CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208609Orig1s000

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 # 208609
Product Name: 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:	06/30/2017
Study/Trial Completion:	04/30/2018
Final Report Submission:	01/31/2019
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 was until very recently 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.

Reference ID: 4062051

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

Reference ID: 4062051

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

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PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

Reference ID: 4062051

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 # 208609
Product Name: 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:	06/30/2017
Study/Trial Completion:	01/30/2018
Final Report Submission:	12/31/2018
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 was until very recently 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.

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

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

Reference ID: 4062051

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

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

Required

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

Reference ID: 4062051

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

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PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

Reference ID: 4062051

00PMR/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 # 208609
Product Name: 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:	06/30/2017
Study/Trial Completion:	04/30/2018
Final Report Submission:	02/28/2019
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 was until very recently 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.

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

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

Reference ID: 4062051

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

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

Required

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

Reference ID: 4062051

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

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PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

Reference ID: 4062051

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 # 208609
Product Name: 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:	06/30/2017
Study/Trial Completion:	03/31/2019
Final Report Submission:	03/31/2020
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 was until very recently 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.

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 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.

Reference ID: 4062051

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 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

Reference ID: 4062051

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

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PMR/PMC Development Coordinator:

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

_____
(signature line for BLAs)

Reference ID: 4062051

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 # 208609
Product Name: Ephedrine sulfate

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

PMR/PMC Schedule Milestones:

Final Protocol Submission:	N/A
Study/Trial Completion:	08/30/2017
Final Report Submission:	02/28/2018
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 was until very recently 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.

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."

Reference ID: 4062051

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.

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 genetic toxicology study (b) (4).

Reference ID: 4062051

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

Reference ID: 4062051

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)

Reference ID: 4062051

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/s/

KIMBERLY A COMPTON
02/27/2017

JUDITH A RACOOSIN
02/27/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

PLLR Labeling Memorandum

Date: June 2, 2016

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: 208609

Applicant: Akorn, Inc

Indication(s) (b) (4) clinically important hypotension in the setting of anesthesia

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Submission Date: September 15, 2015

Consult Date: January 12, 2016

Reference ID: 3951723

Materials Reviewed:

- DAAAP consult request dated January 12, 2016
- Application submission on September 15, 2015
- Applicant's response to Division's information request of January 16, 2016, dated January 29, 2016
- Ephedrine sulfate Labeling submitted on January 29, 2016
- Consult Review by DBRUP in DARRTS on January 30, 2014
- DPMH ephedrine sulfate injection labeling review by C. Mastroyannis, NDA208289, dated April 21, 2016, DARRTS Ref ID 3920401

Consult Question:

DAAAP requests that DPMH review and provide comments on the content and format of the maternal health sections [8.1, 8.2, 8.3] 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 January 12, 2016, 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).

REGULATORY HISTORY

Ephedrine sulfate is indicated for the treatment of clinically important hypotension in the setting of anesthesia and is a previously unapproved drug. 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. This is a 505(b)(2) Application.

BACKGROUND

Drug Characteristics[1]

Ephedrine is a sympathomimetic agent with mixed α- and ß-adrenergic agonist properties. Ephedrine stimulates heart rate and cardiac output, causes prominent vasoconstriction, variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Half-life of oral ephedrine is 5.9 hours. The molecular weight of ephedrine sulfate is 428.54

Ephedrine sulfate injection is supplied as 1 mL ampules of 50 mg/mL ephedrine sulfate in water.

Pregnancy and Lactation Labeling

On June 30, 2015, the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,"[2] also known as

[1] Ephedrine sulfate injection Labeling. Section 11 Description and 12: Clinical Pharmacology. Submission January 29, 2016

Reference ID: 3951723

the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. 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 Rule [3] format to include information about the risks and benefits of using these products during pregnancy and lactation.

DAAAP sent Akorn an information request (IR) on January 16, 2016, to request that the Applicant provide:

- a review and summary of all available published literature regarding ephedrine use in pregnant and lactating women
- a review and summary of relevant cases reported in Akorn's pharmacovigilance database
- an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry (if applicable)
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

In response, the Applicant submitted on January 29, 2016,

- an analysis of cases reported to a summary of published literature with cross-reference to the location of the requested information in the NDA
- labeling containing revisions to sections 8.1 (pregnancy), and 8.2 (lactation).

The Applicant also confirmed that there is no existing pregnancy registry for this product.

REVIEW

A review of the Applicant's response to the IR provided information consistent with a recent DPMH review of a similar product. No additional information was presented. Therefore, DPMH labeling recommendations are consistent with the prior DPMH review of ephedrine injection. The reader is referred to the Labeling Review Consult by DPMH in DARRTS on April 21, 2016, for detailed discussion on ephedrine sulfate injection use in pregnancy and lactation.

CONCLUSIONS

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

---

[2] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014)

[3] 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).

Reference ID: 3951723

Pregnancy, Section 8.1

- The "Pregnancy" subsection of ephedrine sulfate labeling was formatted in the PLLR format to include "Risk Summary," and "Clinical Considerations" (b) (4)

Lactation, Section 8.2

- The "Lactation" subsection of ephedrine sulfate labeling was formatted in the PLLR format to include the "Risk Summary"

(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.

[4] 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

Nothing to be stated in HIGHLIGHTS regarding pregnancy and lactation

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on the use of EPHEDRINE SULFATE injection are insufficient to determine a drug associated risk of major birth defects or miscarriage. However, there are considerations (b) (4) *[see Clinical Considerations]*. Animal reproduction studies have not been conducted with ephedrine sulfate.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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 (b) (4) 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 (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. (b) (4) 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.

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/s/

CHRISTOS MASTROYANNIS
06/27/2016

TAMARA N JOHNSON
06/27/2016

LYNNE P YAO
06/30/2016

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:	June 13, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208609
Product Name and Strength:	Ephedrine Sulfate Injection 50 mg/mL
Submission Date:	June 10, 2016
Applicant/Sponsor Name:	Akorn
OSE RCM #:	2016-99-1
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 label and carton labeling for Ephedrine Sulfate Injection (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 label and carton labeling for Ephedrine Sulfate Injection is acceptable from a medication error perspective. We have no further recommendations at this time.

[1] Schlick, J. Label and Labeling Review for Ephedrine Sulfate injection (Akorn) (NDA 208609). 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); 2016 FEB 16. 10 p. OSE RCM No.: 2016-99.

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/s/

JAMES H SCHLICK
06/14/2016

BRENDA V BORDERS-HEMPHILL
06/14/2016

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

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

Memorandum

Date: June 09, 2016

To: Kimberly Compton, 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 208609
Ephedrine Sulfate Injection for Intravenous Use
Professional Labeling Review

As requested in DAAAP's consult dated December 31, 2015, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for Ephedrine Sulfate Injection. The substantially complete prescribing information was provided to OPDP on June 8, 2016, via email by Matthew Sullivan with the file name "N 208-609 PI from EDR (5-17-16) USE FOR EDITS (2).docx".

OPDP has provided comments on the substantially complete prescribing information, container and carton labeling in the attached documents below.

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.

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/s/

KOUNG U LEE
06/09/2016

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 505(b)(2) NDA 208609
Applicant/Sponsor:	Flamel Ireland Limited Akorn Inc
OSE RCM #:	2016-340

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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 and Akorn Inc 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. Information should also be included in the Akorn label.

(b) (4)

Reference ID: 3908344

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

Information about potential fetal acidosis should be included in the Akorn label so that it contains similar information to that which is proposed by Flamel.

DPV II recommends the following:

1. (b) (4)

2. Information describing potential fetal acidosis should be included in both proposed labels.

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

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3908344

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 and Akorn Inc 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 and Akorn Inc 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]

Reference ID: 3908344

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 Appendix8.3 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

Reference ID: 3908344

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

Reference ID: 3908344

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)**	**Appears in Akorn Draft Labeling (rev. 1/2016)**
Hypotension	39	IR	IR
Acute Kidney Injury	31	No	No[†]
Maternal Exposure During Pregnancy	22	IR; (SP) labeled for may cause fetal harm	IR; (SP) labeled for crossing the placenta, not known whether it can cause fetal harm
Bradycardia	20	Yes; AR	Yes; AR
Cardiac Arrest	17	No	Yes; OD

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)	Appears in Akorn Draft Labeling (rev. 1/2016)
Oliguria	17	No	No
Tachycardia	16	Yes; AR	Yes; AR, OD
Hypertension	14	Yes; AR	Yes; AR, DI
Arteriospasm Coronary	12	No	No
Anaphylactic Shock	11	No	No
Drug Abuse	11	No	No†
Drug Ineffective	11	U	U
Dyspnoea	11	No	No
Ventricular Tachycardia	11	No	Yes; OD (labeled for ventricular arrhythmia)
Blood Pressure Decreased	10	IR	IR
Haematuria	10	No	No
Colitis Ischaemic	9	No	No
Foetal Exposure During Pregnancy	9	IR, (SP) labeled for may cause fetal harm	IR, (SP) labeled for crossing the placenta, not known whether it can cause fetal harm
Heart Rate Decreased	9	IR	IR
Metal Poisoning§	9	No	No
Nausea	9	Yes; AR	Yes; AR, OD
Parkinsonism§	9	No	No
Vomiting	9	Yes; AR	Yes; AR, OD
Headache	8	No	No; AR, OD
Oxygen Saturation Decreased	8	No	No
Pyrexia	8	No	No
Stress Cardiomyopathy	8	No	No
Angioedema	7	No	No
Anuria	7	No	No
Anxiety	7	No	Yes; OD
Caesarean Section	7	IR	IR
Confusion Postoperative	7	No	No†
Drug Interaction	7	Yes; DI	Yes; DI
Exposure During Pregnancy	7	U; (SP) labeled for may cause fetal harm	U; (SP) labeled for crossing the placenta, not known whether it can cause fetal harm
Hypothermia	7	No	No
Loss of Consciousness	7	No	Yes; OD
Mental Status Changes	7	No	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)	Appears in Akorn Draft Labeling (rev. 1/2016)
Postoperative			
Metabolic Alkalosis	7	No	No†
Premature Baby	7	No	No
Unevaluable Event	7	U	U†
Abdominal Distension	6	No	No
Acute Pulmonary Oedema	6	No	No
Confusional State	6	No	No†
Electrocardiogram ST Segment Depression	6	No	No
Haemodynamic Instability	6	IR	IR
Heart Rate Increased	6	No	Yes; AR
Myocardial Infarction	6	No	Yes; OD
Shock	6	No	No†
Sinus Tachycardia	6	Yes; AR (labeled as tachycardia)	Yes; AR, OD (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.

(b) (4) 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)	Appears in Akorn Draft Label (rev. 1/2016)
Cardiac Arrest	8	No	Yes; OD
Hypotension	6	IR	IR
Overdose	4	Yes; OD	Yes; AR, 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)	Appears in Akorn Draft Label (rev. 1/2016)
Mydriasis	3	No	Yes; CP
Toxicity To Various Agents	3	No; U	No; U
Apparent Death	2	U	U
Blister	2	No	No
Bradycardia	2	Yes; AR	Yes; AR, SP
Caesarean Section	2	No; IR	No; IR
Circulatory Failure Neonatal	2	No	No
Coma	2	No	No
Death Neonatal	2	No	No
Drug Ineffective	2	No; U	No; U
Drug Interaction	2	Yes; DI	Yes; DI
Drug Screen Positive	2	No	No
Foetal Death	2	No	No
Foetal Exposure During Pregnancy	2	U; (SP) labeled for may cause fetal harm	U; (SP) labeled for crossing the placenta, not known whether it can cause fetal harm
Haemodialysis	2	No	Yes; labeled for acute renal failure
Haemodynamic Instability	2	IR	IR
Haemoglobin Decreased	2	No	No
Hypertension	2	Yes; AR	Yes; AR, DI
Incorrect Route Of Drug Administration	2	No	No
Maternal Drugs Affecting Foetus	2	U; (SP) labeled for may cause fetal harm	U; (SP) labeled for crossing the placenta, not known whether it can cause fetal harm
Necrosis	2	No	No
Premature Baby	2	IR	IR
Pulmonary Oedema	2	No	No
Rash Erythematous	2	No	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

Reference ID: 3908344

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=3[1]) 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.

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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.

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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, 2015[11]; Dyer, 2012[12]; Lin, 2012[13], Loubert, 2012[14]; Cooper, DW, 2012[15]; Veeser, 2012[16]; and Habib, 2013[17]. 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, 2013[19], 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, 2013[20]; and, Koksal, 2012[21].

C. Publications describing renal stones complexed with ephedrine in patients using cough medication such as guaifenesin. These include: Cockerill, 2013[22]; 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

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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. Information should also be included in the Akorn label.

(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 fetal acidosis should be included in the Akorn label so that it contains similar information to that which is proposed by Flamel.

6 RECOMMENDATIONS

DPV II recommends the following:

1. (b) (4)

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2. Information describing potential fetal acidosis should be included in both proposed labels.

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

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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.

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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-BAYER-200916143BCC
10816706	2	GB-WATSON-2015-02088		7197685	1	GB-BAUSCH-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-AVENTIS-2010SA018155
11112226	1	TR-BAYER-2015-214651		7346037	4	FR-PFIZER INC-2010042758
11112341	1	TR-BAYER-2015-215141		7360978	1	20100127
11112417	1	TR-BAYER-2015-215232		7361640	2	2010SP017804
11112478	1	TR-BAYER-2015-215293		7366505	2	FR-ASTRAZENECA-2010SE17451
11112518	1	TR-BAYER-2015-215315		7370793	2	557465
11112549	1	TR-BAYER-2015-215360		7371413	1	FR-ABBOTT-10P-056-0639712-00
11112579	2	TR-BAYER-2015-215378		7381035	2	B0650935A
11112689	1	TR-BAYER-2015-215405		7393704	1	JHP201000154
11112725	1	TR-BAYER-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-AVENTIS-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-AVENTIS-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-AVENTIS-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-BAYER-200613088BCC		9494905	2	FR-ASTRAZENECA-2013SE66510
6117418	1			9557204	1	FR-BAXTER-2013BAX036594
6118452	1	US-BAYER-200613473BCC		9629833	4	JP-BAXTER-2013BAX038710
6163443	1	US-BAYER-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

APPEARS THIS WAY ON ORIGINAL

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, remifentanil, 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, remifentanil, 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.

11723816[29] – 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

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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 (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

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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 27-Sep-2010. 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.

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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.

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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

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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 # 10468691[30] 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, remifentanil, 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 # 10793994[31] 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 # 6430905[32] 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 # 6948967[33] 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 # 8432146[34] 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 # 10152018[35] 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 Bezoldt-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 # 6061329[36] 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 ad 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 6724541[37] 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

Reference ID: 3908344

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

Case # 7038455[38] 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 # 7768539[39] 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 11919053[40] 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 7410175[41] 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 # 6924235[42] 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 study[43] 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 study[44] 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.

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/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

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:	February 16, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208609
Product Name and Strength:	Ephedrine Sulfate Injection 50 mg/mL
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Akorn
Submission Date:	September 15, 2015
OSE RCM #:	2016-99
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

Reference ID: 3887689

1 REASON FOR REVIEW

As part of the approval process for Ephedrine Sulfate Injection, 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)*	N/A E
Other	N/A F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified areas of concern with the labels and labeling that can be optimized to minimize the risk for medication errors.

Container Label and Carton Labeling

The carton labeling includes the statement "For (b) (4) Intravenous, (b) (4) use", and the container label contains a similar statement (b) (4) However, the prescribing information indicates the proposed route of administration is for intravenous use (b) (4) (b) (4) On the container label, (b) (4) should be changed to "intravenous" to prevent potential confusion with "IJ" (intrajugular), "IU", or "IN" (intranasal).[1] We provide recommendations in Section 4.2.

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2016 JAN 25]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Also, because the proposed product will require dilution prior to intravenous administration, the statement "Dilute before use" should be included on the principal display panel (PDP) of the container label and carton labeling to minimize the risk that the product is given undiluted.[2]

(b) (4)

Thus, we provide a recommendation in Section 4.2 to address only the carton labeling.[3]

Prescribing Information

Akorn does not provide preparation for administration instructions regarding dilution of the solution prior to use in the Dosing and Administration Section. Thus, we provide recommendations in Section 4.1 to address this. Section 16, How Supplied Section does not indicate that any unused contents should be discarded and we provide recommendations in Section 4.1. Section 16, How Supplied Section does not indicate the package type for the ampule and we defer to CMC to determine the proper package type.

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[3] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

4 CONCLUSION & RECOMMENDATIONS

We identified areas of concern with the labels and labeling that can be optimized to minimize the risk for medication errors. We provide comments in Section 4.1 and 4.2 to address this.

4.1 RECOMMENDATIONS FOR THE DIVISION

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

1. Highlights of Prescribing Information, Dosage and Administration
   a. We provide a recommendation in Appendix G.3 to include the statement "Must dilute before use" to minimize the risk of giving the solution undiluted.
2. Full Prescribing Section, Dosage and Administration - 2
   a. We recommend Akorn include information that the solution be diluted prior to use, and instructions on how to dilute the medication including diluents that can be used in the dilution process.
3. Full Prescribing Section, How Supplied Section -16
   a. We provide a recommendation in Appendix G.3 to indicate that any unused portion should be discarded.

4.2 RECOMMENDATIONS FOR AKORN

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

A. <u>Container Labels</u>

1. The Prescribing Information indicates that the proposed route of administration is for intravenous use [redacted] (b) (4) [redacted] we recommend you revise the statement on the principal display panel (PDP) to "For Intravenous Use". We recommend the use of "intravenous" in the statement rather than [redacted] (b) (4) has been reported in postmarketing error cases and is discouraged by the Institute of Safe Medication Practices (ISMP).[1]

B. <u>Container Labels and Carton Labeling</u>

1. Because this solution requires dilution prior to administration, we recommend the statement "Must Dilute Before Use" be placed on the principal display panel below the route of administration statement to minimize the risk of the product being administered without dilution.

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2016 JAN 25]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

C. <u>Carton Labeling</u>

1. Consider revising the statement " 1mL Single-Dose Ampules, 10 Ampules (1 mL each)" to read "1 mL Single Dose Ampules – Discard Unused Portion, 10 Ampules (1 mL each)" to minimize the risk of any unused portion being used on another patient.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ephedrine Sulfate Injection that Akorn submitted on September 15, 2015.

Table 2. Relevant Product Information for Ephedrine Sulfate Injection	
Initial Approval Date	N/A
Active Ingredient	Ephedrine Sulfate
Indication	Treatment of hypotension in the setting of anesthesia
Route of Administration	Intravenous
Dosage Form	Injection
Strength	50 mg/mL
Dose and Frequency	(b) (4)
How Supplied/Container Closure	Ampule in a carton containing 10 ampules
Storage	Room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 15, 2016 we searched the L:drive and AIMS using the terms, Ephedrine to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews.[1,2] We re-read these previous reviews to help inform this one.

[1] Schlick, J. Label and Labeling Review for Ephedrine Sulfate (Eclat) NDA 208289. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 17. RCM No.: 2015-1556.

[2] Miller, C. Postmarket Medication Error Memorandum for Ephedrine Sulfate (Nexus Pharma). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 08. RCM No.: 2015-2602

Reference ID: 3887689

APPENDIX G. LABELS AND LABELING

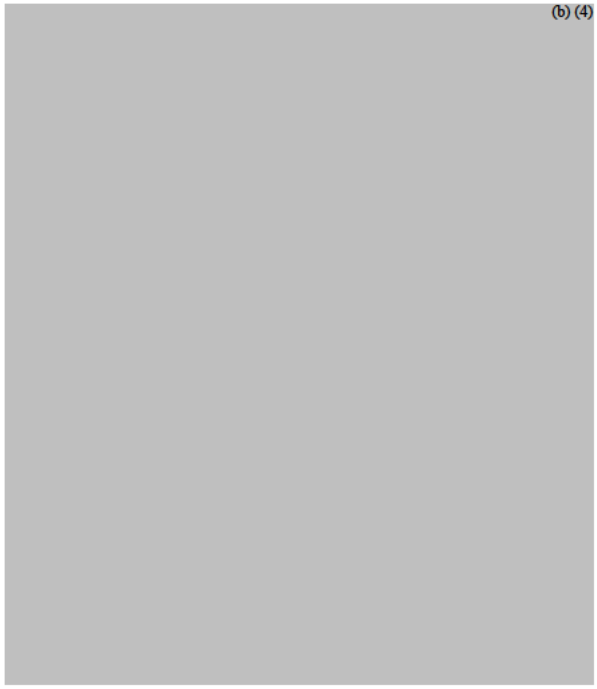
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Ephedrine Sulfate Injection labels and labeling submitted by Akorn on September 15, 2015.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Container Label



[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

G.3 Proposed Changes to Prescribing Information (PI)

(b) (4)



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/s/

JAMES H SCHLICK
02/16/2016

BRENDA V BORDERS-HEMPHILL
02/17/2016

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 # 208609	NDA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: Ephedrine Sulfate Injection, USP Dosage Form: Injection Strengths: 50 mg/mL		
Applicant: Akorn, Inc. Agent for Applicant (if applicable): K. Gary Barnette, PhD,Camargo Pharmaceutical Services, LLC		
Date of Application: 9/15/15 Date of Receipt: 9/15/15		
PDUFA Goal Date: 7/15/16 (if 10 mos)	Action Goal Date (if different):	
Filing Date: 11/14/15	Date of Filing Meeting: 10/29/15	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☒ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): [redacted] (b) (4) clinically important hypotension in the setting of anesthesia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Reference ID: 3863258

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***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***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 118164 (PIND only)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

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to the supporting IND(s) if not already entered into tracking system.				
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)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☐	☒	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☒	☐		

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questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• 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)].**	☐	☒		
• 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)]?** ***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.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***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

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.

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/oopd/index.cfm***	☐	☒		
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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a	☐	☒	☐	

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racemic drug previously approved for a different therapeutic use?				
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		The Sponsor submitted a statement saying that no clinical studies were conducted for this NDA and so there are no financial arrangements to disclose.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

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Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* : TBD	☐	☐	☒	Determined NOT to be an NME after internal discussion with appropriate parties since has been marketed for a number of years.
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage 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.*	☒	☐		PeRC scheduled for 5/18/16
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

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Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☒	☐	☐	
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? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

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Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	No other consults were requested by the team.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		Firm held only a PIND meeting with the Division
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 29, 2015

BACKGROUND: The drug is a marketed, unapproved product that has many years of use in the injectable form and in cough and cold products, via monograph. The firm has submitted a 505b2, with references only to literature. They are proposing an indication (b) (4) clinically important hypotension in the setting of anesthesia. The application will be reviewed on a standard clock with a PDUFA goal of 7/15/16.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Compton	Y
	CPMS/TL:	Matt Sullivan	Y
Cross-Discipline Team Leader (CDTL)	Rigo Roca		Y
Division Director/Deputy	Sharon Hertz		Y
Office Director/Deputy	Curt Rosebraugh		N
Clinical	Reviewer:	Alla Bazini	Y
	TL:	Rigo Roca	Y
Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Yun Xu	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	N/A (no clinical studies)	
	TL:	David Petullo	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	Y
	TL:	Newton Woo/Dan Mellon	Y (both)
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Julia Pinto	Y

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	RBPM:	Steve Kinsley	Y
• Drug Substance	Reviewer:	Jeffrey Medwid	N
• Drug Product	Reviewer:	Art Shaw	N
• Process	Reviewer:	Peter Krommenhoek	N
• Microbiology	Reviewer:	Denise Miller	N
• Facility	Reviewer:	Rose Xu	N
• Biopharmaceutics	Reviewer:	Angella Lu/Albert Chen (TL)	Y (both)
• Immunogenicity	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	TBD	
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	TBD	
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines			
• OUDLC/OC	Reviewer:	Barbara Wise	Y
	TL:		
• OSE Project Management	Reviewer:	Lisa Skarupa	Y
	TL:	Darrell Jenkins	N

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Other attendees	None		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? 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):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO The Sponsor requested a biowaiver for the proposed product. This ephedrine product is for IV administration so its bioavailability appears self-evident (i.e., 100 percent).
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No clinical studies (literature reference only)	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

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If no, for an NME NDA or original BLA, include the reason. For example: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	○ Reason:
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? N/A (no study sites)	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

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Comments:	
PRODUCT QUALITY (CMC) **Comments**: Will have IRs for 74 day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter

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APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• 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?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☒ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Sharon Hertz

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): ~2/15/16

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):
Filing: 11/14/15
74 day letter to issue by: 11/28/15
MC to be held by: 2/15/16
WU to be held by: 6/10/16
PeRC to be held by: 6/10/16
Primary Rvw Complete by: 6/10/16
Secondary Rvws Complete by: 6/17/16
Send lblg and PMRs to applicant by: 6/17/16
Issue DR ltrs by: 6/24/16

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CDTL Rvw due by: 6/24/16 Beging PMR disc'n w/applicant by: 6/24/16 Pkg to Signatory by: 6/24/16 PDUFA Goal: 7/15/16 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	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).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

Reference ID: 3863258

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

/s/

KIMBERLY A COMPTON
12/19/2015

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: NDA 208609

Application Type: New NDA

Name of Drug/Dosage Form: Ephedrine Sulfate Injection, USP 50mg/mL

Applicant: Akorn, Inc.

Receipt Date: September 15, 2015

Goal Date: July 15, 2016

1. Regulatory History and Applicant's Main Proposals

The Sponsor submitted a 505(b)(2) NDA for ephedrine sulfate injection 50mg/mL, indicated (b) (4) clinically important hypotension in the setting of anesthesia. This is a marketed unapproved drug product. The sponsor is referencing published 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

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 18, 2015. The resubmitted PI will be used for further labeling review.

Reference ID: 3849397

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

NO 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:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *The line is typically placed at the bottom of the TOC (bottom of 1st page), not at the top of the FPI 1st page*

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

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Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **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:

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.

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

N/A 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

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:

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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:

Reference ID: 3849397

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 Lactation
8.3 Females and Males of Reproductive Potential
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:

N/A

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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

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 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: *The firm has proposed alternate language because they are a marketed unapproved drug. It is being discussed within the team and with SEALD and the ADL. If the decision is not made by the time the 74 day letter is ready to issue, any request for amendment to the proposed language will be sent under separate cover.*

NO 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."

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Comment: *The firm has proposed alternate language because they are a marketed unapproved drug. It is being discussed within the team and with SEALD and the ADL. If the decision is not made by the time the 74 day letter is ready to issue, any request for amendment to the proposed language will be sent under separate cover.*

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 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:

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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.

Reference ID: 3849397

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

/s/

KIMBERLY A COMPTON
11/19/2015