

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208289Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208289
Product Name: Akovaz (Ephedrine Sulfate)

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

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2016
Study/Trial Completion: 08/2017
Final Report Submission: 05/2018
Other: _____ MM/DD/YYYY

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 ephedrine on fertility and early embryonic 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 ephedrine on fertility.

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.

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)
- 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

Continuation of Question 4

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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208289
Product Name: Akovaz (Ephedrine Sulfate)

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

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2016
Study/Trial Completion: 05/2017
Final Report Submission: 03/2018
Other: _____ MM/DD/YYYY

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 ephedrine 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 adequate data to address the effects of ephedrine on embryo-fetal development.

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.”

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.

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 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)
- 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

Continuation of Question 4

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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208289
Product Name: Akovaz (Ephedrine Sulfate)

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

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2016
Study/Trial Completion: 08/2017
Final Report Submission: 06/2018
Other: _____ MM/DD/YYYY

11. 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 ephedrine 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 adequate data to address the effects of ephedrine on embryo-fetal development.

12. 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.

13. 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?

14. 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)
- 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

Continuation of Question 4

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

15. 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208289
Product Name: Akovaz (Ephedrine Sulfate)

PMR/PMC Description: Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2016
Study/Trial Completion: 07/2018
Final Report Submission: 07/2019
Other: _____ MM/DD/YYYY

16. 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 ephedrine on pre- 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 adequate data to address the effects of ephedrine on pre- and post-natal development.

17. 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 pre- 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.

18. 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?

19. 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 pre- 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)
- 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

Continuation of Question 4

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

20. 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208289
Product Name: Akovaz (Ephedrine Sulfate)

PMR/PMC Description: Conduct an in vivo micronucleus assay with ephedrine sulfate.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>N/A</u>
	Study/Trial Completion:	<u>07/2016</u>
	Final Report Submission:	<u>01/2017</u>
	Other:	<u>MM/DD/YYYY</u>

21. 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. In several in vitro genotoxicity assays, ephedrine tested negative in the Ames, chromosomal aberrations, and mouse lymphoma assay. The evidence to-date suggests low likelihood of genotoxic potential for ephedrine; however, definitive in vivo data are needed to confirm this. Although prior clinical experience does not address the effect of ephedrine on the potential for genotoxicity, given the long clinical experience and negative results from several in vitro genotoxicity assays, 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 adequate data to address the in vivo genotoxic potential of ephedrine.

22. 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.”

An in vivo genetic toxicology study is generally required as part of a standard battery of genotoxicity assays to evaluate the genotoxicity potential of a drug substance. This study is required to also 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.

23. 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?

24. 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 genetic 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)
- 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

Continuation of Question 4

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

25. 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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

/s/

AYANNA S AUGUSTUS
04/28/2016

JUDITH A RACOOSIN
04/28/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 208289	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Akovaz Established/Proper Name: ephedrine sulfate Dosage Form: solution Strengths: 50 mg/mL		
Applicant: Famel Ireland Limited		
Date of Receipt: June 30, 2015		
PDUFA Goal Date: April 30, 2016		Action Goal Date (if different): April 29, 2016
RPM: Ayanna Augustus		
Proposed Indication(s): treatment of clinically important hypotension in the setting of anesthesia		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	All sections of the label
Vazculep (NDA 204300)	Warnings and Precautions

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The sponsor provided a bridge between their drug product and the drug products used in the referenced literature. The Sponsor identified ephedrine as the (-)-enantiomer for the efficacy references and showed that the formulations are comparable to their drug product formulation. More detailed information is provided below, not in italics.

The table below compares Flamel’s ephedrine product to the ephedrine products described in the literature submitted in support of this NDA submission. As confirmed by the Chemistry Manufacturing and Controls (CMC) review team for this application, all ephedrine formulations described in the table below are appropriately comparable to Flamel’s ephedrine product.

Table 1 Comparison of Éclat’s Proposed Formulation to Cited Manufactured Parenteral Formulations (per mL)

Company	Ephedrine Salt	Quantity of Ephedrine Salt	Water for injection qs	Other Ingredients
Éclat	Sulfate	50 mg	Yes	Glacial acetic acid or sodium hydroxide (as (b) (4))
(b) (4)	Sulfate	50 mg	Yes	Sodium hydroxide and/or hydrochloric acid qs pH
(b) (4)	Sulfate	50 mg	Yes	N/A
(b) (4)	Sulfate	30 mg	Yes	Sodium chloride (b) (4)

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(b) (4)	Hydrochloride	30 mg	Yes	Sodium chloride Dilute hydrochloric acid (b) (4)
	Hydrochloride	15 mg – 30 mg	Yes	N/A
	Hydrochloride	10 mg – 50 mg	Yes	Sodium chloride
	Hydrochloride	50 mg	Yes	N/A
	Hydrochloride	50 mg	Yes	(b) (4)

qs: sufficient quantity

(Source: NDA 208289 Applicant’s table page 5 of Summary of Biopharmaceutic Studies)

Although Akovaz is a product comprised of ephedrine sulfate, some of the publications submitted in support of this NDA are in the form of ephedrine hydrochloride instead of the ephedrine sulfate form.

There is a small difference in the amount of ephedrine base present in ephedrine sulfate when compared to ephedrine hydrochloride. A 50 mg dose of ephedrine sulfate contains 38 mg of ephedrine base. A 50 mg dose of ephedrine hydrochloride contains 41 mg of ephedrine base. This difference is small enough that a comparison of the dosing of ephedrine hydrochloride to ephedrine sulfate should not require additional calibration. For example, the proposed dose of Akovaz is a bolus of 5 to 10 mg. Five milligrams of ephedrine sulfate contains 3.8 mg of ephedrine base; 5 mg of ephedrine hydrochloride contains 4.1 mg of ephedrine base.

In Table 5 on pages 6 and 7 of their Summary of Biopharmaceutic Studies, the applicant explains their strategy for determining the identity of the ephedrine product used to support efficacy. The purpose of including the table in this document is to demonstrate the effort put forth by the applicant to determine the identity of the ephedrine product in the publications submitted to support the efficacy of Akovaz.

This table is pictured below.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

Table 2 Drug Product Identification for Clinical Efficacy Studies with Parenteral (-) Ephedrine Administration

Citation	+/-	Salt	Manufacturer	Contact History
Adigun et al. 2010	(-)	HCl	(b) (4)	Adigun TA indicated via email that he used ephedrine hydrochloride. (b) (4) indicated via email that the drug was from (b) (4). (b) (4) indicated via email that the drug consists of only the (-)isomer. Label states that API is Ephedrine Hydrochloride Ph Eur; the current Ph Eur monograph is for the (-)isomer.
Belzarena 2006	(-)	Sulfate	(b) (4)	Belzarena SD indicated via email that he used a product by (b) (4). A web document containing drug information indicates that (b) (4) product (b) (4) contains “Ephedrine Sulfate ((b) (4) (b) (4))”. A web document from the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency) indicates that (b) (4) corresponds to CAS 299-42-3. The CAS Registry number 299-42-3 corresponds to (1R,2S)-(-)Ephedrine.
Bhattarai et al. 2010	(-)	HCl	(b) (4)	Bhattarai B indicated via email that the ephedrine was from (b) (4). (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(-)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Dolci et al. 2011	(-)	HCl	(b) (4)	Dolci M indicated that he most probably used Ephedrine HCl from (b) (4). He also indicated that the active principle corresponds by law to the Ph Eur, which describes the minus enantiomer only (1R, 2S). Dolci M also indicated he also may have used Ephedrine Bichsel at some point. A web document from SwissMedic confirms that both Ephedrine Bischsel and Ephedrine Streuli contain “Ephedrini hydrochloridum”, which corresponds to the (-)enantiomer according to the Ph. Eur.
Ganeshanavar et al. 2011	(-)	HCl	(b) (4)	Ganeshanavar A indicated via email that he used ephedrine hydrochloride manufactured by (b) (4) and that this product met the Indian Pharmacopia standards. (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(-)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Kansal et al. 2005	(-)	HCl	(b) (4)	Mohta M indicated via email that they used ephedrine hydrochloride from (b) (4). (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(-)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Kasaba et al. 2000	(-)	HCl	Unknown	(b) (4) (a pharmacist at (b) (4) Hospital) indicated that the hospital has used ephedrine in the form of (1R,2S)-2-Methylamino-1-phenylpropan-1-ol-monohydrochloride and that it has not changed since 1998.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

Citation	+/-	Salt	Manufacturer	Contact History
Kitchen et al. 2014	(-)	HCl	(b) (4)	Kitchen CC indicated via email that the ephedrine used was from (b) (4). (b) (4) indicated that the products on the market (including (b) (4)) are made of the enantiomer (1R,2S)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.
Lecoq et al. 2010	(-)	HCl	(b) (4)	Lecoq JPH indicated via email that he used ephedrine hydrochloride from (b) (4). An email from (b) (4) indicated that the ephedrine hydrochloride is only “levogyre”. Levorotary compounds are indicated with a (-) as a prefix, indicating that the product was the (-)enantiomer only.
Meersschaert et al. 2002	(-)	HCl	Unknown	Coriat P indicated via email that the ephedrine used in their study was comprised of only the levogyre isomer. He also indicated that the salt form was hydrochloride.
Meng et al. 2011a & Meng et al. 2011b	(-)	Sulfate	(b) (4)	(b) (4) confirmed via email that (b) (4) has been their primary wholesaler of ephedrine since prior to 2009 to the present. A label on DailyMed confirms that (b) (4) repackages product from (b) (4) which is ephedrine sulfate, USP, which indicates the (-)enantiomer only.
Nag 2010	(-)	HCl	(b) (4)	This reference provides a picture of the box of ephedrine used in the study, which was identified as (b) (4). (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(-)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Ngan Kee et al. 2001 Ngan Kee et al. 2008b	(-)	Sulfate	(b) (4)	Ngan Kee WD indicated via email that he used ephedrine sulfate from (b) (4) in all studies. (b) (4) indicated via email that the product is (-)ephedrine.
Nissen et al. 2010	(-)	HCl	(b) (4)	Secher NH identified an ephedrine hydrochloride product from (b) (4) as the product used in the study. (b) (4) indicated that the products on the market (including (b) (4)) are made of the enantiomer (1R,2S)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.
Pennekamp et al. 2011	(-)	HCl	(b) (4)	(b) (4) indicated via email that they used ephedrine hydrochloride from (b) (4). A web document from the CBG Medicines Data Bank shows that the ephedrine is the (-)enantiomer.
Prakash et al. 2010	(-)	HCl	(b) (4)	Prakash S indicated via email that they used ephedrine hydrochloride from (b) (4). (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(-)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.

(Source: NDA 208289 Applicant’s Table 5 pages 6 and 7 of Summary of Biopharmaceutic Studies)

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

Because all of the ephedrine products in Table 1 of this document are considered to be appropriately comparable to Flamel’s ephedrine product, the literature submitted by Flamel presented in the table below is considered to be reliable to support the efficacy of ephedrine.

Table 3 Citations that can be used to support the efficacy of Akovaz because the ephedrine product can be appropriately compared to Akovaz

Citation	Salt	Manufacturer	# of subjects receiving ephedrine
Adigun et al. 2010	HCl	(b) (4)	31
Belzarena 2006	Sulfate		38
Bhattarai et al. 2010	HCl		30
Ganeshanavar et al. 2011	HCl		30
Kansal et al. 2005	HCl		30
Kitchen et al. 2014	HCl		9
Lecoq et al. 2010	HCl		21
Meng et al. 2011a	Sulfate		29
Meng et al. 2011b			
Nag 2010	HCl		50
Ngan Kee et al. 2001	Sulfate		23
Ngan Kee et al. 2008	Sulfate		74
Nissen et al. 2010	HCl		12
Pennekamp et al. 2011	HCl		7
Prakash et al. 2010	HCl		30

The CMC review team contends that Flamel has submitted adequate information on the identity of the ephedrine products in the submitted literature.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
*If “NO,” proceed to question #5.
 If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES NO

If “**NO**” to (a) proceed to question #11.

If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

AYANNA S AUGUSTUS
04/28/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: March 11, 2016 **Date consulted:** August 13, 2015

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD,
Director, Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: Ephedrine sulfate injection,

NDA: 208289

Applicant: Flamel Ireland Limited

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: For the treatment of clinically important hypotension in the setting of anesthesia

Materials Reviewed:

- DAAAP consult request dated August 13, 2015
- Applicant's response to Division's information request of September 18, 2015, dated November 10, 2015
- Ephedrine sulfate Labeling submitted on November 12, 2015
- NDA submission on June 30, 2015
- Consult Review by DBRUP in DARRTS on January 30, 2014

Consult Question:

DAAAP requests that DPMH review and provide comments on the content and format of the maternal health sections of the prescribing information (PI).

INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on August 13, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of ephedrine sulfate injection to comply with the Pregnancy and Lactation Labeling Rule format (PLLR).

Ephedrine sulfate is a sympathetic agonist with both α - and β -adrenergic activity. It causes prominent vasoconstriction, resulting in an increase in blood pressure. There is no Reference Listed Drug (RLD) for ephedrine sulfate.

Ephedrine sulfate injection for intravenous administration is the same formulation of injectable ephedrine that has been used for years for maintaining blood pressure in the operating suite despite not having FDA approval for this use. The Applicant is relying on the published literature to substantiate the safety and efficacy of the drug product and is also using information included in DMF (b) (4) and the USP monograph for ephedrine sulfate injection to support their filing for the indications of (b) (4) the treatment (b) (4) of hypotension associated (b) (4) anesthesia.

REGULATORY HISTORY

In 1938 the FD&C Act was established and required that drugs be proven safe before coming to the market. The Kefauver-Harris Amendments to the Act in 1962 required that drugs also had to be proven efficacious before they could be approved. Drugs that had been approved under NDA's between 1938 and 1962 and were on the market could stay on the market but would be reviewed and "approved". In 1966, FDA contracted to the National Academy of Sciences/National Research Council and, in 1968, FDA set up a process called Drug Efficacy Study Implementation (DESI), to implement the recommendations of these reviews. Ephedrine sulfate injection is currently marketed in the U.S. although it has not been granted FDA approval (it is a DESI drug). Oral ephedrine is currently marketed as an over the counter (OTC) product in compliance with the Final Monograph for OTC Bronchodilator Drug Products. The injectable products are not currently scheduled under the Controlled Substances Act. If NDA 208289 is approved, ephedrine sulfate injection will be available as prescription only.

The proposed indication is for treatment of clinically important hypotension in the setting of anesthesia. The drug will be used in controlled settings, i.e. the surgical suite. Furthermore, the drug will be used acutely for the management of hypotensive episodes and not for its other stimulant properties.

The NDA for ephedrine sulfate injection (208289) was submitted on June 30, 2015.

DAAAP sent (b) (4) an information request on September 18, 2015 to provide:

- A review and summary of all available published literature regarding ephedrine sulfate
- A review and summary from your pharmacovigilance database,
- Interim ongoing or final report on a closed pregnancy registry (if applicable).

- A revised labeling incorporating the above information (in Microsoft Word format) that complies with Pregnancy and Lactation Labeling Requirements (PLLR),

Ephedrine use in Labor and Delivery

Ephedrine has been used for decades during surgical procedures to maintain blood pressure, including extensive use during cesarean section deliveries in patients receiving spinal anesthesia. Therefore, maternal and fetal exposures (during delivery) have been very common. Spinal anesthesia is accompanied by decreased vascular resistance that causes decreased venous return to the heart. Pressure placed on the vena cava from a gravid uterus further exacerbates the venous return and may contribute to hypotension during spinal anesthesia. The incidence of hypotension after spinal anesthesia during pregnancy is reported to be about 80%.¹ Prolonged maternal hypotension may cause impaired fetal oxygenation and fetal acidosis. Another potential risk of the drug product is that of a direct ephedrine impact on the fetal circulation. Because of the vasoconstrictive effect, it can decrease the umbilical artery pH. Although there is some evidence that umbilical artery pH may be impacted by exposure to high doses of ephedrine, fetal outcomes of low APGAR and low umbilical artery pH were not adversely affected in this setting. In different studies, in patients who underwent cesarean sections under spinal anesthesia and had received IV fluid loading prior to anesthesia, and in whom the blood pressure dropped below 20% of the pre anesthesia values, bolus doses of ephedrine successfully reversed to above the threshold criteria in all patients. Potential neonatal effects were evaluated with Apgar scores at 1 and 5 minutes post-delivery and evaluation of umbilical arterial and venous acid-base status parameters. APGAR scores were >7 and in the majority of them umbilical artery pH values were ≥7.2.^{2,3,4} No patients have been reported with umbilical artery pH of <7. Ephedrine crosses the placenta⁵ and increases fetal catecholamine concentrations. Intravenous ephedrine administered to correct maternal hypotension during spinal anesthesia may increase the fetal heart rate.⁶ In some cases, fetal/neonatal tachycardia has been observed. A review by the Applicant in the FAERS SOC Pregnancy, Puerperium, and Perinatal Conditions did not identify any complications related to effects of ephedrine on the fetal circulation. The reader is referred to the Applicant's pharmacovigilance report that is being discussed later in this review. For more detailed discussion, the reader is referred to a consult by Dr. Barbara Wesley in DARRTS dated January 30, 2014. The current recommendations from the American Society of Anesthesiologists (ASA) state that either intravenous ephedrine or phenylephrine (another α -adrenergic agonist) may be used for treating hypotension during neuraxial anesthesia. In the absence of maternal bradycardia, consider selecting phenylephrine because of improved fetal acid-base status in uncomplicated pregnancies.⁷

¹ Kloor S, Roth R, Hofmann T, et al. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. *Acta Anaesthesiol Scand* 2010;54:909-921

² Yousefshahi, F et. al: M.D. The Effect of Ephedrine on Fetal Outcome in Treatment of Maternal Hypotension Caused by Spinal Anesthesia During Cesarean Section. *Journal of Family and Reproductive Health*. 2010;4 (4): 149-154

³ Balcan, A et al. Abstract 11AP2-9

⁴ Ngan Kee, WD et al: A Dose-Response Study of Prophylactic Intravenous Ephedrine for the Prevention of Hypotension During Spinal Anesthesia for Cesarean Delivery: *Anesth Analg* 2000;90:1390-5

⁵ Ward MG, Hughes SC, Shnider SM, et al. Placental transfer of ephedrine. *Anesthesiol* 1979;51(S3):S307

⁶ Wright RG, Shnider SM, Levinson G, et al. The effect of maternal administration of ephedrine on fetal heart rate and variability. *Obstet Gynecol* 1981;57:734-738

⁷ Practice guidelines for Obstetric Anesthesia. An Updated Report by the American Society of Anesthesiologists

Drug Characteristics⁸

Ephedrine is a sympathomimetic agent with mixed α - and β -adrenergic agonist properties. Ephedrine sulfate injection is a sterile solution for intravenous injection. It must be diluted before administration as an intravenous bolus.

Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Half-life of oral ephedrine is 3-6 hours depending on the mean urine pH.

Pregnancy and Lactation

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁹ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹⁰ format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

LITERATURE REVIEW

EPHEDRINE SULFATE USE IN PREGNANCY

Clinical Data

The applicant performed a literature search in PubMed. Multiple publications for pregnancy and ephedrine were identified. DPMH also conducted a review of PubMed, ReproTox¹¹, and TERIS¹² for published literature regarding ephedrine and use in pregnancy. A summary of the findings in these publications is presented below.

- No increase in the frequency of congenital anomalies was found among the infants of 373 women who used ephedrine during the first four months of pregnancy in the Collaborative Perinatal Project.¹³
- In a study evaluating the association of use of vasoconstricting agents and development of gastroschisis, ephedrine was not identified as significantly associated with the malformation.¹⁴

Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology, October 2015

⁸ Ephedrine sulfate injection Labeling. Section 11 Description and 12: Clinical Pharmacology. Submission November 12, 2015

⁹ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹⁰ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

¹¹ ReproTox database, Truven Health analytics, Micromedex solutions, 2016

¹² TERIS database, Truven Health Analytics, Micromedex Solutions, 2016.

¹³ Heinonen, O.P.; Slone, D. and Shapiro, S.: Birth Defects and Drugs in Pregnancy. Littleton, Mass.: John Wright-PSG, 1977, pp 346, 347, 439, 491.

¹⁴ Werler MM, Mitchell AA, Shapiro S: First trimester maternal medication use in relation to gastroschisis. *Teratology*. 1992,45:361-367.

- In the population-based Hungarian Congenital Abnormality Registry, statistically significant increases in birthweight and gestational age were observed in 112 infants whose mothers used for several weeks suppositories containing ephedrine in combination with other products like camphor, chloralhydrate, menthol, atherol millefolii and procaine for hemorrhoid treatment during pregnancy.¹⁵
- In a study of 565 women in the Danish National Birth Cohort, the authors evaluated only the association of a prescription diet drug (Letigen) containing ephedrine (20 mg) and caffeine (200 mg) with spontaneous abortion (SAB) during early pregnancy. They did not identify an increased risk of spontaneous abortions when the drug was used.¹⁶ The authors did not look for an association between the drug and malformations, which constitutes a limitation of this study.
- A case report has described a child born with limb reduction defects whose mother took ephedrine throughout the first trimester.¹⁷
- The administration of ephedrine during labor has been reported to alter fetal heart rate and beat-to-beat variability, but this exposure has not been associated with adverse fetal effects.^{18,19,20,21,22}
- A study comparing the use of ephedrine and phenylephrine with epidural anesthesia during cesarean delivery found that patients given ephedrine had significant increases in heart rate, cardiac output, and cardiac index with decreased systemic vascular resistance upon umbilical cord clamping. These effects were not observed with phenylephrine use. The study authors suggested that phenylephrine was a better choice than ephedrine during cesarean delivery.²³
- Matsuoka *et al.* presented the findings of a detailed anatomicopathologic examination of an aborted human fetus of a mother who had previously taken four tablets of Tedral (130 mg theophylline, 25 mg ephedrine, 8 mg phenobarbital) for an upper respiratory tract infection at 30 days of development. The fetus showed marked growth retardation and the authors stated that the possibility of a teratogenic effect of Tedral during early pregnancy is possible. It is known that theophylline can produce tachycardia and arrhythmia in humans and can produce cardiovascular anomalies such as ventricular

¹⁵ Czeizel, A.E. and Toth, M.: Birth weight, gestational age and medications during pregnancy. *Int. J. Gynaecol. Obstet.* 1998, 60:245-249.

¹⁶ Howards PP, Hertz-Picciotto I, Bech BH, Nohr EA, Andersen A-MN, Poole C, Olsen J: Spontaneous abortion and a diet drug containing caffeine and ephedrine: a study within the Danish national birth cohort. *PLoS One* 2012,7(11):e50372.

¹⁷ Gilbert-Barness E, Drut RM: Association of sympathomimetic drugs with malformations. *Vet Human Toxicol* 2000,42:168-171.

¹⁸ Hollmen AI et al: Intervillous blood flow during caesarean section with prophylactic ephedrine and epidural anaesthesia. *Acta Anaesth Scand.* 1984, 28:396-400.

¹⁹ Hollmen AI et al: Regional anaesthesia and uterine blood flow. *Ann Chir Gynaecol.* 1984, 73:149-52.

²⁰ Wright RG, Shnider SM, Levinson G, et al.: The effect of maternal administration of ephedrine on fetal heart rate and variability. *Obstet Gynecol.* 1981, 57:734-738.

²¹ Cherala SR, Mehta D, Greene R: Ephedrine as a marker of intravascular injection in laboring parturients. *Reg Anesth.* 1990, 15: 15-8.

²² Moon HS, Chon JY, Yang WJ, Lee HJ: Intrauterine fetal bradycardia after accidental administration of the anesthetic agent in the subdural space during epidural labor analgesia. A case report. *Korean J Anesthesiol.* 2013, 64(6):529-532.

²³ Quan Z, Tian M, Chi P, Cao Y, Li X, Peng K: Influence of phenylephrine or ephedrine on maternal hemodynamics upon umbilical cord clamping during cesarean delivery. *Int J Clin Pharmacol Ther.* 2013 51(11): 888-894

septal defect.²⁴ The authors postulated that there is synergy of all three drugs in Tedral, and that specific types of defects depend on the date of administration of Tedral relative to gestational age.

Reviewer comment:

DPMH concludes that placebo-controlled or dose-response data on ephedrine bolus for (b) (4) hypotension during delivery are limited, thereby precluding meaningful assessment. (b) (4) use of ephedrine does not appear to be associated with an increased risk of clinically recognized spontaneous abortion or any specific pattern of congenital malformations. Although there are clear effects on the fetus when administered to the mother during delivery, clinical correlates for any potential effects on the neonates from the lower pH values are unknown.

APPLICANT'S PHARMACOVIGILANCE DATABASE REVIEW

An evaluation of FAERS (October 1, 1969 through September 29, 2014) was conducted by the Applicant and submitted in the Applicant's "Response to FDA Information Request" dated November 10, 2015. Search terms used included: inflammation, infection, nipple, duct, intoxication, feeding, lactation, pregnancy events (e.g., pregnancy complication, abortion, termination, stillbirth, labor, delivery, congenital, structural, dysmorphology, malformation, miscarriage, endocrinopathy, neurodevelopment, premature rupture of membranes, premature labor or delivery, postpartum hemorrhage, fetal heart abnormalities), and reproductive potential events (e.g., impairment, delay, maturation). Several possibly relevant terms related to pregnancy and delivery were identified in FAERS, including: breast enlargement (n=1), stillbirth (n=2), premature rupture of membranes (n=2), amniotic cavity infection (n=1), premature delivery (n=7), premature labor (n=2), pre-eclampsia (n=2), placenta accreta (n=1), postpartum hemorrhage (n=3), fetal heart rate deceleration (n=1), fetal disorder NOS (n=1).

Reviewer comment

The limited reported events are non-specific findings that can be explained by underlying pathology. Some of them were present prior to administration of ephedrine during delivery. The applicant did not identify any clinical findings related to ephedrine sulfate injection during delivery that should be included in ephedrine sulfate labeling.

NON-CLINICAL STUDIES²⁵

There are no animal reproductive toxicology studies conducted that meet current pharmacology/toxicology requirements. The studies described here come from published literature. A published embryofetal development study evaluated the effects of ephedrine administered using intraperitoneal doses to rats during the period of organogenesis. The maximum recommended human dose (MHRD) is 0.83 mg/kg (50 mg/60 kg). A dose-related increase in septal defects in the heart was observed in fetal rats at doses over the range of 0.1 to 50 mg/kg. The lowest dose at which septal defects was observed (0.1 mg/kg) is 50-fold higher than the MRHD of ephedrine sulfate based on a mg/m² comparison. In a 2-year carcinogenicity study,

²⁴ Matsuoka R, Gilbert EF, Bruyers H Jr, Optiz JM.: An aborted human fetus with truncus arteriosus communis--possible teratogenic effect of Tedral. Heart Vessels. 1985, 1(3):176-8

²⁵ Ephedrine sulfate injection proposed labeling. Section 13: Nonclinical toxicology

nothing was observed in rats and mice who were administered ephedrine sulfate 2 and 3 times respectively, the MHRD on a mg/m² basis. Ephedrine was also not found to be mutagenic or clastogenic. Fertility studies have not been conducted. The Pharmacology/ Toxicology review considers that the published reproductive toxicology studies were not adequate to fulfill the requirements of an NDA and, therefore, it is recommended that ephedrine sulfate should be evaluated in the standard battery of reproductive toxicology studies. Therefore, no animal reproductive toxicology studies will be included in section 8.1 Pregnancy: Risk Summary and Data of the labeling. The reader is referred to Pharmacology Toxicology review by Marcus Delate, Ph.D. of April 4, 2016 in DARRTS.

Reviewer comment:

The Applicant and DPMH did not identify any nonclinical findings related to ephedrine sulfate and use in pregnancy that will be included in the labeling.

EPHEDRINE SULFATE AND LACTATION

DPMH reviewed Thomas Hale’s book on *Medication and Mother’s Milk*, a breastfeeding expert, regarding ephedrine sulfate and lactation. It is stated that “small amounts of [redacted] ^{(b) (4)} is believed to be secreted into milk although no data is available. On an acute basis, it is not likely to harm a breast-feeding infant. However, it should not be used regularly by breast feeding mothers”. In addition, Dr. Hale raises issues of pediatric concerns with use of the referenced drug. For ephedrine no concerns are identified. He recommends that infants who breast feed on mothers who take ephedrine should be observed for anorexia, irritability, crying, disturbed sleeping patterns and excitement.

A review of LactMed²⁶ shows that it is not known whether ephedrine therapy affects lactation. There is one case report of a baby with disturbed behavior who was exposed through breast feeding to ephedrine and to an antihistamine. The child’s symptoms resolved when breast feeding was discontinued.²⁷

EPHEDRINE SULFATE AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy Testing and Contraception

Studies in humans, as stated earlier, did not associate ephedrine exposure during pregnancy with an increase in malformation risk.^{14,17} However, these data are limited. DPMH recommends at this time that pregnancy testing and contraception recommendations are not needed in labeling.

Infertility

Ephedrine has been used to treat motility problems in the male genital tract. The limited cases reported include a man with idiopathic aperistalsis of the vas deferens²⁸ and a man with

²⁶ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²⁷ Mortimer EA Jr: Drug toxicity from breast milk? *Pediatrics*. 1977, 60:780-1.

²⁸ Tiffany P, Goldstein M: Aperistalsis of the vas deferens corrected with administration of ephedrine. *J Urol*. 1985, 133:1060-1.

ejaculatory failure after retroperitoneal surgery.²⁹ In both cases, a normal ejaculate occurred after drug therapy. [REDACTED] (b) (4)

CONCLUSIONS

Ephedrine sulfate injection labeling has been updated to comply with the PLLR format. A review of the literature revealed no new data with ephedrine sulfate use in pregnant or lactating women. DPMH has the following recommendations for ephedrine sulfate injection labeling:

- **Pregnancy, Section 8.1**

- The “Pregnancy” subsection of ephedrine sulfate labeling was formatted in the PLLR format to include: “Risk Summary,” and “Clinical Considerations”. [REDACTED] (b) (4)

- **Lactation, Section 8.2**

- The “Lactation” subsection of ephedrine sulfate labeling was formatted in the PLLR format to include the “Risk Summary”. [REDACTED] (b) (4)

- [REDACTED] (b) (4)

RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2, of ephedrine sulfate labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the Applicant’s proposed pregnancy and lactation labeling.)

²⁹ Proctor KS, Howards SS: The effect of sympathomimetic drugs on post-lymphadenectomy aspermia. J Urol. 1983, 129:837-8.

³⁰ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

DPMH Proposed ephedrine sulfate injection Pregnancy and Lactation Labeling

(b) (4)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on the use of ephedrine sulfate are insufficient to determine a drug associated risk of major birth defects or miscarriage. However, there are clinical considerations [see *Clinical Considerations*]. Animal reproduction studies have not been conducted with ephedrine sulfate.

(b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Cases of potential metabolic acidosis in newborns at delivery with maternal ephedrine exposure have been reported in the literature. These reports describe umbilical artery pH of ≤ 7.2 at the time of delivery. Monitoring of the newborn for signs and symptoms of metabolic acidosis is (b) (4) to ensure that an episode of acidosis is acute and reversible.

8.2 Lactation

Risk Summary

Limited published literature reports that ephedrine is present in human milk. However, no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPHEDRINE SULFATE injection and any potential adverse effects on the breastfed child from EPHEDRINE SULFATE injection or from the underlying maternal condition.

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

/s/

CHRISTOS MASTROYANNIS
04/21/2016

TAMARA N JOHNSON
04/21/2016

LYNNE P YAO
04/21/2016

**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 Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: April 4, 2016

Reviewers: Laurelle Cascio, PharmD, Safety Evaluator
Division of Pharmacovigilance II

Jane L. Gilbert, MD, PhD, Medical Officer
Division of Pharmacovigilance II

Team Leaders: Sara Camilli, PharmD, BCPS, Safety Evaluator Team Leader
Division of Pharmacovigilance II

Brian Lewis, MD, Medical Officer Team Leader
Division of Pharmacovigilance II

Deputy Division Director: S. Christopher Jones, PharmD, MS, MPH
Division of Pharmacovigilance II

Product Name(s): Ephedrine Sulfate Injection, 50 mg/ml

Subject: All Adverse Events

Application Type/Number: 505(b)(2) NDA 208289
(b) (4)

Applicant/Sponsor: Flamel Ireland Limited
(b) (4)

OSE RCM #: 2016-340

TABLE OF CONTENTS

1	Introduction	3
1.1	Regulatory History	3
1.2	Product Labeling	4
2	Methods and Materials	4
2.1	FAERS Search Strategy	4
2.2	Literature Search	4
3	Results	5
3.1	FAERS Overview	5
3.1.1	FAERS Search Results	5
3.2	Review of Select FAERS Reports	9
3.2.1	Cases Coded with an Outcome of Death	10
3.2.2	FAERS Cases that Reported Unlabeled Adverse Events in High Frequency (≥ 6)	10
3.3	Literature Search	11
4	Discussion	12
5	Conclusion	13
6	Recommendations	13
7	References	15
8	Appendices	18
8.1	Appendix A. Flamel Proposed Labeling Information (DAAAP draft label revised 02/2016)	18
8.2	Appendix B. Akorn Proposed Labeling Information (DAAAP draft label revised 01/2016)	25
8.3	Appendix C. FDA Adverse Event Reporting System (FAERS)	40
8.4	Appendix D. FAERS Case Numbers, FAERS Version Numbers, and Manufacturer Control Numbers	41
8.5	Appendix E. Narrative Summaries of 11 Fatal FAERS Cases Reported With Ephedrine Injection Use	45
8.6	Appendix F. Narrative Summaries of Renal and Cardiac Adverse Event Cases Reported in FAERS	49
8.7	Appendix G. Narrative Summaries of Fetal Acidosis Cases Reported in FAERS (N=6)	58

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review after receiving literature-based 505(b)(2) NDAs from Flamel Ireland Limited (b) (4) for ephedrine sulfate injection for the treatment of clinically important hypotension in the setting of anesthesia. No new clinical safety or efficacy studies were conducted for this application by the sponsors.

Ephedrine has been marketed as an unapproved product in the US since the early 20th century. Given ephedrine's extensive use over time, there is substantial familiarity with its mode of action and potential for adverse events. In light of this familiarity, this Division of Pharmacovigilance (DPV) review represents an effort to make certain that there are no significant adverse events associated with this product which have not come to light previously. To do this, DPV has undertaken a review of case reports in FDA's Adverse Event Reporting System (FAERS) and the published medical literature. Although oral ephedrine products are commercially available in the US, the focus of this review is adverse events associated with ephedrine injection.

In an effort to provide an overview of potential new safety signals that should be incorporated into labeling, we reviewed the most commonly reported adverse events associated with ephedrine injection reported in FAERS and case reports published in recent medical literature. Renal (13 unique cases) and cardiac (28 unique cases) events are the most common events reported with ephedrine injection and we provide summaries of these cases in Appendix 8.6.

The search of the FAERS database retrieved a total of 288 reports (including duplicates). Though there were 29 reports coded with a fatal outcome, after deduplication and excluding cases that were not relevant, there were 11 unique cases describing a fatal outcome with ephedrine injection use. Analysis of these reports did not find any report of death causally linked to the ephedrine injection alone. The most common use for ephedrine injection is severe hypotension. Since cardiovascular adverse events are associated with the indication for ephedrine, DPV expected FAERS reports of ephedrine to be associated with adverse cardiovascular outcomes even if the drug were not a cause of these outcomes.

A search of the recent medical literature identifies no evidence of stroke or cardiac events resulting from ephedrine injection. It does identify a number of publications describing that fetal acidosis, for which we also found six FAERS cases, is more likely to result from use of ephedrine during cesarean section compared with phenylephrine. Though it appears that this fact is well known in the obstetric community it would be useful to include information about the potential for neonatal acidosis in labels for ephedrine. The proposed Flamel label already includes information about the possible adverse event in sections 8 and 9. (b) (4)

(b) (4)
The information in the proposed section 6.2 was based on publically available FAERS data, which does not include the narrative section of the adverse event reports, and the sponsor did not complete a case-level review of the reports to determine whether there was a reasonable basis of causality for the events and ephedrine injection.

No new safety signals for ephedrine injection were identified in FAERS or the published literature.

Information about potential f [REDACTED] (b) (4)
[REDACTED] o that which is proposed by Flamel.

DPV II recommends the following:

1. Removal of [REDACTED] (b) (4) proposal for 6.2 Postmarketing Adverse Reactions
2. Information describing potential [REDACTED] (b) (4)
[REDACTED]
3. DPV II will continue to monitor for all adverse events associated with the use of ephedrine sulfate injection.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review after receiving literature-based 505(b)(2) NDAs from Flamel Ireland Limited (b)(4) for ephedrine sulfate injection for the treatment of clinically important hypotension in the setting of anesthesia. No new clinical safety or efficacy studies were conducted for this application by the sponsors.

Ephedrine has been marketed as an unapproved product in the US since the early 20th century. Given ephedrine's extensive use over time, there is substantial familiarity with its mode of action and potential for adverse events. In light of this familiarity, this Division of Pharmacovigilance (DPV) review represents an effort to make certain that there are no significant adverse events associated with this product which have not come to light previously. To do this, DPV has undertaken a review of case reports in FDA's Adverse Event Reporting System (FAERS) and the published medical literature. Although oral ephedrine products are commercially available in the US, the focus of this review is adverse events associated with ephedrine injection.

1.1 REGULATORY HISTORY

Ephedrine sulfate injection, USP, 50 mg/ml, a sympathomimetic amine, is an unapproved product and currently marketed to counteract the hypotensive effects of spinal or other types of nontopical conduction anesthesia. It is also used as a pressor agent in hypotensive states following sympathectomy, or following overdose with ganglionic-blocking agents, antiadrenergic agents, veratrum alkaloids or other drugs used for lowering blood pressure in the treatment of arterial hypertension.¹ Other unapproved uses include the management of Adams-Stokes Syndrome, bronchial asthma, narcolepsy and depressive states, and myasthenia gravis.²

In 2015, Flamel Ireland Limited (b)(4) submitted literature-based 505(b)(2)NDAs for ephedrine sulfate injection that propose use of the product to increase blood pressure in adults with clinically important hypotension in the setting of anesthesia.

Ephedrine is also available as ephedrine sulfate capsule for use as a bronchodilator, and as a tablet formulation including as ephedrine sulfate with guaifenesin or ephedrine hydrochloride with guaifenesin for use as a bronchodilator and expectorant.³

Oral ephedrine has been misused and abuse by athletes, bodybuilders, weight lifters and others engaged in sports.⁴ On February 11, 2004, the Food and Drug Administration (FDA) issued a final regulation (69 FR 6788) declaring dietary supplements containing ephedrine alkaloids adulterated under section 402(f)(1)(A) of the Federal, Food, Drug, and Cosmetic Act (the Act) because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. The final rule can be viewed at <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-2912.pdf>. Dietary supplements containing ephedrine alkaloids are no longer commercially available in the US.⁵

Ephedrine has been used in clandestine synthesis of methamphetamine and methcathinone.⁶ Federal restrictions to reduce the potential for misuse and abuse of ephedrine include limiting the amount that can be purchased to 3.6 g per day or 9 g per month, requiring storage behind the counter or in a locked cabinet, requiring purchasers to provide approved photographic identification, and requiring retail distributors to maintain a written or electronic logbook of purchases for at least 2 years.⁷ Additional requirements, more stringent than federal restrictions, have been enacted in some states.

1.2 PRODUCT LABELING

The sponsors' proposed labeling are in Appendix 8.1 and 8.2.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 1. The focus of the review was to retrieve adverse event reports for ephedrine injection; therefore our search was limited to injection-related terms.

Table 1. FAERS Search Strategy*	
Date of search	January 20, 2016
Time period of search	1969 - January 20, 2016
Search type	FBIS Quick Query
Product Terms	Product Active Ingredients: ephedrine, ephedrine sulfate, ephedrine hydrochloride, ephedrine levulinate
Routes of Administration	intravenous (not otherwise specified), intravenous bolus, intravenous drip, parenteral
Product Indication Search Terms	anaesth*, anaesth*, surg*
Report Narrative Search Terms	IV, intravenous, anesth*, anaesth*, surg*
* See Appendix 8.3 for a description of the FAERS database.	

2.2 LITERATURE SEARCH

The medical literature was searched with the strategy described in Table 2 and 3.

Table 2. Literature Search Strategy	
Date of search	03/02/2016
Database	PubMed
Search Terms	Ephedrine, Heart, Cardiac, Stroke
Years included in search	Last 5 years
Filters applied	Case Reports, Humans

Table 3. Literature Search Strategy Expanded	
Date of Search	03/14/2016
Database	PubMed
Search Terms	Ephedrine, Adverse, Safety

Years included in search	Last 5 years
Filters applied	Case Reports, Humans

Ephedrine is an older drug with a well-known safety profile and mechanism of action. It is used to alleviate severe hypotension; therefore it was our expectation that concerning adverse events would be cardiac or neurologic. Accordingly, the original search was restricted to case reports that were likely to describe heart attack or stroke (Table 2). However, to make certain that other, unexpected adverse events were not being missed, we conducted a second broader search (Table 3).

Given the long history of ephedrine use there has been a voluminous amount of literature published. Since, however, treatment scenarios have remained relatively constant over time; we expected that clinically significant and less known events would be adequately captured in a 5 year window of time. Therefore the search was restricted to the last 5 years.

3 RESULTS

The results section is divided into three parts: 1) an overview of total counts of FAERS reports, 2) a hands-on review of all cases that reported an outcome of death and any unlabeled adverse events reported in high frequency (i.e. ≥ 6), and (3) a description of the results from the literature searches.

3.1 FAERS OVERVIEW

The FAERS search retrieved 288 reports. These are total counts of FAERS reports and may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports (e.g., oral ephedrine). Reported outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for all reports in this evaluation.

3.1.1 FAERS Search Results

The FAERS search on 01/20/2016 yielded 288 reports.

Table 4. Demographic Characteristics of FAERS Reports for Ephedrine Sulfate Injection received by FDA from January 1, 1969 to January 20, 2016.		
(N=288)*		
Sex	Male	88
	Female	171
	Unknown	29
Age	<17	9
	17-64	187
	≥ 65	56

Table 4. Demographic Characteristics of FAERS Reports for Ephedrine Sulfate Injection received by FDA from January 1, 1969 to January 20, 2016.		
(N=288)*		
	Unknown	36
Country	US	57
	Foreign	231
Serious Outcomes [†] (N=277)	Death	29
	Hospitalized	135
	Life-threatening	61
	Disability	1
	Congenital Anomaly	2
	Other serious	110
Report type	Expedited	273
	Direct	14
	Periodic	1
FDA Received Year	1971 – 1979	2
	1980 – 1989	3
	1990 – 1999	7
	2000 – 2009	93 [§]
	2010 – 2016	183 [§]
* Report counts may include duplicate reports, miscoded reports, or unrelated reports.		
[†] One case may report more than one outcome		
[§] The large majority are foreign reports. For the US reports, FDA received 6 reports (before 2000), 28 reports from(2000-2009) and 23 reports from(2010-2016). For all drugs, FAERS received > 11 million reports since 1969. In 2015 alone, FAERS received >1.7 million new reports. The recent increase in reports for ephedrine is generally consistent with the overall increase in reports for all drugs.		

The most frequently reported MedDRA Preferred Terms (PTs) are shown in the table 5 (all) and table 6 (fatal) reports below.

Table 5. Most Frequently Reported MedDRA PTs with (N≥6) for Ephedrine Sulfate Injection, received by FDA from January 1, 1969 to January 20, 2016, sorted by decreasing number of FAERS reports per PT.		
Total Number of Reports = 288*		
Preferred Term	PT Count (N) Total	Appears in Flamel Draft Labeling (rev. 2/2016)
Hypotension	39	IR
Acute Kidney Injury	31	No
Maternal Exposure During Pregnancy	22	IR; (SP) labeled for may cause fetal harm
Bradycardia	20	Yes; AR
Cardiac Arrest	17	No

Table 5. Most Frequently Reported MedDRA PTs with (N≥6) for Ephedrine Sulfate Injection, received by FDA from January 1, 1969 to January 20, 2016, sorted by decreasing number of FAERS reports per PT.

Total Number of Reports = 288*

Preferred Term	PT Count (N) Total	Appears in Flamel Draft Labeling (rev. 2/2016)	(b) (4)
Oliguria	17	No	
Tachycardia	16	Yes; AR	
Hypertension	14	Yes; AR	
Arteriospasm Coronary	12	No	
Anaphylactic Shock	11	No	
Drug Abuse	11	No	
Drug Ineffective	11	U	
Dyspnoea	11	No	
Ventricular Tachycardia	11	No	
Blood Pressure Decreased	10	IR	
Haematuria	10	No	
Colitis Ischaemic	9	No	
Foetal Exposure During Pregnancy	9	IR, (SP) labeled for may cause fetal harm	
Heart Rate Decreased	9	IR	
Metal Poisoning [§]	9	No	
Nausea	9	Yes; AR	
Parkinsonism [§]	9	No	
Vomiting	9	Yes; AR	
Headache	8	No	
Oxygen Saturation Decreased	8	No	
Pyrexia	8	No	
Stress Cardiomyopathy	8	No	
Angioedema	7	No	
Anuria	7	No	
Anxiety	7	No	
Caesarean Section	7	IR	
Confusion Postoperative	7	No	
Drug Interaction	7	Yes; DI	
Exposure During Pregnancy	7	U; (SP) labeled for may cause fetal harm	
Hypothermia	7	No	
Loss of Consciousness	7	No	
Mental Status Changes	7	No	

Table 5. Most Frequently Reported MedDRA PTs with (N≥6) for Ephedrine Sulfate Injection, received by FDA from January 1, 1969 to January 20, 2016, sorted by decreasing number of FAERS reports per PT.

Total Number of Reports = 288*

Preferred Term	PT Count (N) Total	Appears in Flamel Draft Labeling (rev. 2/2016)	(b) (4)
Postoperative			
Metabolic Alkalosis	7	No	
Premature Baby	7	No	
Unevaluable Event	7	U	
Abdominal Distension	6	No	
Acute Pulmonary Oedema	6	No	
Confusional State	6	No	
Electrocardiogram ST Segment Depression	6	No	
Haemodynamic Instability	6	IR	
Heart Rate Increased	6	No	
Myocardial Infarction	6	No	
Shock	6	No	
Sinus Tachycardia	6	Yes; AR (labeled as tachycardia)	

Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, CP = Clinical Pharmacology, DI = Drug Interactions, OD = Overdosage, PM = Postmarketing, SP = Use in Specific Populations; Other Categories: IR = Indication-related, PR = Procedure-related, U = Uninformative

* Report counts may include duplicate reports, miscoded reports, or unrelated reports.

† We did not consider the sponsor's proposal for 6.2 Postmarketing Adverse Reactions to be labeled events because the proposal was based on publically available FAERS data and the sponsor did not complete a case-level review of the reports to determine whether the events were causally related to ephedrine. These cases are briefly discussed in section 3.2.2.

§ Nine cases described patients who experienced chronic manganese intoxication and parkinsonism after misuse of ephedrine by injecting ephedrone (a homemade mixture of ephedrine, acetylsalicylic acid and potassium permanganate) for the purpose of amphetamine-like euphoria and sexual arousal.

Table 6. MedDRA PTs with N≥2 from FAERS Reports with Fatal Outcomes for Ephedrine Sulfate Injection, received by FDA from January 1, 1969 to January 20, 2016, sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 29 of 288 reports

Preferred Term	PT Count (N) Total	Appears in Flamel Draft Label (rev. 2/2016)	(b) (4)
Cardiac Arrest	8	No	
Hypotension	6	IR	
Overdose	4	Yes; OD	

Table 6. MedDRA PTs with N≥2 from FAERS Reports with Fatal Outcomes for Ephedrine Sulfate Injection, received by FDA from January 1, 1969 to January 20, 2016, sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 29 of 288 reports

Preferred Term	PT Count (N) Total	Appears in Flamel Draft Label (rev. 2/2016)
Mydriasis	3	No
Toxicity To Various Agents	3	No; U
Apparent Death	2	U
Blister	2	No
Bradycardia	2	Yes; AR
Caesarean Section	2	No; IR
Circulatory Failure Neonatal	2	No
Coma	2	No
Death Neonatal	2	No
Drug Ineffective	2	No; U
Drug Interaction	2	Yes; DI
Drug Screen Positive	2	No
Foetal Death	2	No
Foetal Exposure During Pregnancy	2	U; (SP) labeled for may cause fetal harm
Haemodialysis	2	No
Haemodynamic Instability	2	IR
Haemoglobin Decreased	2	No
Hypertension	2	Yes; AR
Incorrect Route Of Drug Administration	2	No
Maternal Drugs Affecting Foetus	2	U; (SP) labeled for may cause fetal harm
Necrosis	2	No
Premature Baby	2	IR
Pulmonary Oedema	2	No
Rash Erythematous	2	No

Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, CP = Clinical Pharmacology, DI = Drug Interactions, OD = Overdosage, PM = Postmarketing, SP = Use in Specific Populations; Other Categories: IR = Indication-related, PR = Procedure-related, U = Uninformative

3.2 REVIEW OF SELECT FAERS REPORTS

Based on the FAERS search results, cases that reported a fatal outcome and those that reported unlabeled adverse events high in frequency (i.e., ≥ 6) were evaluated in a hands-on review.

3.2.1 *Cases Coded with an Outcome of Death*

There were 29 reports in FAERS coded with an outcome of death. Eighteen reports were excluded; 6 were duplicate reports, 8 reported use or abuse of the oral ephedrine formulation (including one case that reported injection of oral ephedrine with propylhexedrine), 2 reported oral pseudoephedrine use, 1 reported an expired lot of ephedrine injection was given after the patient experienced cardiac arrest and 1 reported a literature case that investigated the hypothesis that vasopressors are harmful to patients requiring emergency operative intervention (OR) and concluded that, except for epinephrine, vasopressors during OR were not independently associated with mortality .

After exclusions, there were eleven unique cases reporting a fatal outcome with ephedrine injection use. Five cases reported adult patients who experienced cardiac arrest following administration of multiple medications used in a surgical setting. Four cases reported neonatal (n=3¹) or fetal (n=2) death following administration of multiple medications given to the mother in a surgical setting. One adult case reported a patient who died from a pre-existing medical condition. Another adult case reported a patient who died from an unknown reason following IV administration of an irrigation solution and necrosis of the leg. Our analysis of the 11 cases did not find any reports of death that could be attributed to ephedrine injection alone. Confounding factors included concomitant medications and alternative etiologies (i.e. underlying medical condition, surgical procedure). In addition, some cases did not contain sufficient clinical information for a causal assessment of ephedrine and the adverse event(s). See Appendix 8.5 for individual summaries of the 11 fatal cases.

3.2.2 *FAERS Cases that Reported Unlabeled Adverse Events in High Frequency (≥ 6)*

We reviewed all cases with unlabeled MedDRA PTs reported in more than 6 (≥ 6) reports as listed in Table 4 (Cardiac Arrest, Acute Kidney Injury, Oliguria, Arteriospasm Coronary, Anaphylactic Shock, Drug Abuse, Dyspnoea, Ventricular Tachycardia, Haematuria, Colitis Ischaemic, Metal Poisoning, Parkinsonism, Oxygen Saturation Decreased, Pyrexia, Stress Cardiomyopathy, Angioedema, Anuria, Anxiety, Confusion Postoperative, Hypothermia, Loss of Consciousness, Mental Status Changes Postoperative, Metabolic Alkalosis, Premature Baby, Abdominal Distension, Acute Pulmonary Oedema, Confusional State, Electrocardiogram ST Segment Depression, Myocardial Infarction and Shock). We did not identify a basis for a causal relationship to ephedrine injection in any of these cases. The cases were confounded by concomitant medications, alternative etiology (i.e., underlying medical conditions, procedure-related events), and/or contained insufficient clinical information; thus a causal association with ephedrine injection was not evident. Of the 11 reports of drug abuse; most cases reported injection of ephedrone solution (a homemade mixture of ephedrine, acetylsalicylic acid and potassium permanganate) and the remaining cases reported oral or intranasal ephedrine abuse. In Appendix 8.6, we give case summaries for renal and cardiac events because they are the two

¹ One neonatal pediatric case reported the death of twins.

most commonly reported events in Table 5 and DAAAP requested DPV to evaluate these particular cases.

It should be noted that fetal acidosis was reported in six FAERS cases; however it was not coded as fetal acidosis in five cases, only as bradycardia and maternal exposure during pregnancy. See Appendix 8.7 for case summaries of fetal acidosis reported with ephedrine injection.

3.3 LITERATURE SEARCH

The literature search described in Table 2 retrieved 15 publications. Only two publications were deemed to be relevant: one by Casella (2015)⁸ and a second by To (1980)⁹ which is referenced in Casella.

Casella (2015)⁸. This publication describes 2 athletes using oral ephedrine who developed cardiac events. The first athlete used 10 mg of ephedra (and 100 mg of caffeine) twice daily for approximately one year; he developed rapid sustained VT during a stress test. The second athlete used 60 mgs of ephedra (and 300 mg of caffeine) each day for approximately three months. This athlete developed palpitations and an ECG revealed ventricular bigeminy. Both patients underwent electrophysiologic studies and right ventricular electroanatomic mapping (EAM). EAM showed “low-voltage areas in the right ventricular outflow tract (RVOT). And, the RVOT was identified as the location wherein the irregular rhythms originated. Both patients underwent successful ablation procedures. Endomyocardial biopsies were also performed; these revealed contraction-band necrosis which led the authors to “suspect an overstimulation of the adrenergic system” possibly from ephedrine.

To (1980)⁹ (Abstract only available at this time; full paper on request). This paper describes a young woman with congestive cardiomyopathy of unknown etiology. Subsequently, a history of longstanding “abuse” of (presumably oral) ephedrine is revealed.

An additional publication (Zdanowicz, 2011)¹⁰ describes Takotsubo cardiomyopathy (“broken heart syndrome”) and suggests that adrenergic stimulation such as that which could result from the use of drugs such as ephedrine, adrenaline, phenylephrine, and so on) should be minimized during cesarean section.

It should be noted, that of the three articles mentioned above, only the third (Zdanowicz, 2011)¹⁰ references IV injectable ephedrine; the first two reference oral use of ephedrine.

The remaining publications that were retrieved described cases where ephedrine was used as a rescue medication during events manifesting hypotension.

During the past 5 years only one publication, describing two individuals, has been published describing stroke or cardiac abnormalities associated with ephedrine. This publication also identifies an older case report (To, 1980)⁹. All three reports involve abuse of oral, not ephedrine injection. We conclude there is no evidence in the medical literature of serious cardiac or neurologic events (i.e. stroke) associated with ephedrine injection.

The expanded search, described in Table 3, identified 122 publications. The vast majority described cases where ephedrine was mentioned only as the rescue drug for other events (primarily hypotension) that developed. Relevant articles from this expanded search fell into four substantive categories:

A. Publications asserting that for treatment of hypotension during caesarean section, phenylephrine is preferred to ephedrine since ephedrine may lead to fetal acidosis as measured by low umbilical cord blood pH. These include: Nag, 2015¹¹; Dyer, 2012¹²; Lin, 2012¹³, Loubert, 2012¹⁴; Cooper, DW, 2012¹⁵; Veese, 2012¹⁶; and Habib, 2013¹⁷. It should be noted, though, that Mitra (2013)¹⁸ points out that “though ephedrine crosses the placenta more than phenylephrine and can possibly cause alterations in the fetal physiology, it has not been shown to affect the fetal Apgar [*sic*] or neurobehavioral scores.” Also, Sng, 2013¹⁹, finds no difference in neonatal umbilical cord pH in a randomized controlled trial that he performs.

B. Publications describing how misuse of ephedrine via injection of a compounded substance composed of ephedrine, acetylsalicylic acid, and manganese permanganate, may lead to metal intoxication and neurodegenerative disorders such as Parkinson’s disease. These include: Fudalej, 2013²⁰; and, Koksai, 2012²¹.

C. Publications describing renal stones complexed with ephedrine in patients using cough medication such as guaifenesin. These include: Cockerill, 2013²²; and, Allard, (2013)²³.

D. Publications describing isolated reports of specific adverse events:

- a. Yokose (2013)²⁴ describes a rash resulting from a cough medicine (oral) containing ephedrine.
- b. Efe (2013)²⁵ describes severe ischemia of the glans penis 24 hours after circumcision using a local anesthetic containing ephedrine (.1% xylocaine with ephedrine).
- c. Nagele (2012)²⁶ studies a large number (over 400) of individuals for postoperative evidence of QT prolongation. He identifies a list of drugs associated with QT prolongation and ephedrine is on his list.
- d. Browning (2011)²⁷ describes a case of ephedrine- induced angina (including a rechallenge) resulting from nasal drops containing 0.5% ephedrine.

Of the above publications from the expanded literature search, the only articles involving ephedrine injection include those describing fetal acidosis with ephedrine.

4 DISCUSSION

In an effort to provide an overview of potential new safety signals that should be incorporated into labeling, we reviewed the most commonly reported adverse events associated with ephedrine injection reported in FAERS and case reports published in recent medical literature.

The search of the FAERS database retrieved a total of 288 reports (including duplicates). Though there were 29 reports coded with a fatal outcome, after deduplication and excluding

cases that were not relevant, there were 11 unique cases describing a fatal outcome with ephedrine injection use. Analysis of these reports did not find any report of death causally linked to the ephedrine injection alone. The most common use for ephedrine injection is severe hypotension. Since cardiovascular adverse events are associated with the use scenarios for ephedrine, DPV expected FAERS reports of ephedrine to be associated with adverse cardiovascular outcomes even if the drug was not a cause of these outcomes.

A search of the recent medical literature identifies no evidence of stroke or cardiac events resulting from ephedrine injection. It does identify a number of publications describing that fetal acidosis is more likely to result from use of ephedrine during cesarean section compared with phenylephrine. Though it appears that this fact is well known in the obstetric community (Nag, 2015) it could be useful to include information about the potential for neonatal acidosis in labels for ephedrine. The proposed Flamel label already includes information about the possible adverse event in sections 8 and 9. (b) (4)

(b) (4)

According to the Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, the definition of adverse reactions does not include all adverse events observed during use of a drug. It is limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug (CFR 21 § 201.57(c)(7)). Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.

5 CONCLUSION

No new safety signals for ephedrine injection were identified in FAERS or the published literature.

Information about potential (b) (4) that which is proposed by Flamel.

6 RECOMMENDATIONS

DPV II recommends the following:

1. Removal of (b) (4) proposal for 6.2 Postmarketing Adverse Reactions

2. Information describing potential (b) (4)

3. DPV II will continue to monitor for all adverse events associated with the use of ephedrine sulfate injection.

7 REFERENCES

1. Ephedrine Sulfate [package insert]. Princeton, NJ. Sandoz Inc. May 2010.
2. Ephedrine Sulfate [package insert]. Vernon Hills, IL. Nexus Pharmaceuticals Inc. June 2014.
3. DailyMed. NIH. U.S. National Library of Medicine.
<https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=EPHEDRIN&pagesize=20&page=1>. Accessed March 18 2016.
4. Shekelle P, Morton S, Maglione M et al. Ephedra and ephedrine for weight loss and athletic performance enhancement: clinical efficacy and side effects. Evidence Report/Technology Assessment No. 76 (prepared by Southern California Evidence-based Practice Center, RAND, under Contract No 290-97-0001, Task Order No. 9). AHRQ Publication No. 03-E022. Rockville, MD: Agency for Healthcare Research and Quality, 2003 Feb. (AHRQ Publication No. 03-E022).
5. Food and Drug Administration. Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk; Final Rule. 21 CFR Part 119. Final rule. [Docket No. 1995N-0304] Fed Regist. 2004; 69:6787-6854.
6. AHFS drug information 2003. McEvoy GK, ed. Ephedrine. Bethesda, MD: American Society of Health-System Pharmacists; 2003:1235-41.
7. Food and Drug Administration. Legal requirements for the sale and purchase of drug products containing pseudoephedrine, ephedrine, and phenylpropanolamine. From FDA website:
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm072423.htm>. Accessed March 18, 2016.
8. Casella M et al. Ventricular arrhythmias induced by long-term use of ephedrine in two competitive athletes. *Heart Vessels*. 2015 Mar;30(2):280-3.
9. To LB et al. Ephedrine-induced cardiomyopathy. *Med J Aust*. 1980, 2:35-6.
10. Zdanowicz JA et al. "Broken heart" after cesarean delivery. Case report and review of literature. *Arch Gynecol Obstet*. 2011 Apr;283(4):687-94.
11. Nag, DS et al. Vasopressors in obstetric anesthesia: A current perspective. *World J Clin Cases*. 2015 Jan 16;3(1):58-64.
12. Dyer RA and Biccard BM. Ephedrine for spinal hypotension during elective caesarean section: the final nail in the coffin. *Acta Anaesthesiol Scand*. 2012 Aug;56(7):807-9.
13. Lin FQ et al. Ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean section: an updated meta-analysis. *CNS Neurosci Ther*. 2012 Jul;18(7): 591-7. 2012
14. Loubert C. Fluid and vasopressor management for Cesarean delivery under spinal anesthesia: continuing professional development. *Can J Anaesth*. 2012 Jun;59(6):604-19.
15. Cooper DW. Caesarean delivery vasopressor management. *Curr Opin Anaesthesiol*. 2012 Jun;25(3):300-8.
16. Veesser M et al. Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systemic review and cumulative meta-analysis. *Acta Anaesthesiol Scand*. 2012 Aug;56(8):810-6.

17. Habib AS. Phenylephrine versus ephedrine for the management of hypotension in the obstetric patient; do we have an updated answer? *CNS Neurosci Ther.* 2013 Mar, 19(3):199-200.
18. Mitra JK et al. Changing trends in the management of hypotension following spinal anesthesia in cesarean section. *J Postgrad Med.* 2013 Apr-Jun;59(2):121-6.
19. Sng BL et al. Closed-loop double-vasopressor automated system vs manual bolus vasopressor to treat hypotension during spinal anaesthesia for caesarean section: a randomized controlled trial. *Anaesthesia.* 2014 Jan;69(1):37-45.
20. Fudalej S et al. Manganese-induced Parkinsonism among ephedrine users and drug policy in Poland. *J Addict Med.* 2013 Jul-Aug;7(4):302-3.
21. Koksall A et al. Chronic manganese toxicity due to substance abuse in Turkish patients. *Neurol India.* 2012 Mar-Apr;60(2):224-7.
22. Cockerill PA et al. Acute bilateral ureteral obstruction secondary to guaifenesin toxicity. *Can J Urol.* 2013 Oct, 20(5):6971-3.
23. Allard T et al. Mechanisms of herb-induced nephrotoxicity. *Curr Med Chem.* 2013;20(22):2812-9.
24. Yokose C et al. Maculopapular-type drug eruption caused by Coughcode ®-N combination tablets. *Allergol Int.* 2013 Dec;62(4):519-21.
25. Efe E et al. Successful treatment with enoxaparin of glans ischemia due to local anesthesia after circumcision. *Pediatrics.* 2013 Feb;131(2). Epub 2013 Jan 14.
26. Nagele P et al. Postoperative QT interval prolongation in patients undergoing noncardiac surgery under general anesthesia. *Anesthesiology.* 2012 Aug;117(2):321-8.
27. Browning MG et al. An unusual case of systemic cardiovascular side effects from the application of over-the-counter nasal decongestion drops. *BMJ Case Rep.* 2011 Mar 24; 2011.
28. Ephedrine Sulfate [draft package insert]. (b) (4) Revised date: 01/2016
29. Murphy CJ, McCaul CL, Thornton PC. Maternal collapse secondary to aortocaval compression. *Int-J-Obstet-Anesth* 2015; 24(4):393-394.
30. Shimizu Y et al. Complete atrioventricular block with ventricular asystole following injection of sugammadex. *Tohoku Branch of the Japanese Society of Anesthesiologists.* 2015.
31. Jowik-Plebanek et al. Pheochromocytoma presenting as takotsubo-like cardiomyopathy following deliver. *Endocr-Pract* (2014) 20:233-236.
32. Ootsuji M et al. A case of cardiac arrest associated with coronary artery spasm following anesthesia induction. *Clinical Experience.*
33. Kotake Y et al. Recurrent ST-segment elevation on ECG and ventricular tachycardia during neurosurgical anesthesia. *J of Anesthesia* (2009) Feb; 23:1:115-118.
34. Ono T et al. A case of asystole following povidone iodine administration. *The Japanese Journal of Anesthesiology* (2011) Apr 10;60:4:499-501.
35. Gordon K and Wise R. An usual case of ST elevation. *South Afr J Anaesth Analg* (2013); 19(5):270-273.
36. Simosaka M et al. A case of shift from coronary artery spasm to ventricular fibrillation during general anesthesia. *Journal of Japanese Dental Society of Anesthesiology* (2006); 34:2:203-204.
37. Patel S, Marengo J. Sympathomimetic induced coronary artery vasospasm: Tako Tsubo cardiomyopathy. *Anesthesia and Analgesia* (2008) May; 66:NO.5.

38. Khavandi A et al. Myocardial infarction associated with the administration of intravenous ephedrine and metaraminol for spinal-induced hypotension. *Anaesthesia* (2009) May; 64(5):563-566.
39. Kroll HR et al. Coronary artery spasm occurring in the setting of the oculocardiac reflex. *Journal of Anesthesia* (2010) Oct; 29(5):757-760.
40. Nakanishi M et al. Ventricular tachycardia observed during cesarean section in a patient without structural cardiac disease. *JA Clinical Reports* (2015); 1:1:1-4.
41. Habib AS, Gan TJ. Food and Drug Administration black box warning on the perioperative use of droperidol: A review of the cases. *Anesth Analg* (2003); 96:1377-1379.
42. Kitamura T et al. Severe hypotension as a complication of intramyometrial injection of vasopressin: a case report. *Masui* (2008) Dec; 57(12):1517-20.
43. Study Title: Suprane Inhalation Anesthetic Post Authorization Surveillance Study. Protocol Number: PASS-JA-007. Site Number: SUPS013. Subject Number: SUPS013-023. Subject Initials: Unknown. Study Sponsor: Baxter.
44. Study Name: Double blind, randomized study of oxytocin vs. carbetocin for the prevention of postpartum hemorrhage (PPH) after caesarean section and investigation of effectiveness and cost effectiveness.
45. Cooper D et al. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology* (2002); 79(6):1582-90.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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).

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.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

Case #	Vrsn	MFR Ctrl #	Case #	Vrsn	MFR Ctrl #
10072794	1	2014P1002724	6205371	1	2006GB02391
10075493	2	AU-JNJFOC-20130606643	6301255	1	FR-PFIZER INC-2007033143
10152018	3	2305457	6377991	1	AT-BAYER-200714429GDS
10204393	3	US-PFIZER INC-2014115426	6430905	4	JP-ABBOTT-07P-087-0418256-00
10266628	1	PHHY2014BB079033	6453555	1	2003016450
10299365	1	PHHY2014JP084301	6458780	2	FR-GLAXOSMITHKLINE-B0408169A
10299373	1	PHHY2014JP084267	6458783	1	US-BAXTER-2007BH008049
10299473	1	PHHY2014JP084302	6470268	2	FR-ASTRAZENECA-2007CG01580
10302273	2	FR-ASTRAZENECA-2014SE48850	6476255	1	FR-BAXTER-2007BH009223
10304392	1	BB-RANBAXY-2014US-83299	6615580	1	
10308622	1	HR-GLAXOSMITHKLINE-B1014211A	6622986	1	08H-163-0314111-00
10357247	2	PHHY2014FR093407	6639196	3	PTA2008000003
10357250	1	PHHY2014FR092511	6642916	1	GXKR2008IL03761
10358135	1	FR-JNJFOC-20140718420	6648805	1	08H-163-0314228-00
10410527	1	PHHY2014HR103553	6672460	1	US-ROCHE-544009
10415420	5	JP-ASTRAZENECA-2014SE53576	6672463	1	US-ROCHE-544002
10447302	1		6675025	1	US-TEVA-173008USA
10468026	1	FR-ASTRAZENECA-2014SE68692	6712855	2	TR-BAYER-200822852GPV
10468691	5	JP-009507513-1409JPN010099	6712856	2	TR-BAYER-200822859GPV
10480661	1	FR-MALLINCKRODT-T201403551	6714836	1	TR-WATSON-2008-04446
10505686	2	CH-GE HEALTHCARE MEDICAL DIAGNOSTICS-OMPQ-PR-1409S-1220	6714864	1	TR-BAYER-200822864GPV
10506172	2	JP-009507513-1410JPN002814	6724541	2	US-TEVA-175520USA
10538724	1	FI-BAXTER-2014BAX062617	6743637	1	US-ASTRAZENECA-2008AC02238
10558689	2	JP-BAXTER-2014BAX064127	6784667	1	US-BAUSCH-2008BL004171
10568428	2	JP-009507513-1410JPN003063	6784913	1	FR-ASTRAZENECA-2008CG01434
10611977	1	JP-ABBVIE-14P-087-1312939-00	6863472	1	B0548893B
10636645	1		6868115	1	FR-AVENTIS-200814566FR
10648854	1	FK201405811	6892347	1	FR-ASTRAZENECA-2009CG00168
10725316	1	PHHY2015CA004189	6892484	1	FR-ABBOTT-09P-056-0498241-00
10729395	1	PHHY2015IN004285	6924235	2	JP-BAUSCH-2009BL000694
10729411	1	PHHY2015IN006735	6948967	1	JP-ROXANE LABORATORIES, INC.-2009-RO-00244RO
10755711	1	GB-BAXTER-2015BAX004066	7024922	1	GB-MERCK-0906USA02196

10777528	1	FR-PFIZER INC-2015047681	7038455	1	297777
10790128	3	DE-ASTRAZENECA-2015SE13675	7065229	1	FR-PFIZER INC-2009240360
10790978	1	GB-ABBVIE-15P-167-1344408-00	7110902	1	FR-ASTRAZENECA-2009SE11653
10793994	1	PHHY2015PL014056	7136485	1	CHNY2009GB03502
10795788	1	PHHY2015GB014896	7145896	1	
10813674	1	GB-MYLANLABS-2015M1003511	7168124	1	US-BA YER-200916143BCC
10816706	2	GB-WATSON-2015-02088	7197685	1	GB-BA USCH-2009BL006226
10830449	1	GB-JNJFOC-20150203323	7223756	1	443138
10902792	1	FR-GLAXOSMITHKLINE-FR2015GSK028768	7267104	1	FR-PFIZER INC-2010009668
10910997	1	FR-GLAXOSMITHKLINE-FR2015GSK016031	7274510	2	US-JNJFOC-20100110232
10962622	1	IT-PFIZER INC-2015105613	7326230	1	20100076
10997176	2	FR-SA-2015SA043562	7340756	2	FR-NOVOPROD-306294
11029274	1	US-JNJFOC-20140608166	7341282	3	B0642598A
11080271	4	JP-BAXTER-2015BAX022332	7345412	2	FR-SANOFI-A VENTIS-2010SA018155
11112226	1	TR-BA YER-2015-214651	7346037	4	FR-PFIZER INC-2010042758
11112341	1	TR-BA YER-2015-215141	7360978	1	20100127
11112417	1	TR-BA YER-2015-215232	7361640	2	2010SP017804
11112478	1	TR-BA YER-2015-215293	7366505	2	FR-ASTRAZENECA-2010SE17451
11112518	1	TR-BA YER-2015-215315	7370793	2	557465
11112549	1	TR-BA YER-2015-215360	7371413	1	FR-ABBOTT-10P-056-0639712-00
11112579	2	TR-BA YER-2015-215378	7381035	2	B0650935A
11112689	1	TR-BA YER-2015-215405	7393704	1	JHP201000154
11112725	1	TR-BA YER-2015-215418	7399590	1	FR-ASTRAZENECA-2008CG01327
11327070	3	PHHY2015FR088003	7399699	1	2010SCPR000642
11341593	1	CHPA2015FR009064	7404117	3	B0657755A
11342801	1	FR-FRESENIUS KABI-FK201503740	7404118	3	B0657756A
11348879	2	FR-JNJFOC-20150720033	7405787	2	B0657762A
11365319	1	FR-GLAXOSMITHKLINE-FR2015GSK113868	7410175	1	US-JNJFOC-20100510839
11375967	1	FR-MYLANLABS-2015M1025938	7418673	1	FR-ASTRAZENECA-2010SE27001
11525246	2	FR-JNJFOC-20150912152	7424092	2	FR-ABBOTT-10P-056-0650758-00
11643624	1		7424721	1	FR-ASTRAZENECA-2010SE27131
11645460	3	FR-PFIZER INC-2015348811	7424854	1	FR-SANOFI-A VENTIS-2010SA033927
11684621	2	US-BAXTER-2015BAX057630	7426217	1	FR-PFIZER INC-2010071990
11684973	2	US-NEXUS PHARMA-000001	7426848	1	FR-PFIZER INC-2010071901
11685048	1	US-NEXUS PHARMA-000002	7428017	1	FR-BAXTER-2010BH015780
11685055	1	US-NEXUS PHARMA-000003	7432756	1	GXKR2010KR06595
11714757	2	JP-MYLANLABS-2015M1038569	7436283	1	FR-SANOFI-A VENTIS-2010SA034368
11723816	1	IE-MYLANLABS-2015M1038855	7440746	2	KP-RANBAXY-2010RR-35178

11723817	1	IE-MYLANLABS-2015M1038789	7442971	6	NO-BAXTER-2010BH016546
11723818	1	IE-MYLANLABS-2015M1038854	7449240	1	FR-BAXTER-2010BH016936
11768823	1	FR-BAXTER-2015BAX061538	7450572	1	FR-ASTRAZENECA-2010SE29518
11782722	4	JP-009507513-1511JPN005254	7450986	2	KR-MYLANLABS-2010S1010903
11836115	2	JP-009507513-1512JPN006778	7455229	1	2010TJ0118
11865260	1	FR-BAXTER-2015BAX068728	7476725	1	2010TJ0118FU1
11867832	1	FR-JNJFOC-20151219342	7490829	1	KR-TYCO HEALTHCARE/MALLINCKRODT-T201001578
11875569	1	PHHY2015FR166812	7601715	1	CH-BAXTER-2010BH023693
11879268	1	CH-GLAXOSMITHKLINE-CH2015180940	7606092	2	FR-BAYER-201039232GPV
11919053	1	JP-PAR PHARMACEUTICAL COMPANIES-2016SCPR015089	7617193	2	2010SP048825
3004772	1	91378	7625699	1	US-BAYER-201021450BCC
3360351	1	886-0073-990001	7637584	1	US-JNJCH-2007332486
3396511	2	220562	7644947	1	US-JNJCH-2007332175
3437712	1	20000200122	7728261	1	FR-ASTRAZENECA-2010SE59246
3438533	1	228955	7746393	1	B0691155A
3446035	4	WAES 00035106	7757714	1	US-BAXTER-2011BH000236
3722409	1		7765336	1	NO-BAXTER-2011BH001296
3722941	1	2001075845US	7768539	1	782955
3726547	3	A124377	7801921	1	FR-ASTRAZENECA-2011SE05892
3746295	1		7808325	1	KP-PAR PHARMACEUTICAL, INC-2010SCPR000642
3778096	3	B0261797A	7850751	1	IDA-00496
3787355	1	PHRM2002FR01125	7902595	2	JP-ASTRAZENECA-2011SE21195
3800555	1	2002CG00695	7934062	2	FR-PFIZER INC-2011091365
3801471	1	2002CG00694	7946598	1	FR-ASTRAZENECA-2011SE27416
3813179	1	M0497-2002	7966775	3	FR-BAXTER-2011BH017150
3888282	1	B0289377A	7975279	2	2011SP021439
3902449	1	FR-GLAXOSMITHKLINE-B0289377A	7989667	3	2011SP023020
3945701	1	03H-118-0217321-00	8065018	2	JP-ABBOTT-11P-087-0841776-00
3970274	1	03H-163-0222865-00	8107413	1	US-BAXTER-2011BH027009
4036325	1	2003116374	8161490	1	FR-JNJFOC-20080400073
4044653	1	03H-087-0242555-00	8169584	3	JP-ABBOTT-11P-087-0859740-00
4096323	1	GB-GLAXOSMITHKLINE-B0324054A	8197090	2	FR-ASTRAZENECA-2011SE62766
4121077	1	7688	8293076	1	2011SP050935
4164939	1	PHRM2004FR02207	8428991	1	DE-ASTRAZENECA-2012SE11912
4193051	1	2004050539	8432146	1	JP-ROXANE LABORATORIES, INC.-2012-RO-00721RO
4199580	1	04H-163-0270361-00	8450822	2	FR-ABBOTT-12P-056-0912897-00
4202380	1	NUBN20040014	8452216	2	FR-ASTRAZENECA-2012SE15405
4213100	2	PHRM2004FR02770	8469210	2	DE-RANBAXY-2012US-53791

4250669	1		8581419	1	US-BAXTER-2012BAX006330
4327923	1		8590062	1	GXBR2012US001425
4486038	1	BX8612	8602452	5	FR-NOVOPROD-352947
4503810	1	36110	8613976	1	1295348
4639778	1		8648730	1	FR-ABBOTT-12P-056-0951074-00
5177731	1		8684563	2	JP-BAXTER-2012BAX009263
5431756	1	600397201	8835512	1	FR-ASTRAZENECA-2012SE76321
5518064	1	F9601038DHE	8898437	1	CH-009507513-1211CHE002470
5518075	1	F9601079DHE	9063272	1	FR-JNJFOC-20130117047
5657157	1	PHRM2004FR03208	9306205	2	FR-GLAXOSMITHKLINE-B0892343A
5661737	1	FR-GLAXOSMITHKLINE-B0349467A	9334528	2	JP-BAXTER-2013BAX014718
5681264	1	2004CG02203	9342692	1	FR-ASTRAZENECA-2013SE40804
5715961	1		9343862	1	2013P1006706
5769679	1	200010404RHF	9347077	1	FR-GLAXOSMITHKLINE-B0896826A
5817694	1	2005GB01081	9358500	2	CH-009507513-1306CHE006416
5881818	1	PHRM2005FR02454	9361806	3	CH-JNJFOC-20130608468
5883772	1	2005CG01437	9364547	1	1749725
5975437	1		9376935	1	PHHY2013FR066914
5984416	1	06H-167-0304600-00	9380704	2	FR-BAXTER-2013BAX024389
5984424	1	06H-167-0304599-00	9393811	4	FR-BAXTER-2013BAX025564
5985329	1	06H-167-0304607-00	9393923	1	FR-BAXTER-2013BAX025570
5985332	1	06H-167-0304597-00	9396422	1	FR-NICOBRDEVP-2013-11853
5985334	1	06H-167-0304598	9400485	1	2013P1011215
6005146	2	NO-A VENTIS-200612310GDDC	9407281	1	FR-ASTRAZENECA-2013SE51859
6025486	1	FR-JNJFOC-20060402566	9454723	1	FR-PFIZER INC-2013228468
6049412	1	06H-163-0307930-00	9458896	4	FR-GLAXOSMITHKLINE-B0913208A
6061329	2	JP-ABBOTT-06P-087-0334627-00	9459145	2	US-JHP PHARMACEUTICALS, LLC-JHP201300506
6100240	1	CA-BA YER-200613088BCC	9494905	2	FR-ASTRAZENECA-2013SE66510
6117418	1		9557204	1	FR-BAXTER-2013BAX036594
6118452	1	US-BA YER-200613473BCC	9629833	4	JP-BAXTER-2013BAX038710
6163443	1	US-BA YER-200614481BCC	9713721	1	ZA-MYLANLABS-2013S1026142
6173352	1	06H-163-0310993-00	9721858	1	GB-ASTRAZENECA-2001AP01628
6173356	1	06H-163-0310990-00	9822035	1	PR-AE13-001220
6199573	1	GB-JNJFOC-20061204553	9850502	2	FR-JNJFOC-20140111056
6199985	1	GB-GLAXOSMITHKLINE-B0451449A	9910887	1	FR-ASTRAZENECA-2014SE09975
6201687	1	GB-PURDUE-GBR_2006_0002705	9917145	1	IT-WATSON-2014-02724

8.5 APPENDIX E. NARRATIVE SUMMARIES OF 11 FATAL FAERS CASES REPORTED WITH EPHEDRINE INJECTION USE

10568428 – a 72-year-old male suffered cardiac arrest after given ephedrine with multiple medications (IV injections of sugammadex, rocuronium bromide, flomoxef sodium, phenylephrine hydrochloride, ephedrine, aprotinin, calcium chloride, factor xiii, fibrinogen, thrombin, albumin, nicardipine, fentanyl, remifentanyl, propofol, flumazenil, and mepivacaine) during a pylorus-preserving pancreaticoduodenectomy. He had a medical history of cancer of duodenal papilla and asymptomatic cerebral infarction (left parietal lobe), depression, arteriosclerosis and a liver disorder (unspecified). Within 20 minutes after anesthesia was completed, the patient's consciousness decreased and he could open his eyes only with verbal stimuli. Ventricular fibrillation developed and 6 doses of adrenaline were given and defibrillation was attempted for 4 times. Ventricular fibrillation led to asystole (cardiac arrest developed). The cause of death was determined to be acute myocardial infarction. No autopsy was performed.

Reviewer's Comment: This case was confounded by the use of multiple medications and the patient's underlying condition (hypotension) for which ephedrine was given.

10777528 – a fetus (14 weeks + 6 days post LMP) died after it was transplacentally exposed to ephedrine and multiple concomitant medications (methylprednisolone sodium succinate, lidocaine, propofol, remifentanyl, paracetamol, ketoprofen, droperidol, morphine, ondansetron, nefopam, tramadol, amoxicillin/potassium clavulanate, metoclopramide) and Pneumo 23 following surgery for cochlea implant insertion for the mother.

Reviewer's Comment: This case was confounded by the use of multiple medications.

11723816²⁹ – a literature case reported fetal death of twins after the mother received ephedrine for decreased blood pressure during fetoscopic surgery for twin-twin transfusion syndrome at 20 weeks of gestation. The 26-year-old female also received bupivacaine, epinephrine, phenylephrine, propofol and suxamethonium-chloride during the procedure. The mother had a history of polyhydramnios, morbid obesity and symptoms of aortocaval compression from the first trimester. During the procedure, she experienced hypotension, dizziness, nausea, loss of consciousness. Six minutes after receiving combined spinal-epidural (CSE) anaesthesia, it was decided to perform hysterotomy and emergency caesarean delivery of the twins. She was transferred to the ICU and extubated six hours later. She made a complete recovery; however, her twins died shortly after delivery.

Reviewer's Comment: This case is confounded by the use of multiple medications and alternative etiologies (medical condition of twin-twin transfusion syndrome and surgical procedure).

5881818 – A 29-year-old female suffered cardiac arrest after receiving ephedrine IV for hypotension during a caesarean section. She had a premature rupture of membranes and irregular contractions and was admitted to the maternity unit. Concomitant medications included amoxicillin, dinoprostone, synthetic oxytocin, ropivacaine, sulprostone, and epinephrine. A living baby boy was delivered. She experienced low hemoglobin, which decreased from 10.6 to

5.8 g/dl), arterial hypotension, hemodynamic instability, and underwent a hysterectomy. The hemodynamics continued to deteriorate and she suffered cardiac arrest and a massive acute pulmonary edema. Treatment for the events was without effect, resuscitation attempts failed and the mother died a few hours later. Autopsy (partial results available) showed a healthy coronary artery, a macroscopically normal heart muscle, and lung overload without alveolar lesions.

Reviewer's comment: This case is confounded by multiple medications and an underlying medical condition.

7442971 - A 60-year-old female patient with pre-existing liver failure died due to an unknown reason. The patient was given 0.9% sodium chloride irrigation solution by IV route of administration rather than irrigation for 2 hours before the error was discovered. After 5-6 hours, the patient developed a red rash on the leg which developed into a blister that burst. The patient developed necrosis. She was also administered the following medications: Fentanyl, Prothromplex, esomeprazole, propofol, fentanyl, terbutaline, calcium chloride, phenylephrine, terlipressine and ephedrine (unknown route and formulation). The reporter was uncertain which medications were administered through the same cannula as the sodium chloride. Treatment was not reported. The patient died at an unknown time after the irrigation solution was given by IV route of administration. It was not reported whether an autopsy was performed.

Reviewer's comment: This case lacked clinical detail (cause of death), therefore an association between ephedrine and the cause of death cannot be determined.

7617193 – A case of fetal death was reported after the mother was treated with ephedrine for hypotension. The mother experienced contractions at 28 weeks of pregnancy, leading to discovery of modified cervix. She also experienced tachycardia, bleeding and fissure of bag of waters, dyspnea, chest pain, pulmonary embolism and sepsis. Concomitant medications included erythromycin, betamethasone, nifedipine, phenylephrine, hydroxyethyl amidon, and atosiban. It was reported that “the cause of fetal death may have been related to a combination of several factors: to prematurity, maternal-fetal infection, cardiac failure, possibly promoted by particular sensitivity to nifedipine and to progression of sepsis, causing low rates and a deficiency in oxygenation of the fetus, which could also have aggravated fetal tissue acidosis.”

Reviewer's comment: This case of fetal death was confounded by multiple concomitant medications and alternative etiologies (i.e. prematurity, infection, and sepsis).

7801921 – This is a case of circulatory failure and death of a neonate (gestational age 36 weeks) following a cesarean section with ephedrine use. The mother was 30 years old and had a history of two spontaneous abortions, gestational diabetes, and arterial hypertension treated with Avlocardyl and Loxen. On [REDACTED]^{(b)(6)}, labor started spontaneously. Epidural anesthesia was started at 10:00 am. At 10:30 am, the amniotic sac broke. The fluid was bloody. The foetal heart rate decreased and it was decided to perform cesarean section using epidural anesthesia. At 12:00 am, Naropeine, Sufenta and Xylocaine were administered. After the epidural failed to provide sufficient anesthesia, general anesthesia was initiated. At 01:00 pm, Celocurine, Tracrium, Diprivan and Ephedrine were given. Maternal blood pressure decrease was stable. The Apgar score was at 0/0/3 with heart rate at 60/min. Ventilation with positive pressure and external

cardiac massage were performed. Oxygen saturation remained low (30-40). The neonate was intubated and received adrenalin by the intracheal route (10 min after he was born), then Curosurf (30 min after he was born) leading to transient mild improvement. Oxygen saturation remained low (30-40). Then, lip and skin purpura developed. The neonate began to struggle with the ventilator leading to sedation of the child with Sufenta. At 03:00 pm, resuscitation was stopped. Thorax X-ray did not evidence pneumothorax but showed white lungs. Anatomopathological investigation of placenta did not show obvious lesions but disclosed simple hemorrhagic suffusions, possibly secondary to the labour. Post-mortem physical examination of neonate did not reveal any malformation or dysmorphia. Fetal autopsy only showed supernumerary spleen. Histological investigation of heart and encephalon was pending. A drug interaction between Avlocardyl, Loxen, Naropeine, Sufenta, Xylocaine, Celocurine, Tracrium, Diprivan and Ephedrine was suspected by the reporter.

Reviewer's comment: This case is confounded by multiple medications.

8197090 – A 78-year-old male suffered cardiac arrest after receiving ephedrine hydrochloride IV for hypotension during a mitral valve replacement surgery on (b) (6). Concomitant medications included propofol, sufentanil citrate, cisatracurium besilate, phenylephrine. Cardiopulmonary resuscitation was performed and the patient received treatment with adrenaline and noradrenaline. Surgery was cancelled and rescheduled for (b) (6). Ephedrine was not reported as a drug that was re-administered during the second surgical procedure. The patient died from vasoplegic and cardiogenic shock 16 days after the second procedure.

Reviewer's comment: This case was confounded by multiple concomitant medications and underlying condition (hypertension).

8648730 - A 63-year-old female suffered a fatal cardiac arrest and ventricular tachycardia on the same day he received ephedrine with multiple anesthetics and cefazolin for right hip replacement procedure. Multiple electric shocks were performed and echocardiography revealed fibrillation. She was treated with adrenaline and xylocaine, but the patient died. It was unknown if an autopsy was performed.

Reviewer's comment: This case was confounded by multiple concomitant medications and the patient's underlying condition (hypotension).

9393923 – A 71-year-old male experienced anaphylactic reaction and grade III circulatory shock after receiving ephedrine IV and multiple other concomitant medications for an unspecified procedure. The patient had a medical history of perioperative collapse (an anesthetic complication), Type II diabetes mellitus, anorexia, arterial hypertension, and pancreatic neoplasm. He was treated with injection of adrenaline. On an unknown date, the patient experienced worsening of general status and metastatic pancreatic neoplasm. The patient died one month later.

Reviewer's comment: The role of ephedrine in the occurrence of anaphylaxis and shock in the case is unclear due to lack of reporting details and concomitant administration of many other drugs.

9721858 – A 50-year-old male experienced cardiac arrest and died after receiving ephedrine for anesthesia for surgery to remove a mole on his back. The patient had no significant medical history, no history of cardiac problems and was considered “totally fit.” Concomitant medications given during surgery included propofol, midazolam, vecuronium, and enflurane. Fentanyl, glycopyrronium, and neostigmine were given on an unknown date. The cause of death was cardiac arrest. An autopsy was not performed.

Reviewer’s comment: This case is confounded by multiple concomitant medications and the lack of clinical information (i.e. events leading up to cardiac arrest and death) precludes a causality assessment.

8.6 APPENDIX F. NARRATIVE SUMMARIES OF RENAL AND CARDIAC ADVERSE EVENT CASES REPORTED IN FAERS

RENAL EVENTS: ACUTE KIDNEY INJURY, ANURIA AND OLIGURIA (N=13)

There were 11 unique cases that reported acute kidney injury with ephedrine injection use. Of these 11 acute kidney injury cases, four cases also reported oliguria and three cases reported anuria. Two additional cases reported anuria: one case reported renal insufficiency and the other did not report renal dysfunction. In all 13 cases, ephedrine was administered during a surgical procedure in combination with multiple concomitant medications that confounded the association between ephedrine and acute kidney injury, anuria and oliguria.

Acute Kidney Injury (N=11)

Eleven cases reported acute kidney injury with ephedrine injection use.

Case # 10302273 reported a 40-year-old female who received ephedrine with multiple general anesthetics, amoxicillin-clavulanic acid, and ketoprofen for a cystectomy and enterocystoplasty. She had a history of tetraplegia. On the day of the procedure, the patient experienced hemodynamic failure, anuria, oliguria, cardiac failure, and acute renal failure. The patient was discharged from the hospital 21 days later. At the time of the report, she recovered from acute renal failure, oliguria, and anuria.

Case # 10358135 reported a 68-year-old male who received ephedrine with multiple general anesthetics, tramadol, nefopam, ketoprofen, dexamethasone, furosemide, and amoxicillin and clavulanate potassium for a cystectomy and enterocystoplasty. His medical history included a bladder neoplasm. The patient experienced acute renal failure and lost 8 liters of blood during the 6 hour procedure. He was treated for the events and recovered from acute renal failure on an unspecified date.

Case # 10997176 reported a 39-year-old male who received ephedrine with multiple general anesthetics, enoxaparin, paracetamol, tramadol, nefopam, droperidol, atropine, neostigmine, and morphine for a left nephrectomy. He experienced thrombotic microangiopathy, acute renal failure and oliguria the day after the procedure. He was treated for the events and recovered without sequelae from acute renal failure and thrombotic microangiopathy.

Case # 11327070 reported a 65-year-old female who received ephedrine with multiple general anesthetics, amoxicillin and clavulanic acid, ofloxacin, ketoprofen, dexamethasone, ketamine, paracetamol, tramadol, droperidol, and atropine for a cystectomy. The following day, she developed acute kidney failure. The outcome at the time of reporting for the event acute kidney failure was condition improving.

Case # 6868115 reported a 70-year-old female who received ephedrine, furosemide and bumetanide while hospitalized for a right ventricular failure associated with lower limb edema. Concomitant drugs were not reported. Seven days later, she developed anuria and acute renal insufficiency. The patient was treated for the events and she recovered within one week.

Case # 7366505 reported a 51-year-old female who received ephedrine, Tagamet, propofol, and morphine, for a breast tumor excision. Concomitant medications included amlodipine and valsartan, gliclazide and lipanthyl. Her medical history included Addison-Biermer anemia, rheumatic purpura, type II diabetes mellitus, arterial hypertension, chronic alcoholism and a breast tumor. Two days after the surgery, she experienced oliguria and vomiting. Five days after surgery, acute renal failure was confirmed and acute hemolytic anemia associated with hyperbilirubinaemia was discovered on blood work-up. Seven days after surgery, the patient was recovering from acute renal failure while outcome of acute hemolytic anemia was unknown. An autoimmune disease was suspected but not confirmed.

Case # 7404118 reported a 34-year-old female who received ephedrine with multiple general anesthetics, amoxicillin and clavulanate potassium, enoxaparin, neurontin, betadine and dexamethasone for a myomectomy and peritoneal cyst removal by laparotomy. The day of the surgery she experienced oliguria and hematuria. Acute renal failure was diagnosed. The patient was discharged eight days after the procedure. At the time of reporting, acute renal failure, oliguria and hematuria were resolved without sequelae.

Case # 7418673 reported a 47-year-old female who received ephedrine with multiple general anesthetics, amoxicillin and clavulanic acid, enoxaparin, ketamine, gabapentin, normacol, nefopam, and morphine for an unspecified surgical procedure. On the day of surgery, she experienced oliguria. The following day, she experienced acute renal failure with metabolic acidosis and hyperkalemia. She was treated with dialysis and intermittent non-invasive ventilation. The patient was discharged 17 days after the surgical procedure. At the time of reporting, she recovered from acute pulmonary edema and oliguria while acute renal failure and macroscopic hematuria was improving.

Case # 7449240 reported a 78-year-old female who received ephedrine with multiple general anesthetics, amoxicillin and clavulanic acid, nefopam, paracetamol, gabapentin, and normacol for a bilateral annexectomy by laparotomy due to an ovarian cyst. She had a medical history of rheumatoid arthritis, hypertension, ovarian cyst and hernia of the linea alba. Upon arrival to the recovery room, the patient experienced oliguria. Two days later, renal insufficiency worsened and in the following days, the event improved with treatment. The patient was discharged six days after the surgical procedure. The patient was seen by the physician 15 days after discharge for regression of renal insufficiency. At an unknown date, the patient recovered from oliguria and was recovering from acute renal insufficiency.

Case # 9458896 reported a 31-year-old female who received ephedrine with multiple general anesthetics, tagamet, cefazolin, neosynephrine, tranexamic acid, carbetocin, fibrinogen, factor VII, sulprostone, and suxamethonium. She was pregnant with twins and labor started at 36 weeks and 6 days gestation. She was admitted for hemorrhagic shock after postpartum hemorrhage was complicated by oligoanuric acute renal insufficiency with hyperkalemia. Acute renal insufficiency was treated with hemodialysis. She received a second dialysis two days later. Eight days later, a probable acute tubular necrosis was suspected.

Case # 9850502 reported a 55-year-old male who received ephedrine with multiple general anesthetics, cefoxitin, tramadol, paracetamol for a colostomy. His medical history included

acute renal insufficiency diagnosed 5 years prior to the procedure and streptococcus bacteremia since 10 days prior to the procedure. Concomitant medications included baclofen, clonazepam, enoxaparin, ornithine oxoglurate, oxybutynin, pravastatin, amoxicillin and clavulanic acid, acetylsalicylate lysine, and atenolol. The day after the surgery, the patient developed acute renal insufficiency. Tramadol and cefoxitin treatment was discontinued and the patient recovered on an unspecified date.

Anuria (N=5)

There were five unique cases of anuria reported with ephedrine injection. Three of the five cases also reported acute kidney injury described above (Case 10302273, 6868115, and 9458896).

Case # 3970274 reported a 41-year-old female experienced anuria, hypertension, respiratory distress, chest tightness, neck tightness, loss of consciousness, thrashing, combativeness, nausea, vomiting and loss of voice after receiving ephedrine for a vaginal hysterectomy. Concomitant medications included “an epidural block”, fentanyl and naloxone. The patient was sedated with propofol due to the events and required intermittent urinary catheterizations over the next 24 hours, at which the anuria resolved. The patient fully recovered from all events. The reporter believed ephedrine was related to the events.

Case # 7341282 reported a 47-year-old female experienced acute respiratory distress and septic shock three days after receiving ephedrine and anuric renal insufficiency seven days after receiving ephedrine for a gastroplasty. The patient received multiple concomitant medications during the surgical procedure. She was treated with antibiotics for the septic shock and dialysis for the renal insufficiency.

Oliguria (N=4)

There were four unique cases of oliguria reported with ephedrine injection. All four cases reported acute kidney injury and are described above (Cases 10302273, 7404118, 7418673, and 7449240)

Cardiac Events: Cardiac Arrest, Arteriospasm Coronary, Ventricular Tachycardia, Stress Cardiomyopathy, Electrocardiogram ST Segment Depression, Myocardial Infarction (N=28)

Cardiac Arrest (N=12)

There were 13 unique cases of cardiac arrest reported with ephedrine injection. Of the 13 cases, one case lacked temporal association: cardiac arrest occurred prior to the administration of ephedrine. Therefore we excluded this case. Ephedrine, given for hypotension, precludes assessment of whether ephedrine was ineffective or worsened cardiovascular decompensation. In the remaining 12 cases, ephedrine was administered during a surgical procedure in combination with multiple concomitant medications. The 12 cases were confounded by the concomitant medications or an underlying medical condition that preclude an association between ephedrine and cardiac arrest.

Case # 10468691³⁰ is a literature case that reported an 83-year-old male who received ephedrine for decreased blood pressure during a colostomy and thoracic drainage for rectal cancer, multiple

pulmonary metastases, and right pleural effusion. Concomitant medications included multiple anesthesia medications, cefmetazole, phenylephrine, and sugammadex. Approximately 2 minutes after receiving sugammadex, his heart rate dropped and he went into cardiac arrest due to complete atrioventricular block. He was treated with epinephrine and resuscitation and a transvenous pacing catheter was inserted. Sixty-six days after surgery, the patient was discharged from the hospital with independent gait without sequelae. The reporting physician felt that the events were related to sugammadex.

Case # 10506172 reported an 82-year-old male who received ephedrine for decreased blood pressure for an unspecified surgical procedure. The patient had no medical history of an arrhythmia. Concomitant medications included multiple anesthesia medications, cefmetazole, fentanyl, remifentanyl, and sugammadex. Approximately 30 minutes after receiving sugammadex, the patient developed cardiac arrest. Transient high-grade atrioventricular block developed. A temporary pacing catheter was inserted. On an unspecified date, cardiac arrest resolved. The reporting physician considered ephedrine and multiple other medications as other suspect drugs to the cause of the events.

Case # 10568428 is a case with a fatal outcome summarized above in Appendix E of a 72-year-old male who received ephedrine (for decreased blood pressure) with multiple concomitant medications for a pancreaticoduodenectomy and experienced cardiac arrest. The reporting physician felt that sugammadex, rocuronium and nicardipine were related to the cause of cardiac arrest.

Case # 10793994³¹ is a literature case that reported a 32-year-old female who received ephedrine with multiple concomitant medications for a caesarean section. During the pregnancy she was in good health without any signs or symptoms of catecholamine excess. A healthy male infant was delivered. Ten hours after the operation, she started to complain of headache and progressive shortness of breath. The dyspnea progressed to pulmonary edema followed by cardiac arrest. Cardiopulmonary resuscitation was given and the patient's condition was stabilized. Over subsequent days, she was diagnosed with pheochromocytoma. The author speculated that metoclopramide might have provoked a hypertensive crisis which could be associated with pheochromocytoma hemorrhage, although the exact mechanism is unclear.

Case # 11685055 reported a 67-year-old male who received ephedrine for hypotension and decreased heart rate during surgery of a left AV fistula. Concomitant medications included midazolam, propofol, phenylephrine, glycopyrrolate and atropine. During surgery, his heart rate and blood pressure decreased and remained low despite receiving ephedrine. The patient was treated with glycopyrrolate and epinephrine. Chest compression was performed for asystole. Ephedrine was withdrawn. The outcome of the events was unknown.

Case # 5431756 reported a 3-year-old child who experienced cardiac arrest prior to receiving an expired lot of ephedrine. This case lacked temporal association.

Case # 5881818 is a case with a fatal outcome summarized above in Appendix E of a 29-year-old female who received ephedrine (for arterial hypotension) with multiple concomitant medications during a caesarean section.

Case # 6430905³² is a literature case that reported a 69-year-old male who received ephedrine (for hypotension) and multiple concomitant medications during a resection of the gastric remnant for stump cancer. After anesthesia was induced, the patient experienced 1st degree AV block, QRS prolongation, and ST segment elevation followed by ventricular tachycardia (VT) and cardiac arrest. The patient was treated for the events and an implantable defibrillator was placed. A second resection was performed successfully 28 days after the previous surgery, without any fatal arrhythmia. The authors suspect myocardial ischemia caused by coronary artery spasm was the cause of the VT.

Case # 6642916 is a literature case (uncited source) that reported a 59-year-old male who received ephedrine (for hypotension) with multiple concomitant medications for a cochlear implantation. Relevant medical history included hypertension and atypical chest pain at rest. During the procedure, the patient developed hypotension, ST-segment elevation, ventricular tachycardia and cardiac arrest. The patient was treated for the events and the surgery was cancelled. The patient was discharged on nifedipine and aspirin and remained asymptomatic at a 9 month follow-up. The authors suspect the patient's underlying condition, repeated doses of suxamethonium chloride and ephedrine as possible explanations for the events.

Case # 6948967³³ is a literature case of a 60-year-old female who received ephedrine and phenylephrine after multiple episodes of hypotension occurred during a neck clipping of an unruptured cerebral aneurysm. Concomitant medications included multiple general anesthetics. Twenty minutes after the incision, the patient developed bradycardia, atrioventricular block, ST elevation and T wave inversion with hypotension. She was diagnosed with coronary vasospasm. Three episodes of ECG changes occurred with ST elevation and ventricular tachycardia and the patient was treated with lidocaine for each episode, with the addition of epinephrine and defibrillation for the third episode. Thirty minutes after the third event, cardiac arrest following hypotension occurred and was successfully treated. The authors suspected propranolol, prostaglandin E1, and propofol may have contributed to the coronary spasm.

Case # 8432146³⁴ is a literature case of a 71-year-old female who received ephedrine (for decreased blood pressure and heart rate) and multiple anesthetics during a cystectomy. After anesthesia was induced, 1% lidocaine was administered through an epidural catheter and the surgeon began to disinfect the vaginal area with povidone iodine. Two minutes later, the patient developed a dark brown rash in the lower abdominal area and her systolic BP and heart rate dropped. The patient was treated with atropine and ephedrine, but they were not effective. Systolic blood pressure and heart rate decreased to 33 mmHg and 30 beats/min, respectively, and asystole and ventricular fibrillation occurred. Sinus rhythm was restored, the patient's condition was stabilized and the rash resolved. The authors suspect that the anaphylactic reaction that led to asystole may have been caused by povidone iodine.

Case # 8648730 is a case with a fatal outcome summarized above in Appendix E of a 63-year-old female who received ephedrine (for unknown reason) with multiple concomitant medications for a hip replacement.

Case # 9721858 is a case with a fatal outcome summarized above in Appendix E of a 50-year-old male who received ephedrine (for unknown reason) with multiple concomitant medications for removal of a mole on his back.

Arteriospasm Coronary (N=9)

There were nine unique cases of arteriospasm coronary reported with ephedrine injection. Two of the nine cases are described in the cardiac arrest summary of cases (Case # 6642916 and 6948967). In some cases, the reporter/author stated ephedrine may have contributed to the event, although other confounding factors (i.e. concomitant medications, underlying condition) were reported.

Case # 10152018³⁵ is a literature case of a 61-year-old female who experienced a coronary artery vasospasm during an elective acromioplasty. The patient was a chronic smoker with low magnesium levels. She received multiple concomitant medications during the procedure and five minutes after her anesthesia induction, the patient became acutely hypotensive. The hypotension was resistant to repeated doses of ephedrine and phenylephrine, therefore adrenaline was given. Significant ST elevation was noted and the surgery was postponed. She remained stable and the event was recognized as case of acute myocardial ischemia with a subsequent ST elevation. The patient was diagnosed with coronary artery vasospasm. The authors suspected various causes of the vasospasm: the Bezold-Jarisch reflex secondary to the positioning, ephedrine use, adrenaline bolus, histamine release induced by fentanyl, and a brief period of hyperventilation. Smoking, low magnesium levels and vecuronium use were also considered as causes for the coronary artery vasospasm.

Case # 4199580 is a literature case (uncited source) of a 42-year-old male who experienced coronary artery vasospasm, acute myocardial infarction, and ventricular tachycardia after taking ephedrine for hypotension during a femoral-popliteal bypass. He took cocaine four days prior to his surgery and he received spinal anesthesia on the day of the surgery. The patient developed ventricular tachycardia and chest pain within 30 seconds after he was given ephedrine. He was treated for the events and converted to sinus rhythm. He was advised to refrain from cocaine and nine weeks later he underwent an uneventful femoral-popliteal bypass. The authors suspected ephedrine and cocaine use to be precipitating factors of the vasospasm.

Case # 6061329³⁶ is a literature case of a 67-year-old male who experienced coronary artery spasm and ventricular fibrillation after receiving ephedrine for hypotension in addition to multiple concomitant medications for neck dissection. The patient was treated for the events and after surgery he had normal ECG and cardiac enzymes. A repeat operation was undertaken 44 days later. During the second surgery, the patient developed hypotension and ST segment elevation again. Ventricular fibrillation again occurred after administration of ephedrine and epinephrine. The authors suspected ephedrine to be the cause of the coronary artery spasm and ventricular fibrillation.

Case 6724541³⁷ is a literature case of a 35-year-old female who developed Tako-Tsubo cardiomyopathy, ST segment depression, and pulmonary edema after receiving ephedrine (for decreased blood pressure) with multiple concomitant medications for labor induction. She was treated for the events and her symptoms resolved, and resolution of wall motion changes was

expected. An excess of catecholamines was suspected by the authors to play a causal role in Tako-Tsubo cardiomyopathy.

Case # 7038455³⁸ is a literature case of a 31-year old female who developed coronary vasospasm, myocardial infarction and tachycardia after receiving ephedrine and metaraminol for spinal-induced hypotension. The authors suspect ephedrine and/or metaraminol was associated with a myocardial infarction due to coronary vasospasm and tachycardia.

Case # 7768539³⁹ is a literature case of a 41-year-old male who developed coronary artery spasm, myocardial ischemia and perioperative myocardial infarction after receiving ephedrine and atropine for sinus bradycardia. The patient received multiple concomitant medications during a bilateral strabismus repair. The authors stated that the combination of the vagal hyperactivity that occurred during the ocular muscle manipulation and the use of ephedrine led to myocardial ischemia and perioperative myocardial infarction.

Case # 8065018 reported a 66-year-old male who developed coronary vasospasm, ST elevation, and ventricular tachycardia with premature ventricular contractions 35 minutes after receiving ephedrine (for hypotension) during preparation for a right aortofemoral bypass and thromboembolectomy. The patient received multiple concomitant medications for general anesthesia. His relevant medical history included untreated hypertension and hyperlipidemia, arteriosclerosis obliterans, iliac artery thrombosis, axillary thrombosis, femoral artery bypass, thromboembolectomy, and he was a longtime smoker. He continued to experience hemodynamic instability and ECG changes and was treated with additional doses of ephedrine, lidocaine, noradrenaline, isosorbide dinitrate, dopamine, and diltiazem. After the patient was stabilized a femoro-femoral bypass and thromboembolectomy was performed. No further ECG changes were observed during surgery and he was extubated without complications and transferred to the cardiac care unit. The patient developed coronary artery spasm again following intraluminal administration of acetylcholine. He was treated with nitroglycerin and did not suffer further cardiac attacks during his hospital stay. Nifedipine was prescribed for the prevention of coronary artery spasm and treatment of hypertension. No further symptoms of coronary artery spasm occurred.

Ventricular Tachycardia (N=10)

There are 10 unique cases that reported ventricular tachycardia with ephedrine injection. Six (cases 10152018, 4199580, 6430905, 6642916, 6948967, and 8648730) of the 10 cases also reported cardiac events arteriospasm coronary and/or cardiac arrest which are described above. All of the cases were either confounded by concomitant medications or underlying conditions or lacked sufficient clinical detail in order to thoroughly evaluate the case.

Case 10611977 reported a 52-year-old female who experienced multifocal ventricular tachycardia (torsade de pointes) and bigeminal extrasystoles with ephedrine treatment during a cerebral aneurysm clipping in the head. Her relevant medical history included subarachnoid hemorrhage. The patient received general anesthesia. A preoperative blood test showed hypokalemia and ECG revealed a slight ST segment depression but QTc was within normal range. Multiple doses of phenylephrine and ephedrine were given for low blood pressure. One minute after the second dose of ephedrine, ventricular extrasystoles developed and two minutes

later the patient progressed to torsade de pointes. The patient returned to normal sinus rate with cardiac massage. The following day, an echocardiography showed no abnormality. The reporters suspect catecholamine, hypokalemia, sympathetic nerve stimulation (such as operative stress), and sevoflurane to be causative factors for the events.

Case 11919053⁴⁰ is a literature case that reported a 32-year-old female experienced ventricular tachycardia after receiving ephedrine (for decreased blood pressure) and multiple concomitant medications during a cesarean section. The child was delivered 17 minutes after the start of anesthesia. After the birth, 17 minutes after the start of oxytocin and methylergometrine maleate (25 minutes after ephedrine was given), ventricular tachycardia appeared. The oxytocin infusion was stopped immediately and the arrhythmia resolved and did not reappear. The authors concluded that the combination of combined spinal and epidural anesthesia (CSEA), ephedrine, oxytocin and ergometrine may cause ventricular tachycardia in a patient without structural cardiac disease.

Case 6049412 is a literature case (uncited source) that reported a 26-year-old pregnant female with normal coronary arteries experienced acute coronary syndrome, chest pain, ventricular tachycardia, ST abnormalities, elevated cardiac enzymes and ischemic myocardial injury after receiving ephedrine injection to prevent secondary hypotension. The case lacked clinical detail (i.e. time to onset of event, type of procedure, concomitant medications). The authors stated that ephedrine was the cause of the acute coronary syndrome.

Case 7410175⁴¹ is a literature case that reported a 53-year-old male who received ephedrine and multiple concomitant medications during a cystoscopy, stent placement and percutaneous nephrolithotomy. Two minutes after receiving droperidol and dolasetron the patient experienced ventricular tachycardia. An ECG after the event showed sinus rhythm, intraventricular conduction delay and flattened T wave. An ECG the following day was normal. The outcome of the ventricular tachycardia was unknown and had recovered from intraventricular conduction delay and flattened T waves on an unspecified date.

Stress Cardiomyopathy (N=3)

There were three unique cases of stress cardiomyopathy reported with ephedrine injection. Two of the three cases were described in the cardiac arrest and arteriospasm coronary summary of cases (Cases 10793994 and 6724541). The remaining case (Case 6675025) reported a 31-year-old female who developed hypotension and bradycardia during a caesarean section delivery under spinal anesthesia. After receiving ephedrine, atropine, and phenylephrine she developed stress-induced cardiomyopathy. Although the authors felt that ephedrine, phenylephrine, and atropine precipitated stress-induced cardiomyopathy (SIC), SIC is theorized to be induced by many factors including stress (e.g. and operative procedure), and excess catecholamines.

Electrocardiogram ST Segment Depression (N=3)

There were three unique cases of electrocardiogram ST-segment depression reported with ephedrine injection. One of the three cases was described in the cases with a fatal outcome (Case 10568428). All of the cases were confounded by concomitant medications or an underlying condition.

Case # 6924235⁴² is a literature case that reported a 30-year-old female who experienced increased blood pressure and heart rate, premature ventricular contraction and ST-segment depression after receiving atropine and ephedrine during a laparoscopic myomectomy. The patient was administered atropine and ephedrine after the patient experienced decreased blood pressure and heart rate following an intramyometrial injection of vasopressin. Concomitant medications included general anesthetic drugs. The patient was treated with nicorandil, lidocaine, sevoflurane, nitrous oxide, mepivacaine and was discharged five days later. The physicians suspect that vasopressin was associated with the severe hypotension reported in this case.

Case 8684563 is derived from a study⁴³ that reported a 77-year-old female experienced ST-segment depression after receiving ephedrine (for hemostasis) and desflurane during a surgical operation of partial peripyloric gastrectomy and gastric cancer resection. The patient also received multiple concomitant general anesthetic drugs. The event resolved upon treatment with nicorandil. The reporting physician suspected desflurane, ephedrine, and an undetermined dehydration may have caused the tachycardia and increased heart rate which induced ST depression. The reporter also speculated the patient's underlying diabetes mellitus may have caused an ischemic heart disorder.

Myocardial Infarction (N=7)

There were seven unique cases of myocardial infarction reported with ephedrine injection. Five of the cases (Cases 10152018, 10568428, 4199580, 7038455 and 7768539) also described cardiac events (cardiac arrest, arteriospasm coronary, electrocardiogram ST segment depression) described above. All of the cases were confounded by concomitant medications and/or an underlying condition.

Case # 7197685 is derived from a study⁴⁴ that reported a 28-year-old female who experienced a myocardial infarction and tachycardia after receiving ephedrine, phenylephrine, and carbetocin for a caesarean section due to spontaneous rupture of membranes. The patient also received spinal anesthesia and cefuroxime. Following the administration of carbetocin, the patient became tachycardic and developed ST depression, which resolved without treatment. She was discharged three days later, which is the normal discharge time after a caesarean section. The anesthetist felt that ephedrine was not responsible for the events since it was stopped and the tachycardia and MI occurred after treatment with carbetocin.

Case # 9557204 reported a 62-year-old male who experienced a myocardial infarction on the same day that ephedrine was administered for an unknown indication. He received multiple anesthetics and amoxicillin and clavulanic acid during the left trans-tibial amputation. After the induction of anesthesia, the patient presented with hypotension, pulseless electrical activity and cardiorespiratory arrest due to anaphylactic shock. Adrenaline was administered and surgery was stopped. A stent was placed in the right coronary artery and the patient was transferred to surgical intensive care unit. Amiodarone was given for atrial fibrillation. Anaphylactic shock was confirmed and the patient recovered from this event, however the outcome of the cardiorespiratory arrest and myocardial infarction was not reported.

8.7 APPENDIX G. NARRATIVE SUMMARIES OF FETAL ACIDOSIS CASES REPORTED IN FAERS (N=6)

Case # 7617193 reported a 29-year-old female presented with contractions, tachycardia, bleeding, and “amniotic sac cracking” at 28 weeks pregnant. She was treated with erythromycin, betamethasone, nifedipine. The following day, she experienced low blood pressure, then maternal reactive tachycardia and was treated with ephedrine, phenylephrine, and hydroxyethyl amidon. The following morning the patient again experienced contractions and tachycardia, in addition to dyspnea. Tocolysis was performed with Atosiban, however, Atosiban was ineffective and the patient’s amniotic sac ruptured. During labor she experienced dyspnea and tachycardia and was treated with oxygen. A female baby was delivered in a state of apparent death with ph in favor of tissue acidosis, despite normal fetal rhythm and clear amniotic fluid during labor. Intensive resuscitation was performed after the birth, but it failed to revive the baby. Regarding the mother, she experienced worsening of tachycardia and dyspnea, ongoing dyspnea and thoracic pain. An angioscan revealed condensation of the left pulmonary base and very small bilateral pleural effusion, compatible with overload. She was transferred to the cardiology intensive care unit, due to her oxygen dependence, the persistence of the dyspnea and thoracic pain, increased troponin (2 and then 3) and increased B-type natriuretic peptide. The reporter suspected the fetal death to be related to a combination of several factors: “prematurity, maternal-foetal infection, cardiac failure, possibly promoted by particular sensitivity to nifedipine and to progression of sepsis, causing low rates and a deficiency in oxygenation of the fetus, which could also have aggravated fetal tissue acidosis.”

Cases # 5984416, 5984424, 5985329, 5985332, 5985334

These five cases derived from a study reported in the literature.⁴⁵ The purpose of the article was to compare the incidence of fetal acidosis at elective cesarean delivery when an infusion of phenylephrine, or ephedrine sulfate, or both, was given to maintain maternal systolic arterial pressure during spinal anesthesia. Fetal acidosis was less frequent in the phenylephrine group and less frequent in the combination group than in the ephedrine group. The study concluded that giving phenylephrine alone by infusion at cesarean delivery was associated with a lower incidence of fetal acidosis and maternal nausea and vomiting than giving ephedrine alone. There was no advantage to combining phenylephrine and ephedrine because it increased nausea and vomiting, and it did not further improve fetal blood gas values, compared with giving phenylephrine alone.

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

/s/

LAURELLE CASCIO
04/04/2016

JANE L GILBERT
04/05/2016

SARA L CAMILLI
04/05/2016

SARA L CAMILLI on behalf of BRIAN M LEWIS
04/08/2016
Proxy for Dr. Brian Lewis.

STEVEN C JONES
04/08/2016

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

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

Memorandum

Date: April 1, 2016

To: Ayanna Augustus, Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 208289
AKOVAZ (ephedrine sulfate) Injection for Intravenous Use
Professional Labeling Review

As requested in DAAAP's consult dated July 9, 2015, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for AKOVAZ (ephedrine sulfate) Injection. The substantially complete prescribing information was provided to OPDP on March 28, 2016, via email by Ayanna Augustus with the file name "[\\fdafs01\ode2\DAAAP\NDA and sNDA\NDA 208289\(Ephedrine sulfate Flamel\)\Labeling\proposed-tracked 03 28 16.docx](#)".

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we made comments on pages 1, 2 and 7 of the substantially complete prescribing information.

OPDP has no comments on the carton and container labeling submitted February 3, 2016.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KOUNG U LEE
04/01/2016



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 25, 2016

To: Sharon Hertz, MD, Director, Division
of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, PhD, Director
Controlled Substance Staff

From: James Hunter, RPh., MPH, Pharmacist Reviewer, Controlled Substance
Staff

Subject: **Topic:** General consult
Application: NDA 208289 - Ephedrine Sulfate Injection (Ephedrine
Sulfate Injection, USP) Sterile 50 mg/mL solution for intravenous
injection.
Proposed Indication: Treatment of clinically important hypotension in
the setting of anesthesia.
Sponsor: Flamel Ireland Limited (Flamel)

Materials reviewed: 1. Submission dated June 30, 2015. 1.11.4 Abuse Potential Assessment.
NDA 208289 (ephedrine).
2. Meeting minutes. Meeting between Eclat representatives and FDA on
April 23, 2015.

Table of Contents

A. BACKGROUND:1

B. CONCLUSIONS:2

C. RECOMMENDATIONS TO DIVISION:2

Background:

This memorandum is in response to a CSS consult dated July 09, 2015, from the Division of Analgesics, Anesthetics, and Addiction Products (DAAAP) for NDA 208289, a 505(b)(2) New Drug Application for ephedrine sulfate injection, under development by Flamel Ireland Limited. DAAAP is requesting review from a CSS perspective and to attend scheduled team and labeling meetings.

The Sponsor has developed ephedrine sulfate injection, USP as a sterile 50 mg/mL solution for intravenous injection. Ephedrine sulfate is a sympathomimetic drug with mixed adrenergic agonist activity. The proposed indication is for the treatment of clinically important hypotension in the setting of anesthesia. Ephedrine sulfate may be administered as additional boluses, as needed, not to exceed a total dosage of 50 mg.

Unapproved versions of ephedrine sulfate injection have been marketed for many decades. The sponsor claims that the formulation for Ephedrine Sulfate Injection, USP is the same as that for the FDA unapproved injectable products that have been used for years. The sponsor is relying solely on the published literature for evidence of safety and effectiveness.

As requested in a pre-NDA meeting on April 23, 2015, Éclat, an affiliate of the sponsor Flamel, provided an overview of the abuse potential of the formulation as a Multiple Module Information Amendment located in Section 1.11.4.1. This overview includes a description of the drug product, and a literature review on the abuse potential of ephedrine. Éclat also conducted a search of the published literature, and did not find evidence indicating that parenteral ephedrine has been directly abused. The sponsor proposes that the product not be scheduled under the Controlled Substances Act.

Conclusions:

1. We agree with the sponsor that ephedrine sulfate injection poses minimal risk for abuse and should not be scheduled under the Controlled Substances Act. Further, we agree with the sponsor that treatment of clinically important hypotension in the setting of anesthesia and availability only by prescription should result in the drug being used in highly controlled settings, such as surgical suite, and limited dispensing in a hospital setting.
2. As relayed to the sponsor previously, the importation and manufacturing of this product is subject to the controls imposed by the Combat Methamphetamine Epidemic Act of 2005, as a List 1 chemical. This Act mandates that U.S. Drug Enforcement Administration (DEA) establish total annual requirements, and individual import, manufacturing, and procurement quotas for this product.

C. Recommendations to Division:

1. CSS recommends that the sponsor be reminded to discuss the projected needs of ephedrine with the DEA Office of Diversion Control because the importation and manufacturing of ephedrine is subject to the controls imposed by the Combat Methamphetamine Epidemic Act of 2005.

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

/s/

JAMES R HUNTER
03/28/2016

MICHAEL KLEIN
03/28/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 29, 2016
Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 208289
Product Name and Strength: Akovaz(Ephedrine Sulfate) Injection
50 mg/mL
Submission Date: January 26, 2016
Applicant/Sponsor Name: Éclat
OSE RCM #: 2015-1556-1
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling for Akovaz (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container labels and carton labeling for Akovaz are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Schlick J. Label and Labeling Review for Akovaz (NDA 208289). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 17. 22 p. OSE RCM No.: 2015-1556.

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

/s/

JAMES H SCHLICK
01/29/2016

BRENDA V BORDERS-HEMPHILL
02/01/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 17, 2015

Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 208289

Product Name and Strength: Akovaz (Ephedrine Sulfate) Injection
50 mg/mL

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Éclat Pharmaceuticals

Submission Date: June 30, 2015

OSE RCM #: 2015-1556

DMEPA Primary Reviewer: James Schlick, RPh, MBA

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

As part of the approval process for Akovaz (Ephedrine) Injection, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A C
ISMP Newsletters	N/A D
FDA Adverse Event Reporting System (FAERS)	E
Unapproved Ephedrine Products	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

FAERS cases

Our evaluation of the FAERS cases identified 14 cases relevant to this review (Appendix E).

We received four cases related to confusion between ephedrine and epinephrine. In three of the cases, the error reached the patient. Outcomes reported included hypertension and chest pain. We identified the following root causes for these errors:

- Ephedrine and Epinephrine next to each other in Automated Dispensing cabinet
- Nurse Confused Epinephrine vial for Ephedrine vial

A root cause was not reported in two of the cases. It is likely that the confusion in these cases can be attributed to the fact that both names begin with the same letter string 'Ep' and end with the same letter string 'rine'. Thus, the names often appear near each other on automated dispensing cabinet selection screens and may be stored near each other in the automated dispensing cabinets, leading to product selection errors. Additionally, both medications are used in the same practice setting, increasing the risk for confusion. Of the four cases that we received, the most recent case was reported in June 2003 (Case# 3966105). Since this case, it is likely that hospitals have taken steps to mitigate the confusion between these two medications

based on previous reports. Therefore, we do not recommend any changes at this time, but we will continue to monitor for these types of errors through post-market surveillance.

We received nine cases related to the confusion between ephedrine and another product where the root cause was due to similar packaging within a company's product line and used in the same setting of care. These errors did not reach the patient. However, we assess the labels and labeling of Éclat's other product lines to determine if they are similar and can be improved to mitigate confusion.

Labels and Labeling

We evaluated the labels and labeling of Éclat's two other product lines- Bloxiverz (neostigmine) and Vazculep (phenylephrine)- to determine if the Akovaz packaging is similar. See Appendix G for a comparison. We determined that the Akovaz 50 mg/mL and the Vazculep 10 mg/mL labels and carton labeling are similar because they both use a similar color to present the strength statement and both are 1 mL single dose vials. See Appendix G.4 for a side by side comparison. We have received post-market errors with Vazculep and Bloxiverz packaging because the presentation of the strengths used similar colors (b)(4) was used for both product lines) and the trade dress was similar. To mitigate this risk, Éclat changed the strength presentation color for the Vazculep 50 mg/5 mL strength to mitigate confusion with the Bloxiverz 10 mg/10 mL strength.¹ We provide a recommendation in Section 4.1 to address this.

4 CONCLUSION & RECOMMENDATIONS

We identified confusion between ephedrine and epinephrine ampule and vial products. However, the most recent case we received was in 2003. Thus, we have no recommendations at this time, but we will continue to monitor for these types of errors through post-market surveillance. We also determined that the Akovaz 50 mg/mL and the Vazculep 10 mg/mL are in the same container closure systems (1 ml single dose vial) with similar labels and labeling. We provide a recommendation in Section 4.1 to address this.

4.1 RECOMMENDATIONS FOR ÉCLAT

We recommend the following be implemented prior to approval of this NDA:

Carton Labeling and Container Labels

1. There is inadequate differentiation between the labels and labeling for the 1 ml single dose Akovaz 50 mg/mL vials and the 1 mL single dose Vazculep 10 mg/mL vials. Consider the use of different colors, colored boxing of the strength statement, or some other means to provide adequate differentiation between the container labels and carton labeling.

¹ Schlick J. Postmarketing Review for Vazculep (NDA 204300) and Bloxiverz (NDA 204078). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 April 02. 24 p. OSE RCM No.: 2015-245.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Akovaz that Éclat Pharmaceuticals submitted on June 30, 2015.

Table 2. Relevant Product Information for Akovaz	
Initial Approval Date	N/A
Active Ingredient	Ephedrine Sulfate
Indication	Treatment of clinically important hypotension in the setting of anesthesia
Route of Administration	Intravenous
Dosage Form	Injection
Strength	50 mg/mL
Dose and Frequency	5 mg to 10 mg via intravenous bolus. Dose adjusted to achieve appropriate blood pressure. Ephedrine must be dilute to 5 mg/mL solution prior to administration
How Supplied/ Container Closure	50 mg/mL in a single dose 1 mL vial
Storage	Room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 9, 2015, we searched the L: drive using the terms, ephedrine to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not yield any previous reviews.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on July 9, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.²

Table 3: FAERS Search Strategy	
Date Range	July 9, 2015
Product	ephedrine [active ingredient]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

² 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>.

E.2 Results

Our search identified 128 cases, of which 14 described errors relevant for this review.

Table 4: Reported Characteristics for FAERS Medication Error Cases Possibly Associated with Ephedrine Injection Labels and Labeling (n=14).	
Appendix E.3 lists the 14 FAERS case numbers	
<i>Reported Characteristic</i>	<i>Number of Cases</i>
<i>Medication Error Type</i>	
<i>Wrong drug dispensed or selected (Reached the patient)</i>	3
<i>Transcription error</i>	1
<i>Label/Packaging Complaint (Error did not reach patient)</i>	10
<i>Reason for Error</i>	
<i>Small Ampule Size makes label hard to read</i>	1
<i>Similar packaging within Company's product line</i>	9
<i>Ephedrine and Epinephrine next to each other in Automated Dispensing cabinet</i>	1
<i>Nurse Confused Epinephrine vial for Ephedrine vial</i>	1
<i>Reason not reported</i>	2
<i>Setting of Use</i>	
<i>Outpatient</i>	0
<i>Inpatient</i>	14
<i>Outcomes</i>	
<i>Serious</i>	1
<i>Non-Serious</i>	0
<i>Not Reported</i>	2
<i>Not reported Because error did not reach patient</i>	11

We excluded 114 cases because they described:

- Intentional overdose or intentional misuse
- Medication error not related to ephedrine
- Error case related to oral products containing ephedrine
- Foreign cases
- Adverse event related ephedrine, but no medication error occurred

- Unable to determine root cause of medication error
- Errors related to compounding pharmacy products

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

	Case #	Vrsn	FDA Initial Recd Date	Narrative
1.	3491141	1	6/19/2000	Print size on Ephedrine Ampule is too small. May Lead to ERROR with this drug. [compare Taylor product label with the more READABLE Abbott products NDC 0074-3073-31] drug maladministration
2.	3574302	1	11/22/2000	Ephedrine placed into 3000 liter saline bag for irrigation on a shoulder scope. The medicine that should have been used was Epinephrine. Mistake was caught after one, one liter bag had been infused. drug maladministration
3.	3613990	1	2/21/2001	Ephedrine placed into 3000 liter. Saline bag for irrigation on a shoulder scope instead of Epinedrine. Liter bag was used for irrigation until error was discovered. Surgeon and physician notified during case. drug maladministration
4.	3722501	1	10/15/2001	Similar packaging of Ephedrine 50mg/ml and Midazolam 5mg/ml by (b) (4) There was almost an administration error by an anesthesiologist Drug Maladministration

5.	3952471	1	5/23/2003	<p>Unfortunately, we do have a look alike issue with (b) (4) products:</p> <ol style="list-style-type: none"> 1. Ketorolac 30mg/ml 1ml vial NDC # 55390048101 (Lot # 417769, Exp 12/04) 2. Ephedrine 50mg/ml 1ml vial NDC # 55390087501 (Lot # 393494 Exp 9/05) <p>Both of the vials are the same size with the same grey cap and fairly Close coloration on the labels. Also, both vials are amber in color. It is interesting because it appears that the vials for this size just changed to amber. We have another lot (Lot # 368803 Exp 7/04) where they are clear!</p> <p>That really helps differentiate them from the ephedrine vials. The clear vials are about 12.5-13mm in diameter whereas the amber vials are 16mm in diameter. I wonder if they changed their manufacturer for their vials. Of course the names differ, but the vials are so close that this is a problem.</p> <p>(b) (4) may have changed to amber vials for the ketorolac 30mg vials since the 60mg vials are clear and have a purple cap. The obviously didn't refer to their ephedrine vials or other product lines vials when they made that decision. I can't remember if ISMP noted this changed or not, so I will send it to them.</p> <p>If we can't get (b) (4) to change the caps, size, or labeling, then we probably need to change companies for either the ephedrine vials or the ketorolac 30mg vials/</p>
6.	3961983	1	6/17/2003	<p>medication error</p> <p>Our anesthesiologist have identified a potential medication error. The manufacturer of ephderine also produces ketorolac. The ephderine has been delivered in a brown-glass vial with a grey flip-top, and white label with black lettering, and a shade of purple outlining. The ketorolac has been packaged in a clear-glass vial until recently. The ketorolac is now in a look-a-like vial; the outlining is a different shade of purple. Recommend changing colors of cap or labeling to help prevent errors that may happen when a provider is in a rush such as an emergent situation. We have temporarily place a label with a look-a-like warning in the vial.</p>

7.	3966105	1	6/27/2003	<p>medication error</p> <p>This report is being submitted on behalf of the reporter by ISMP: We also just had an ephedrine/epinephrine event in laboring patient. Drugs were next to each other in PYXIS drawer (both on override). Doc asked for ephedrine, hurried nurse drew up epinephrine and handed it to primary nurse who administered the epi. Pt suffered period of hypertension and chest pain, baby delivered ok a little later and Mom was ok.</p>
8.	3969748	1	7/9/2003	<p>MEDICATION ERROR SEE IMAGE</p> <p>This report is being submitted on behalf of the reporter by ISMP; The attached file is a photo that depicts a potential problem that our anesthesiologists noted. The manufacturer of KETOTOLAC has recently changed color of the vial to a brown glass because this medication requires protection from sunlight. However, manufacturer also produces EPHEDRINE and packages the drug in a similar vial. Both vials: are brown glass; are the same size; have grey protective caps; have white labels; have typed text with slightly different shades of purple.</p> <p>The manufacturer is (b) (4).</p> <p>We are in the process of developing a safe work-around and may have to order from a different supplier.</p> <p>MEDICATION ERROR SEE IMAGE</p>
9.	4049576	1	12/23/2003	<p>A Pharmacist received a call from an ICU nurse stating that she needed more ephedrine in order to draw up the ephedrine dose the physician had ordered. Having read the warnings from ISMP regarding potential errors between ephedrine and epinephrine, the Pharmacist questioned the nurse. She stated that she was holding an amp of ephedrine in her hand and that it was 1 mg/ml and her dose was for 10 mg. knowing that ephedrine is available as a 50 mg vial, the Pharmacist asked the nurse to verify that she indeed was holding ephedrine. The nurse again confirmed that she was holding ephedrine and had a second person view the ampule and both agreed that it was ephedrine. At this point, the Pharmacist went down to the nursing station with an ephedrine 50 mg vial and pointed out to the nurse that what she was holding in her hand was epinephrine 1:1000 or 1 mg/ml which is different than ephedrine.</p> <p>Medication Error</p>

10.	4186193	1	7/30/2004	<p>During a procedure the Anesthesiologist was to use midazolam and ephedrine. After removing the "flip" tops of each of these drugs he placed them on a counter. During the procedure to sedate the patient he was to administer midazolam and grabbed one of the vials which appeared identical. The wrong medication was retrieved but it was fortunate he read the label before administration.</p> <p>Medication Error</p>
11.	5875875	1	9/6/2005	<p>abstracted by FDA rep CRNA wanted midazolam but opened Ephedrine Different Color Labeling for Cardiac drugs or Drugs used in shock vs Benzo medication error partially illegible see image (per FDA rep)</p>
12.	6394372	1	8/23/2007	<p>I work in a hospital pharmacy. We found a potential error before it reached the patient. The patient was prescribed ephedrine IV and the patients drawer was filled with compazine (generic) vials. The vials are in similar packaging. The packaging is as follows: <div style="background-color: #cccccc; padding: 2px; text-align: center;">(b) (4)</div> prochlorperazine 10 mg/2mL vial (dark amber) (Compazine) <div style="background-color: #cccccc; padding: 2px; text-align: center;">(b) (4)</div> Ephedrine 50 mg/mL vial (dark amber) Both vials are highlighted in bright orange. THE only distinguishing factor is the color of the cap, which our institution sometimes puts a warning sticker on the top if dosage is less than dose is vial. Submitted via ISMP We found a potential error before it reached the patient. Both vials are highlighted in bright orange. The only distinguishing factor is the color of the cap, which our institution sometimes puts a warning sticker on the top if dosage is less than dose is vial. medication error</p>
13.	6506285	1	12/6/2007	<p>Potential for error - mix-up between ephedrine & prochlorperazine injectable vials - both from <div style="background-color: #cccccc; padding: 2px; text-align: center;">(b) (4)</div>. Submitted via ISMP N/A Unknown medication error</p>

14.	6506291	1	12/6/2007	<p>Upon obtaining a vial of ephedrine - it was discovered that a vial of midazolam was in the same stock in the Acudose unit in our OR. The correct medication was chosen - but the error was noted as well. The storage error probably occurred during stocking of the Acudose; where the midazolam was accidentally included w/ a number of ephedrine vials. The two vials look very similar - has the same manufacturer, identical writing style; however one vial has a maroon cap w/ red strip on the label (ephedrine), and the other has a red cap w/ maroon strip on the label (midazolam). Submitted via ISMP</p> <p>The error did not reach a patient - but had the potential too. The storage error probably occurred during stocking of the Acudose; where the midazolam was accidentally included w/ a number of ephedrine vials. The two vials look very similar - has the same manufacturer, identical writing style; however one vial has a maroon cap w/ red strip on the label (ephedrine), and the other has a red cap w/ maroon strip on the label (midazolam).</p> <p>Medication Error</p>
-----	-------------------------	---	-----------	---

E.4 Description of 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 postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX F. Unapproved Ephedrine Injection Products

F.1 Methods

We searched the Electronic Drug Registration and listing System (eDRLS) database for ephedrine sulfate injection products on August 21, 2015 using the following search terms and filters:

- Non-proprietary name contains “ephedrine”
- Dosage Form equals “Injection, Solution”
- Dosage Form equals “Injection”

F.2 Results

We identified the following labelers and currently marketed unapproved products

PRODUCT NDC	START MARKETING DATE	LABELER NAME	
(b) (4)			

F.3

The electronic Drug Registration and Listing System (eDRLS) was established to support the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

<http://dqcp.fda.gov/pls/dqcp/f?p=105:1:103424780719536::NO::>

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JAMES H SCHLICK
09/17/2015

BRENDA V BORDERS-HEMPHILL
09/17/2015

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 # 208289 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: n/a Established/Proper Name: ephedrine sulfate injection, USP Dosage Form: solution Strengths: 50 mg/mL		
Applicant: Flamel Ireland Limited Agent for Applicant (if applicable): The Weinberg Group		
Date of Application: June 30, 2015 Date of Receipt: June 30, 2015 Date clock started after UN: n/a		
PDUFA/BsUFA Goal Date: April 30, 2016		Action Goal Date (if different): April 29, 2016
Filing Date: August 29, 2015		Date of Filing Meeting: August 11, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input checked="" type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For the treatment of clinically important hypotension in the setting of anesthesia		
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" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none">• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)• The product is a Qualified Infectious Disease Product (QIDP)• A Tropical Disease Priority Review Voucher was submitted• A Pediatric Rare Disease Priority Review Voucher was submitted	
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 (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <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 Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <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)
<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): 116266

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the 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</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>)			
	<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>	Payment of other user fees:			
	<input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>			
	<input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• 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)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• 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)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested:					
Note: An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<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)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <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> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: 7/9/15</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

2

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

Version: 6/15/2015

7

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

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

4

<p>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?⁵</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				

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

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

If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 19, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 23, 2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 11, 2015

BACKGROUND: The Sponsor submitted a 505(b)(2) NDA for ephedrine sulfate injection which is a marketed unapproved drug product, for the treatment of clinically important hypotension in the setting of anesthesia. The sponsor is referencing literature to support the safety and efficacy of their drug product.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ayanna Augustus	y
	CPMS/TL:	Parinda Jani	n
Cross-Discipline Team Leader (CDTL)	Rigoberto Roca		y
Division Director/Deputy	Rigoberto Roca		y
Office Director/Deputy			
Clinical	Reviewer:	Amelia Lockett	y
	TL:	Rigoberto Roca	y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Srikanth Nallani	n
	TL:	Yun Xu	y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Freda Cooner	n

	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	y
	TL:	Newton Woo	y
	Superviosr:	Dan Mellon	y
Statistics (carcinogenicity)	Reviewer:		
	TL:	Freda Cooner	n
Product Quality (CMC) Review Team:	ATL:	Julia Pinto	y
	RBPM:	Steven Kinsley	y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:	Vidula Kolhatkar	y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Koung Lee	y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	James Schlick	n
	TL:	Vicky Borders-Hemphill	n
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Jim Hunter	y
	TL:	Michael Klein	n
Other reviewers/disciplines			
Office of Unapproved Drug Labeling Compliance		Michael Ghobrial	n
		Barbara Wise	y
		Art Simone	y
		Sally Loewke	n
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees	Kelly Kitchens		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Provide information on the source, enantiomer identification and formulation comparison of the sponsor's product with the products used in the reference literature</p>
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none">• Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
---	--

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: clinical studies were not conducted for this NDa</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Rigoberto Roca	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): December 7, 2016	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<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"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<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"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

APPEARS THIS WAY ON ORIGINAL

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

/s/

AYANNA S AUGUSTUS
08/24/2015

PARINDA JANI
08/25/2015

CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 208289

Applicant: Flamel Ireland Ltd. Date: June 30, 2015

Drug Name: ephedrine sulfate
injectable

IND Number:

Checklist	Yes	No	N/A	Comment
What is the regulatory history of this application?				Not a scheduled substance, DEA listed chemical
Abuse potential assessment is required if any of the following are true for a drug:				
It affects the CNS	x			
It is chemically or pharmacologically similar to other drugs with known abuse potential	x			
It produces psychoactive effects such as sedation, euphoria, and mood changes	x			
Is the drug a new molecular entity?		x		
Is this a new or novel drug formulation?		x		
Content of NDA abuse potential section:¹				
<i>Module 1: Administrative Information and Prescribing Information</i>				
1.1.1.4 Multiple Module Information Amendment contains:				
<ul style="list-style-type: none"> A summary, interpretation, and discussion of abuse potential data provided in the NDA. 	x			Brief summary
<ul style="list-style-type: none"> A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential. 	x			limited
<ul style="list-style-type: none"> A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA 	x			
<i>Module 2: Summaries</i>				
2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.	x			limited
<i>Module 3: Quality</i>	x			
3.2.P.1 Description and Composition of the Drug Product - describes any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).		x		No studies performed
Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?		x		
3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.				
Is this an extended release or abuse-resistant formulation?		x		

CSS Filing Checklist for NDA/BLA or Supplement

Checklist	Yes	No	N/A	Comment
<i>Module 4: Nonclinical Study Reports</i>				
4.2.1 Pharmacology		x		
4.2.1.1 Primary Pharmacodynamics - contains study reports (<i>in vitro</i> and <i>in vivo</i>) describing the binding profile of the parent drug and all active metabolites.				
Are <i>in vitro</i> receptor binding studies included?		x		
Are functional assays included?		x		
4.2.3.7.4 Dependence – section includes:		x		
<ul style="list-style-type: none"> • A complete discussion of the nonclinical data related to abuse potential. • Complete study reports of all nonclinical abuse potential studies. 		x		
Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA		x		
Was a self administration study conducted?				
Was a conditioned place preference study conducted?				
Was a drug discrimination study conducted?				
Was a physical dependence study conducted?				
<i>Module 5: Clinical Study Reports</i>		x		
5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.				
Human abuse potential study:				
Was a human abuse potential study conducted?				
Are all the primary data included in the NDA?				
Is a Statistics consult necessary?				
Other Clinical trials:				n/a
Is there evidence of drug accountability issues or overt evidence of misuse, abuse, or diversions?				
Are all abuse/misuse Case Report Forms submitted [addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study]?				
Does Compliance need to be consulted re: site inspection for data integrity or other issues?		x		
5.3.6.1 Reports of Postmarketing Experience - includes information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product	x			Sponsor's literature search confined to ephedrine injectable. Contained in 1.11.4 Multiple Module Information Amendment.
Did you review the scientific literature?	x			Module 1.11.4

CSS Filing Checklist for NDA/BLA or Supplement

Checklist	Yes	No	N/A	Comment
Did you conducted a search of databases and other information related to misuse, abuse, and addiction?				
Is there evidence for any of the following:				
Accidental overdose in the patient population and vulnerable populations		x		None described in NDA
Overdose associated with misuse and abuse		x		Sponsor states none found in literature with marketed injectable product
Unintended pediatric exposures to product		x		None described in NDA
Labeling issues				
Drug disposal issues?		x		In hospital use during anesthesia as needed
Postmarketing activities [PMRs, PMCs, REMS]				
		x		None described
Scheduling activities				
		x		

Is NDA FILEABLE from a CSS perspective?

yes _____

If the Application is not fileable, state the reasons and provide comments to be sent to the Applicant.

1.

2.

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

None noted

CSS Reviewer: James R. Hunter, RPh., MPH	Date: 08-10-2015
Team Leader:	Date:
Director:	Date:

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

/s/

JAMES R HUNTER
08/10/2015

ALAN I TRACHTENBERG
08/21/2015

MICHAEL KLEIN
08/24/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208289

Application Type: New NDA

Name of Drug/Dosage Form: Ephedrine Sulfate Injection

Applicant: Flamel Ireland Limited
c/o The Weinberg Group, Inc.

Receipt Date: June 30, 2015

Goal Date: April 30, 2016

1. Regulatory History and Applicant's Main Proposals

The Sponsor submitted a 505(b)(2) NDA for ephedrine sulfate injection which is a marketed unapproved drug product, for the treatment of clinically important hypotension in the setting of anesthesia. The sponsor is referencing literature to support the safety and efficacy of their drug product.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

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

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment: *not yet approved.*

Boxed Warning (BW) in Highlights

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

Comment:

- N/A** 13. The BW 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 and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC 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 in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. 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 in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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 in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. 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

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW 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 and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- N/A** 39. When clinical trials adverse reactions data are 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 practice.”

Comment: ******Literature based NDA******

- N/A** 40. When postmarketing adverse reaction data are 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 Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

AYANNA S AUGUSTUS
07/30/2015

PARINDA JANI
07/30/2015