

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204078Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

NDA 204078

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PMR/PMC Description: Conduct an in vitro assay using Chinese hamster ovary cells to evaluate the potential for neostigmine methylsulfate to produce chromosomal damage.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/02/2013</u>
	Study Completion:	<u>02/03/2014</u>
	Final Report Submission:	<u>05/01/2014</u>
	Other:	<u>N/A</u>

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the genotoxic potential of this drug, given the long clinical experience these studies were deemed acceptable as post-marketing requirements.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Genetic toxicology studies are conducted to ascertain the potential for a compound to interact with and damage DNA. DNA damage is believed to contribute to the potential for carcinogenicity. For a drug product indicated for acute use, carcinogenicity studies are generally not required in the absence of a genotoxic cause for concern. The goal of the study is to evaluate the genotoxic potential of neostigmine using the current standard battery of studies. The results will be used to update the drug product label and may identify concerns that would require additional studies.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?  
If the study or trial will be performed in a subpopulation, list here.

The study is a genetic toxicology study that will be conducted to complete the standard battery of studies as per ICH S2(R1).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

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Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

NDA 204078

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PMR/PMC Description: Conduct an in vivo mouse micronucleus assay for chromosomal damage for neostigmine methylsulfate.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/02/2013</u>
	Study/Trial Completion:	<u>02/03/2014</u>
	Final Report Submission:	<u>05/01/2014</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the genotoxic potential of this drug, given the long clinical experience these studies were deemed acceptable as post-marketing requirements.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Genetic toxicology studies are conducted to ascertain the potential for a compound to interact with and damage DNA. DNA damage is believed to contribute to the potential for carcinogenicity. For an acute drug product, carcinogenicity studies are generally not required in the absence of a genotoxic cause for concern. The goal of the study is to evaluate the genotoxic potential of neostigmine using the current standard battery of studies. The results will be used to update the drug product label. ICH guidelines require three different assays to assess genotoxicity. To date the Sponsor has only conducted one of these assays (the in vitro bacterial reverse mutation assay or Ames test).

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?  
If the study or trial will be performed in a subpopulation, list here.

The study is a genetic toxicology study.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

*Continuation of Question 4*

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

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- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

NDA 204078

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PMR/PMC Description: Conduct a fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/14/2014</u>
	Study/Trial Completion:	<u>03/02/2015</u>
	Final Report Submission:	<u>12/30/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of neostigmine on fertility and early embryonic development, given the long clinical experience these studies were deemed acceptable as a post-marketing requirement. At the time of approval, the drug product label will indicate that there are no data to address the effects of neostigmine on fertility, and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A fertility and early embryonic development study is generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

Deleted: 5/29/2013

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?  
If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo fertility and early embryonic development study in the rat model.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials

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- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

NDA 204078

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PMR/PMC Description: Conduct an embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/14/2014</u>
	Study/Trial Completion:	<u>10/01/2014</u>
	Final Report Submission:	<u>08/03/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
- Unmet need
  - Life-threatening condition
  - Long-term data needed
  - Only feasible to conduct post-approval
  - Prior clinical experience indicates safety
  - Small subpopulation affected
  - Theoretical concern
  - Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of neostigmine on embryo-fetal development, given the long clinical experience these studies were deemed acceptable as post-marketing requirements. At the time of approval, the drug product label will indicate that there are no data to address the effects of neostigmine on teratogenicity, and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Two embryo-fetal developmental toxicology studies (rat and rabbit models) are generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

Deleted: 5/29/2013

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?  
If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo embryo-fetal developmental toxicology study using the rat model.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

*Continuation of Question 4*

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Deleted: 5/29/2013

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

NDA 204078

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PMR/PMC Description: Conduct an embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/01/2014</u>
	Study/Trial Completion:	<u>01/30/2015</u>
	Final Report Submission:	<u>11/30/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
- Unmet need
  - Life-threatening condition
  - Long-term data needed
  - Only feasible to conduct post-approval
  - Prior clinical experience indicates safety
  - Small subpopulation affected
  - Theoretical concern
  - Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of neostigmine on embryo-fetal development, given the long clinical experience this study was deemed acceptable as a post-marketing requirement. At the time of approval, the drug product label will indicate that there are no data to address the effects of neostigmine on teratogenicity, and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Two embryo-fetal developmental toxicology studies (rat and rabbit models) are generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

Deleted: 5/29/2013

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?  
If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo embryo-fetal developmental toxicology study using the rabbit model.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Deleted: 5/29/2013

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

NDA 204078

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PMR/PMC Description: Conduct a peri- and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/14/2014</u>
	Study/Trial Completion:	<u>12/30/2015</u>
	Final Report Submission:	<u>12/30/2016</u>
	Other:	<u>N/A</u>

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of neostigmine on peri- and post-natal development, given the long clinical experience this study was deemed acceptable as a post-marketing requirement. At the time of approval, the drug product label will indicate that there are no data to address the effects of neostigmine on peri- and post-natal development, and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A peri- and post-natal developmental toxicology study is generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

Deleted: 5/29/2013

8. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)?  
If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo peri- and post-natal developmental toxicology study using the rat model.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

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Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

10. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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ALLISON MEYER  
05/30/2013

JUDITH A RACOOSIN  
05/30/2013

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	<b>BLOXIVERZ™ (neostigmine methylsulfate) injection, for intravenous use</b>
Applicant	Éclat Pharmaceuticals, LLC
Application/Supplement Number	NDA 204078
Type of Application	Original
Indication(s)	For the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery (b) (4)
Established Pharmacologic Class <sup>1</sup>	Cholinesterase Inhibitor
Office/Division	ODE II/DAAAP
Division Project Manager	Allison Meyer
Date FDA Received Application	July 31, 2012
Goal Date	May 31, 2013
Date PI Received by SEALD	May 30, 2013
SEALD Review Date	May 30, 2013
SEALD Labeling Reviewer	Abimbola Adebawale
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A (not applicable):** This item does not apply to the specific PI under review.

# Selected Requirements of Prescribing Information

## Highlights (HL)

### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPERCASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *White space is missing before the Product Title, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions and Use in Specific Populations headings in HL.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:** *Under the Use in Specific Populations heading in HL, the reference is missing for the first bulleted item.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required

## Selected Requirements of Prescribing Information

• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

- YES** 10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

- N/A** 12. All text must be **bolded**.

**Comment:**

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

**Comment:**

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

**Comment:**

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

**Comment:**

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

**Comment:**

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

**Comment:**

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:** *The required statement in the Indications and Usage section of HL should read as: “BLOXIVERZ is a cholinesterase inhibitor indicated for the reversal of the effects...” not “BLOXIVERZ, a cholinesterase inhibitor, is indicated for the reversal of the effects...”(see 21CFR 201.57 (a) (6)).*

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

**Comment:**

## Selected Requirements of Prescribing Information

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- N/A** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment: *Horizontal line between TOC and FPI is missing. Insert.*

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

## Selected Requirements of Prescribing Information

Comment:

**YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

**YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

**YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

**YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

### Full Prescribing Information (FPI)

#### GENERAL FORMAT

**YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

**YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

**NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>

## Selected Requirements of Prescribing Information

<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:*** There are periods after the numbers for the section and subsection headings. Delete the periods after the numbers in both the FPI and the TOC (see table above).

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

***Comment:***

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

***Comment:***

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

***Comment:***

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

***Comment:***

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

***Comment:***

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

***Comment:***

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

***Comment:***

## Selected Requirements of Prescribing Information

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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ABIMBOLA O ADEBOWALE  
05/30/2013

LAURIE B BURKE  
05/30/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: May 13, 2013

Reviewer: Jung Lee, RPh  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: (b) (4) (Neostigmine Methylsulfate Injection, USP),  
5 mg/10 mL (0.5 mg/mL) and 10 mg/10 mL (1 mg/mL)

Application Type/Number: NDA 204078

Applicant: Éclat Pharmaceuticals, LLC

OSE RCM #: 2013-891

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and insert labeling for (b) (4) (Neostigmine Methylsulfate) (NDA 204078) for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND AND REGULATORY HISTORY

Neostigmine Methylsulfate injection, USP is a parasympathomimetic agent that has been used by anesthesiologists for decades for the reversal of neuromuscular blockade after surgery. There are currently no FDA approved formulations of Neostigmine Methylsulfate injection on the market. The proposed formulation of Neostigmine Methylsulfate injection, USP will contain the preservative, phenol, which is different from the previously marketed U.S. formulations. NDA 204078 was submitted by the Applicant on July 31, 2012.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the February 13, 2013 labeling submission.

- Active Ingredient: Neostigmine Methylsulfate Injection, USP
- Indication of Use: Cholinesterase inhibitor indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strengths: 5 mg/10 mL (0.5 mg/mL) and 10 mg/10 mL (1 mg/mL)
- Dose and Frequency: Initial Dose – 30 mcg/kg; additional doses may be given up to a total of 70 mcg/kg (or 5 mg, whichever is less); doses should be injected slowly over a period of at least 1 minute
- How Supplied: Ten 10 mL multiple dose vials; Vials will be individually packaged in cardboard cartons with the package insert. The cartons are then shrink wrapped in packages of 10.
- Storage: 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Protect from light. Store in carton until time of use
- Container and Closure System: (b) (4)

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched FDA Adverse Event Reporting System (FAERS) database for neostigmine medication error reports. We also reviewed the (b) (4) labels and package insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

<b>Table 1: FAERS Search Strategy</b>	
Date	August 28, 2012 to April 12, 2013 (since last AERS search was conducted August 28, 2012)
Drug Names	Active Ingredient: Neostigmine
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified one case.

### 2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 22, 2013 (Appendix B)
- Carton Labeling submitted April 22, 2013 (Appendix C)
- Insert Labeling submitted February 13, 2013

### 2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed (b) (4) (OSE Review #2012-1763 dated November 15, 2012) and we looked at the reviews to ensure all our recommendations were implemented. The significant revisions implemented by the Applicant include the (b) (4)

Any previous recommendations not implemented in this latest label submission will be restated in this review along with any new recommendations.

---

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

### 3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the (b) (4) product design as well as the associated label and labeling.

#### 3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, one neostigmine medication error case remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Appendix D provides a listing of the case number summarized in this review.

##### 3.1.1 Wrong Drug (n=1)

One case of wrong drug was identified in which Zemuron was given instead of neostigmine. The patient was not harmed and required very little time for the drug to wear off. According to the report, the root cause was attributed to the fact the vials were stored close to each other inside the anesthesia cart and both vials have a similar yellow top.

We evaluated the label and labeling for Zemuron and our proposed product, (b) (4) to determine if their labels and labeling were adequately differentiated. Both products have a similar vial size of 10 mL; however, Zemuron's vial consists of a yellow cap while the proposed product, (b) (4)

In addition, Zemuron's container label consists of a bottom label (black font on a white background) and a top label (black font on a red background). The top red label is intended to be peeled off the vial for attachment to a prepared syringe. In contrast, (b) (4) container label consists of black font on a white background with a gray color block highlighting the 5 mg/10 mL strength statement and a red color block highlighting the 10 mg/10 mL strength statement, both of which are printed in white font. Overall, despite the similar vial size (10 mL) of (b) (4) and Zemuron, we find there is enough differentiation between the labels and labeling and lid colors between these two products that this would not lead to confusion.

#### 3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

We reviewed the proposed package insert, container label, and carton labeling and determined the proposed label and labeling can be improved to increase the readability and prominence of important information. As previously stated in OSE Review #2012-1763, we noted (b) (4)

As such, it is likely that

<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

using “milligrams” (or the abbreviation “mg”) will lead to less confusion and calculation errors because the proposed concentration (0.5 mg/mL and 1 mg/mL) incorporates the ‘milligram’ unit of measurement and commonly used drug databases (hardcopy and electronic) also reference the unit of measurement in milligrams (e.g., Facts and Comparisons, Clinical Pharmacology, and MicroMedex).”

#### 4 RECOMMENDATIONS

The Applicant submitted revised carton and container labeling on April 22, 2013 following a request from the Agency on April 19, 2013. DMEPA will request any recommendations not addressed from the previous review (OSE review #2011-4219) as well as some additional recommendations be implemented to improve the readability and promote the safe use of the product prior to approval of this NDA supplement:

##### 4.1 COMMENTS TO THE DIVISION

DMEPA provides the following recommendations from OSE review #2012-1763 for consideration by the review division prior to approval of this NDA:

###### A. Insert Labeling

1. Revise the units of measurement for the recommended dosing to only present milligrams or mg/kg [REDACTED] (b) (4).  
[REDACTED] Milligram is the unit of measurement that is commonly used in drug databases (e.g., Facts and Comparisons, Clinical Pharmacology, and MicroMedex) and is used to designate the product’s strength.
2. In the How Supplied Sub-Section of the Full Prescribing Information portion of the labeling, revise the description of the vial size to reflect the packaging type. For example, revise the statement [REDACTED] (b) (4) to read “10 mL multiple dose vials supplied in packages of 10.”

##### 4.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to the approval of this NDA.

###### A. All Container Labels and Carton Labeling (5 mg/10 mL and 10 mg/10 mL)

1. Revise the presentation of the proprietary name from all upper case letters [REDACTED] (b) (4) to title case [REDACTED] (b) (4) to improve readability.
2. Revise the presentation of the proprietary name [REDACTED] (b) (4) for clarity and to improve readability.
3. [REDACTED] (b) (4)
4. Remove or decrease the size and prominence of the company name and logo so that it does not distract from important identifying drug information. The company name and logo is problematic because it is currently equally or

more prominent than the established name on the container label and the proprietary and established name on the carton labeling.

- B. Container Label (5 mg/10 mL and 10 mg/10 mL)
  - 1. Include a space between the number and unit. For example, 5 mg/10mL should read 5 mg/10 (space) mL and 10 mg/10mL should read 10 mg/10 (space) mL.
  - 1. Reformat the strength statement to appear in a stacked format to help with the readability of this information. The format of the strength statement should appear similar to the currently proposed format on the carton labeling.
  - 2. Relocate and revise the “Rx ONLY” statement from the principal display panel to the side panel and to appear as “Rx Only.”
- C. Carton Labeling (5 mg/10 mL and 10 mg/10 mL)
  - 1. Include a space between the number and unit. For example, 5 mg/10mL should read 5 mg/10 (space) mL and 10mg/10mL should read 10 (space) mg/10 (space) mL.
  - 2. Relocate the “Manufactured for” statement on the principal display panel to the side panel to help increase the readability of the most important information.
  - 3. Relocate the route of administration statement, “For Intravenous Use,” to appear above the net quantity statement similar to the presentation of the statement on the container label.

If you have further questions or need clarifications, please contact Teena Thomas, project manager, at 301-796-0549.

## **APPENDICES**

### **APPENDIX A. DATABASE DESCRIPTIONS**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/  
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JUNG E LEE  
05/13/2013

JAMIE C WILKINS PARKER  
05/13/2013

SCOTT M DALLAS  
05/14/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 13, 2013

**To:** Allison Meyer  
Senior Regulatory Project Manager  
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

**From:** Eunice Chung-Davies, PharmD., Regulatory Review Officer  
Office of Professional Drug Promotion (OPDP)

**Subject:** OPDP's comments for NDA 204078  
(b)(4) (neostigmine methylsulfate injection)

---

On May 1, 2013, OPDP received a consult request from DAAAP to review the proposed package insert for (b)(4) (neostigmine methylsulfate injection)

OPDP has reviewed the proposed labeling using the following version of the proposed package insert:

- Neostigmine 5 1 13 clean.doc (emailed from Allison Meyer on May 1, 2013)

Upon review of the proposed labeling, OPDP offers the following comments.

If you have any questions regarding the package insert, please contact Eunice Chung-Davies at 301-796-4006 or [eunice.chung-davies@fda.hhs.gov](mailto:eunice.chung-davies@fda.hhs.gov).

Enclosure:  
Marked up Package Insert

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/s/  
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EUNICE H CHUNG-DAVIES  
05/13/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date	November 15, 2012
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, R.Ph. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strength(s)	(b) (4) (Neostigmine Methylsulfate) Injection, USP 0.5 mg/mL and 1 mg/mL
Application Type/Number	NDA 204078
Applicant	Éclat Pharmaceuticals, LLC
OSE RCM #:	2012-1763

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for (b) (4) (NDA 204078) for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND

Currently there are no approved formulations of Neostigmine Methylsulfate Injection in the marketplace. If approved, this may be the first such product available.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the August 1, 2012 label and labeling submission.

- Active Ingredient: Neostigmine Methylsulfate Injection, USP
- Indication of Use: cholinesterase inhibitor indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery
- Route of Administration: intravenous
- Dosage Form: Injection
- Strength: 0.5 mg/mL and 1 mg/mL
- Dose and Frequency: initial dose – 30 mcg/kg; additional doses may be given up to a total of 70 mcg/kg (or 5 mg, whichever is less); doses should be injected slowly over a period of at least 1 minute
- How Supplied: Ten 10 mL multiple dose vials; Vials will be individually packaged in cardboard cartons with the package insert. The cartons are then shrink wrapped in packages of 10
- Storage: 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Protect from light. Store in carton until time of use
- Container and Closure System: (b) (4)

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Neostigmine Injection medication error reports. We also reviewed the (b) (4) container label, carton and insert labeling submitted by the Applicant.

## 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

<b>Table 1: AERS Search Strategy</b>	
Date	April 18, 2012 through August 28, 2012 (since last AERS search was conducted April 18, 2012)
Drug Names	active ingredient: Neostigmine verbatim term: Neostig% verbatim term: Prostig%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database searches identified 2 reports. Each report was reviewed for relevancy and duplication. After individual review, both reports were not included in the final analysis for the following reasons:

- Complaint regarding the practice of referring to the drug names ‘neosynephrine’ and ‘neostigmine’ as simply “neo” in the medical community; and
- Overdose of Vecuronium where Neostigmine was identified as a concomitant drug and not involved in a medication error

## 2.2 LITERATURE SEARCH

We searched the ISMP publications on September 4, 2012 for additional cases and actions concerning Neostigmine. There were no additional cases identified.

## 2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 1, 2012 (Appendix A)
- Carton Labeling submitted August 1, 2012 (Appendix B)
- Insert Labeling submitted August 1, 2012 (no image)

---

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

## 2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed an internal signal analysis involving label confusion (OSE 2008-22 dated January 15, 2008) between Neostigmine and Etomidate labels (manufacturers American Regent and Ben Venue Laboratories, respectively). We did not find similarity among the labels and there was no further assessment.

## 2.5 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

In our evaluation of the proposed container label and carton labeling, (b) (4)  
the identifying product information is presented in black font on a white background (b) (4)

We note the Dosage and Administration section of the insert labeling uses 2 different units of measurement (e.g., the recommended initial dose is 30 *mcg*/kg; additional doses up to a total dose of 70 *mcg*/kg [or 5 *mg*, whichever is less]). Typically, we recommend consistency in the units of measure throughout product labeling to avoid medication errors due to miscalculation or misinterpretation. As such, it is likely that using “milligrams” (or the abbreviation “mg”) will lead to less confusion and calculation errors because the proposed concentration (0.5 mg/mL and 1 mg/mL) incorporates the ‘milligram’ unit of measurement and commonly used drug databases (hardcopy and electronic) also reference the unit of measurement in milligrams (e.g., Facts and Comparisons, Clinical Pharmacology, and MicroMedex). In addition, we note the proposed container label and carton labeling (b) (4)

However, the Dosage and Administration section does not (b) (4) Thus, DMEPA discussed our concerns with the review division (b) (4) on the container label and carton labeling. The review division agreed that the (b) (4) and the dosing should be presented in unit of milligrams solely (b) (4)

Finally, in our evaluation of this proposed package configuration, the vial sizes and strengths appear to be appropriate for this drug product and are reasonable in view of the recommended dosing and indication of use. Additionally, the NDC numbers stated in the How Supplied section of the insert labeling reflect the different package sizes.

## 3 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label/labeling and to bring the presentation of information up to current standards. See Section 4 below.

## 4 RECOMMENDATIONS

### 4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

#### A. Insert Labeling

1. Revise the units of measurement for the recommended dosing to only present milligrams or mg/kg [REDACTED] (b) (4).  
[REDACTED] Milligrams is the unit of measurement that is commonly used in drug databases and is used to designate the product's strength.
2. In the How Supplied Sub-Section of the Full Prescribing Information portion of the labeling, revise the description of the vial size to reflect the packaging configuration. For example, revise the statement [REDACTED] (b) (4) [REDACTED] to read "10 mL multiple dose vials supplied in packages of 10".

### 4.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to the approval of this NDA:

#### B. All Container Labels and Carton Labeling (0.5 mg/mL and 1 mg/mL)

1. Ensure that the letters of the established name are at least half as large as the letters comprising the proprietary name on all strengths and packaging configurations taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. [REDACTED] (b) (4)
3. [REDACTED] (b) (4)
4. After the established name, add the total drug content (TDC) to reflect the total amount of drug available for use in one 10 mL vial. The TDC should then be followed by the concentration per milliliter within parenthesis and in smaller sized font in accordance with the USP General Chapter <1> Injections. For example,

(Neostigmine Methylsulfate Injection, USP)  
10 mg/10 mL  
(1 mg/mL)

5. Ensure space is allocated for placement of the lot number and expiration date for this drug product.
  6. Revise the strength statement “1.0 mg/mL” to read “1 mg/mL” on all label and labeling for this proposed strength. The use of trailing zeros is error prone because the reader may overlook the decimal point resulting in dosing errors.
  7. Decrease size and prominence of the company name and logo so that it does not distract from important identifying drug information. The company name and logo is problematic, because it currently more prominent than the established name on the container label and the proprietary and established name on the carton labeling.
- C. Container Label (10 mL vial, 0.5 mg/mL and 1 mg/mL)
1. Following the statement “For Intravenous Use” (located on the principal display panel), add the statement, “ Multiple Dose Vial” to indicate the container type for this product.
  2. Relocate the “Mfg for” statement to the side panel to help increase the readability of the most important information. If additional space is needed on the side panel, then consider deleting the “See USP Controlled Room Temperature” and or “Directions for Use: See Package Insert” statement(s).
- D. Carton Labeling
1. Revise the net quantity statement and package type to appear as “10 mL Multiple Dose Vial”, and relocate the statements away from the strength. Generally the net quantity and package type statement appears in the lower portion or in the upper right hand corner of the principal display panel.
  2. Unbold the “Rx Only” statement.
  3. The proprietary name and established name are separated by an intervening red line. In accordance with 21CFR 201.10(a), the proprietary name, and established name should appear together without any intervening written, printed, or graphic matter. Revise this label to remove the line separating the proprietary name and the established name.
  4. Revise the statement (b) (4) to read as separate statements consistent with recommendation C1.

If you have further questions or need clarifications, please contact Danyal Chaudhry, OSE Project Manager, at 301-796-3813.

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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**Appendix H:** ISR numbers of cases discussed in this review

ISR# 8508089-5

ISR# 8588188-2

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/s/  
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DENISE V BAUGH  
11/15/2012

LUBNA A MERCHANT  
11/15/2012

SCOTT M DALLAS  
11/16/2012

CAROL A HOLQUIST  
11/16/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 204078 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: <span style="background-color: #cccccc; color: #000080;">(b) (4)</span> (proposed) Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection Strengths: 0.5 mg/mL and 1.0 mg/mL		
Applicant: Eclat Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: July 31, 2012 Date of Receipt: July 31, 2012 Date clock started after UN:		
PDUFA Goal Date: May 31, 2013	Action Goal Date (if different):	
Filing Date: September 29, 2012	Date of Filing Meeting: September 11, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): <span style="background-color: #cccccc; color: #000080;">(b) (4)</span>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" 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: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> 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"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input 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  Other:	<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) <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): 106574				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, 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 no, 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			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		x		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<b>User Fee Status</b>  <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 Unacceptable for Filing (UN) letter and contact user fee staff.</i>		<b>Payment for this application:</b>  <input checked="" type="checkbox"/> Paid <input 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>		<b>Payment of other user fees:</b>  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)  (NDAs/NDA Efficacy Supplements only)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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 is 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)]?			x		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>			x		
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<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>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b>			x		

<a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		x		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		x		
<b>If yes</b> , 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	
<b>Format and Content</b>				
<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)  X CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	x			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	x			

<sup>1</sup>  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<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)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	x			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	x			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA 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></p>				
<p><b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b></p>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> 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	

<p><b>Controlled Substance/Product with Abuse Potential</b></p>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u>  Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u>  Date of consult sent to Controlled Substance Staff:</p>			x	

<p><b>Pediatrics</b></p>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	xx			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	x			
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			x	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			xx	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		xx		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		x		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? <sup>4</sup>	x			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)?	x			5/16/12

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>Date(s):</b> 5/16/12				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>		x		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		x		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** September 11, 2012

**BLA/NDA/Supp #:** 204078

**PROPRIETARY NAME:** (b) (4) (proposed)

**ESTABLISHED/PROPER NAME:** Neostigmine Methylsulfate

**DOSAGE FORM/STRENGTH:** Injection/0.5 mg/mL and 1.0 mg/mL

**APPLICANT:** Eclat Pharmaceuticals

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** (b) (4)

**BACKGROUND:** Neostigmine has been submitted as a literature based 505(b)(2) NDA.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Allison Meyer	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Chris Breder		Y
Clinical	Reviewer:	Art Simone	Y
	TL:	Chris Breder	Y
Clinical Pharmacology	Reviewer:	Suresh Naraharansetti	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Huiqing Hao	Y

	TL:	Dan Mellon	Y
Product Quality (CMC)	Reviewer:	Edwin Jao	Y
	TL:	Prasad Peri	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Erica Pfeiler	Y
	TL:	John Metcalfe	N
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
Other reviewers: Biopharmaceutics	Elsbeth Chikhale		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></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"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></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
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></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><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></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"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<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
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	<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
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<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
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li> <li>    <b>If no</b>, was a complete EA submitted?   <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> <li>    <b>If EA submitted</b>, consulted to EA officer (OPS)?   <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable
<u><b>Quality Microbiology (for sterile products)</b></u>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)   <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></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><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></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><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Bob Rappaport or Rigoberto Roca

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<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"> <li>• 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)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Allison Meyer

9/27/12

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Regulatory Project Manager

Date

---

Chief, Project Management Staff

Date

## 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.

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

/s/  
-----

ALLISON MEYER  
10/10/2012

PARINDA JANI  
10/10/2012

**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:** 7/11/2012

**Reviewer(s):** Martin Pollock, Pharm. D., Safety Evaluator  
James Kaiser, M.D., Medical Officer Team Leader  
Division of Pharmacovigilance II (DPV-2)

**Team Leader:** Lauren Choi, Pharm. D., DPV-2

**Deputy Division Director:** Bindi Nikhar M.D., DPV-2

**Product Name(s):** Neostigmine (injection)

**Subject:** All adverse events

**NDA Number:** 204078

**Applicant/Sponsor:** Eclat Pharmaceuticals

**OSE RCM #:** 2012-239

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## EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has received a literature-based NDA (204078) for neostigmine injection, a currently marketed unapproved product. The sponsor's proposed indication is for reversal of neuromuscular blockade. DAAAP requested a review of AERS<sup>1</sup> and the published literature for postmarketing adverse events associated with neostigmine in order to determine if there is any new information that should be incorporated into the sponsor's proposed neostigmine label.

Our review of AERS data identified 217 reports. Neostigmine was used for NMB reversal in most (69%) cases, followed by various other indications (22%; most common: GI tract stimulation); this information was not reported in the remaining 9% of the cases. The most common reactions were cardiac and respiratory events such as cardiac arrest and respiratory depression which are known events consistent with the cholinergic activity of neostigmine. Our analysis of all events reported in this case series, including fatalities, did not identify any new safety issue, for which the proposed label can be strengthened or new events could be added. There were 34 deaths reported in this case series, all of which were not directly related to neostigmine. Given that neostigmine is commonly administered in a setting of surgery along with many other medications, attribution to neostigmine could not be established in many of the AERS cases.

We found 52 reports from our literature search.<sup>2</sup> We found events that were labeled or consistent with what is labeled. This did not reveal any new safety concerns not addressed in the sponsor's proposed label. Reversal of nondepolarizing NM block was the most common indication (n=23); most common other indication was treatment of nonmechanical intestinal obstruction (n=15). There were 7 deaths of various causes. Four occurred days to weeks after neostigmine administration; one occurred nearly a day after completion of abdominal surgery; one occurred during an illness that was postulated to have resulted in an overdose; and one occurred after bradycardia in a patient with myasthenia gravis. Labeled events for proposed indicated use or other indications included cardiac events, (e.g. asytle, bradycardia, hypotension), anaphylaxis, and bronchospasm. In addition, cases were reported of increased or decreased neostigmine effects attributed to renal failure, other drugs, and abnormal cholinesterase activity.

As there were no safety risks identified from AERS and literature that merit changing the proposed neostigmine label, we have no recommendations beyond routine safety monitoring at this time.

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<sup>1</sup>Adverse Event Reporting System

<sup>2</sup>For published articles of a patient(s) experiencing an adverse event(s) after receiving neostigmine that the sponsor did not submit to this NDA and or were not present in AERS (for which there were 44 citations representing 48 patients).

## 1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has received a literature-based NDA (204078) for neostigmine injection, a currently marketed unapproved drug product. The sponsor's (Eclat Pharm) proposed indication is for reversal of neuromuscular blockade. No new clinical safety or efficacy studies have been conducted for this application. Safety-related information from the sponsor's proposed label is in Appendix 8.1. DPV-2 has reviewed neostigmine adverse events (AEs) from AERS and the published literature in order to determine if there is any new safety information that should be incorporated into the sponsor's proposed neostigmine label.

## 2 METHODS

### 2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched as shown in Table 2.1

<b>Table 2.1 AERS Search Strategy*</b>	
Date of search	1/25/12
Time period	1/1/69 to 1/25/12
Product Term	Neostigmine (active ingredient search)
MedDRA Search Terms	None; all events were retrieved

\*See Appendix 8.5 for the description of the AERS database.

### 2.2 LITERATURE SEARCH

The literature search was conducted as shown in Table 2.2

<b>Table 2.2 Literature Search Strategy</b>	
Date of search	3/28/12
Database	PubMed
Search Terms	In title: "neostigmine" and "adverse"
Years included in search	Unrestricted
Language	English

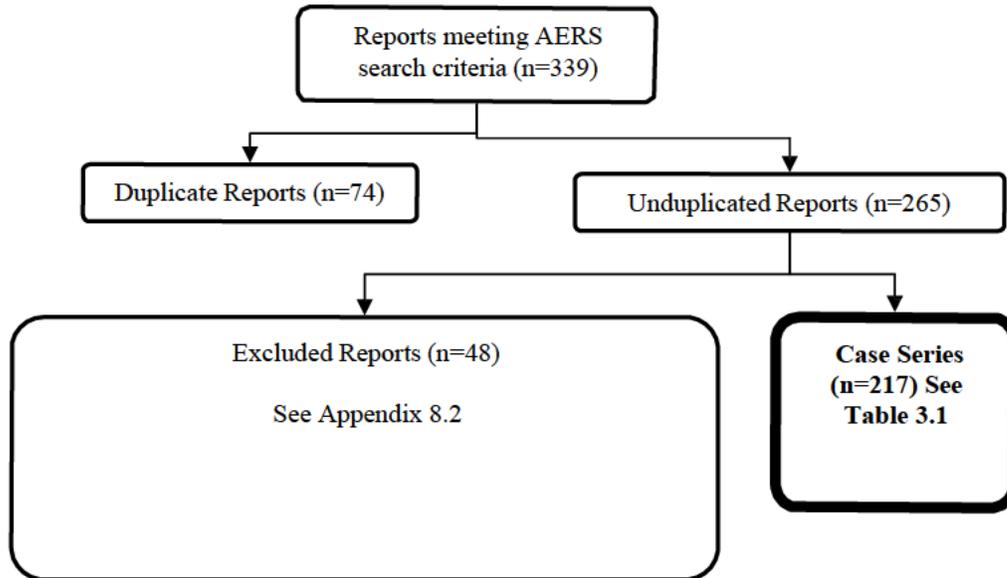
We retained for further review literature case reports and reports of deaths in clinical studies that had not been submitted to the NDA or to the postmarketing adverse event reporting system (AERS).

### 3 RESULTS

#### 3.1 AERS CASES

##### 3.1.1 AERS CASE SELECTION

Figure 3.1.1 AERS CASE SELECTION



The analysis of all events reported in this case series did not find any new safety issue for which the proposed label can be strengthened or new events could be added. Confounding factors in AERS cases include concomitant medications, medical history (surgical or procedural complications occurring before neostigmine administration), and/or the lack of sufficient clinical information.

##### 3.1.2 LABELED EVENTS FROM AERS FOR ALL INDICATIONS

The most commonly reported indication in our neostigmine AERS case series (n=217) was neuromuscular blocker (NMB) reversal (n=150; 69%). The remaining cases reported other (n=47; 22%) or unknown indications (n=20; n=9%). Almost one-half (21/47; 45%) of the ‘other’ indications were for GI tract stimulation; the remaining were amenorrhea (12), myasthenia gravis (9), spinal anesthesia (3), and urinary retention (1).<sup>3</sup>

There were 726 reported events for all indications, approximately half of which are labeled. (Table 3.1.2.1)

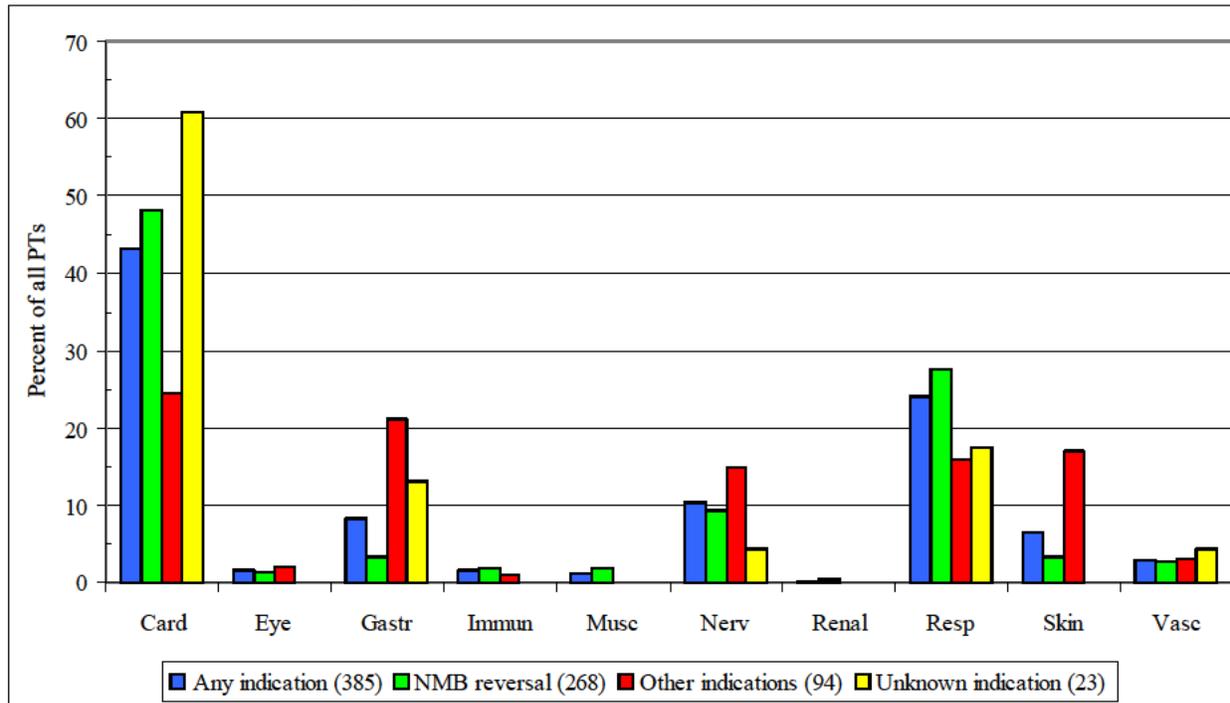
<sup>3</sup>One of the 47 ‘other’ indications was inadvertent neostigmine administration (medication error).

**Table 3.1.2.1 All events by reported indication and label status**

Indication	Events	Labeled	Unlabeled
NM reversal	512	268	244
Other	174	94	80
Unknown	40	23	17
Total	726	385	341

The *labeled* events (n=385), by reported indication, are shown in Figure 3.1.2.

**Figure 3.1.2. Labeled neostigmine events by SOC (system organ class) and reported indication**



Across all indications, the three most common groups of events (in descending order) were cardiac, respiratory and nervous. There was a disproportionate number of reported events for “*other indications*” under gastrointestinal, nervous and skin SOCs. This is due to a cluster of 10 cases where neostigmine was used for amenorrhea in patients who experienced (and recovered from) ‘dysphagia, nausea, cold sweat and asthenia’ after the administration of the drug.

The labeled events as PTs (preferred terms) are listed in Table 3.1.2.2.

**TABLE 3.1.2.2 LABELED EVENTS AS PTS<sup>4</sup> BY INDICATION<sup>5</sup>**

	Reported indication		
	NMB Reversal	Other	Unknown
<b>SOC (All)</b>	268	94	23
<b>Cardiac SOC (All)</b>	129	23	14
Cardio and/or respiratory arrest	27	4	9
Bradycardia or decreased heart rate	23	8	
Tachycardia or heart rate increased	19	2	
Arrhythmias (ventricular, atrial, NOS)	18	2	2
Hypotension or blood pressure decreased	14	4	1
Atrioventricular block	13		1
EKG abnormal	10		
Myocardial infarction	2		
<b>Resp SOC (All)</b>	74	15	4
Oxygen saturation decreased/hypoxia	15		
Respiratory arrest, depression, distress or failure	13	3	2
Dyspnoea or apnoea	12	3	1
Bronchospasm or laryngospasm	7	4	1
Respiratory acidosis	4		
Cyanosis	3	2	
Hypercapnia	3		
Increased bronchial secretion/laryngoedema	3		
Stridor or wheezing	3		
Cough	2		
Hypoventilation	2		
Respiration abnormal	2	1	
<b>Nervous SOC All</b>	25	14	1
Sedation, somnolence or asthenia	10	11	1
Coma or LOC	7	1	
Convulsion	3		
<b>GI SOC (All)</b>	9	20	3
Nausea or vomiting	4	11	2
Abdominal pain/pain	2	2	
Diarrhoea	2	3	
<b>Skin SOC (All)</b>	9	16	
Rash/erythema/urticaria	7	3	
<b>Vascular SOC (All)</b>	7	3	1
Shock/circulatory collapse	5		1
Flushing	2		
<b>Immune SOC (All)</b>	5	1	
Anaphylaxis/hypersensitivity	5		
<b>Musc SOC (All)</b>	5		
Muscle spasms/twitching	4		

<sup>4</sup>Blank cells mean zero reports.

<sup>5</sup>Within any particular SOC, related-PTs were grouped together. For NMB reversal, PTs with a single report are not listed.

	Reported indication		
	NMB Reversal	Other	Unknown
<b>Eye SOC (All)</b>	4	2	
Miosis/visual changes	4	2	

### 3.1.3 NMB REVERSAL (n=150)

Demographic and other information from the cases reporting neostigmine use for NMB reversal are in Table 3.1.2.3

<b>Age</b> (132)	Mean (46.6); median( 49.5); range (2 months to 87 years); pediatric (15)
<b>Sex</b> (135)	Female (69); male (66)
<b>Received year</b> (150)	1970's (4); 1980's (5); 1990's (34); 2000's (80); 2010-11 (27)
<b>Country</b> (150)	U.S. (89); foreign (61)
<b>Report type</b> (150)	Direct (51); periodic (8); expedited (91; literature [39])
<b>Serious Outcomes</b> (126) <sup>6</sup>	Death (18); hospitalization (46); life-threatening (29); disability (5); Other (63)
<b>Recovery [for non-fatal, (132)]</b>	Yes (104); no (1); unknown (27)
<b>Time to event onset</b> [excluding drug ineffective, (95)]	<60 <b>minutes</b> : <60 (n=53; range 1 to 45 min) ≥1 and <24 <b>hours</b> : (n=30; 1 to 20 hours) ≥1 <b>day</b> : (n=12; 1 to 7 days)
<b>Dose</b> (57)	Within recommended: yes (51); no (6; [low 4], high [2])
<b>Procedure</b> (101)	Top 3: GI/abdominal (43); ENT (15); reproductive (12); complete list of procedures is in Appendix 8.4
<b>Anticholinergic co-administration</b> (100)	Glycopyrrolate (64); atropine (36)
<b>NMB that neostigmine reversed</b> (132) <sup>7</sup>	Vecuronium (39); rocuronium (34); succinylcholine (20); atracurium (19); pancuronium (7); cisatracurium (5) curare-related (4); <sup>8</sup> mivacurium (3); doxacurium (1); alcuronium (1)

the 18 fatalities (adult, n=17; unknown age, n=1). Most of the fatalities (13/18; 72%) were caused by cardio and/or respiratory arrest (labeled); three other cases were due to agranulocytosis,<sup>9</sup> anaphylaxis, and multi-organ failure (MOF), respectively. The MOF case (54-year-old female) was confounded by ~25% of her body being burned in a house fire and having received 27 other drugs besides neostigmine.<sup>10</sup> In the

<sup>6</sup>Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events; *Cases are not mutually exclusive.*

<sup>7</sup>Not mutually exclusive.

<sup>8</sup>d-tubocurarine (3); curare (1).

<sup>9</sup>Although the role of neostigmine cannot be excluded, this 68 year-old female underwent mastectomy and contributing factors could have been any prior breast cancer treatment (e.g. chemotherapy, radiation). Agranulocytosis onset was on Day 8. (neostigmine given on Day 1) and death was on Day 14 during which time other unknown factors could have contributed.

<sup>10</sup>Literature report: Kitamura R, Takeda A, Uchinum E. A case of burn with toxic epidermolysis. *Jap. J. Burn Injuries* 2008;34:89-85.

remaining 2 cases, where the cause of death was not reported, contributing factors were age (75, 87 years), cardiovascular disease (both) and cancer (lung and lymphoma, respectively).

Where known (n=12), 9 patients died within a few days (2-5 days; n=4)<sup>11</sup> to weeks (2-6 weeks; n=5) after neostigmine administration. It is unlikely that a short acting drug like neostigmine could have contributed significantly to the deaths in many of these cases. One of the 9 patients was an 84 year-old female who underwent an unknown procedure, and it was uncertain if she received glycopyrrolate, which was ordered by her physician to counter neostigmine-induced bradycardia. Not receiving this drug could have contributed to the patient's cardiac arrest.

Although, in the remaining 3 of 12 cases, fatal cardio-respiratory arrests<sup>12</sup> occurred on the same day as neostigmine administration, they were all confounded. Two had cardiovascular disease; in the third case, the contributory role of neostigmine could not be discerned from the other concomitant anesthetics administered. Where known (n=4), most (n=3) of the neostigmine dosing was according to the label.<sup>13</sup>

There were 15 pediatric cases. Two-thirds of the patients (n=10) experienced cardiac and/or respiratory events (n=7) or hypersensitivity reactions (n=3) which are labeled<sup>14</sup>. In 2 of the cases with cardiac and/or respiratory events (involving 3 and 16 year-olds), their underlying conditions (AV conduction abnormality<sup>15</sup> and Brugada syndrome<sup>16</sup> respectively) were contributory factors. Four other patients experienced somnolence (1), amnesia/visual acuity reduced (1), aggression/sleep disorder (1), and proteinuria/hematuria (1) respectively; in all cases, there were other drugs and/or an underlying medical condition that could have contributed. The last case involved a 13-month old female, who received a slightly higher (1.14 times) than the recommended dose, and recovered from her extended period (3.5 hrs) of post surgical paralysis (lack of effect). Where known (n=13), all but one<sup>17</sup> recovered from the reported events. Patients' age ranged from 2 months to 16 years; median was 6 years. The most common procedures (n=9) were ENT (n=4) and GI/abdominal (n=3). Neostigmine dosage (n=7), was mostly (n=6) according to the label.

Sixty-nine percent (103/150) of the cases reported unlabeled events. Table 3.1.2.4 lists the unlabeled events *that have a count of 2 or more cases*.

**Table 3.1.2.4 Unlabeled events (n≥2) reported with neostigmine use for NMB reversal**

SOC	Events
Blood (12)	Lymphocyte abnormalities (2); hemoglobin changes (2); decreased protein parameters (2); coagulation abnormalities (2)

<sup>11</sup>In one, a medication error was suspected as glycopyrrolate was intended to be given, but may not have been administered.

<sup>12</sup>Autopsy for one said cause of death was myocardial infarction.

<sup>13</sup>A 47-year-old 48 kg male (experienced cardio-respiratory arrest; history of hypertension and asthma) received 1.26 times the maximal 40 mcg/kg labeled neostigmine dose after having plastic surgery. This patient was given *three* NMB's (succinylcholine, mivacurium and doxacurium) which may explain the excessive neostigmine dose.

<sup>14</sup>Or can be a consequence of a labeled event.

<sup>15</sup>Heard CMB; perioperative considerations in a newly described subtype of congenital long QT syndrome; *Paed. Anaesthes.* 1998;8:93:96.

<sup>16</sup>Kloesel B, Ackerman J, Sprung J, Marr, BJ, Weingarten TN. Anesthetic management of patients with Brugada syndrome: a case series and literature review. *Can. J Anesthes* 2011;58:824-836. From Kloesel 2011: Brugada syndrome manifests as ECG changes (e.g. ST elevation and incomplete bundle branch block). Brugada syndrome is often associated with syncope and sudden death.

<sup>17</sup>A 6-year-old (with a history of flu, fever and cough 2 weeks prior) became comatose after an appendectomy; limited information prevents any further assessment.

Cardiac (15)	Blood pressure increased (11)
Gastrointestinal (7)	GI hemorrhage (2)
General (61)	Drug ineffective (36) <sup>18</sup> ; drug interaction (7); pyrexia (3); malignant hyperthermia (3); injection site complication (3); edema (3); multi-organ failure (2)
Hepatobiliary (14)	Hepatic failure or injury (3); hepatitis (3); bilirubin increased (2); cholestasis or cholelithiasis (2); increased LFT (2)
Infection (3)	Sepsis (2)
Injury and poisoning (35)	Post procedural complication (11); delayed recovery from anesthesia or prolonged NM block (9); medication error-related (6); anesthetic complication (4)
Metabolic (7)	Metabolic acidosis (3)
Musculoskeletal (8)	Rhabdomyolysis-related (3)
Nervous (23)	Paralysis or hypotonia (7); unresponsive to stimuli or hypoaesthesia (5); serotonin syndrome (2); dyskinesia (2)
Psychiatric (10)	Anxiety related <sup>19</sup> (6)
Renal (12)	Hematuria (3); oliguria (2); renal infarct or thrombosis (2)
Respiratory (18)	Pulmonary edema (5); breath sounds abnormal (2); bronchial or pulmonary hemorrhage (2)
Skin (7)	Blister or drug eruption (2)

Adverse events from the General SOC (62 PTs; n=50<sup>20</sup>) and Injury and poisoning SOC (35 PTs; n=29) were the most commonly reported.

For the General SOC, Drug ineffective (n=36 PTs; n=31) was the most reported event<sup>21</sup> which occurred throughout the past 22 years (1990-1999, n=13; 2000-2012, n=18). There was no mention of any pharmaceutical testing data for any of the 31 drug ineffective cases. In most (6/7) of the drug interactions, there were multiple medications administered and there was no pharmacological basis for neostigmine's involvement in the case (e.g., in one case,<sup>22</sup> paroxetine and fentanyl were most likely responsible [for the serotonin syndrome]). The last drug interaction case (prolonged neuromuscular block) reported the use of neostigmine and donepezil (also an anticholinesterase). The patient received succinylcholine (followed by pancuronium); however, the patient's low pseudocholinesterase level was a confounder.

For the Injury and Poisoning SOC the following PTs were most commonly reported: *post procedural complication, delayed recovery from anesthesia and/or prolonged NM block or anesthetic complication*. In most (n=18) cases, the reported PTs in this SOC did not add any clinical information to the other more specific PTs reported in the same case (e.g. in one case, the reported event 'cardiac arrest' was the *post procedural complication*). There were 6 cases where the Injury/Poisoning SOC terms (*delayed recovery from anesthesia and or prolonged NM block*) were the only terms describing the delayed response to NMB reversal.

<sup>18</sup>Includes the following PTS: drug effect decreased, drug effect delayed, drug ineffective, drug resistance, product quality resistance, therapeutic product ineffective, drug effect increased, and drug effect prolonged. The last two terms (n=2, n=1 respectively from 3 patients) referred to an excessive effect of the NMB. Neostigmine was also reported as a suspect drug, in addition to the NMBA decreased effect of neostigmine could not be excluded.

<sup>19</sup>Includes PTs: anxiety, irritability, listless, restlessness, stress

<sup>20</sup>The second 'n' is the number of cases (patients).

<sup>21</sup>29 US and 2 foreign.

<sup>22</sup>One was literature report: Gokcinar D, Karabeyoglu I, Ucar H, Gogus N; Postoperative nystagmus and anisocoria due to serotonin toxicity; *Acta Anaesthes. Scand.* 2006;53:694-695.

There were 4 cases that were coded as medication errors; one was fatal (mentioned above). Another case (dyspnea) claimed that the vial did not contain neostigmine, there was no testing done to confirm. The remaining 2 cases reported bradycardia and tachycardia, respectively; the first case reported neostigmine contamination of atropine (via use of the same needle during preparations) and the second case reported that neosynephrine was mistakenly given with neostigmine.<sup>23</sup>

### 3.1.4 OTHER INDICATIONS (n=47)

Thirty-seven of 47 cases (78%) reported unlabeled events. Table 3.1.2.5 lists unlabeled events *that have a count of 2 or more cases*.

**Table 3.1.2.5 Unlabeled events (n≥2) for other indications**

SOC	Events
Cardiac (3)	Blood pressure increased (2)
Gastrointestinal (31)	Dysphagia (11); diverticular or intestinal perforation (4); abdominal infection (3); oral lesion (3)
General (8)	Drug interaction (2); multi-organ failure (2)
Injury and poisoning (11)	Medication error-related (4); anesthetic complication (3); procedural complication (2)
Renal (4)	Renal failure (3)
Respiratory (5)	Pneumonia (2)

Two SOCs, Gastrointestinal (31 PTs; n=19) and Injury and poisoning (11 PTs; n=9), contained the most unlabeled events. The most commonly reported event in Table 3.1.2.5 is *dysphagia*, which has been explained in Section 3.1.2. Two of the diverticular/intestinal perforations are discussed below (fatalities). The remaining two perforations were more likely due to other drugs (sodium polystyrene sulfonate/sorbitol and thiopental,<sup>24</sup> and prednisolone<sup>25</sup>, respectively).

One of the 2 medication errors (4 PTs; n=2) is described below (fatality). The other case involved a 64-year-old female with ileus who received neostigmine 3 mg instead of 1 mg; she recovered from her bronchospasm.

There were seven fatalities, 6<sup>26</sup> involving medical use and 1 involving an inadvertent administration. The reported neostigmine indication (n=6) was GI tract stimulation (GTS, n=5) and myasthenia gravis (n=1). All had confounding medical history and/or concomitant medications as mentioned below:

More than half (n=4) were due to respiratory-related causes including pulmonary edema, bronchial pneumonia, pulmonary embolism (all unlabeled) and cardio-respiratory arrest (labeled). Each of these 4 cases had contributing medical history including cardiac failure, pulmonary embolism, emphysema, and/or pneumonia. Two patients died from multi-organ failure (MOF);

<sup>23</sup>3 neostigmine ampules were intended to be used; 2 of the 3 vials erroneously ended being neostigmine.

<sup>24</sup>Trottier V, Drolet S, Morcos MW. Ileocolic perforation secondary to sodium polystyrene sulfonate in sorbitol use. *Can. J. Gastroenterol* 2009;10:689-690. This patient's refractory seizures were treated with a 2 day thiopental infusion. Ileus has been reported to occur after this barbiturate coma-treatment.

<sup>25</sup>Mariasy R, Shapiro A, Mitchell T. Bowel perforation in a patient receiving prednisolone for myasthenia gravis. *Post Grad Med J.* 1989;65:428-429

<sup>26</sup>All were adults; age known for 4: median 71 years; range 52 to 91 years.

n=2). In one MOF<sup>27</sup> (GTS, indication), contributing factors were suspected prior GI-tract stenosis and concomitant lactulose administration.<sup>28</sup> The other MOF involved a medication error and a 1-day old infant,<sup>29</sup> born with pulmonary stenosis. Neostigmine (Prostigmin) was given to the mother prior to birth instead of dinoprostone (Prostine). The last fatality (GTS, indication) was due to intestinal perforation for which the reporters stated was more likely due to prior radiation therapy and antineoplastic toxicity than neostigmine.<sup>30</sup>

The time of neostigmine administration to death was reported in 5 of 7 cases as same day (n=3), 1 week (n=1) and 35 days (n=1). The case with the longest duration (35 days) involved a 61-year-old male who received neostigmine infusion for 10 days during which time he experienced cardiac and renal events; he died 25 days after the end of the infusion. The patient had contributing medical history that included colon cancer, cirrhosis, pancreatitis, and hypertension.

There were 3 pediatric cases (one fatal, mentioned above). The remaining 2 cases were confounded by contributing medical history (yes, n=1; unk, n=1) and other medications (n=2).

In the second case, a 3 month-old male (unknown medical history) received a 73 mcg/kg neostigmine dose s.c. to stimulate peristalsis and experienced bradycardia and cyanosis and recovered. Chloramphenicol eye drops, which could have contributed to the event, were also given.

In the 3<sup>rd</sup> case, an attorney reported that a pediatric patient (age unknown) has multiple malformations and chromosomal abnormalities including *Mobius syndrome* from *in-utero* exposure to neostigmine, medroxyprogesterone, and tetracycline, that were all taken within an 11 day period.<sup>31</sup> The mother had a history of pelvic inflammatory disease and received neostigmine for ‘last menses’. This case was from 1986 and the ‘delayed menstruation’ was treated with neostigmine, due to the drug’s cholinergic effect on the uterine endometrium.<sup>32</sup>

### 3.1.5 INDICATION UNKNOWN (N=20)

Ten of 20 cases (50%) reported unlabeled events.

Table 3.1.2.6 lists these unlabeled events *that have a count of 2 or more cases*.

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<sup>27</sup>Literature report: Mollema R, Spijkstra JJ, Polderman KH, Gelissen HP, Girbes AR. Perforation of the colon after administration of neostigmine. *Intensive Care Med.* 2004 Apr;30(4):730. Epub 2004 Feb 24.

<sup>28</sup>Neostigmine is labeled as contraindicated in patients with... mechanical obstruction. .... Lactulose can be associated with intestinal obstruction: van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, van Roon EN. Laxation of critically ill patients with lactulose or polythylene glycol: a two center randomized, double-blind, placebo-controlled trial. *Crit. Care Med.* 2007;35:2726-2731.

<sup>29</sup>All of the other fatalities were adults (age known for 4: median 71 years; range 52 to 91 years).

<sup>30</sup>Literature report: Takashita atsushi, Akutagawa Kan, Noda Nachiro et al. an autopsy case of localized hepatic atrophy with veno-occlusive disease after radiation therapy. Western regional meeting of the Japan Society of Hepatology Dec 7-8, 2001; *Acta Hepatologica Japonica* 2002; 42 (S2) 583

<sup>31</sup>Drug(s) exposure was about 12 weeks after mother’s last menstrual period.

<sup>32</sup>Soskin S, Wachten H, Hechter O. The treatment of delayed menstruation with prostigmine. *JAMA* 1940; 114:2090-2091.

**Table 3.1.2.6 Unlabeled events (n≥2) for unknown indication**

SOC	Events
Injury and poisoning (3)	Overdose (2) <sup>33</sup>
Psychiatric (4)	Completed suicide (3)
Renal (2)	Renal failure or tubular necrosis (2) <sup>34</sup>

Almost one-half (9/20) of the cases were fatal:

All 9 cases had one or more confounding factors of medical history (yes, n=3; unknown, n=6) and contributing other medications (yes, n=5; unknown=4). The time of neostigmine administration to death was reported as same day (n=2) and 14 days (n=1); this information was not provided in the remaining 6 cases.

Most (n=7) of the deaths were due to cardio and/or respiratory arrest (CRA). In 1 of 7 cases, a 41-year-old male committed *suicide* from an acute multi-drug exposure that included neostigmine.<sup>35</sup> The other drugs were mostly anesthesia-related.<sup>36</sup> Two of 7 were pediatric cases: A 5-month old (unknown sex and weight) who had a history of ‘not thriving’ and was alkalotic had an ‘upper GI series’; the patient received 0.15 mg neostigmine i.m.<sup>37</sup> The autopsy found the endotracheal tube in the esophagus. The second pediatric case involved a 16-year-old who committed *suicide* from multi-drug ingestion (including neostigmine [dose form and dosage unknown]<sup>38</sup>).

Neostigmine appeared to be used ‘medically’ in 3 other CRA cases (GI-procedure, n=2<sup>39</sup>). These cases were confounded by multiple concomitant medications, renal impairment (CrCl 25 mL/min), and unknown medical history. The last CRA lacked sufficient clinical information to determine whether neostigmine was used for medical or non-medical use, as well as if there were other confounding factors.

Two fatalities were not coded as due to cardio-respiratory arrest: A 45-year-old female committed suicide by overdose of neostigmine (dose form and dosage unknown) and methyl dopa. A 25-year-old male had toxic epidermal necrolysis<sup>40</sup> after receiving neostigmine i.v. and 19 other drugs and subsequently died (unknown time and cause).

<sup>33</sup>Single patient, fatal.

<sup>34</sup>Single patient, non-fatal. The 64-year-old male experienced non-fatal renal failure and tubular necrosis 5 days after neostigmine administration, Unknown medical history, administration of other anesthesia and atracurium (for an unknown indication) over the 5 days were confounding factors.

<sup>35</sup>Bronstein AC, Spyker DA, Cantilena LR, Green JL et al. 2007 Annual Report of the American Association of Poison Control Centers National Poisoning and Exposure Database (NSPDS) 25th Annual Report; Clin Toxicol 2008;46:927-1057.

<sup>36</sup>Propofol, succinylcholine, cisatracurium, midazolam and venlafaxine.

<sup>37</sup>Although it is possible that neostigmine was used to stimulate the gut for the GI procedure, there was a lack of any specific information regarding the indication.

<sup>38</sup>Litovitz TL, Klein-Schwartz W, Rodgers GC, Cobaugh DJ et al. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System; Am. J. Emerg. Med. 2002;20:391-452.

<sup>39</sup>It was not known if neostigmine was used as part of the anesthetic regimen or for another use (treating the GI-related condition (e.g. ileus).

<sup>40</sup>Also coded as dermatitis exfoliative.

## 3.2 LITERATURE SEARCH

On March 28, 2012 we searched PubMed for English-language literature using “neostigmine” in the title and the word “adverse” as an unrestricted search term. We retained for further review case reports and reports of deaths in clinical studies that had not been submitted to the NDA or to the postmarketing adverse event reporting system (AERS). The search resulted in 52 reports of cases, ranging in publication date from 1948 through 2011, including 2 death cases found in references. The plurality of these (23) concerned patients who received the drug for the reversal of a nondepolarizing neuromuscular block after surgery. The most common nonindicated use was treatment of nonmechanical intestinal obstruction (15 reports); others included test dose after cardiac transplantation, reversal of depolarizing neuromuscular blockade, treatment of puffer fish poisoning; use in myasthenia gravis, overdose of neostigmine; in one case, the indication was unclear.

The adverse events reported in association with neostigmine, either the indicated use or various nonindicated uses, were labeled events or consistent with labeled events. These included asystole, bradycardia, atrioventricular block, hypotension, excess salivation, and nausea, abdominal pain, anaphylaxis, and bronchospasm. One of the cardiovascular reports was a fetus who experienced a drop in heart rate, with no other adverse event, after the mother was treated with neostigmine. In addition, cases were reported of increased or decreased pharmacological effects attributed to renal failure (5 patients), hypokalemia, concomitant use of medications (beta blockers (4), verapamil (1), methyldopa (1), or reduced or atypical cholinesterase activity (4). There was case of anaphylaxis (a labeled event) in which the role of neostigmine was supported by a skin prick test.

The following are the deaths reported in the PubMed search. Two of the cases involved indicated use, one in a patient with a neuromuscular disease. Three were reported in patients receiving neostigmine for nonmechanical intestinal obstruction. In all of the fatalities, except the one preceded by bradycardia, the cause of death was not proximal to the administration of neostigmine.

- Buzello et al. (1982) report the death of a 57 year-old woman with dystrophia myotonica who died of bronchopneumonia, hypoxemia, hypercapnea, and recurrent bradyarrhythmia approximately 3 weeks after neostigmine had been given for a proposed indicated use, reversal of pancuronium neuromuscular blockade following a cholecystectomy. She had been extubated at 5 days following her procedure, then reintubated 12 hours later.

*Comment: This death occurred in a patient with neuromuscular disease, and it occurred weeks after reintubation.*

- Middleton (1957) report a death of a patient from shock 23 hours after reversal of apnea with neostigmine during surgery for a gunshot wound to the abdomen. The authors did not attribute the death to neostigmine, but concluded that neostigmine had reversed apnea that they attributed to neomycin.
- Van der Spoel et al (2001) reported the death of a patient with endocarditis and multiple organ failure treated in a clinical study with neostigmine (0.4-0.8 mg/hour for 24 hours) for colonic ileus who died with intestinal necrosis on day 7 after inclusion into the study. The authors state, “At this stage, no conclusions can be drawn regarding the risks and benefits of neostigmine on colon (micro-circulation)” and that “continuous infusion of 0.4-0.8 mg/h of the neostigmine promotes defecation in the critically ill, ventilated patients with an ileus of the colon, and is well-tolerated.”

An additional two deaths were reported in literature and referred to in the AERS case series. Both were in patients treated for nonindicated uses, and in both cases, the death followed a pharmacologically known effect of neostigmine.

- Briggs (1969) reported the death of a 9 year-old girl who had been treated with neostigmine, 15 mg daily for 2 years for megacolon, who became apneic and died. The author postulated that the underlying condition caused an accumulation of neostigmine and resulted in an overdose.
- Merrill (1948) reported the death of a patient with myasthenia gravis who died after a test dose of neostigmine. The death was preceded by bradycardia.

*Reviewer's comment:* The review of adverse events, including deaths, in our literature search did not uncover new safety concerns not addressed in the proposed label.

## 4 DISCUSSION

Our AERS review examined all neostigmine adverse events reported over the past 40 years in an effort to provide a comprehensive assessment of the spontaneous postmarketing safety data. We did not restrict our search for any particular type of 'indication'<sup>41</sup> and our finding that most of the reported use was for NMB reversal makes our data more applicable for the sponsor's NDA application for the same indication. The larger proportions of *labeled* events in the cardiac, respiratory and nervous SOCs are compatible with the cholinergic activity of neostigmine. Our review of all unlabeled events did not find any that were compelling enough to be a new 'signal', requiring addition to the proposed neostigmine labeling.

The published literature search of adverse events reported in association with neostigmine, either for NMB reversal or various nonindicated uses, primarily retrieved labeled events and deaths due to various causes that appeared to be unrelated to neostigmine. The review of these adverse events, including deaths, did not reveal any new safety concerns not addressed in the proposed label.

## 5 CONCLUSIONS

No safety risks were identified from AERS and literature that merit changing the proposed neostigmine label.

## 6 RECOMMENDATIONS

DPV will continue routine monitoring of all adverse events reported in association with neostigmine.

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<sup>41</sup>Neostigmine is currently an unapproved product.

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## 8 APPENDICES

### 8.1 NEOSTIGMINE LABELING (SAFETY RELATED INFORMATION)

<b>SOC</b>	<b>Event</b>
Card	atrioventricular block (as arrhythmia)
Card	bradycardia (as arrhythmia)
Card	cardiac arrest
Card	cardiac arrhythmias
Card	electrocardiogram changes (non specific)
Card	Hypotension
Card	nodal rhythm (as arrhythmia)
Card	tachycardia (as arrhythmia)
Eye	miosis
Eye	visual changes
Gastr	Emesis
Gastr	Flatulence
Gastr	Nausea
Gastr	oral secretion (as increased)
Gastr	peristalsis (as increased)
Genrl	death (overdose)
Genrl	drug interaction (certain aminoglycosides)
Genrl	Headache
Genrl	Weakness
Immun	allergic reaction
Immun	Anaphylaxis
Musc	Arthralgia
Musc	muscle cramp
Musc	muscle spasm
Musc	muscle weakness (overdose)
Nerv	cholinergic crisis (overdose)
Nerv	Convulsions
Nerv	Dizziness
Nerv	Drowsiness
Nerv	Dysarthria
Nerv	loss of consciousness
Renal	urinary frequency
Resp	bronchial secretions (as increased)
Resp	Bronchospasm
Resp	Dyspnea
Resp	pharyngeal secretion (as increased)
Resp	respiratory arrest
Resp	respiratory depression

<b>SOC</b>	<b>Event</b>
Resp	respiratory impairment (via muscles, overdose)
Skin	Diaphoresis
Skin	Rash
Skin	Urticaria
Vasc	Flushing
Vasc	Syncope

## 8.2 EXCLUDED AERS CASES (N=48)

Reason for Exclusion	N
Neostigmine not administered	18
Event occurred before neostigmine administration	7
Not enough info to determine nature of event	5
Cannot determine relationship of neostigmine and event	5
Image illegible or not available in AERS	4
Not likely due to neostigmine because of long time to onset	3
Event most likely related to another drug	3
Ophthalmic neostigmine not likely cause of systemic or generalized event	2
Fictitious patient	1

### 8.3 PROCEDURES FOR NMB REVERSAL (N=101)

<b>Procedure</b>	<b>N</b>
GI/abdominal	43
ENT	15
Reproductive	12
Musculoskeletal	9
Urogenital	8
Cardiovascular	6
Respiratory	4
Skin	3
Normal volunteer	1

## **8.4 ADVERSE EVENT REPORTING SYSTEM (AERS)**

### **Adverse Event Reporting System (AERS)**

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

**8.5 AERS CASE, ISR AND MANUFACTURER  
CONTROL NUMBERS**

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