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RESEARCH**

APPLICATION NUMBER:

209963Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-1
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue development to support pediatric dosing in children under 3 years of age.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: 12/2017
Final Protocol Submission: 06/2018
Study/Trial Completion: 11/2018
Final Report Submission: 02/2019

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Cocaine is known to have CNS effects, and published literature indicate that cocaine can alter brain development and male reproductive tissue development, including testicular necrosis. The effects of cocaine on early brain development and male reproductive function in a suitable animal model should be completed prior to studies in human pediatric patients.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

Draft protocol submission dates should be included in order to provide adequate time for the Agency to review and respond to the protocol and ensure adequacy.

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

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Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-2
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue development to support pediatric dosing in children 3 years of age to less than 17 years of age.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	12/2017
Final Protocol Submission:	06/2018
Study/Trial Completion:	11/2018
Final Report Submission:	02/2019

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Cocaine is known to have CNS effects, and published literature indicate that cocaine can alter brain development and male reproductive tissue development, including testicular necrosis. The effects of cocaine on the early brain development and male reproductive function in a suitable animal model should be completed prior to studies in human pediatric patients.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

Draft protocol submission dates should be included in order to provide adequate time for the Agency to review and respond to the protocol and ensure adequacy.

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-3
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a multicenter, sequential age-group study to evaluate the pharmacokinetic and safety profiles of a single topical administration of GOPRELTO for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in pediatric subjects two years of age to less than 17 years of age.

2. PMR/PMC Schedule Milestones^{2, 3}

PK and safety study in pediatric subjects from two years of age to less than 17 years of age.

Draft Protocol Submission: 02/2018
Final Protocol Submission: 11/2018
Study/Trial Completion: 12/2020
Final Report Submission: 06/2021

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The goal of this study is to assess the pharmacokinetic and safety profiles of GOPRELTO for the induction of local anesthesia of the mucous membranes in patients two years of age to less than 17 years of age undergoing diagnostic procedures and surgeries on or through the nasal cavities.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-4
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a multicenter study to evaluate the pharmacokinetic profile, efficacy, and safety of a single topical administration of GOPRELTO for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in pediatric patients from birth to less than two years of age.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	10/2020
Final Protocol Submission:	04/2021
Study/Trial Completion:	12/2023
Final Report Submission:	06/2024

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The goal of this study is to assess the pharmacokinetic profile, efficacy, and safety, of GOPRELTO for the induction of local anesthesia of the mucous membranes in pediatric patients from birth to less than two years of age undergoing diagnostic procedures and surgeries on or through the nasal cavities.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do **not** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-5
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: 01/2018
Final Protocol Submission: 04/2018
Study Completion: 10/2018
Final Report Submission: 03/2019

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Review of the submitted published literature did not identify adequate data to characterize the impact of cocaine on female fertility and early embryonic development. The existing literature does indicate that cocaine can alter female reproductive hormone levels and impact the estrus cycle; therefore, there is clear potential that cocaine could impact female fertility.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

Cocaine is currently a marketed unapproved drug product. The plasma levels of cocaine associated with this drug product are relatively low, and the existing data in animals that suggests adverse effects is likely far greater than the levels a patient would be exposed to. However, definitive data do not exist to ideally inform labeling. In the interim, the product labeling will include data about the potential adverse effects

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

reported in the literature.

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

The proposed study is a standard nonclinical study to address this potential hazard.

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do **not** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-6
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: 12/2017
Final Protocol Submission: 03/2018
Study/Trial Completion: 05/2018
Final Report Submission: 10/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Review of the submitted published literature did not identify adequate data to characterize the impact of cocaine on embryo-fetal development. The existing literature does indicate that cocaine can result in teratogenicity, however, all of the standard endpoints and adequate toxicokinetic data do not exist to permit a definitive characterization of the potential for adverse effects.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ **Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ **Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ **PREA PMR:** Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ **FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ **PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☒ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☒ Other reason (describe in text box below)

Cocaine is currently a marketed unapproved drug product. The plasma levels of cocaine associated with this drug product are relatively low and the existing data in animals that suggests adverse effects is likely far greater than the levels a patient would be exposed to. However, definitive data do not exist to ideally inform labeling. In the interim, the product labeling will include data about the potential adverse effects

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

reported in the literature.

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

a. **The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]**

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ ☒ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

Rat embryo-fetal studies are the standard approach to characterize the teratogenic potential of a compound.

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☒ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-7
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: 12/2017
Final Protocol Submission: 03/2018
Study/Trial Completion: 06/2018
Final Report Submission: 11/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Review of the submitted published literature did not identify adequate data to characterize the impact of cocaine on embryo-fetal development. The existing literature does indicate that cocaine can result in teratogenicity; however, all of the standard endpoints and adequate toxicokinetic data do not exist to permit a definitive characterization of the potential for adverse effects.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ **Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ **Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ **PREA PMR:** Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ **FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ **PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☒ Other reason (describe in text box below)

Cocaine is currently a marketed unapproved drug product. The plasma levels of cocaine associated with this drug product are relatively low, and the existing data in animals that suggests adverse effects is likely far greater than the levels a patient would be exposed to. However, definitive data do not exist to ideally inform labeling. In the interim, the product labeling will include data about the potential adverse effects

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

reported in the literature.

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

a. **The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]**

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☒ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

Rabbit embryo-fetal development studies are standard studies to assess the teratogenic effects of a compound.

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-8
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional assessments, and reproductive capacity of the offspring.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: 03/2018
Final Protocol Submission: 06/2018
Study/Trial Completion: 02/2019
Final Report Submission: 08/2019

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Review of the submitted published literature did not identify adequate data to characterize the impact of cocaine on pre- and postnatal development. The existing literature does indicate that cocaine can result in subtle adverse effects likely of CNS origin in the offspring of animals; however, all of the standard endpoints and adequate toxicokinetic data do not exist to permit a definitive characterization of the potential for adverse effects.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☒ Other reason (describe in text box below)

Cocaine is currently a marketed unapproved drug product. The plasma levels of cocaine associated with this drug product are relatively low, and the existing data in animals that suggests adverse effects is likely far greater than the levels a patient would be exposed to. However, definitive data do not exist to ideally

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

inform labeling. In the interim, the product labeling will include data about the potential adverse effects reported in the literature.

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

a. **The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]**

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

Rat pre- and postnatal development studies are standard studies to permit evaluation of the effects of in utero exposure to drugs and exposures during lactation on development of the offspring.

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

Draft protocol submission dates should be included in order to provide adequate time for the Agency to review and respond to the protocol and ensure adequacy.

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA # 209963
PMR/PMC Set (####-#) 3241-9
Product Name: GOPRELTO
Applicant Name: Genus Life Sciences
ODE/Division: ODE II/DAAAP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Submit a complete histopathological assessment from the 14-day rat intranasal toxicology study testing (b) (4) (Study Number 256501 or 558503) and revise the final study report accordingly.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study Completion: 12/2017
Final Report Submission: 01/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

(b) (4)

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☒ Other reason (describe in text box below)

Cocaine is currently a marketed unapproved drug product; however, it is not known if this impurity is present in the currently marketed or previously marketed drug products. The drug substance has been used in clinical studies submitted to the Agency under IND, but because these specifications will likely be used to set the USP standards, definitive data are required.

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?

[Select either “Yes” or “No” and provide the appropriate responses.]

☒ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

The tissues have already been retained, they simply have to be cut and evaluated by a trained pathologist.

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?

[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)

TYPE OF CLINICAL TRIAL

- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
- ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **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.**

See DARRTs signature block.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

See DARRTS signature block.

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

/s/

DIANA L WALKER
12/14/2017

JUDITH A RACOOSIN
12/14/2017

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

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

Memorandum

Date: September 26, 2017

To: Renee L. Petit-Scott, M.D.
Division Anesthesia, Analgesia, Addiction Products (DAAAP)

Diana L. Walker, PhD
Sr. Regulatory Project Manager, (DAAAP)

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

CC: Sam Skariah, PharmD
Team Leader
OPDP

Subject: OPDP Labeling Comments for COCAINE HYDROCHLORIDE TOPICAL SOLUTION for intranasal use, CII

NDA: 209963

In response to DAAAP's consult request dated December 5, 2016, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Cocaine HCl Topical Solution for intranasal use.

PI: OPDP's comment on the proposed labeling are based on the substantially complete draft PI received by electronic mail from DAAAP on August 25, 2017 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 3, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (301) 240-402-8686 or Koung.lee@fda.hhs.gov.

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

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

/s/

KOUNG U LEE
09/26/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 209963	NDA Supplement #:	Efficacy Supplement Type:
Proprietary Name: GOPRELTO Established/Proper Name: Cocaine Hydrochloride Nasal Solution Dosage Form: Solution Strengths: 4%, 40 mg/mL Route of Administration: intranasal		
Applicant: Genus Lifesciences Inc.		
Date of Receipt: November 23, 2016, Major Amendment July 31, 2017		
PDUFA Goal Date: December 23, 2017		Action Goal Date (if different): December 14, 2017
RPM: Diana Walker		
Proposed Indication: Induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults.		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

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

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature in support of the nonclinical pharmacology, PK, single- and repeated-dose toxicity, reproductive and developmental toxicology, and carcinogenicity potential of cocaine.	Sections (b) (4)
Published literature regarding pregnancy and lactation.	Sections 8.1 and 8.2
Published literature to support clinical safety.	Section 5
Published literature to support clinical pharmacology.	Section (b) (4)
Published literature describing Abuse, Dependence, and Overdosage.	Sections 9 and 10

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

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹.

[See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The Applicant is relying upon an extensive literature review for this drug product. The clinical studies cited employed similar doses, concentrations, and formulations of cocaine administered via the same route and method of administration.

The nonclinical literature cited are scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the Applicant's drug product and the doses used in the reported studies are scientifically relevant to the proposed human dose. The Applicant provided literature data to support the conclusion that the doses tested were equivalent to and greater than the doses and exposures that would be obtained via the proposed drug product.

RELIANCE ON PUBLISHED LITERATURE

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

YES ☒ NO ☐

If “**NO**,” proceed to question #5.

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

YES ☐ NO ☒

If “**NO**,” proceed to question #5.

If “**YES**,” list the listed drug(s) identified by name and answer question #4(c).

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

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

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

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

YES ☐ NO ☒

If “**NO**,” proceed to question #10.

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

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

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☐

If “YES”, please list which drug(s).

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

b) Approved by the DESI process?

YES ☐ NO ☐

If “YES”, please list which drug(s).

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

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

If “YES”, please list which drug(s).

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

d) Discontinued from marketing?

YES ☐ NO ☐

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

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

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

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

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

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

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

YES ☐ NO ☒

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

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

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

Pharmaceutical equivalent(s):

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

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

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

YES ☐ NO ☒

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

One of the alternatives is approved for the same indication and one of the alternatives is approved for a similar indication

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

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

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

Pharmaceutical alternative(s): Narcan (NDA 016636): approved for a similar indication
Approved generics to Narcan are listed in the Orange Book

Evzio (NDA 205787): approved for the same indication

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

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

YES ☐ NO ☐

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

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

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

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

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

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

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If “NO”, please contact the applicant and request the documentation.

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

Date(s):

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

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

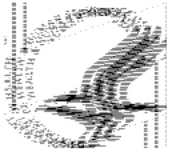
***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

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

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

/s/

DIANA L WALKER
12/14/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and
Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
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PLLR Labeling Memorandum

Date: August 14, 2017 **Date consulted:** December 5, 2016

From: Jane Liedtka, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader
Division of Pediatric and Maternal Health

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

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

Drug: GOPRELTO (Cocaine Hydrochloride Topical Solution)

NDA: 209963

Applicant: Genus Lifesciences, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: Cocaine Hydrochloride Topical Solution is an ester-based anesthetic indicated for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults.

Materials Reviewed:

- DPMH consult request dated December 5, 2016, DARRTS Reference ID 4022929.

- Sponsor's submitted background package for NDA 209963, submitted on November 23, 2016.
- DPMH consult review of Adzenys ER (amphetamine extended-release oral suspension), NDA 204325. Jane Liedtka, M.D. June 27, 2017, DARRTS Reference ID 4116325.

Consult Question:

“DAAAP is requesting that PMHS please assist us in reviewing the labeling for the new PLLR format.”

INTRODUCTION

On December 5, 2016, DAAAP consulted DPMH to provide input for appropriate labeling of the pregnancy and lactation sections of GOPRELTO (Cocaine Hydrochloride Topical Solution) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY

- On November 23, 2016, (b) (4) submitted a New Drug Application (NDA) for NDA 209963, GOPRELTO (Cocaine Hydrochloride Topical Solution)
- On May 10, 2017 the company notified the FDA that they had changed their name to Genus Lifesciences, Inc.
- GOPRELTO (Cocaine Hydrochloride Topical Solution) is an ester-based anesthetic indicated for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults.
- Cocaine hydrochloride topical solution is currently an unapproved marketed drug.
- The original submission contained an adequate review of the literature to support PLLR labeling.

BACKGROUND

Cocaine Hydrochloride Topical Solution and Drug Characteristics¹

- Contains 160 mg/4 mL (40 mg/mL= 4%) cocaine hydrochloride, an amino ester local anesthetic and a vasoconstrictor.
- Molecular weight is $\approx$ 340 Daltons
- Prevents conduction in nerve fibers by reversibly blocking sodium channels and preventing the transient rise in sodium conductance necessary for generation of an action potential
- Vasoconstrictor activity is related to its local blockade of norepinephrine presynaptic reuptake and subsequent potentiation of norepinephrine released by adrenergic nerve terminals onto the local vasculature

¹ GOPRELTO proposed package insert

- Following intranasal application of two 40 mg pledgets applied to each nasal cavity (160 mg cocaine hydrochloride total dose) for 20 minutes, the geometric mean (SD) cocaine C_{max} was 43.2 (1.73) ng/mL.
- 84-92% bound to human plasma proteins, binding primarily to alpha-1-acid glycoprotein (AAG) and albumin
- Mean elimination half-life of cocaine was 1.0 to 1.7 hours; with longer plasma sampling (32 hours) and a highly sensitive assay, mean half-life values of 5.0 to 8.0 hours were observed at very low plasma concentrations
- Most common adverse reactions (>0.5%) occurring in patients treated with Cocaine Hydrochloride Topical Solution were: headache, epistaxis, and anxiety

Anesthesia during Pregnancy and Lactation

In 2015 the American Academy of Pediatrics (AAP) in conjunction with FDA, the American Society of Anesthesiologists, and other organizations, issued a consensus statement regarding a concern that general anesthetic and sedative drugs administered to infants and toddlers may be associated with neurotoxicity based on animal studies and studies in children.² A subsequent supplemental statement was released when preliminary data from a clinical trial assessing the effects of a short exposure to anesthesia (less than an hour) in children less than six months of age showed no difference in cognitive development at two years of age.³ Animal studies have shown long-term, possibly permanent, injury to the developing brain caused by repeated or prolonged exposure to these products. Animal studies showed abnormalities in behavior, learning, and memory. The effect of exposure to anesthetic drugs in young children is unknown; however, some but not all studies have suggested that problems similar to those seen in animals could also occur in infants and toddlers who have repeated or prolonged exposure (greater than three hours).⁴ The studies in children have limitations that preclude the ability to conclude whether the effects were due to the anesthetic drugs or to other factors, such as the surgery or related illness.

According to the division clinical team, use of topical cocaine hydrochloride solution applied intra-nasally is considered “local anesthesia” and is not expected to affect the fetal or neonatal brain. Therefore, the above warnings noted in the Drug Safety Communication (DSC) and safety labeling change (SLC) do not apply to this product for this indication.

DATA REVIEW

Pregnancy

Nonclinical Experience

According to the Applicant’s proposed label, (b) (4)

² <http://smarttots.org/wp-content/uploads/2015/10/ConsensusStatementV910.5.2015.pdf>

³ <http://smarttots.org/wp-content/uploads/2015/11/CSsupplement11.9.2015.pdf>

⁴ Per DAAAP meeting 11-30-2016

For further details, the reader is directed to the Nonclinical Review by BeLinda A. Hayes, PhD.

Applicant's Review of Literature

According to the Applicant,

The published literature was searched using PubMed and ToxNet, with various combinations of the following search terms: cocaine, pregnant, pregnancy, fetus, fetal, *in utero*, infant, prenatal, placenta, placental abruption, growth, vasculature, hemorrhage, infarct, lactation, milk, breastmilk, fertility, reproduction, hormone, testis, spermatogenesis, sperm. Over 2300 citations for pregnancy-related terms, 833 citations for reproduction-related terms, and 134 citations for lactation-related terms were returned and were reviewed for relevancy. Books and databases concerning effects of drugs during pregnancy (Schaefer et al., 2015⁵; Briggs and Freeman, 2015⁶; Reprotox, 2016⁷) and lactation (LactMed, 2016⁸) were also consulted. Review articles and meta-analyses were used to refine the information and collect additional references.

No clinical studies have been conducted with topical cocaine HCl in pregnant women, and there are no studies in the published literature evaluating therapeutic use of cocaine as a local anesthetic in pregnancy.

Published literature on effects of cocaine use as a substance of abuse during pregnancy have been used to assess the potential risks of cocaine HCl, although it is likely that prenatal cocaine exposure and duration would be much greater when used as a drug of abuse with the intent of inducing CNS effects compared with a single, topical, therapeutic administration of cocaine HCl.

Applicant's Conclusions Regarding Congenital Anomalies

Initial case reports and limited case series describing pregnancy outcomes of prenatal cocaine exposure emerged during the 1980s and 1990s in response to a dramatic increase in cocaine abuse in the United States.⁶ These early reports

⁵ Schaefer C, Peters P, Miller RK, Eds. *Drugs during Pregnancy and Lactation Treatment Options and Risk Assessment*, Third Edition. Elsevier, London, 2015, ISBN 978-0-12-408078-2.

⁶ Briggs GG, Freeman RK, eds. *Drugs in Pregnancy and Lactation*, Tenth Edition. Wolters Kluwer Health, Philadelphia, 2015.

⁷ Reprotox Database. Cocaine Summary [CAS Number 50-36-2].

<https://reprotox.org/member/agents/17236>. Last updated 12/22/2015. Accessed 2/24/2016.

⁸ LactMed Record, Cocaine (CASRN:50-36-2). <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2>, last revision date 26 Feb 2016. Accessed 10 Oct 2016.

linked prenatal cocaine exposure to malformations in urogenital organs^{9, 10, 11} and in a range of other organ systems^{12, 13, 14}. However, as briefly described below, no specific cocaine-associated morphologic syndrome or pattern of defects was identified^{15, 16} and subsequent well-controlled epidemiologic studies did not confirm the association between cocaine use and minor or major congenital anomalies^{6, 17, 17, 18, 19}... Based on these studies and others, it is now generally accepted that cocaine is not a direct human teratogen, and that early studies were significantly confounded by small sample sizes, various socioeconomic factors, and concomitant use of other drugs (polydrug use) during pregnancy^{20, 20}.

Applicant's Conclusions regarding other Adverse Pregnancy Outcomes

Increased incidences of stillbirths, premature delivery, membrane rupture, placental abruption, reduced intrauterine growth/small birthweight and/or head circumference have also been linked with cocaine use in the published literature^{15, 18, 21, 21, 22}. Again, there is uncertainty around whether these effects can be directly attributed to prenatal cocaine exposure, or whether effects are confounded by polydrug use and other socioeconomic factors^{21, 23, 23, 24}.

⁹ Chavez GF, Mulinare J, Cordero JF. Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. JAMA 1989; 262:795-798.

¹⁰ Chasnoff IJ, Chisum GM, Kaplan WE. Maternal cocaine use and genitourinary tract malformations. Teratology. 1988; 37:201-204.

¹¹ Lutiger B, Graham K, Einarson TR, Koren G. Relationship between Gestational Cocaine Use and Pregnancy Outcome: A Meta-Analysis. Teratology. 1991; 44:405-414.

¹² Hoyme HE, Jones KL, Dixon SD, Jewett T, Hanson JW, Robinson LK, Msall ME, Allanson JE. Prenatal cocaine exposure and fetal vascular disruption. Pediatrics. 1990; 85:743-747.

¹³ Kapur RP, Shaw CM, Shepard TH. Braine hemorrhages in cocaine-exposed human fetuses. Teratology. 1991; 44:11-18.

¹⁴ Bingol N, Fuchs M, Diaz V, Stone RK, Gromisch DS. Teratogenicity of cocaine in humans. J Pediatrics. 1987; 110:93-96.

¹⁵ Little BB, Wilson GN, Jackson G. Is there a cocaine syndrome? Dysmorphic and anthropometric assessment of infants exposed to cocaine. Teratology. 1996; 54:145-149.

¹⁶ Behnke M, Eyler FD, Garvan CW, Wobie K. The search for congenital malformations in newborns with fetal cocaine exposure. Pediatrics. 2001; 107(5):E74.

¹⁷ Minnes S, Robin NH, Alt AA, Kirchner HL, Satayathum S, Salbert BA, Ellison L, Singer LT. Dysmorphic and anthropometric outcomes in 6-year-old prenatally cocaine-exposed children. Neurotoxicol Teratol. 2006; 28:28-38.

¹⁸ Behnke M, Eyler FD, Conlon M, Wobie K, Woods NS, Cumming W. Incidence and description of structural brain abnormalities in newborns exposed to cocaine. J Pediatr. 1998; 132(2):291-4.

¹⁹ Addis A, Moretti ME, Ahmed Syed F, Einarson TR, Koren G. Fetal effects of cocaine: an updated meta-analysis. Reprod Toxicol. 2001; 15:341-369.

²⁰ Cressman AM, Natekar A, Kim E, Koren G, Bozzo P. Cocaine abuse during pregnancy. J Obstet Gynaecol Can. 2014; 36(7):628-31.

²¹ Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. J Addict Dis. 2010; 29(2):245-58.

²² Sprauve ME, Lindsay MK, Herbert S, Graves W. Adverse perinatal outcome in parturients who use crack cocaine. Obstet Gynecol. 1997; 89:674-8.

²³ Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, Development, and Behavior in Early Childhood Following Prenatal Cocaine Exposure: A Systematic Review. JAMA. 2001; 285(12): 1613-1625.

²⁴ Lambert BL and Bauer CR. Developmental and behavioral consequences of prenatal cocaine exposure: a review. J Perinatol. 2012; 32(11):819-828.

The studies most relevant to assessment of risks related to a single, intranasal administration of cocaine hydrochloride as a topical anesthetic are those in which the extent of prenatal exposure has been evaluated. Several studies have attempted to quantitate the extent of prenatal cocaine exposure through measurement of cocaine in meconium at birth, or the presence/amount of cocaine benzoylecgonine [BE] (metabolite in meconium) in maternal or infant hair. These studies have generally shown no adverse pregnancy outcomes in groups exposed to low levels of cocaine during pregnancy^{18, 25, 26, 27}.

According to the Applicant, based on this information, there is **no concern** for adverse pregnancy outcomes, including fetal malformations, or reductions in birthweight, infant length or head circumference, with a single administration of cocaine hydrochloride applied topically for therapeutic purposes.

Reviewer's Comment

*Though I do not agree with the Applicant that "there is **no concern** for adverse pregnancy outcomes, including fetal malformations or reductions in birthweight, infant length or head circumference, with a single administration of cocaine hydrochloride applied topically for therapeutic purposes", I acknowledge that the concern is low. The clinical pharmacology team estimates that only about 4 % of the dose of 160 mg of cocaine is systemically absorbed. With a one time exposure of ≈ 6.4 mg of cocaine the above mentioned adverse events associated with chronic illicit exposure seem unlikely. The rest of the Applicant's analysis (beyond the "no concern" statement) is a reasonable summary based on my reading of the published literature and the collected information in the databases.*

Applicant's Conclusions regarding other Adverse Pregnancy Outcomes (continued)

A large number of studies evaluating effects of prenatal cocaine exposure on postnatal growth and development through infancy, childhood and adolescence have been reported in the published literature.

Some studies, but not others, have shown effects on physical growth, intelligence/academic achievement, language skills, and behavioral regulation, but interpretation of these studies is difficult due to confounding factors of socioeconomic status, parenting skills, environmental risk factors, polydrug use, etc.²⁵ (reviewed in: Lambert and Bauer, 2012). In general, carefully controlled neurobehavioral studies and meta-analyses have not identified serious adverse postnatal effects of chronic prenatal cocaine exposure alone. However, subtle

²⁵ Eyler FD, Behnke M, Conlon M, Woods NS, Wobie K. Birth outcome from a prospective, matched study of prenatal crack/cocaine use: I. Interactive and dose effects on health and growth. *Pediatrics*. 1998; 101(2):229-37.

²⁶ Bateman DA and Chiriboga CA. Dose-response effect of cocaine on newborn head circumference. *Pediatrics*. 2000 Sep; 106(3):E33.

²⁷ Kuhn L, Kline J, Ng S, Levin B, Susser M. Cocaine Use during Pregnancy and Intrauterine Growth Retardation: New Insights Based on Maternal Hair Tests. *Am J Epidemiol*. 2000;152:112-119.

changes in neurodevelopmental outcomes cannot be excluded^{21, 22, 24}, with effects on postnatal growth being the most probable.²⁵

Given the subtle nature of these effects, confounding lifestyle factors, and the uncertainty around duration and extent of exposure, these studies are not considered relevant for assessing fetal risk with the intended single, topical administration of cocaine hydrochloride.

Reviewer's Comment

The Applicant's analysis is a reasonable summary based on my reading of the published literature and the collected information in the databases.

Applicant Review of Pharmacovigilance Database

In a letter dated December 14, 2016 the Applicant stated:

(b) (4) has reviewed the FAERS database output for both cocaine topical solution and cocaine, as of November 10, 2016, and there are no reports of pregnancy with either drug listed.

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "Topical Cocaine solution 4% and pregnancy," "Topical Cocaine solution 4% and pregnant women," "Topical Cocaine solution 4% and pregnancy and birth defects," "Topical Cocaine solution 4% and pregnancy and congenital malformations," "Topical Cocaine solution 4% and pregnancy and stillbirth," "Topical Cocaine solution 4% and spontaneous abortion" and "Topical Cocaine solution 4% and pregnancy and miscarriage." No relevant articles were identified. DPMH then conducted a search of published literature in PubMed and Embase using the search terms "cocaine" rather than topical cocaine solution 4% and 3000 publications were identified. The summaries of information regarding cocaine in Micromedex²⁸ and Briggs and Freeman²⁹ *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk* were consulted to try to better refine the publications that were relevant.

One of the articles identified (in addition to numerous articles already cited by the Applicant) was a systematic review of 31 studies regarding maternal antenatal cocaine exposure and adverse perinatal outcomes published by Gouin³⁰ *et al* in 2011, which concluded that prenatal cocaine exposure is significantly associated with preterm birth, low birthweight, and small for gestational age infants. Tables with details of the studies that were included in the Gouin *et al*³¹ publication are reproduced as Attachment A.

²⁸ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 6/12/17.

²⁹ Briggs, GG, Freeman, RK, & Yaffe, SJ. (2015). *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

³⁰ Gouin K, Murphy K, Shah PS, *et al*. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and meta-analyses. *Am J Obstet Gynecol* 2011; 204:340.e1-12.

Another relevant article published in 2014 by Cressman³¹ *et al* states the following in the abstract:

... We identified risks to the pregnancy and baby in women abusing cocaine during pregnancy. These include preterm birth, placenta-associated syndromes (e.g. placental abruption, preeclampsia, and placental infarction), and impaired fetal growth. Long term neurodevelopmental and cognitive deficits include (but are not limited to) poorer language development, learning and perceptual reasoning, behavioral problems, and adverse effects on memory and executive function. However, these results should be interpreted cautiously because cocaine abuse may be accompanied by many other maternal and sociodemographic risk factors, so it is difficult to ascertain the effect of cocaine alone.

Reviewer's Comment

This limitation (inability to separate out effects of confounders) is repeatedly cited as a problem with the majority of publications that identified adverse developmental outcomes associated with cocaine use during pregnancy. Another common limitation is the inability to define a minimum exposure associated with adverse outcomes since most abusers do not know what quantity of cocaine they have used. Studies that attempted to at least refine exposure by amount or duration of use (for example-first trimester exposure only versus exposure throughout pregnancy) did suggest that there was a dose effect with more severe findings associated with use throughout pregnancy including the third trimester.^{32,33} Some studies suggested the timing and pattern (binging versus chronic use) of abuse determined the type of adverse developmental outcomes that were seen.^{34, 35}

Conclusion

Although there are no available data on the use of intranasal cocaine hydrochloride solution in pregnant women to inform a drug-associated risk for major congenital malformations or miscarriage, adverse maternal and fetal/neonatal outcomes have been seen in the setting of chronic illicit cocaine abuse during pregnancy. See DPMH proposed labeling below for further details.

³¹ Cressman AM, Natekar A, Kim E, Koren G, Bozzo P. Cocaine abuse during pregnancy. J Obstet Gynaecol Can. 2014; 36(7):628-31.

³² Richardson GA & Day NL: Maternal and neonatal effects of moderate cocaine use during pregnancy. Neurotoxicol Teratol 1991; 13:455-460.

³³ Graham K, Feigenbaum A, Pastuszak A, et al: Pregnancy outcome and infant development following gestational cocaine use by social cocaine users in Toronto, Canada. Clin Invest Med 1992; 15:384-394.

³⁴ Burkett G, Yasin SY, Palow D, et al: Patterns of cocaine binging: effect on pregnancy. Am J Obstet Gynecol 1994; 171:372-379.

³⁵ Towers CV, Pircon RA, Nageotte MP, et al: Cocaine intoxication presenting as preeclampsia and eclampsia. Obstet Gynecol 1993; 81:545-547.

Lactation

Applicant's Review of the Literature

According to the Applicant, the published literature was searched using PubMed and ToxNet, with various combinations of the following search terms: cocaine, lactation, milk, breastmilk. 134 citations for lactation-related terms were returned and were reviewed for relevancy. Books and databases concerning effects of drugs during pregnancy lactation (LactMed,³⁶) were also consulted. Review articles and meta-analyses were used to refine the information and collect additional references.

Applicant's Conclusions Regarding Lactation

- No studies have been conducted by the sponsor or exist in the published literature on the therapeutic use of cocaine in nursing mothers or effects on a breastfed infant.
- Infants are sensitive to the adverse effects of cocaine³⁶. Adverse events have been reported in infants ingesting cocaine through breast milk or when directly applied to the nipples, including convulsions, hypertension, tachycardia, agitation and irritability.^{10,37,38,39}
- Limited studies in the published literature in cocaine abusers have shown high levels of cocaine in breast milk, and cocaine is likely to achieve higher concentrations in breast milk than in blood.⁴⁰
- Cocaine has been detected in the breast milk of cocaine abusers at widely varying concentrations.^{41, 42}
- Cocaine accumulation in breast milk is presumed to be related to ion trapping due to the lower pH of milk compared with serum (6.9 vs 7.4, respectively),

³⁶ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed June 12, 2017.

³⁷ Chaney NE, Franke J, Wadlington WB. Cocaine convulsions in a breast-feeding baby. *J Pediatr* 1988; 112(1):134-5.

³⁸ Chasnoff IJ, Lewis DE, Squires L. Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987; 80(6):836-8.

³⁹ Cressman AM, Koren G, Pupco A, Kim E, Ito S, Bozzo P. Motherisk Update: Maternal cocaine use during breastfeeding. *Canadian Family Physician*. 2012; 58:1218-1219.

⁴⁰ Dickson PH, Lind A, Studts P, Nipper HC, Makoid M, Therkildsen D. The routine analysis of breast milk for drugs of abuse in a clinical toxicology laboratory. *J Forensic Sci*. 1994; 39(1):207-14.

⁴¹ Winecker RE, Goldberger BA, Tebbett IR, Behnke M, Eyler FD, Karlis JL, Wobie K, Conlon M, Phillips D, Bertholf RL. Detection of cocaine and its metabolites in breast milk. *J Forensic Sci*. 2001; 46(5):1221-1223.

⁴² Dickson PH, Lind A, Studts P, Nipper HC, Makoid M, Therkildsen D. The routine analysis of breast milk for drugs of abuse in a clinical toxicology laboratory. *J Forensic Sci*. 1994; 39(1):207- 14.

and the pKb for cocaine of 8.6,⁴³ and this phenomenon is expected to occur in humans⁴² and animals.⁴⁴

- Dickson, *et al.*⁴⁰ (1994) estimated the milk to blood (m/b) ratio of cocaine in humans as a function of ion trapping (m/b $\approx$ 20) and used this ratio to estimate cocaine concentrations in milk relative to maternal plasma levels. Corresponding estimated infant dose and steady state plasma concentrations (C_{ss}) were then calculated assuming 100% oral bioavailability, an infant clearance rate of 23 mL/min for a 4.55 kg infant, and 100 mL of milk ingested in a typical feeding.
- Using the cocaine m/b ratio of 20 (Dickson⁴⁰ 1994), the Applicant estimated that a C_{max} of 43 ng/mL (estimated C_{max} from clinical trials with GOPRELTO) would equate to a maximum milk concentration of 860 ng/mL, and that an infant would ingest $\approx$ 86 ug of cocaine in a typical feeding (100mL). Assuming 100% bioavailability, a 3-hour period between feedings, and the clearance value used by Dickson⁴⁰ (1994), the steady state plasma concentration (C_{ss}) in the infant would be approximately 21 ng/mL (using the equation: C_{ss} = Dose/[clearance * dosing period]). RX0041-002 is intended as a single dose application. Therefore, maternal plasma and milk levels would fall after dosing, and infant exposure would be correspondingly reduced in subsequent feedings.
- No amount infant exposure to cocaine is considered safe.
- It is advisable for a nursing mother treated therapeutically with cocaine hydrochloride to refrain from breastfeeding for 24 to 48 hours after administration, and to pump and discard her milk during this period. This is consistent with recommendations for mothers who intermittently abuse cocaine (likely for CNS stimulation) while breastfeeding.^{39, 45}

DPMH's Review of Literature

DPMH conducted a search of Medications and Mother's Milk¹⁹, the Drugs and Lactation Database (LactMed)³⁶, Micromedex²⁸, and of published literature in PubMed and Embase using the search terms "cocaine and lactation" and "cocaine and breastfeeding." No reports of adequate and well-controlled studies of cocaine use in lactating women were found. Clinical data regarding cocaine and lactation are limited to case reports^{37, 38} and support a recommendation to avoid breastfeeding when exposure has occurred.

In *Medications and Mother's Milk*⁴⁶, Thomas Hale, a breastfeeding expert, states the following regarding cocaine use during lactation:

Significant secretion into breastmilk is suspected with a probable high milk/plasma ratio... Topical application to the nipples is extremely

⁴³ Bailey DN. Cocaine and cocaethylene binding to human milk. Am J Clin Pathol 1998; 110:491-494.

⁴⁴ Wiggins RC, Rolsten C, Ruiz B, Davis CM. Pharmacokinetics of cocaine: basic studies of route, dosage, pregnancy and lactation. Neurotoxicology. 1989;10: 367-382.

⁴⁵ Jones W. Cocaine use and the breastfeeding mother. Pract Midwife. 2015; 18(1):19-22.

⁴⁶ Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15th edition. HalePublishing, L.P. 2012

dangerous and contraindicated³⁷...Oral, intranasal and smoking of crack cocaine is dangerous and definitely contraindicated. Breastfeeding mothers should avoid cocaine absolutely. In those individuals who have ingested cocaine, a minimum pump and discard period of 24 hours is recommended for clearance³⁹.

Cocaine is referenced in LactMed³⁶. The summary of use states:

No data are available on the medical use of cocaine in nursing mothers. However, because of its chemical nature, high concentrations of cocaine are expected in milk^{40, 43}. Cocaine and its metabolites are detectable in breastmilk, although data are from random breastmilk screening of mothers who used cocaine recreationally rather than controlled studies. Cocaine breastmilk concentrations have varied over 100-fold in these reports. Newborn infants are extremely sensitive to cocaine because they have not yet developed the enzyme that inactivates it⁴⁷ and serious adverse reactions have been reported in a newborn infant exposed to cocaine via breastmilk... A breastfeeding abstinence period of 24 hours has been suggested for women who occasionally use cocaine while breastfeeding, based on the rapid elimination of cocaine by the mother³⁹.

Under the section “Effects on Lactation and Breastmilk” in LactMed³⁶ on cocaine it states:

Long-term cocaine use can result in chronic, low-level hyperprolactinemia.^{48, 49, 50} The prolactin level in a mother with established lactation may not affect her ability to breastfeed.

Micromedex notes the following; “Infant risk has been demonstrated... Regarding therapeutic use of cocaine as a topical anesthetic for surgical procedures, temporary bottle feeding for the early postoperative period can eliminate infant exposure.”

Conclusion

Based on limited case reports in published literature, cocaine is present in human milk at widely varying concentrations. Cocaine’s pharmacochemical characteristics (low molecular weight, pH) suggest that high concentrations of cocaine are expected in breast milk. In addition, adverse effects (vomiting, diarrhea, irritability, mydriasis, tachycardia, tachypnea, cyanosis, increased sucking reflex, increased deep tendon reflexes, hyperactive Moro reactions, tremulous extremities, seizures, and a high pitched cry) have been reported in

⁴⁷ Anderson PO: Drug use during breast-feeding. Clin Pharm 1991; 10:594-624.

⁴⁸ Mello NK, Mendelson JH. Cocaine’s effects on neuroendocrine systems: clinical and preclinical studies. Pharmacol Biochem Behav. 1997; 57:571-99.

⁴⁹ Elman I, Lukas SE. Effects of cortisol and cocaine on plasma prolactin and growth hormone levels in cocaine-dependent volunteers. Addict Behav. 2005; 30:859-64.

⁵⁰ Patkar AA, Hill KP, Sterling RC et al. Serum prolactin and response to treatment among cocaine-dependent individuals. Addict Biol. 2002; 7:45-53.

breastfed infants exposed to cocaine via breast milk. The long-term effects on infants exposed to cocaine through breast milk are unknown. Therefore, DPMH agrees with the applicant that breastfeeding is not recommended during use of cocaine hydrochloride 4% solution and for (b) (4) 48 hours after administration (6x the half-life) of the solution.

Females and Males of Reproductive Potential

Nonclinical Experience

According to the Applicant's proposed label, (b) (4)

[REDACTED]

According to the Applicant's proposed label, (b) (4)

[REDACTED]

The reader is referred to the full Pharmacology/Toxicology review by BeLinda A. Hayes, Ph.D. for further details.

Applicant Review of the Literature

According to the Applicant, the published literature was searched using PubMed and ToxNet, with various combinations of the following search terms: cocaine, fertility, reproduction, hormone, testis, spermatogenesis and sperm. 833 citations for reproduction-related terms were returned and were reviewed for relevancy.

The Applicant concluded that (b) (4)

[REDACTED]

DPMH Review of the Data and Conclusion

DPMH reviewed cocaine and effects on fertility in the published literature in PubMed and Embase using the search terms "cocaine and fertility" and "cocaine and infertility. A small number of relevant articles were identified. The findings regarding effects on

fertility in males were inconsistent. Earlier publications reported varied deleterious effects on sperm concentration and motility but these were not confirmed in later reports.

A single publication based on a small sample size found a possible effect on fertility in females (Mueller⁵¹ *et al*). However, there were confounders (incidence of pelvic inflammatory disease) that were not controlled for in this study.

Based on the inconsistent findings, the limitations inherent in these studies and the fact that the majority of findings were seen with chronic abuse of cocaine, it is not possible to accurately define the risk of an effect on fertility with a single intranasal exposure for anesthesia. I recommend that Section 8.3 be omitted from labeling. See Table 1 below for a summary of these articles.

⁵¹ Mueller BA *et al*. Recreational Drug Use and the Risk of Primary Infertility. *Epidemiology*.1990; 1:195-200.

Table 1: Published literature on Cocaine's Effect on Fertility

Citation	Type of Study	Population	Findings	Confounders
Bracken ⁵² MB <i>et al</i> 1990	Variant of case-cohort (nested case-control)	1657 male patients attending an infertility clinic 1984-1987 1309 (79%) participated	Use of cocaine within 2 years of their first semen analysis has been found to be twice as common among men with sperm counts < 20 X 10 ⁶ mL (odds ratio [OR] = 2.1, 95% confidence interval [CI] 1.0, 4.6). Duration of cocaine use for five or more years was more common in men with low sperm motility (OR = 2.0, 95% CI 1.0, 4.1) and in those with low concentrations and a large proportion of abnormal forms.	Tobacco, alcohol, marijuana and lysergic acid diethylamide (LSD) use higher in cocaine group, Cocaine group with ↑ history of varicocele, undescended testicle and prostate infection
Mueller ⁵¹ BA <i>et al</i> 1990	Case-control	300 female patients attending an infertility clinic 1979-1981	Risk of infertility from a tubal abnormality associated with cocaine use was greatly increased (RR = 11.1, 95% CI = 1. 7, 70.8).	Adjustment made for tobacco use Cocaine group 3 X more likely to have history of Pelvic Inflammatory Disease
Hurd ⁵³ WW <i>et al</i> 1992	In-vitro study	Human semen samples from 18 healthy volunteers exposed to cocaine	Cocaine exposure decreased the percentage of motile sperm in a concentration-dependent manner with a maximum decrease of 23% at 10 ⁻⁴ M but had no effect on other motility characteristics. Cocaine decreased bovine mucus penetration by 12% at high cocaine concentrations (10 ⁻⁴ M), but increased penetration by 69% at low concentrations (10 ⁻⁹ M).	None reported
Yelian ⁵⁴ FD <i>et al</i> 1994	In-vitro study	Human semen samples exposed to cocaine	After a short exposure (15 minutes) to cocaine, the sperm motion kinematic parameters, straight line velocity and linearity, were decreased in the high concentration groups. However, after a longer exposure (2 hours) to cocaine, the differences were no longer significant. Cocaine treatment did not alter spermatozoa intracellular calcium levels. Most importantly, human sperm treated with cocaine at a high concentration were fully capable of penetrating zona-free hamster oocytes.	None reported
Semplaski ⁵⁵ M <i>et al</i> 2014		38 cocaine-exposed males presenting for a fertility exam 2008–2012	Few (< 1%) men in our infertile population reported the use of cocaine, and the frequency of use was low...infrequent cocaine use seems to have limited impact on semen parameters	90% with concurrent use of marijuana (32), ecstasy (9), LSD (2), heroin (1) and anabolic steroids for bodybuilding (3), also ↑ history of sexually transmitted diseases and tobacco

⁵² Bracken MB *et al*. Association of cocaine use with sperm concentration, motility, and morphology. Fertility and Sterility. 1990; 53(2):315-322.

⁵³ Hurd WW *et al*. The effect of cocaine on sperm motility characteristics and bovine cervical mucus penetration. Fertil Steril. 1992; 57:178-82.

⁵⁴ Yelian FD *et al*. The effects of in vitro cocaine exposure on human sperm motility, intracellular calcium, and oocyte penetration. Fertil Steril. 1994; 61(5): 915-921.

⁵⁵ Semplaski MK *et al*. Cocaine Use in the Infertile Male Population: A Marker for Conditions Resulting in Subfertility. Curr Urol. 2014;8:38–42.

RECOMMENDATIONS

DPMH revised the HPI and sections 8.1, 8.2 and 17 in GOPRELTO (cocaine hydrochloride topical solution) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed GOPRELTO (Cocaine Hydrochloride Topical Solution) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----
Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of (b) (4) cocaine hydrochloride solution in pregnant women to (b) (4) a drug-associated risk (b) (4) maternal and fetal/neonatal outcomes have been seen in women with chronic cocaine abuse during pregnancy (b) (4) (see Data).

Comment [LJ1]: At the time of this review, The pharmacology/toxicology team had not completed revisions of the nonclinical data language

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

(b) (4)

Data

Human Data

There are no available data on the use of intranasal cocaine hydrochloride solution in pregnant women to inform a drug-associated risk (b) (4) There are published data describing adverse developmental outcomes in women with chronic cocaine abuse during pregnancy. The published case-control and observational studies examining the effect of in utero cocaine exposure on fetal growth

parameters, after controlling for confounding variables, found exposure was associated with reduced fetal growth compared with non-drug-abuse populations.

Published data from a large number of studies of women with chronic cocaine abuse during pregnancy are inconsistent in their findings with regard to (b) (4)

The applicability of the findings from these studies of chronic abuse in pregnancy to a single topical exposure is limited.

Animal Data

To be inserted by Nonclinical

8.2 Lactation

Risk Summary

Based on limited case reports in published literature, cocaine is present in human milk at widely varying concentrations. Based on its pharmacochemical characteristics, high concentrations of cocaine are expected in breast milk with systemic exposure. The applicability of these findings to a single topical exposure with limited systemic absorption is unclear. (b) (4)

The long-term effects on infants exposed to cocaine through breast milk are unknown. There are no data on the effects of cocaine hydrochloride solution on milk production. Because of the potential for serious adverse reactions in breastfed infants, advise a woman that breastfeeding is not recommended during treatment with cocaine hydrochloride solution and (b) (4) pump and discard breastmilk for (b) (4) 48 hours after (b) (4) of cocaine hydrochloride solution.

17 Patient Counseling Information

Lactation

Advise a woman that breastfeeding is not recommended during treatment with cocaine hydrochloride solution and (b) (4) pump and discard breastmilk for (b) (4) 48 hours after administration of cocaine hydrochloride solution.

Attachment A

Table 2: Gouin K, Murphy K, Shah PS, *et al.*: Summary of Included Studies of Cocaine Exposure and Pregnancy Outcomes

Author	Year of study	Type of study	Setting of study	Population	Exposure assessment (when, how)	Outcomes assessed	Confounders adjusted for	Results	Quality assessment (risk of bias)
Bingol <i>et al</i> ⁶	1984-85	Prospective cohort with unmatched controls (similar for MA, SES, tobacco, ethnicity)	2 large inner-city hospitals in New York City (Harlem, Bronx)	Poor inner-city women at delivery	Neonate urine at birth	PTD, BW			Low
MacGregor <i>et al</i> ¹⁵	1983-86	Retrospective cohort with matched controls (MA, parity, SES, tobacco, med complications)	Single center, Chicago	Pregnant women receiving care at the Perinatal Center for Chemical Dependence of Northwestern University	NS ? Maternal self-report antenatally	LBW, PTD, SGA, BW, GA			Low
Cherukuri <i>et al</i> ¹⁶	1986	Retrospective cohort with matched controls (MA, parity, PNC, SES, race, ROH)	Single center, Brooklyn NYC	Patient delivering at Kings County Hospital, on public assistance	Maternal self-report at delivery	LBW, PTD, SGA, BW, GA			Low
Chouneau <i>et al</i> ¹⁷	1986	Retrospective cohort with unmatched controls	Single center, large teaching hospital, NYC	Pregnant at L + D who did not receive ANC	Maternal urine toxicology at admission	BW, GA			Low
Fulroth <i>et al</i> ¹⁸	NS	Prospective cohort with unmatched controls	Single center, Oakland	All infants delivered at Highland General Hospital, Oakland	Maternal self-report or urine at admission and neonate urine	PTB			Moderate
Hadeed, Siegel ¹⁹	1984-87	Prospective cohort with matched controls (MA, parity, tobacco, SES, ethnicity)	Single center, Hollywood Presbyterian Center in Los Angeles, California	Pregnant women receiving government subsidized medical care	Maternal and infant urine immediately after birth	BW, GA			Low
Little <i>et al</i> ²⁰	1987	Retrospective cohort with unmatched controls	Single center, Dallas, Texas	Mother of infant born at Parkland Memorial Hospital	Self-report (SW) and chart review	PTD, SGA, BW, GA			Low
Neerhof <i>et al</i> ²¹	1985-88	Prospective cohort with unmatched controls	Single center, Chicago	All patients admitted to L + D (screening policy)	Maternal urine at admission and neonate urine	PTD, SGA, BW, GA			Moderate
Zuckerman <i>et al</i> ²²	1984-87	Prospective cohort with unmatched controls	Single center, Boston	Recruited at women's and adolescent prenatal clinic (52% Medicaid, low income)	Interview and maternal urine antenatally and PP	BW, GA			Low
Gilligley <i>et al</i> ²³	1987-88	Retrospective cohort with matched controls (race, discharge date)	Single center, Perinatal unit, University of California, Davis, Sacramento	Admission OB service of UCDMC; urban, 93% Medicaid or no insurance, diverse ethnicity (routine testing)	Maternal urine at admission ± neonate urine	LBW, PTB, BW, GA	Multiple regression with smoking	-129g associated with tobacco use	Low
Calhoun, Watson ²⁴	1987-88	Prospective cohort with matched controls (parity, SES, MA)	Single center, L + D, Portland	Indigent, low rate of ANC, no insurance	Maternal and infant urine at admission	PTB, SGA, BW, GA			Moderate
Cohen <i>et al</i> ²⁵	1986-87	Retrospective cohort with matched controls (MA, race, parity)	Single center, San Francisco General hospital	Toxic screen from L + D or nursery, 88% black	Maternal and/or neonatal urine at admission	LBW, PTB, BW, GA			Minimal
Kelley <i>et al</i> ²⁶	NS	Retrospective cohort with controls matched (age of infant, race, sex, SES)	Single center, pediatric well-child clinic, large urban teaching hospital, Boston	Infant 1wk-26 mo, 80% black, 96% Medicaid	Maternal self-report at delivery or neonate urine	LBW, PTB, SGA, BW, GA			Moderate

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. *Am J Obstet Gynecol* 2011.

(continued)

Author	Year of study	Type of study	Setting of study	Population	Exposure assessment (when, how)	Outcomes assessed	Confounders adjusted for	Results	Quality assessment (risk of bias)
McCalla et al ²⁷	1988-89	Cross-sectional cohort with unmatched controls	Single center, municipal hospital, NYC	Inner-city	Maternal urine at admission $\pm$ neonate urine	LBW, GA	Regression analysis for: PNC, MA, parity, tobacco, ROH	For smoking, $-125.0g$ ($P = .04$) for BW and -0.37 wks ($P = .18$) for GA	Low
Richardson, Day ²⁸	1983-86	Prospective cohort with unmatched controls	Single center, Magee-Womens Hospital, interview each trimester	Young, single, low income women attending public prenatal clinic	Maternal self-report antenatally	BW, GA, LBW, SGA			Moderate
Spence et al ²⁹	NS	Prospective cohort with unmatched controls	Single center, Hahnemann University Hospital, Philadelphia	Consecutive admission in L + D, routine screen	Maternal urine at delivery	PTB, BW			Low
Bateman, et al ³⁰	1985-86	Prospective cohort with unmatched controls	Single center, Harlem Hospital, NYC	Inner-city	Maternal self-report or infant urine	LBW, PTB, BW, GA	GA, MA, gravidity, race, sex, PNC, syphilis, tobacco, ROH, marijuana, PCP, opiates	Regression coefficient $-121g$ ($P < .005$)	Low
Forman et al ³¹	1990-91	Prospective cohort with unmatched controls	3 centers, Toronto	Mother-infant pairs in 3 nurseries, 69% white	Neonate urine and hairs	BW	Tobacco - LBW BW	LBW: 50% of smokers vs 8% of nonsmokers $2899 \pm 750g$ (C+T) $3423 \pm 612g$ (C only) 3414 ± 564 (No exp)	Low
Rosengren et al ³²	1990	Prospective cohort with unmatched controls	2 urban centers, Hartford, Connecticut	Consecutive newborns, urban and suburban population	Neonate meconium	LBW, PTB, BW			Moderate
Eyler et al ³³	1987-88	Retrospective cohort with matched controls (race, MA, parity, GA at PNC, ROH, tobacco)	Single center, regional hospital (referral center), Florida	Women using rural county public health unit (min access rehab), Medicaid, low income	Maternal history or urine or neonate urine	LBW, PTB, GA, BW			Low
Kliegman et al ³⁴	1990-91	Prospective cohort with unmatched controls	Single center, large urban university-based maternity hospital, Cleveland	Anonymous screen, unselected population	Maternal urine at delivery or postpartum	LBW, PTD	Race, MA, ROH, marijuana, tobacco, PNC, primiparous, history of PTB	Multivariate logistic models adjusted OR, 9.90 (0.53-1.84)	Low
Neuspiel et al ³⁵	1992	Retrospective cohort with unmatched controls	Single center, public hospital, Bronx, NYC	NS	Maternal urine at admission and neonate cord blood	BW, GA	Cotinine, smoking history	$-204g$ ($P = .15$)	Moderate
Singer et al ³⁶	NS	Retrospective cohort with matched controls (race, SES)	NS	AA, low SES, public assistance	Maternal urine and self-report antenatally	LBW, BW, GA			Low
Miller et al ³⁷	1990	Retrospective cohort with matched controls (race, age, parity, month of delivery)	Single center, New Orleans	Large urban center, inner-city, indigent population	Maternal urine at delivery	BW, GA, PTB, SGA	Tobacco PNC	BW/Tobacco + :2759 $\pm$ 462 (45) for cocaine vs 2824 $\pm$ 876 (75) for controls BW/Tobacco - :3051 $\pm$ 602 (17) for cocaine vs 3078 $\pm$ 853 (167) for controls GA/Tobacco + : 38.4 $\pm$ 2.5 (45) for cocaine vs 37.6 $\pm$ 4.4 (75) for controls GA/Tobacco - : 39.0 $\pm$ 1.6 (16) for cocaine vs 38.4 $\pm$ 4.3 (164) for controls	Minimal

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. *Am J Obstet Gynecol* 2011.

(continued)

Author	Year of study	Type of study	Setting of study	Population	Exposure assessment (when, how)	Outcomes assessed	Confounders adjusted for	Results	Quality assessment (risk of bias)
Shiono et al ³⁸	1984-89	Prospective cohort with unmatched controls	Multicenter (7 centers) university-based prenatal clinics in US (Oklahoma, Louisiana, Texas, Tulane, Washington, Harlem)	Multietnic, from Vaginal Infections and Prematurity study	Maternal serum or self-report antenatally or at delivery	LBW, PTB	Frequency use Blood concentration Tobacco ROH Marijuana	Logistic regression for smoking LBW OR, 1.1 (0.6-2.2) PTB OR, 1.5 (0.9-2.6)	Low
Kistin et al ³⁹	1988	Retrospective cohort with unmatched controls	Multicenter (12 centers) Univ Illinois hospital perinatal network	Patient delivering in a hospital of the network	Self-report or maternal or neonate urine at delivery	LBW, PTB, SGA	Race Age Gravidity		Low
Sprauve et al ⁴⁰	1992	Retrospective cohort with unmatched controls	Single center, Atlanta	Inner-city, indigent, routine voluntary urine drug screening	Maternal urine at any time during pregnancy or within 1 wk of delivery	LBW, PTB, SGA	ROH, tobacco, weight, age, PNC, PTB	LBW: 1.59 (1.03-2.43) PTB: 0.88 (0.63-1.22) SGA: 1.7 (1.24-2.32)	Low
Richardson et al ⁴¹	1988-93	Prospective cohort with unmatched controls	Single center, PNC clinic Magee-Women's hospital, Pittsburgh	Inner-city, low income	Maternal self-report antenatally and PP	PTB, LBW, SGA	PNC		Low
Bandstra et al ⁴²	1990-93	Retro and prospective cohort with unmatched controls	Single center, Miami prenatal cocaine study	AA, inner-city, low SES	Maternal self-report and urine, infant urine and meconium	LBW, BW, GA	Tobacco	BW -0.006 (-0.012-0.000) P = .038 GA 0.008 (0.002-0.014) P = .10	Moderate
Ogunyemi, Hernandez-Loera ⁴³	1991-2000	Retrospective cohort with matched controls	Single center, Los Angeles	All deliveries at this institution	Maternal toxicology screen PP	BW, GA, PTB, SGA	Tobacco	PTB coefficient regression 0.045(0.06) (-0.08 to -0.17)	Moderate
Bada et al ⁴⁴	NS	Retrospective cohort with unmatched controls	Multicenter (4 centers) Providence, Miami, Memphis, Detroit	Database Maternal Lifestyle Study	Maternal self-report or neonate meconium	LBW, PTB, SGA	Tobacco	LBW 5.57 (3.06-7.91) PTB 3.66 (0.87-6.53) SGA 13.79 (10.08-17.33)	Low

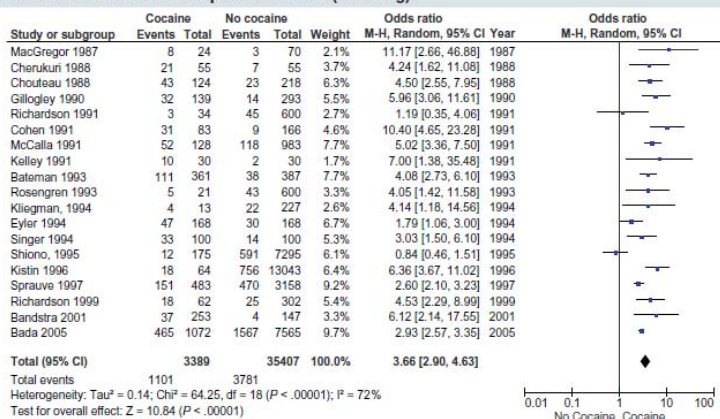
AA, African American; ANC, antenatal care; BW, birthweight; exp, exposure; GA, gestational age; L+D, labor and delivery suites; LBW, low birthweight; MA, maternal age; NS, not specified; Ob, obstetrics; PNC, prenatal care; PP, postpartum; PTB, preterm birth; PTD, preterm delivery; ROH, alcohol; SES, socioeconomic status; SGA, small for gestational age; UCDMC, University of California Davis Medical Center.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

Subgroup Analyses

FIGURE 2

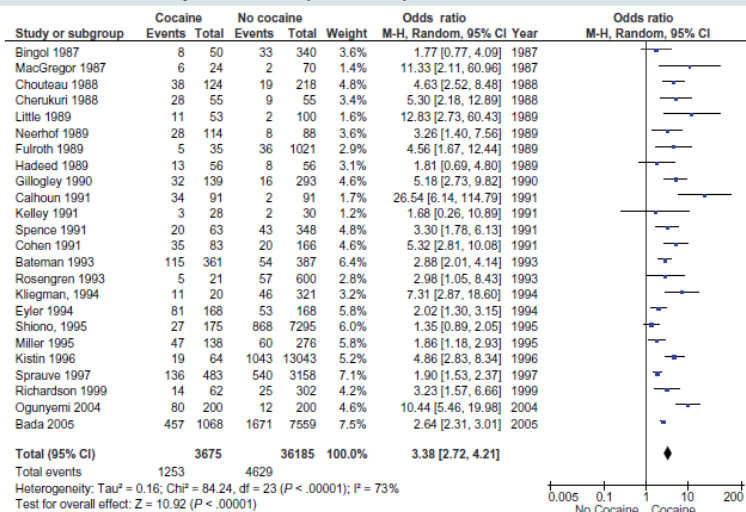
Effect of antenatal cocaine exposure on LBW (<2500 g)



LBW, low birthweight.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

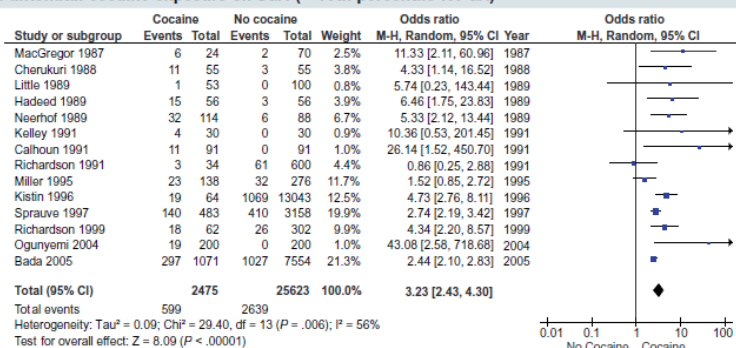
FIGURE 3
Effect of antenatal cocaine exposure on PTB (<37 weeks)



PTB, preterm birth.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

FIGURE 4
Effect of antenatal cocaine exposure on SGA (<10th percentile for GA)

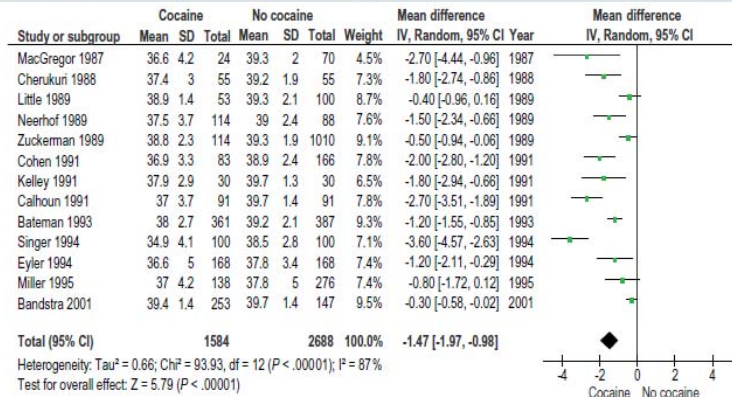


GA, gestational age; SGA, small for gestational age.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

FIGURE 5

Effect of antenatal cocaine exposure on GA at delivery (weeks)

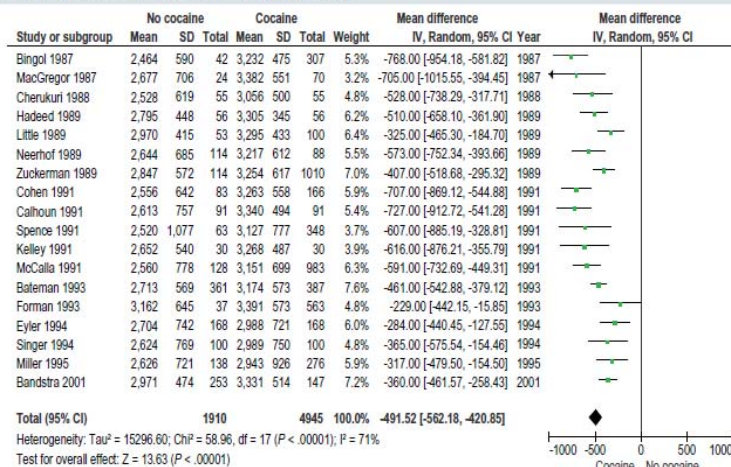


GA, gestational age.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

FIGURE 6

Effect of antenatal cocaine exposure on BW (grams)



BW, birthweight.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

TABLE 2
Sensitivity/subgroup analysis

Variable	Group	PTB		LBW	
		n studies/ participants	OR (95% CI)	n studies/ participants	OR (95% CI)
Year of study	≤1991	13/3791	4.29 (3.11–5.92)	8/3032	5.23 (3.72–7.34)
	>1991	11/36069	2.93 (2.28–3.76)	11/35764	3.02 (2.32–3.93)
Method of exposure assessment	Self-report	11/32123	2.97 (2.25–3.93)	12/32160	3.21 (2.29–4.48)
	Objective	13/7737	3.80 (2.59–5.57)	7/6636	4.62 (3.09–6.89)
Type of cohort	Retrospective	13/28711	3.69 (2.75–4.95)	12/14501	3.97 (3.05–5.17)
	Prospective	11/11149	3.09 (2.13–4.48)	7/24295	3.28 (1.96–5.47)
Quality assessment (risk of bias)	Minimal/low	18/37341	2.99 (2.42–3.70)	15/37081	3.66 (2.85–4.70)
	Moderate	6/2519	5.44 (2.73–10.85)	4/1715	3.71 (1.72–7.99)
Type of controls	Matched	10/2387	4.35 (2.59–7.30)	7/1481	4.72 (2.67–8.34)
	Unmatched	14/37473	2.94 (2.34–3.69)	12/37315	3.37 (2.59–4.39)

CI, confidence interval; LBW, low birthweight; OR, odds ratio; PTB, preterm birth.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. *Am J Obstet Gynecol* 2011.

APPENDIX 1

Risk of bias assessment for observational studies

Bias	None	Low	Moderate	High	Can't tell
Selection	- Consecutive unselected population - Sample selected from general population rather than a select group - Rationale for case and control selection explained - Follow up or assessment time explained	- Sample selected from large population but selection criteria not defined - A select group of population (based on race, ethnicity, residence, etc) studied	- Sample selection ambiguous but sample may be representative - Eligibility criteria not explained - Rationale for case and controls not explained - Follow up or assessment time not explained	- Sample selection ambiguous and sample likely not representative - A very select population studied making it difficult to generalize findings	
Exposure assessment	Direct questioning (interview) or completion of survey by mother regarding her BW or GA	Assessment of exposure from global dataset (National register, Vital statistics)	Extrapolating data from population exposure sample (with some assumptions) and not direct assessment at any time	Indirect method of assessment (obtaining data from others and not from mother or father)	
Outcome assessment	Assessment from hospital record, birth certificate or from direct question to mother regarding BW of infant	- Assessment from administrative database (national register, vital statistics) - Direct question to mother regarding gestational age	Assessment from "open-ended" questions (was your infant early? or premature? or small? or before due date)	Assessment from nonvalidated sources or generic estimate from overall population	
Confounding factor	Controlled for common confounders	Only certain confounders adjusted	Not controlled for confounders		
Analytical	- Analyses appropriate for the type of sample - Analytical method accounted for sampling strategy in cross-sectional study - Sample size calculation performed and adequate sample studied	- Analyses not accounting for common statistical adjustment (eg, multiple analyses) when appropriate - Sample size calculation not performed, but all available eligible patients studied - Sample size calculated and reasons for not meeting sample size given	Sample size estimation unclear or only subsample of eligible patients studied	Analyses inappropriate for the type of sample/study	
Attrition	0-10% attrition and reasons for loss of follow-up explained - All subjects from initiation of study to the final outcome assessment were accounted for	0-10% attrition and reasons for loss of follow-up not explained 11-20% attrition, reasons for loss of follow-up explained	11-20% attrition but reasons for loss of follow-up not explained >20% attrition but reasons for loss of follow-up explained - All subjects from initiation of study to final outcome assessment not accounted for	>20% attrition, reasons for loss of follow-up not explained	

BW, birthweight; GA, gestational age.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

APPENDIX 2

Studies quality assessment (risk of bias) of included studies of cocaine exposure

Author	Type of study	Selection bias	Exposure assessment bias	Outcome assessment bias	Confounding factor bias	Analytical bias	Attrition bias	Overall assessment bias
Bingol et al ⁴	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Low	Low
MacGregor et al ¹⁵	Cohort with matched controls	Low	None	None	Low	Low	None	Low
Cherukuri et al ¹⁶	Retrospective cohort with matched controls	Low	None	None	Moderate	Low	None	Low
Chouteau et al ¹⁷	Retrospective cohort with unmatched controls	Low	None	None	Moderate	Low	None	Low
Fulroth et al ¹⁸	Cohort with unmatched controls	Moderate	None	None	Moderate	Low	None	Moderate
Hadeed, Siegel ¹⁹	Retrospective cohort with matched controls	Low	Low	None	Low	Low	None	Low
Little et al ²⁰	Retrospective cohort with unmatched controls	Low	None	None	Low	Low	None	Low
Neerhof et al ²¹	Prospective cohort with unmatched controls	Moderate	None	None	Moderate	Low	None	Moderate
Zuckerman et al ²²	Prospective cohort with unmatched controls	Low	Low	None	Low	Low	Low	Low
Gillogley et al ²³	Retrospective cohort with matched controls	Low	None	None	Low	Low	Moderate	Low
Calhoun, Watson ²⁴	Prospective cohort with matched controls	Moderate	Low	None	Low	Low	None	Moderate
Cohen et al ²⁵	Retrospective cohort with matched controls	Low	None	None	Low	Low	None	Minimal
Kelley et al ²⁶	Retrospective cohort with matched controls	Low	None	None	Moderate	Low	ns	Moderate
McCalla et al ²⁷	Cross-sectional cohort with unmatched controls	Low	None	None	Low	Low	Moderate	Low
Richardson and Day ²⁸	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Moderate	Moderate
Spence et al ²⁹	Prospective cohort with unmatched controls	Low	None	None	Moderate	Low	Low	Low
Bateman et al ³⁰	Prospective cohort with unmatched controls	Low	None	None	None	Low	ns	Low
Forman et al ³¹	Prospective cohort with unmatched controls	Low	None	None	Low	Low	None	Low
Rosengren et al ³²	Prospective cohort with unmatched controls	Low	None	None	Moderate	Low	None	Moderate
Eyler et al ³³	Retrospective cohort with matched controls	Low	Low	None	None	Low	ns	Low
Kliegman et al ³⁴	Cohort with unmatched controls	Low	None	None	None	Low	ns	Low
Neuspiel et al ³⁵	Retrospective cohort with unmatched controls	Low	None	None	Low	Low	Moderate	Moderate
Singer et al ³⁶	Retrospective cohort with matched controls	Low	None	none	Low	Low	ns	Low
Miller et al ³⁷	Retrospective cohort with matched controls	None	None	None	None	Low	Low	Minimal
Shiono et al ³⁸	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Low	Low
Kistin et al ³⁹	Retrospective cohort with unmatched controls	Low	None	None	Low	Low	None	Low
Sprauve et al ⁴⁰	Retrospective cohort with unmatched controls	Low	None	None	None	Low	Low	Low
Richardson et al ⁴¹	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Low	Low
Bandstra et al ⁴²	Retrospective and prospective cohort with unmatched controls	Low	Low	None	None	Low	Moderate	Moderate
Ogunyemi, Hernandez-Loera ⁴³	Retrospective cohort with matched controls	Moderate	Low	None	Low	Low	Low	Moderate
Bada et al ⁴⁴	Retrospective cohort with unmatched controls	Low	None	None	None	Low	Low	Low

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. *Am J Obstet Gynecol* 2011.

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/s/

JANE E LIEDTKA
08/15/2017

MIRIAM C DINATALE
08/15/2017

LYNNE P YAO
08/18/2017

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:	August 9, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209963
Product Name and Strength:	Cocaine Hydrochloride Topical Solution 4% (40 mg/mL)
Applicant/Sponsor Name:	Genus Lifesciences, Inc.
Submission Date:	August 3, 2017
OSE RCM #:	2016-2721-2
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling for Cocaine Topical Solution (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to subsequent recommendations from the Office of Pharmaceutical Quality (OPQ) to the Sponsor. OPQ requested that the Sponsor include an equivalent statement for the cocaine base and that the strength be expressed as '40 mg/mL' in addition to the '4%' strength expression. The container labels and carton labeling also contain revisions from our previous review, which we found acceptable in a previous memorandum.^{a,b}

^a Schlick J. Label and Labeling Review for Cocaine Hydrochloride Topical Solution (NDA 209963). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 11. RCM No.: 2016-2721.

^b Schlick J. Label and Labeling Review MEMO for Cocaine Hydrochloride Topical Solution (NDA 209963). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 22. RCM No.: 2016-2721-1.

2 CONCLUSION

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

APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 3, 2017

Container labels



Carton labeling



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/s/

JAMES H SCHLICK
08/09/2017

OTTO L TOWNSEND
08/09/2017



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

Date: August 8, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia and Addiction Products

Through: Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Cocaine Hydrochloride Topical Solution
NDA 209,963 (IND 118,527)
Indication: Induction of local anesthesia when
performing diagnostic procedures and surgeries on or through
the mucous membranes of the nasal cavities in adults
Dosage: 4% solution (40 mg/ml)
Sponsor: (b) (4)
PDUFA Goal Date: August 19, 2017

Materials reviewed: NDA 209,963 (11/23/17)

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2	CONCLUSIONS AND RECOMMENDATIONS	2

1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) to the Controlled Substance Staff (CSS) to evaluate and revise the proposed text for Section 9 (Drug Abuse and Dependence) and Section 10 (Overdose) of the drug label for Cocaine Hydrochloride Topical Solution (4% solution, 40 mg/ml) under NDA 209,963. The Sponsor is (b) (4)

This NDA is submitted as a 505(b) 2, so there are no abuse-related nonclinical or clinical studies for CSS to review.

Cocaine Hydrochloride Topical Solution is proposed for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults. The recommended dose of Cocaine Hydrochloride Topical Solution is two pledgets, each containing 40 mg of cocaine hydrochloride, applied to each nasal cavity. Each of four pledgets (1.3 cm x 4 cm) absorbs 1 ml of cocaine hydrochloride, equivalent to 40 mg cocaine hydrochloride, for a total dose of 160 mg. The total dose for any one procedure or surgery should not exceed 160 mg cocaine hydrochloride. The preparation of the pledgets involves pouring the full contents of one 4 ml (160 mg) bottle of Cocaine Hydrochloride Topical Solution into a medicine cup. The four cottonoid pledgets are soaked until the solution is fully absorbed. Following soaking, two pledgets are placed against the septum in each nasal cavity and left in place for up to twenty minutes. The pledgets are removed and discarded prior to the procedure or surgery.

Cocaine has two primary mechanisms of action. Its centrally-mediated effects (including euphoria) are due to its action as a triple reuptake inhibitor that blocks the transporters for dopamine, norepinephrine and serotonin in the brain. Its ability to produce local anesthesia is the result of its ability to block sodium channels. The human effects of cocaine are well-characterized and represented in the text proposed below for Sections 9 and 10 regarding acute responses, development of physical dependence and overdose.

2. Conclusions and Recommendations

The Sponsor submitted no abuse-related studies in this NDA. However, cocaine has been a Schedule II drug under the Controlled Substances Act since 1970, with known and well-characterized abuse potential. Therefore, the drug label for this product will need to include Section 9 (Drug Abuse and Dependence) and Section 10 (Overdose).

CSS has the following proposal for the text for these two label sections:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Cocaine Hydrochloride Topical Solution contains cocaine, a Schedule II controlled substance.

9.2 Abuse

Cocaine Hydrochloride Topical Solution contains cocaine, a substance with a high potential for abuse. Cocaine Hydrochloride Topical Solution can be misused and abused, which can lead to addiction. Cocaine Hydrochloride Topical Solution may also be diverted for abuse purposes [see *Warnings and Precautions* (5.1)].

Drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. Drug abuse of a substance may occur without progression to drug addiction. “Drug-seeking” behavior is very common in persons with substance use disorders.

Drug abuse and addiction are conditions that are separate and distinct from physical dependence and tolerance [see *Dependence* (9.3)]. Health care providers should be aware that abuse and addiction may occur in the absence of symptoms indicative of physical dependence and tolerance.

Individuals who abuse stimulants may use Cocaine Hydrochloride Topical Solution for abuse purposes. Adverse events associated with abuse of cocaine include euphoria, excitation, irritability, restlessness, anxiety, paranoia, confusion, headache, psychosis, hypertension, stroke, seizures, dilated pupils, nausea, vomiting, and abdominal pain. Intranasal abuse can produce damage to the nostrils (e.g., ulceration and deviated septum). Abuse of cocaine can result in overdose, convulsions, unconsciousness, coma, and death [see *Overdosage* (10)].

Cocaine Hydrochloride Topical Solution, like all prescription drugs with abuse potential, can be diverted for non-medical use into illicit channels of distribution. In order to minimize these risks, effective accounting procedures should be implemented, in addition to routine procedures for handling controlled substances.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Cocaine Hydrochloride Topical Solution is approved for topical single use during diagnostic procedures and surgeries, so physical dependence and withdrawal symptoms are unlikely to develop. Although Cocaine Hydrochloride Topical Solution is not indicated for chronic therapy, repeated misuse or abuse of this product may lead to physical dependence.

(b) (4)

10 OVERDOSAGE

No cases of overdose with Cocaine Hydrochloride Topical Solution were reported in clinical trials. Blood pressure and heart rate increases were greater with Cocaine Hydrochloride Topical Solution 8% than with Cocaine Hydrochloride Topical Solution

(b) (4)

In the case of an overdose, consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to cocaine varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of cocaine overdose associated with illicit use of cocaine reported in literature and based on reports in FDA's Adverse Events Reporting System (AERS) database include death, cardio-respiratory arrest, cardiac arrest, respiratory arrest, tachycardia, myocardial infarction, agitation, aggression, restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Because cocaine is significantly distributed to tissues and rapidly metabolized, dialysis and hemoperfusion are not effective. Acidification of the urine does not significantly enhance cocaine elimination.

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/s/

KATHERINE R BONSON
08/08/2017

SILVIA N CALDERON
08/08/2017

Clinical Inspection Summary

Date	July 25, 2017
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Diana Walker, Ph.D., Regulatory Project Manager Renee Petit-Scott, M.D., Medical Officer Leah Crisafi, M.D., Medical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Applications	NDA 209963
Applicant	Genus Lifesciences, Inc. (b) (4)
Drug	Cocaine Hydrochloride Topical Solution, 4% (b) (4)
New Molecular Entity	No
Review Priority	Standard
Proposed Indication	Local anesthesia of nasal cavities (adults)
Consultation Date	January 17, 2017
CIS Goal Date	August 4, 2017
Action Goal Date	September 20, 2017
PDUFA Due Date	September 23, 2017

I. OVERALL ASSESSMENT OF FINDINGS

Study CTS 2013011 was audited at four good clinical practice (**GCP**) inspections of (b) (4) a contract research organization (**CRO**) for study management, and three clinical investigator (**CI**) sites (two CIs, one with two sites): (1) Site 602, John McGrath (Marlton, New Jersey); (2) Site 702, Robert Pulchaski (Columbia, South Carolina); and (3) Site 703, Robert Pulchaski (Lugoff, South Carolina). The CRO inspection (b) (4) was triggered by the (initial) inability to verify the NDA data at CI sites. In resolving this finding, the sponsor discovered and promptly corrected an error in the NDA data as originally prepared and presented by (b) (4), the transposition of two study medication dose groups (4% and 8%).

For all four inspections, no significant GCP deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequately GCP-compliant, including sponsor/CRO oversight of study conduct. (b) (4) data presentation error appeared to be isolated, readily corrected, and limited to this study. All audited data were acceptably verifiable against source records and case report forms (**CRFs**). The data from the three inspected CI sites appear reliable as reported in the NDA.

II. BACKGROUND

This 505(b)(2) NDA from Genus Lifesciences, Inc. (b) (4) supports the use of Cocaine Hydrochloride Topical Solution, 4% (pending trade name (b) (4) for “the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults.” Study CTS 2013011 supporting this NDA was initially sponsored by (b) (4) before the sponsorship was transferred to (b) (4). The study was audited at good clinical practice (GCP) inspections of a CRO and three CI sites.

Study CTS 2013011

A Phase III Investigation of Topical Application of RX0041-002 on Safety and Efficacy in Local (Topical) Anesthesia for Diagnostic Procedures and Surgeries on or Through the Accessible Mucous Membranes of the Nasal Cavities

This randomized controlled trial (RCT) was conducted between 2014 and 2015 in over 648 subjects enrolled at nine CI sites in the United States (US). The primary study objective was to evaluate the efficacy of the investigational product (IP, RX0041-002) as a single-application topical anesthetic for use immediately prior to diagnostic or surgical intranasal procedures (e.g., nasal endoscopy, intranasal biopsy, and sinus debridement).

Subject selection and randomization: The study subjects consisted of men and women (age ≥18 years) requiring any of the indicated intranasal procedures and able to feel/report pain in the anterior nasal septum. Eligible subjects were randomized in 3/3/1 ratio, respectively, to: (1) 4% IP (IP-4); (2) 8% IP (IP-8); and (3) placebo.

Study treatment and efficacy assessment: The study medication was topically administered to the intranasal mucous membrane using 4 cotton pledgets (2 per nostril), each measuring 1.3 x 4 cm and soaked with about 1 mL of the study medication. For each subject/nostril, treatment success (primary endpoint) was evaluated as follows:

- *Analgesic success* was defined as a pain score of 0 (no pain) on Visual Numeric Rating Scale (VNRS), assessed immediately after applying the study medication using the Von Frey Filament Test (VFFT).
- After completing VFFT at baseline (pre-procedure), the identity of the study medication was unblinded (placebo versus IP) while the dose remained blinded (IP-4 versus IP-8). All placebo subjects were offered an active anesthetic (CI judgment and choice) in completing the indicated diagnostic/surgical procedure.
- *Treatment success* was defined as analgesic success followed by adequate analgesia throughout the diagnostic/surgical procedure without the need for rescue medication (subject request and CI judgment). The evaluation of treatment success was limited to those subjects given the IP and achieving analgesic success.

The major study analyses consisted of comparisons of treatment success (rates) between placebo and: IP-4 (primary), and IP-8 (secondary). Safety monitoring (during, one hour after, and at 7 days after procedure) included: adverse events (AEs), vital signs, nasal examination, ability to smell, pulse oximetry, and electrocardiography (ECG).

III. INSPECTION OUTCOMES: Audit of Study CTS 2013011

Clinical Investigator Site ⁽¹⁾		Site / Enrollment ⁽²⁾	Inspection Outcome
1	Robert Puchalski, M.D. 710 Rabon Road Columbia, South Carolina	Site 702 107 subjects	April 3 – 7, 2017 NAI
2	Robert Puchalski, M.D. 15 Exchange Drive Lugoff, South Carolina	Site 703 171 subjects	April 3 – 7, 2017 NAI
3	John McGrath, M.D. 3 North Maple Avenue, Suite D Marlton, New Jersey	Site 602 102 subjects	May 16 – 18, 2017 NAI ⁽³⁾
Contract Research Organization			Inspection Outcome
(b) (4)			

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations

VAI = Voluntary Action Indicated, minor deviations from regulations

OAI = Official Action Indicated, major deviations from regulations

- ⁽¹⁾ These CI sites were selected for GCP inspection based on: (large) subject enrollment, (high) site-specific efficacy outcome, and (relatively few reported) AEs.
- ⁽²⁾ Case records were selected for detailed review based on subject data favoring NDA approval (high placebo-adjusted efficacy and/or few AEs). Data verification (against on-site source records) included the following NDA listings:
 - VNRS pain intensity scores: Listing 16.2.6.1
 - AEs: Listings 16.2.7.1, 16.2.7.6a, and 16.2.7.6b
 - protocol deviations: Listing 16.2.2
- ⁽³⁾ For the CRO (b) (4) and CI Site 602 (John McGrath), the establishment inspection report (EIR) has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. An addendum to this clinical inspection summary (CIS) may be forwarded to the review division if new significant findings are discovered at completion of EIR review; otherwise, OSI's written correspondence to the inspected entity (to be copied to review division) indicates completion of EIR review and confirmation of the findings reported in this CIS.

1. Robert Puchalski, M.D. (Site 702; Columbia, SC)

Study CTS 2013011, Site 702: 107 subjects were screened, 72 were enrolled, and 72 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for the following 12 subjects (selected as noted above, Table footnote 2): Subjects 03, 11, 19, 33, 35, 38, 39, 50, 52, 55, 75, and 92.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor protocol deviations were considered unlikely to be significant:

- Body temperature measurement intervals inconsistent with study protocol (more frequent than specified, 3 subjects)
- Inadequate documentation of: (1) no childbearing potential, and (2) no ibuprofen use within 2 days before Day 1 (same single subject)

Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the NDA.

2. Robert Puchalski, M.D. (Site 703; Lugoff, SC)

Study CTS 2013011, Site 703: 171 subjects were screened, 112 were enrolled, and 112 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for the following 15 subjects (selected as noted above, Table footnote 2): Subjects 12, 13, 23, 35, 41, 52, 53, 62, 72, 91, 92, 95, 102, 168, and 169.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor protocol deviations were considered unlikely to be significant:

- Body temperature measurement intervals inconsistent with study protocol (2 subjects)
- Inadequate documentation of no albuterol use within 2 days before Day 1 (one subject)

Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the NDA.

3. John McGrath, M.D.

Study CTS 2013011, Site 602: 102 subjects were screened, 89 were enrolled, and 89 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for the following 12 subjects (selected as noted above, Table footnote 2): Subjects 01, 24, 27, 44, 46, 57, 58, 59, 62, 70, 76, and 94.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor protocol deviations were considered unlikely to be significant:

- Pledgets removed 2 minutes later than as specified in study protocol (4 subjects)
- Blood pressure measurement intervals inconsistent with study protocol (12 subjects)
- Incomplete screening laboratory testing and/or ECG (3 subjects)
- Enrollment with hematology test results below reference range (2 subjects)

Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the NDA.

(b) (4)

This CRO inspection was triggered by the inability to verify the NDA data (specifically, randomized treatment assignment to IP-4 and IP-8) at CI Sites 702 and 703 (Puchalski). In resolving this unexpected finding, the sponsor discovered an error in the NDA data as originally prepared and presented by (b) (4), the transposition of two study medication dose groups (4% and 8%). The sponsor promptly corrected the error and submitted to the NDA (April 19, 2017) a report of corrective and preventive action (**CAPA**).

Study CTS 2013011: (b) (4) monitored the CI sites, managed and analyzed the study data, and prepared the clinical study report. In follow up of the CAPA error, this CRO inspection included a detailed audit of the major control points for data management:

- Software development (or procurement, including licensure) and maintenance
- Local software validation, including data entry and internal audit
- Standard operating procedures (**SOP**) for data and database management

No significant GCP deficiencies were observed and a Form FDA 483 was not issued. The CAPA error appeared to be an isolated human data input/programming error, readily corrected without complication.

- In setting up study tables, dummy (programming) codes were apparently used accidentally in lieu of the actual randomization codes.
- (b) (4) identified and updated all relevant SOPs (for quality assurance and data management) to prevent error recurrence. The CAPA error appeared to be limited to this study (confirmation for all future studies on-going at inspection close-out).

(b) (4) monitoring of the CI sites appeared adequate, including monitoring for any evidence of unblinding. All audited NDA data were adequately verifiable against CRFs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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CC:

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DAAAP / Medical Team Leader / Leah Crisafi
DAAAP / Medical Officer / Renee Petit-Scott
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/s/

JONG HOON LEE
07/25/2017

JANICE K POHLMAN
07/25/2017

KASSA AYALEW
07/26/2017

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:	May 24, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209963
Product Name and Strength:	Cocaine Hydrochloride Topical Solution 4% (40 mg/mL)
Applicant/Sponsor Name:	Genus Lifesciences, Inc.
Submission Date:	May 22, 2017
OSE RCM #:	2016-2721-1
DMEPA Primary Reviewer:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling for Cocaine Hydrochloride Topical Solution (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for Cocaine Hydrochloride Topical Solution are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Schlick J. Label and Labeling Review for Cocaine Hydrochloride Topical Solution (NDA 209963). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 11. RCM No.: 2016-2721.

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/s/

JAMES H SCHLICK
05/24/2017

OTTO L TOWNSEND
05/24/2017

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:	May 11, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209963
Product Name and Strength:	Cocaine Hydrochloride Topical Solution 4% (40 mg/mL)
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genus Lifesciences, Inc.
Submission Date:	November 23, 2016 and May 1, 2017
OSE RCM #:	2016-2721
DMEPA Primary Reviewer:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

We are responding to a request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). DAAAP wants us to evaluate the proposed Cocaine Topical Solution labels and labeling. Thus, we review the labels and labeling to identify error prone content and provide comments.

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	C N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Background on Marketed, Unapproved Products

The FDA encourages manufacturers of unapproved products, like cocaine topical solution, to submit data to NDA for review. The FDA reviews the data to assess if the proposed product meets modern safety standards. Genus Lifesciences submitted their marketed product via the 505(b)(2) pathway, but there is no reference drug identified in the Application.

Container Label and Carton Labeling

We identified the following in our risk assessment of the container label and carton labeling:

- The font size of the dosage form statement 'Topical solution' on the carton's principal display panel is smaller than the established name. The font size needs to be larger to improve its prominence.
- Health care practitioners can misinterpret the statement 'Not for injection or Ophthalmic Use' on the principal display panel. We have received post-marketing reports that negative statements (e.g. Not for) may have the opposite of the intended meaning because the word 'not' can be overlooked. Hence, health care practitioners misinterpret the statement as an affirmative statement.

- The Sponsor did not include the package type ‘single-use’ on the container label and carton labeling.

Prescribing Information

We identified the following in our risk assessment of the Prescribing Information:

- Highlights of Prescribing Information and Full Prescribing Information – *Dosage and Administration* Sections
 - The text on how many pledgets are applied in each nostril is unclear.
 - Information on soaking the pledget does not appear before information on the placement of the pledget in the nasal cavities. The appropriate sequence of steps will help minimize preparation errors. The instructions to use a medicine cup to pour the solution into the cup, prior to soaking the pledgets are error prone. The confusing instructions could cause someone to administer the drug accidentally via the oral route.
 - In the Full Prescribing Information, Dosage and Administration Section -The size of the pledgets to be used is not given, and the section does not indicate that the pledgets are not co-packaged with the drug. In addition, it is unclear if the 1.3 cm x 4 cm pledget dimensions noted in the section are standard sizes that are widely available.
- Highlights of Prescribing Information – Dosage Forms and Strengths Section
 - The Labeling Development Team (LDT) Labeling Review Tool^a recommends that the total volume of the bottle- 4 mL – be included in the section.
- Full Prescribing Information – Dosage Forms and Strengths Section
 - The LDT Labeling Review Tool recommends the description of the topical solution (i.e. clear, green colored liquid) be included in the section.
 - The LDT Labeling Review Tool recommends the appropriate package term (i.e. single-use) be included in the section.
- Full Prescribing Information – How Supplied/Storage and Handling Section
 - The packaging type ‘single-use’ is not in this section.

We provide recommendations in Sections 4.1 and 4.2 to address our findings of the container label, carton labeling, and prescribing information.

^aFDA Labeling Development Team – Labeling Review Tool. Available at:
<http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/UCM541522.pdf>

4 CONCLUSION & RECOMMENDATIONS

We identified areas of concern with the container labels, carton labeling, and prescribing information that can be optimized for clarity. We provide comments in Sections 4.1 and 4.2 to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. We have several recommendations to improve the clarity of the information presented and to conform to the LDT Labeling Review Tool. See Appendix H for our track changed recommendations.

4.2 RECOMMENDATIONS FOR GENUS LIFESCIENCES

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

A. Container Label and Carton Labeling

1. Revise the statement 'Not for Injection or Ophthalmic Use' on the principal display panel to 'For Topical Use Only. Not for Injection or Ophthalmic Use'. We have received post-marketing reports that negative statements (e.g. Not for) without a preceding positive statement may be read accidentally as the opposite of the intended meaning. The reader can overlook the word 'not', and interpret the statement as an affirmative statement.
2. We recommend you include the package type 'single-use' on the principal display panel to inform users the bottle is for a single administration.

B. Carton Labeling

1. Revise the font size of the dosage form statement 'Topical Solution' on the principal display panel to a larger font. A larger font size will increase the prominence of this important information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cocaine Hydrochloride Topical Solution that Genus Lifesciences submitted on May 1, 2017.

Table 2. Relevant Product Information for Cocaine Hydrochloride Topical Solution	
Initial Approval Date	N/A
Active Ingredient	Cocaine Hydrochloride
Indication	Induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults.
Route of Administration	Intranasal
Dosage Form	Topical Solution
Strength	4% (40 mg per mL)
Dose and Frequency	160 mg per procedure. Pledget Preparation: 4 pledgets are soaked in 4 mL of the topical solution in a small container to obtain 1 mL (40 mg) per pledget. Administration: Apply two pledgets to each nasal cavity for four pledgets (160 mg).
How Supplied/ Container Closure	A clear, green colored liquid available as a 4% (40 mg) topical solution. One 4 mL bottle packed in a carton.
Storage	Room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 26, 2017, we searched the L:drive and AIMS using the terms, cocaine to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 26, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: cocaine

D.2 Results

Our search did not identify any articles related to this review.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On April 26, 2017, we searched FAERS using the criteria in the table below and identified 103 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^b We excluded 103 cases because they described intentional misuse or intentional overdose

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	April 26, 2012 to April 26, 2017
Product Name:	Cocaine
Product Active Ingredient (PAI):	Cocaine
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

E.2 Results

Our search did not identify any cases relevant to this review.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

^b The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

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,^c along with postmarket medication error data, we reviewed the following Cocaine Hydrochloride Topical Solution labels and labeling submitted by Genus Lifesciences on November 23, 2016 and May 1, 2017.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Container Label

(b) (4)



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
05/11/2017

OTTO L TOWNSEND
05/11/2017

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	209963
Brand Name	-
Generic Name	Cocaine Hydrochloride Topical Solution (RX0041-002)
Sponsor	(b) (4)
Indication	For the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults
Dosage Form	Topical solution for intranasal use
Drug Class	Amino ester local anesthetic
Therapeutic Dosing Regimen	160 mg: Two pledgets, each containing 40 mg of cocaine hydrochloride, applied to each nasal cavity. The total dose for any one procedure or surgery should not exceed 160 mg cocaine hydrochloride.
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	> 320 mg (4 mL of 8% cocaine topical solution, i.e., 320 mg cocaine HCl was well tolerated)
Submission Number and Date	001; 11/23/2016
Review Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Correcting the QT interval for heart rate using population methods such as the Fridericia method works well for drugs that do not affect heart rate; however, there is less confidence in this approach for drugs with substantial heart rate effects (mean changes >10 bpm). In this TQT study, Cocaine Hydrochloride Topical Solution (RX0041-002) caused dose-/concentration-dependent increases in heart rate (Table 1) that impacts the ability to interpret the $\Delta\Delta QTcF$ for the supratherapeutic dose of 320 mg (8% solution).

Table 1: The $\Delta\Delta$ HR Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for RX0041-002 (160 mg and 320 mg) (FDA Analysis)

Treatment Group	Time (hour)	$\Delta\Delta$ HR (bpm)	90% CI (bpm)
RX0041-002 160 mg	0.67	7.0	(4.0; 10.0)
RX0041-002 320 mg	0.33	15.3	(11.6; 19.0)

For the therapeutic dose of 160 mg (4% solution) of RX0041-002, no significant QTc prolongation effect was detected in this TQT study, as the largest upper bound of the two-sided 90% CI excludes 10 ms (Table 2). The heart rate effects at the 320 mg dose (~2.2-fold higher exposures compared to 160 mg) impacts the interpretability of the QTc effects associated with this suprathreshold dose. However, based on the preclinical data and the observed mean $\Delta\Delta$ QTcF of less than 10 ms, it seems unlikely that 320 mg RX0041-002 would cause large increases in QTc (i.e. 20 ms).

The suprathreshold dose in this study has ~2.2-fold exposure margin over the C_{max} with therapeutic dose and the margin is well above the highest exposure scenario of 1.33-fold C_{max} in subjects with severe renal impairment compared to subjects with normal renal function. It is unlikely that the imprecision resulting from the heart rate effect would result in a mean QTc effect greater than 10 ms at this highest exposure scenario (1.33-fold exposure) with therapeutic dose. Further, given that the duration of therapeutic use is acute with single dose administration, we believe there is minimal risk of clinically relevant QTc prolongation at this highest clinically relevant concentrations (highest exposure scenario).

In this randomized, partially blinded, four-period crossover study, 24 healthy subjects received RX0041-002 160 mg (4%), RX0041-002 320 mg (8%), placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of $\Delta\Delta$ QTcF findings for the 160 and 320 mg doses are presented in Table 2 below. The table also shows that the largest lower bound of the two-sided 90% CI for the $\Delta\Delta$ QTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 8, indicating that assay sensitivity was established.

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for RX0041-002 (160 mg and 320 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	$\Delta\Delta$ QTcF (ms)	90% CI (ms)
RX0041-002 160 mg	0.33	4.6	(2.2; 6.9)
RX0041-002 320 mg	0.33	7.1	(4.7; 9.5)
Moxifloxacin 400 mg	4	15.0	(12.4; 17.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 11.5 ms.

Concentration-QT analysis showed a positive slope of concentration- $\Delta\Delta$ QTcF relationship for cocaine concentrations, albeit with the upper bound of 90% CI for

predicted $\Delta\Delta QTcF$ at the geometric mean C_{max} of the two dose groups (160, 320 mg) to be less than 10 ms.

2 PROPOSED LABEL

The sponsor included following QT-related language in their current proposed label.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of Cocaine Hydrochloride Topical Solution on the QTc interval was evaluated in a randomized, placebo- and positive-controlled four-period crossover thorough QTc study in 24 healthy subjects. No clinically relevant QTc prolongation was observed at highest clinically relevant concentrations with single therapeutic dose.

3 BACKGROUND

3.1 PRODUCT INFORMATION

RX0041-002 is an aqueous solution of cocaine hydrochloride being developed for use as a local anesthetic for diagnostic and surgical procedures on or through the mucous membranes of the nasal cavities.

3.2 MARKET APPROVAL STATUS

Information not available.

3.3 PRECLINICAL INFORMATION

Refer to Preclinical Cardiac Safety section in Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

Refer to Clinical Cardiac Safety section in Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of cocaine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 118527. The sponsor submitted the study report CTS2016017 for RX0041-002, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Single-Dose, Partially Blinded, Four-Period, Four-Treatment, Four-Way Crossover Pharmacodynamic and Pharmacokinetic Study of QT/QTc Prolongation Potential of RX0041-002 (Cocaine Hydrochloride Topical Solution)

4.2.2 Protocol Number

CTS2016017

4.2.3 Study Dates

16 June 2016 - 29 June 2016

4.2.4 Objectives

To exclude an effect of RX0041-002 topical solution applied to the nasal membranes on placebo corrected $\Delta QTcF$ exceeding 10 ms at clinically relevant plasma levels using exposure response analysis.

4.2.5 Study Description

4.2.5.1 Design

This was a single-dose, partially blinded, randomized, four-period, four-treatment, crossover study in which 24 healthy adult subjects received separate single doses of RX0041-002 topical solution (8%, equivalent dose of 320 mg), RX0041-002 topical solution (4%, equivalent dose of 160 mg), placebo, and moxifloxacin tablet, 400 mg in four study periods. Each subject received a different treatment in each study period.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Partial blinding. Subjects, investigators, study personnel, and ECG analysts were blinded to Treatments A (RX0041-002 topical solution, 8%), B (RX0041-002 topical solution, 4%), and C (placebo topical solution). Treatment D (moxifloxacin) was open-label.

4.2.5.4 Treatment Arms

RX0041-002 topical solution (8%), RX0041-002 topical solution (4%), placebo, and moxifloxacin tablet, 400 mg

4.2.5.5 Sponsor's Justification for Doses

Not provided.

Reviewer's comment: Highlights of Clinical Pharmacology Table notes that the C_{max} of drug is 16% higher in females as compared to males. The individual clinical pharmacology studies included in the NDA provide following information regarding organ impairment: Geometric mean C_{max} was slightly higher (1.33-fold) in subjects with severe renal impairment compared to those with normal renal function for the same dose. Further, geometric mean C_{max} was similar or lower in moderate/severe hepatic impairment (Child-Pugh B/C) compared to subjects with normal hepatic function for the same dose. Overall, the >2-fold exposure margin provided by the 320 mg supratherapeutic dose would adequately cover the highest clinically relevant concentrations with therapeutic dose of 160 mg.

4.2.5.6 Instructions with Regard to Meals

Subjects were given an assigned treatment (based on the randomization schedule) at a prespecified time in each period, after a 10-hour overnight fast. The subjects fasted for 4 hours thereafter. Water was allowed ad libitum during the study except for 1 hour prior through 1 hour postdose (postdose defined as after pledget insertion/moxifloxacin dose administration). Standard meals were provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter.

Reviewer's Comment: Because the drug will be administered intranasally, food is not likely to cause changes in drug exposure.

4.2.5.7 ECG and PK Assessments

ECG: On each dosing day, ECGs were extracted predose at 3 timepoints (-45, -30 and -15 minutes), and 20 minutes (end of RX0041-002 dose; immediately after pledget removal), 40 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after pledget insertion/moxifloxacin dose.

PK: PK samples were collected predose (approximately 60 minutes before dose administration), and 20 minutes (end of RX0041-002 dose; immediately after pledget removal), 40 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after pledget insertion/moxifloxacin dose.

Reviewer's comment: Acceptable. ECG measurements were collected frequently enough to monitor the effects of drug over a 24-hour interval. Frequent samples were collected around T_{max} of the drug (20 minutes) and metabolites (2-2.5 h) in order to detect changes in the QT interval at maximum drug or metabolite concentrations.

4.2.5.8 Baseline

The average of predose QT/QTc values on Day 1 of each period was used as baseline for that period.

4.2.6 ECG Collection

Continuous 12-Lead digital ECG recording was performed. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

A total of 24 healthy adult subjects (15 females and 9 males) were enrolled and randomized to the study. All of the 24 subjects completed the study and thus were included in the safety, PK, and PD populations.

The average age (SD) of the 24 subjects was 30.5 (6.6) years, ranging from 20 to 39 years. Sixteen of the 24 subjects (16/24, 66.7%) were White and 8 of the 24 subjects (8/24, 33.3%) were Black or African American. Half of the subjects were of ethnic Hispanic or Latino.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

Exposure-response analysis was used for primary analysis. The findings of the study are discussed in section 4.2.7.2.4 and section 4.2.7.4.2.

4.2.7.2.2 Assay Sensitivity

Exposure-response analysis was used for assay sensitivity analysis, which is discussed in section 4.2.7.4.2. Additional analysis of assay sensitivity is discussed in section 4.2.7.2.4.

4.2.7.2.3 Categorical Analysis

From the sponsor's categorical analysis tables, no subject had QTcF > 480 ms. One subject (1/24, 4.2%) in moxifloxacin 400 mg group and one subject (1/24, 4.2%) in placebo group had QTcF > 450 ms.

No subject had change from baseline in QTcF (Δ QTcF) > 60 ms. One subject (1/24, 4.2%) in moxifloxacin 400 mg group had Δ QTcF > 30 ms at one time point.

4.2.7.2.4 Additional Analyses

The "by timepoint" analysis for QTcF was based on a linear mixed-effects model with change from baseline QTcF (Δ QTcF) as the dependent variable, period, sequence, time (categorical), treatment (RX0041-002 4%, RX0041-002 8%, moxifloxacin, and placebo), and time by treatment interaction as fixed effects, and baseline QTcF as a covariate.

After dosing with RX0041-002 320 mg, a small increase of Δ QTcF was observed with mean values around 4 ms to 5 ms at the first 3 timepoints: 4.0 ms, 5.8 ms, and 4.6 ms at 20, 40, and 60 minutes, respectively. Changes were smaller after dosing with RX0041-002 160 mg. Moxifloxacin caused a clear increase of Δ QTcF, which peaked at 14.4 ms at 4 hours post-dosing. After administration of the high dose of RX0041-002 (320 mg), the mean placebo-corrected Δ QTcF ($\Delta\Delta$ QTcF) was 7.0 ms at the timepoint of pledget removal (20 minutes) and 6.8 ms and 4.9 ms at 40 and 60 minutes and mean values thereafter were below 5 ms. At 20 minutes, mean $\Delta\Delta$ QTcF was 4.6 ms after administration of RX0041-002 160 mg, with smaller values at all subsequent timepoints. The peak $\Delta\Delta$ QTcF after dosing of 400 mg moxifloxacin reached 15.2 ms 4 hours post-dosing with rising and falling phases before and after this timepoint. There were no

categorical outliers in terms of QTcF > 450 ms or ΔQTcF > 30 ms after administration of RX0041-002 and no treatment emergent T-wave morphology changes.

A relatively pronounced heart rate effect was seen after application of 320 mg RX0041-002 for 20 minutes with the largest effect (15 bpm) seen at the timepoint of pledget removal (20 minutes).

4.2.7.3 Safety Analysis

No deaths, serious adverse events (SAEs), or other significant AEs occurred during the conduct of the study. No subjects discontinued the study due to AEs.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results for cocaine and metabolites of cocaine (Benzoylecgonine (BE), Ecgonine Methyl Ester (EME) and Norcocaine) are presented in Figure 1. Cocaine appeared rapidly in the plasma following intranasal application of the two dose groups of RX0041-002, and was present in the plasma of all subjects by the end of the 20-minute dosing period. Plasma profiles of the two major metabolites, BE and EME, showed that both were present in the plasma after intranasal administration of RX0041-002, at both dose levels. Peak metabolite levels were reached somewhat later than those of cocaine, with median T_{max} of 2.0-2.5 h for these metabolites. The minor but active cocaine metabolite, norcocaine, was not detectable at any time point in 6 of 24 subjects at the low (160 mg) dose level, and in 1 of 24 subjects at the high (320 mg) dose level.

The C_{max} and AUC values of cocaine and its metabolites were about 2-fold higher following administration of 320 mg dose compared with 160 mg, the intended clinical dose.

The PK results for moxifloxacin are presented in Figure 2. Moxifloxacin was present in the plasma of all subjects after Treatment D (400 mg oral moxifloxacin). Geometric mean plasma levels rose over the first few hours to reach a geometric mean C_{max} of 1,910 ng/mL at a median T_{max} of 3.0 h.

Figure 1. Plasma Concentration-Time Profiles of (Top, Left) Cocaine (Top, Right) Benzoylecgonine, BE (Bottom, Left) Ecgonine Methyl Ester, EME (Bottom, Right) Norcocaine. Shown are the Data From the two Dose Groups

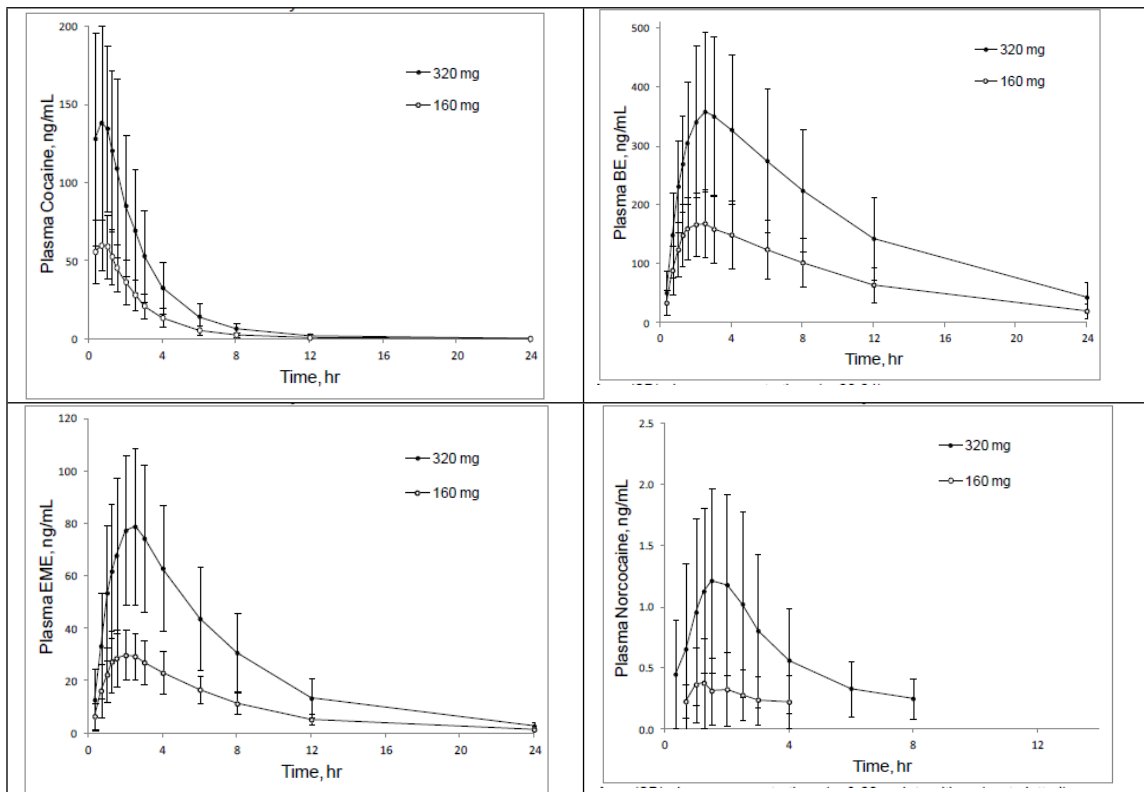
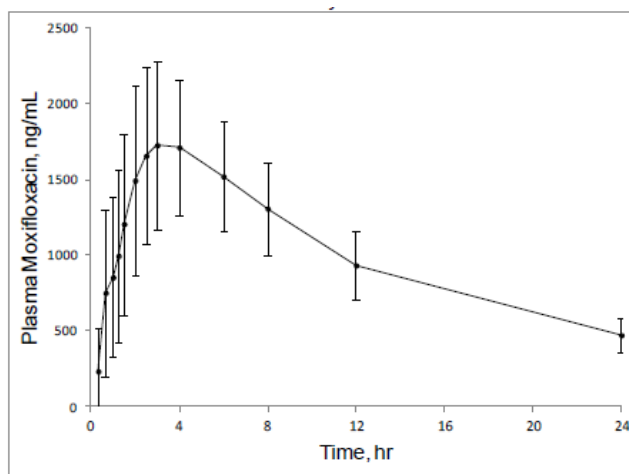


Figure 2. Plasma Concentration Profiles of Moxifloxacin



4.2.7.4.2 Exposure-Response Analysis

Relationship between cocaine concentrations and $\Delta\Delta$ QTcF

The relationship between cocaine plasma concentration and placebo-corrected change-from-baseline QTcF ($\Delta\Delta$ QTcF) were investigated by linear mixed-effects modeling. The following 3 linear models were considered:

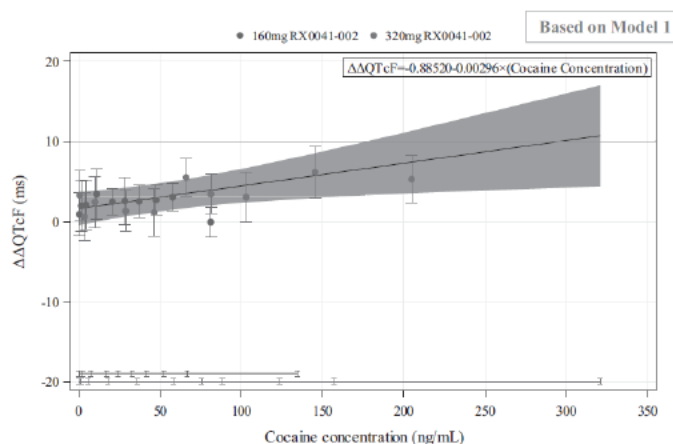
- Model 1 was a linear model with an intercept.
- Model 2 was a linear model with mean intercept fixed to 0 (with variability).
- Model 3 was a linear model with no intercept.

Table 3 summarizes the results of cocaine- $\Delta\Delta$ QTcF analyses. Model 1 was used for further analysis since the model with an intercept was found to fit the data best (i.e., had the smallest AIC among the three candidate models). Figure 3 shows the mean $\Delta\Delta$ QTcF (90% CI) within each cocaine concentration decile on doses of 160 mg and 320 mg, and the model-predicted mean $\Delta\Delta$ QTcF with 90% CI. The estimated slope of the exposure response relationship was 0.028 ms per ng/mL (90% CI: 0.005 to 0.052) with an intercept of 1.633 ms.

Table 3. Exposure-Response Analysis of Cocaine- Associated $\Delta\Delta$ QTcF Prolongation

Model	AIC	Parameter	Estimate (90% CI)	P-Value	Between-Subject Variation
1	3011	Intercept (ms)	1.633 (-0.496; 3.762)	0.2014	5.730
		Slope (ms per ng/mL)	0.028 (0.005; 0.052)	0.0508	0.050
		Residual Variability (ms)	5.580	.	
2	3011	Intercept (ms)		.	5.960
		Slope (ms per ng/mL)	0.037 (0.016; 0.058)	0.0065	0.060
		Residual Variability (ms)	5.580	.	
3	3117	Slope (ms per ng/mL)	0.054 (0.028; 0.079)	0.0018	0.070
		Residual Variability (ms)	6.640	.	

Figure 3. Cocaine Plasma Concentrations vs. $\Delta\Delta Q_{TcF}$ Relationship



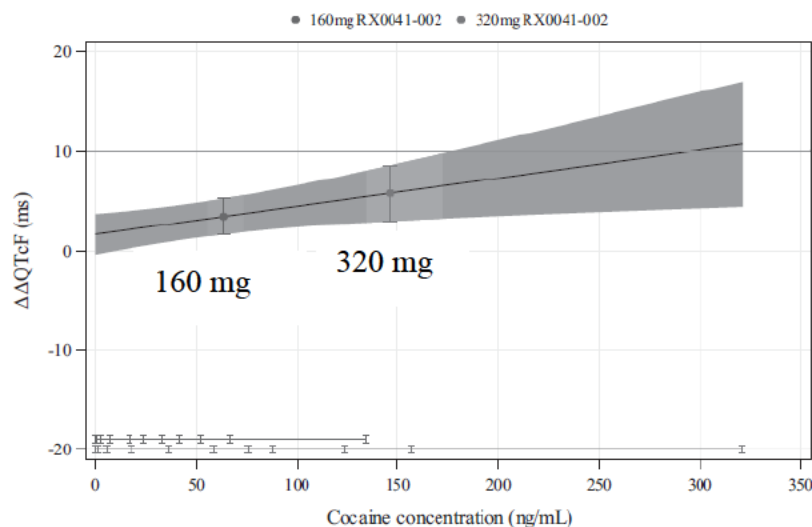
The predicted $\Delta\Delta Q_{TcF}$ at the geometric mean peak cocaine concentrations for RX0041-002 doses of 160 mg and 320 mg is shown in Table 4 and visualized in Figure 4.

Table 4. Predicted $\Delta\Delta Q_{TcF}$ Interval at Geometric Mean Peak Cocaine Concentrations*

Treatment	Geometric Mean (90% CI) cocaine C_{max} (ng/mL)	Predicted $\Delta\Delta Q_{TcF}$ (ms)	90% CI of Q_{TcF} (ms)
160mg RX0041-002	63.78 (55.07; 73.86)	3.44	(1.58; 5.30)
320mg RX0041-002	146.11 (123.39; 173.02)	5.77	(2.83; 8.71)

* Prediction was based on Model 1. The 90% CI of the geometric mean was calculated in the logarithmic domain and presented after back-transformation to the original concentration domain.

Figure 4. Predicted Mean (90% CI) vs $\Delta\Delta Q_{TcF}$ Interval at Geometric Mean Peak Cocaine using Model 1*



* The solid black line with gray shaded area denotes the model-predicted mean (90% CI) $\Delta\Delta Q_{TcF}$. The predicted mean (90% CI) $\Delta\Delta Q_{TcF}$ at the geometric mean (90% CI) C_{max} of cocaine for RX0041-002 doses of 160 mg and 320 mg, respectively are also shown.

Relationship between moxifloxacin concentrations and $\Delta\Delta\text{QTcF}$

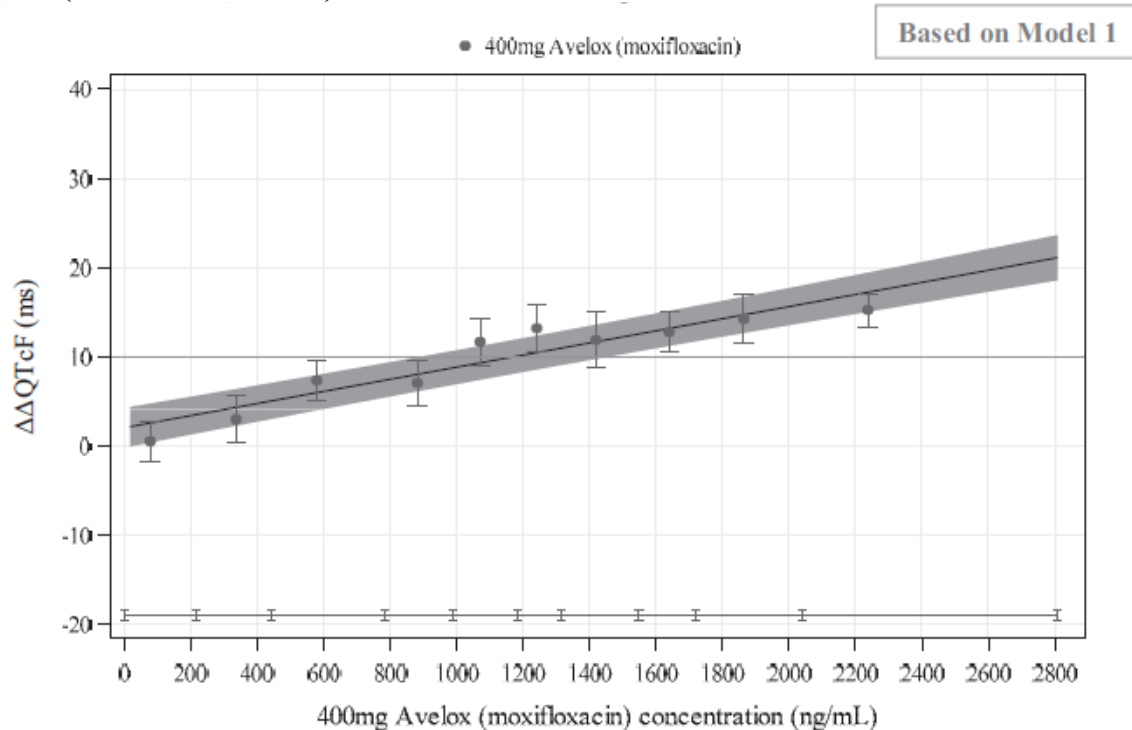
The findings of analyses that explored the relationship between moxifloxacin concentrations and $\Delta\Delta\text{QTcF}$ are shown in Table 5.

Table 5. Exposure-Response Analysis of Moxifloxacin- Associated $\Delta\Delta\text{QTcF}$ Prolongation.

Model	AIC	Parameter	Estimate (90% CI)	P-Value	Between-Subject Variation
1	2054	Intercept (ms)	2.039 (-0.216; 4.294)	0.1357	5.310
		Slope (ms per ng/mL)	0.007 (0.006; 0.008)	0.0000	.
		Residual Variability (ms)	6.400	.	
2	2054	Intercept (ms)	.	.	5.520
		Slope (ms per ng/mL)	0.007 (0.006; 0.008)	0.0000	.
		Residual Variability (ms)	6.410	.	
3	2079	Slope (ms per ng/mL)	0.008 (0.007; 0.010)	0.0000	0.000
		Residual Variability (ms)	6.680	.	

Figure 5 shows the mean $\Delta\Delta\text{QTcF}$ (90% CI) within each moxifloxacin concentration decile, and the model-predicted mean $\Delta\Delta\text{QTcF}$ with 90% CI.

Figure 5. Model Predicted $\Delta\Delta\text{QTcF}$ (Mean and 90% CI) and Observed $\Delta\Delta\text{QTcF}$ (Mean and 90% CI) Across Deciles of Moxifloxacin Plasma Concentrations

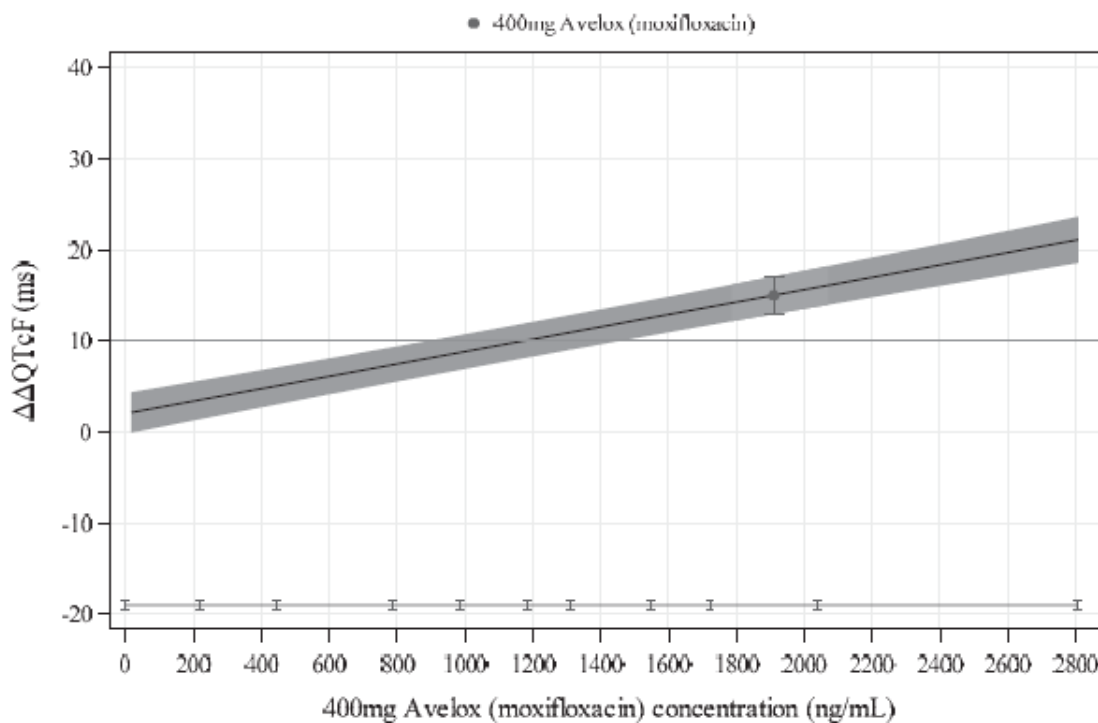


The predicted $\Delta\Delta QTcF$ at the geometric mean peak moxifloxacin concentrations is shown in Table 6 and visualized in Figure 6.

Table 6. Predicted $\Delta\Delta QTcF$ interval at geometric mean peak moxifloxacin concentrations*

Treatment	Geometric Mean (90% CI) of C_{max} (ng/mL)	Predicted $\Delta\Delta QTcF$ (ms)	90% CI of $QTcF$ (ms)
400mg Avelox (moxifloxacin)	1910 (1757.5; 2074.9)	15.0	(12.91; 17.10)

Figure 6. Predicted Mean (90% CI) $\Delta\Delta QTcF$ Interval at Geometric Mean Peak Moxifloxacin Concentrations Using Model 1*



* The solid black line with gray shaded area denotes the model-predicted mean (90% CI) $\Delta\Delta QTcF$. The shaded areas denote the predicted mean (90% CI) $\Delta\Delta QTcF$ at the geometric mean (90% CI) C_{max} of moxifloxacin.

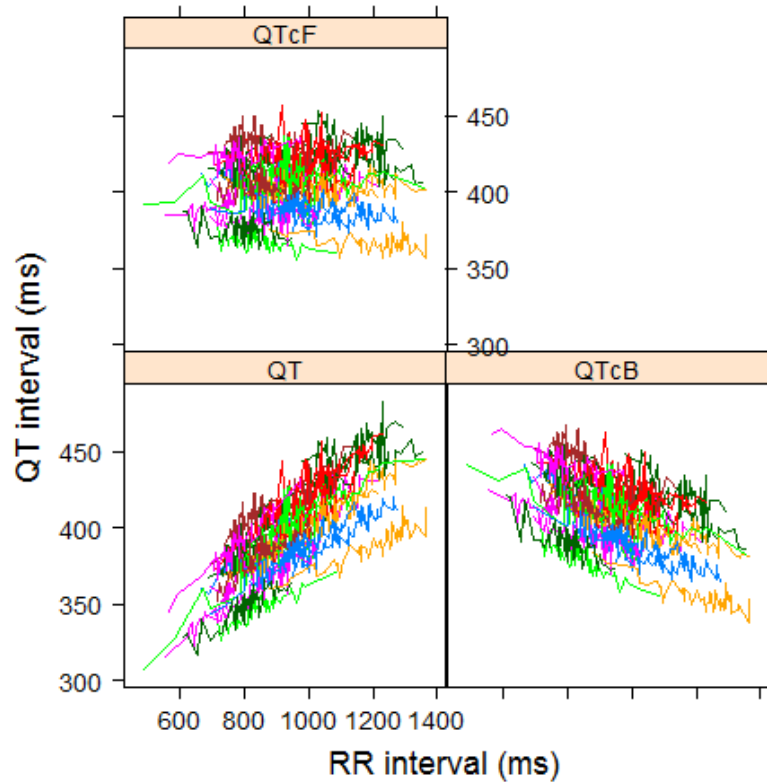
Reviewer's Comments: The analysis conducted by the sponsor is acceptable. The reviewer's independent assessment and findings are discussed in section 5.3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 7. $QTcF$ was used for primary analyses.

Figure 7: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for RX0041-002

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment, sequence, period, time point and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 7: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = B: RX0041-002 160 mg (4%)

	Δ QTcF (ms) RX0041-002 160 mg (4%)	Δ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) RX0041-002 160 mg (4%)	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.33	1.6	-3.0	4.6	(2.2, 6.9)

	ΔQTcF (ms) RX0041-002 160 mg (4%)	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) RX0041-002 160 mg (4%)	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.67	2.4	-1.0	3.4	(1.0, 5.8)
1	2.2	-0.3	2.5	(0.2, 4.9)
1.25	1.7	0.5	1.2	(-1.4, 3.8)
1.5	1.0	0.6	0.4	(-1.8, 2.7)
2	1.5	0.2	1.3	(-0.9, 3.6)
2.5	1.7	1.7	-0.0	(-2.4, 2.3)
3	3.5	0.3	3.2	(0.4, 6.0)
4	1.1	-0.7	1.7	(-0.9, 4.3)
6	-0.9	-3.7	2.8	(-0.7, 6.2)
8	-4.5	-7.0	2.5	(-0.3, 5.3)
12	-2.1	-2.3	0.2	(-2.5, 2.9)
24	-6.0	-5.2	-0.8	(-3.6, 2.0)

**Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = A:
RX0041-002 320 mg (8%)**

	ΔQTcF (ms) RX0041-002 320 mg (8%)	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) RX0041-002 320 mg (8%)	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.33	4.1	-3.0	7.1	(4.7, 9.5)
0.67	5.8	-1.0	6.8	(4.4, 9.3)
1	4.5	-0.3	4.9	(2.5, 7.2)
1.25	2.2	0.5	1.7	(-0.8, 4.3)
1.5	2.1	0.6	1.5	(-0.7, 3.8)
2	1.1	0.2	0.9	(-1.3, 3.2)
2.5	3.0	1.7	1.3	(-1.0, 3.6)
3	2.5	0.3	2.3	(-0.5, 5.1)
4	1.1	-0.7	1.8	(-0.8, 4.4)

	ΔQTcF (ms) RX0041-002 320 mg (8%)	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) RX0041-002 320 mg (8%)	
Time (hour)	LSmean	LSmean	LSmean	90% CI
6	-4.4	-3.7	-0.8	(-4.2, 2.7)
8	-6.0	-7.0	1.0	(-1.8, 3.8)
12	-2.4	-2.3	-0.1	(-2.8, 2.6)
24	-4.6	-5.2	0.6	(-2.2, 3.4)

The largest upper bounds of the 2-sided 90% CI for the mean differences between RX0041-002 160 mg (4%) and placebo, and between RX0041-002 320 mg (8%) and placebo were 6.9 ms and 9.5 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 12.4 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 11.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTcF (ms) Moxifloxacin 400 mg	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
0.33	-3.0	-3.0	-0.0	(-2.4, 2.4)	(-3.3, 3.3)
0.67	4.5	-1.0	5.5	(3.1, 8.0)	(2.2, 8.9)
1	7.5	-0.3	7.8	(5.5, 10.2)	(4.6, 11.0)
1.25	9.1	0.5	8.6	(6.0, 11.1)	(5.0, 12.1)
1.5	8.5	0.6	7.9	(5.7, 10.2)	(4.8, 11.0)
2	9.0	0.2	8.9	(6.6, 11.1)	(5.8, 12.0)
2.5	11.5	1.7	9.8	(7.4, 12.1)	(6.6, 13.0)
3	13.2	0.3	12.9	(10.1, 15.7)	(9.0, 16.8)
4	14.4	-0.7	15.0	(12.4, 17.6)	(11.5, 18.6)
6	7.3	-3.7	11.0	(7.6, 14.5)	(6.3, 15.8)
8	4.5	-7.0	11.5	(8.7, 14.3)	(7.7, 15.4)

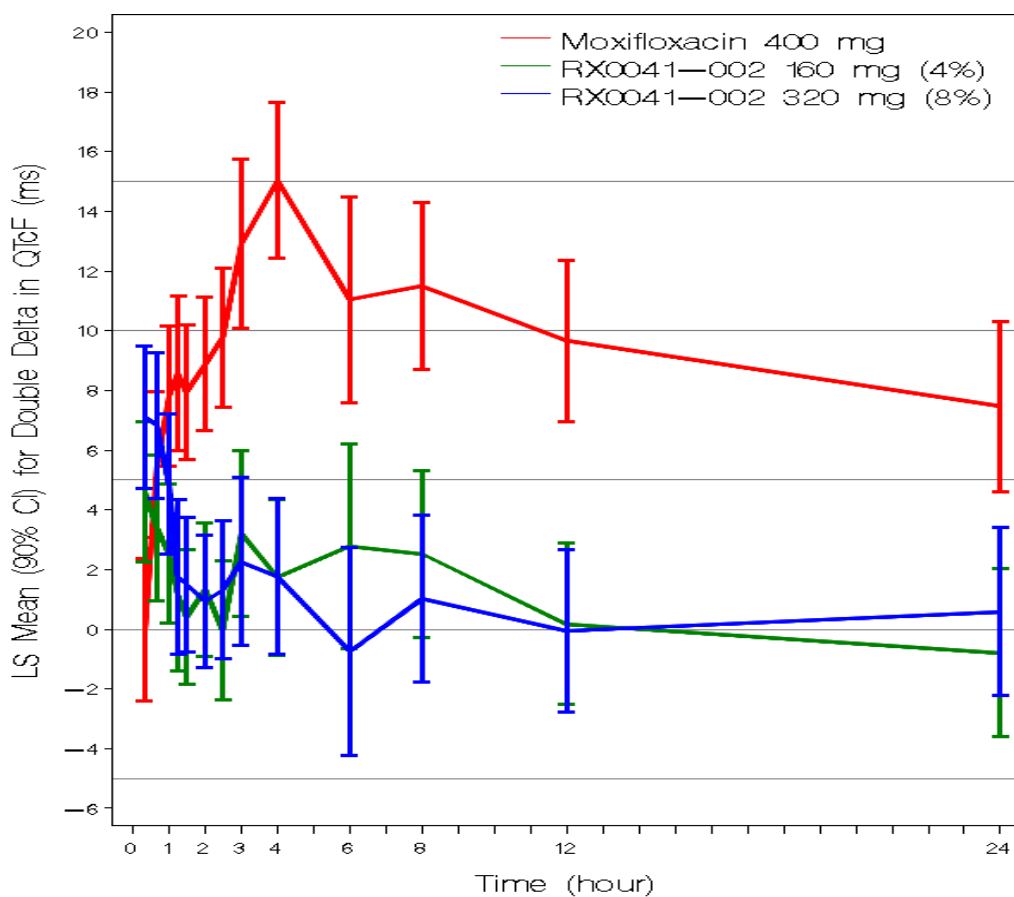
	ΔQ_{TcF} (ms) Moxifloxacin 400 mg	ΔQ_{TcF} (ms) Placebo	$\Delta\Delta Q_{TcF}$ (ms) Moxifloxacin 400 mg		
Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
12	7.3	-2.3	9.7	(7.0, 12.4)	(5.9, 13.4)
24	2.3	-5.2	7.5	(4.6, 10.3)	(3.5, 11.4)

* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 4 time points around moxifloxacin C_{max} .

5.2.1.3 Graph of $\Delta\Delta Q_{TcF}$ Over Time

The following figure displays the time profile of $\Delta\Delta Q_{TcF}$ for different treatment groups. It should be noted that CIs are all unadjusted, including those for moxifloxacin.

Figure 8: Mean and 90% CI $\Delta\Delta Q_{TcF}$ Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

	Total N		QTcF ≤ 450 ms		450<QTcF ≤ 480 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	24	285	23 (95.8%)	284 (99.6%)	1 (4.2%)	1 (0.4%)
Placebo	24	311	23 (95.8%)	310 (99.7%)	1 (4.2%)	1 (0.3%)
Moxifloxacin 400 mg	24	305	23 (95.8%)	303 (99.3%)	1 (4.2%)	2 (0.7%)
RX0041-002 160 mg (4%)	24	309	24 (100%)	309 (100%)	0 (0.0%)	0 (0.0%)
RX0041-002 320 mg (8%)	24	308	24 (100%)	308 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 11: Categorical Analysis of Δ QTcF

	Total N		Δ QTcF ≤ 30 ms		30< Δ QTcF ≤ 60 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	24	311	24 (100%)	311 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	24	305	23 (95.8%)	304 (99.7%)	1 (4.2%)	1 (0.3%)
RX0041-002 160 mg (4%)	24	309	24 (100%)	309 (100%)	0 (0.0%)	0 (0.0%)
RX0041-002 320 mg (8%)	24	308	24 (100%)	308 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the HR mean differences between RX0041-002 160 mg (4%) and placebo and RX0041-002 320 mg (8%) and placebo were 10.0 bpm and 19.0 bpm, respectively. An

HR increasing effect was observed for both RX0041-002 160 mg (4%) and RX0041-002 320 mg (8%) groups.

The outlier analysis results for HR are presented in Table 13.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR

	RX0041-002 160 mg (4%)			RX0041-002 320 mg (8%)		
	Δ HR (bpm)		$\Delta\Delta$ HR (bpm)	Δ HR (bpm)		$\Delta\Delta$ HR (bpm)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.33	10.8	5.4	5.4 (1.8, 9.1)	20.7	5.4	15.3 (11.6, 19.0)
0.67	7.9	0.9	7.0 (4.0, 10.0)	14.1	0.9	13.2 (10.2, 16.2)
1	5.7	-0.1	5.8 (3.2, 8.3)	11.5	-0.1	11.6 (9.1, 14.1)
1.25	5.5	-0.2	5.7 (2.8, 8.6)	9.1	-0.2	9.3 (6.5, 12.2)
1.5	4.8	0.0	4.8 (2.4, 7.1)	9.7	0.0	9.7 (7.3, 12.0)
2	2.4	-0.9	3.3 (1.2, 5.5)	8.4	-0.9	9.3 (7.2, 11.5)
2.5	3.2	1.7	1.5 (-0.7, 3.7)	6.5	1.7	4.8 (2.6, 7.0)
3	3.4	-0.1	3.5 (1.4, 5.6)	6.2	-0.1	6.3 (4.2, 8.4)
4	2.3	1.8	0.5 (-1.6, 2.6)	4.5	1.8	2.7 (0.5, 4.8)
6	7.0	5.8	1.2 (-1.3, 3.7)	8.3	5.8	2.5 (-0.0, 4.9)
8	4.3	4.1	0.3 (-2.1, 2.7)	5.0	4.1	0.9 (-1.5, 3.3)
12	10.4	9.0	1.4 (-1.0, 3.7)	11.3	9.0	2.3 (-0.0, 4.6)
24	4.5	4.2	0.3 (-2.9, 3.5)	5.4	4.2	1.2 (-2.0, 4.4)

Table 13: Categorical Analysis for HR

	Total N	HR $\leq$ 100 bpm	HR>100 bpm	HR>45 bpm	HR $\leq$ 45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	24	24 (100%)	0 (0.0%)	21 (87.5%)	3 (12.5%)
Placebo	24	24 (100%)	0 (0.0%)	24 (100%)	0 (0.0%)
Moxifloxacin 400 mg	24	24 (100%)	0 (0.0%)	22 (91.7%)	2 (8.3%)
RX0041-002 160 mg (4%)	24	24 (100%)	0 (0.0%)	23 (95.8%)	1 (4.2%)
RX0041-002 320 mg (8%)	24	21 (87.5%)	3 (12.5%)	24 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. A PR lowering effect was observed from immediately postdose to 4 hours postdose for RX0041-002 320 mg (8%).

There were no subjects who experienced PR interval greater than 200 ms in any treatment group.

Table 14: Analysis Results of Δ PR and $\Delta\Delta$ PR

	RX0041-002 160 mg (4%)			RX0041-002 320 mg (8%)		
	Δ PR (ms)		$\Delta\Delta$ PR (ms)	Δ PR (ms)		$\Delta\Delta$ PR (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.33	-5.5	-1.0	-4.5 (-7.6, -1.5)	-6.9	-1.0	-5.9 (-9.0, -2.8)
0.67	0.2	1.4	-1.2 (-3.9, 1.4)	-4.2	1.4	-5.6 (-8.2, -2.9)
1	-0.8	0.9	-1.7 (-4.5, 1.2)	-2.8	0.9	-3.7 (-6.6, -0.9)
1.25	-0.1	0.7	-0.8 (-3.3, 1.8)	-2.8	0.7	-3.5 (-6.0, -0.9)
1.5	-0.5	1.3	-1.8 (-4.4, 0.8)	-2.3	1.3	-3.6 (-6.2, -1.0)
2	-1.3	0.1	-1.4 (-4.0, 1.2)	-4.7	0.1	-4.8 (-7.4, -2.2)
2.5	-0.8	-1.2	0.5 (-2.0, 2.9)	-4.2	-1.2	-3.0 (-5.4, -0.6)
3	-0.6	0.0	-0.6 (-2.9, 1.6)	-4.0	0.0	-4.0 (-6.3, -1.8)
4	-0.7	-0.1	-0.7 (-3.1, 1.8)	-3.7	-0.1	-3.7 (-6.1, -1.2)
6	-1.1	-1.6	0.4 (-2.6, 3.5)	-3.4	-1.6	-1.9 (-5.0, 1.2)
8	-2.4	-3.7	1.4 (-1.8, 4.6)	-3.1	-3.7	0.7 (-2.5, 3.9)
12	-1.7	-0.7	-1.0 (-3.9, 1.8)	-0.5	-0.7	0.1 (-2.7, 3.0)
24	-3.5	-2.4	-1.1 (-4.0, 1.8)	-3.6	-2.4	-1.2 (-4.0, 1.7)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15. The magnitude of RX0041-002 on QRS effect was small and mostly insignificant.

The outlier analysis results for QRS are presented in Table 16.

Table 15: Analysis Results of Δ QRS and $\Delta\Delta$ QRS

	RX0041-002 160 mg (4%)			RX0041-002 320 mg (8%)		
	Δ QRS (ms)		$\Delta\Delta$ QRS (ms)	Δ QRS (ms)		$\Delta\Delta$ QRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.33	-0.1	-0.4	0.3 (-0.3, 1.0)	-0.4	-0.4	0.0 (-0.6, 0.7)
0.67	0.1	0.2	-0.0 (-0.5, 0.4)	0.4	0.2	0.2 (-0.3, 0.7)
1	0.2	0.4	-0.2 (-0.8, 0.4)	0.2	0.4	-0.2 (-0.9, 0.4)
1.25	0.3	-0.1	0.5 (0.1, 0.8)	0.2	-0.1	0.3 (-0.0, 0.6)
1.5	0.1	-0.3	0.3 (0.0, 0.7)	0.1	-0.3	0.3 (0.0, 0.7)
2	0.1	0.1	-0.0 (-0.4, 0.3)	0.0	0.1	-0.1 (-0.4, 0.3)
2.5	-0.1	-0.4	0.3 (-0.1, 0.6)	0.3	-0.4	0.6 (0.2, 1.0)
3	-0.2	-0.1	-0.1 (-0.4, 0.2)	0.1	-0.1	0.2 (-0.1, 0.6)
4	-0.1	0.2	-0.3 (-0.9, 0.3)	-0.1	0.2	-0.2 (-0.8, 0.3)
6	-0.4	-0.6	0.2 (-0.4, 0.8)	-0.6	-0.6	0.0 (-0.6, 0.7)
8	0.1	-0.4	0.5 (-0.0, 1.0)	-0.6	-0.4	-0.2 (-0.7, 0.4)
12	0.2	-0.3	0.5 (-0.2, 1.2)	-0.2	-0.3	0.2 (-0.5, 0.9)
24	-0.1	0.4	-0.5 (-1.1, 0.2)	-0.2	0.4	-0.5 (-1.2, 0.1)

Table 16: Categorical Analysis for QRS

	Total N		QRS $\leq$ 110 ms		QRS $>$ 110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	24	285	18 (75.0%)	230 (80.7%)	6 (25.0%)	55 (19.3%)
Placebo	24	311	18 (75.0%)	246 (79.1%)	6 (25.0%)	65 (20.9%)
Moxifloxacin 400 mg	24	305	19 (79.2%)	249 (81.6%)	5 (20.8%)	56 (18.4%)
RX0041-002 160 mg (4%)	24	309	19 (79.2%)	249 (80.6%)	5 (20.8%)	60 (19.4%)
RX0041-002 320 mg (8%)	24	308	18 (75.0%)	260 (84.4%)	6 (25.0%)	48 (15.6%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean concentration-time profiles of cocaine and its metabolites from the two dose groups are shown in Figure 9. Also, the mean concentration-time profile for moxifloxacin is shown in Figure 9.

Figure 9: Mean Concentration-Time Profiles for Cocaine and its Metabolites Ecgonine Methyl Ester (EME), Norcocaine and Benzoylecgonine from Two Dose Groups (4%, 8%). Moxifloxacin Concentration-Time Profile is also shown.

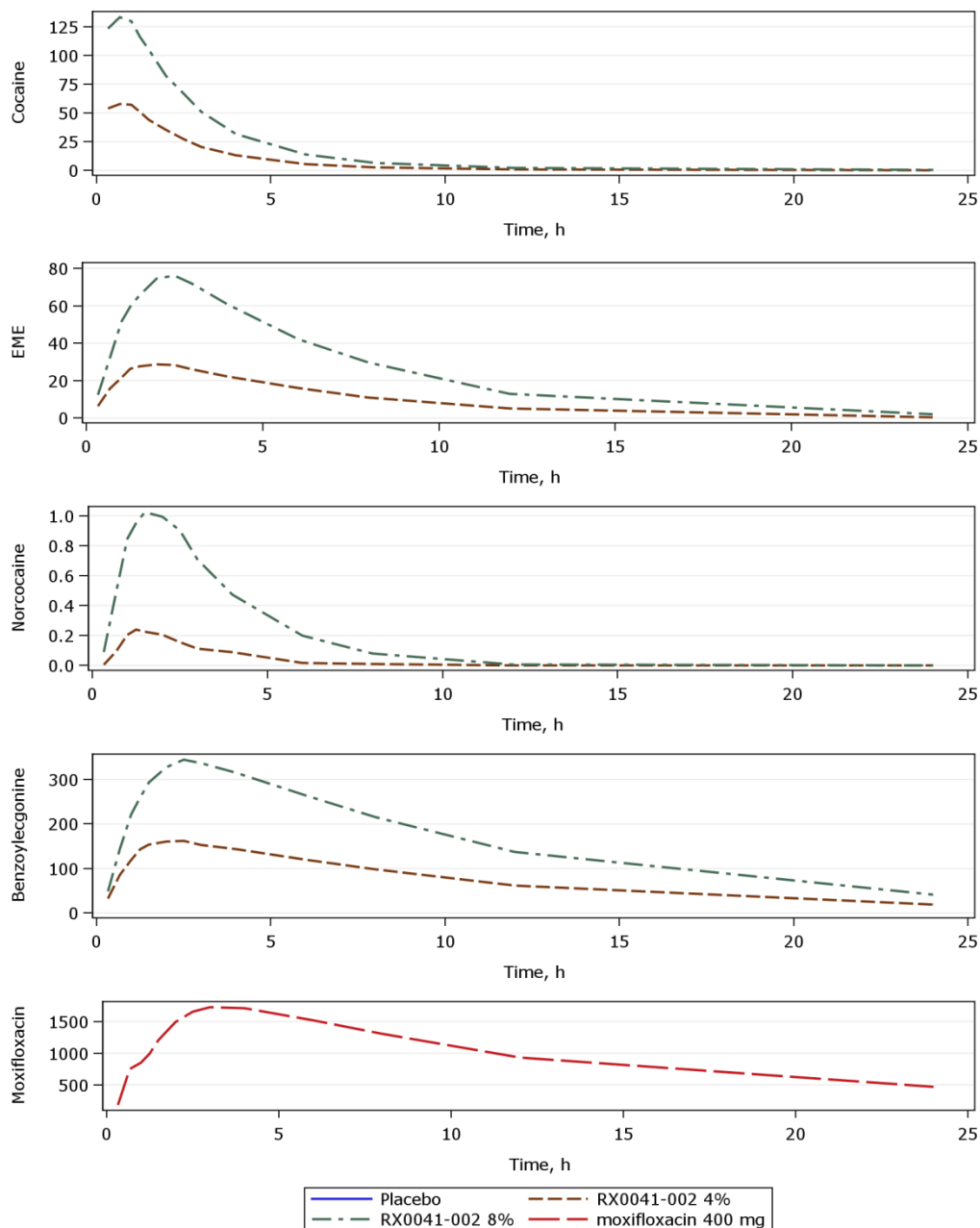
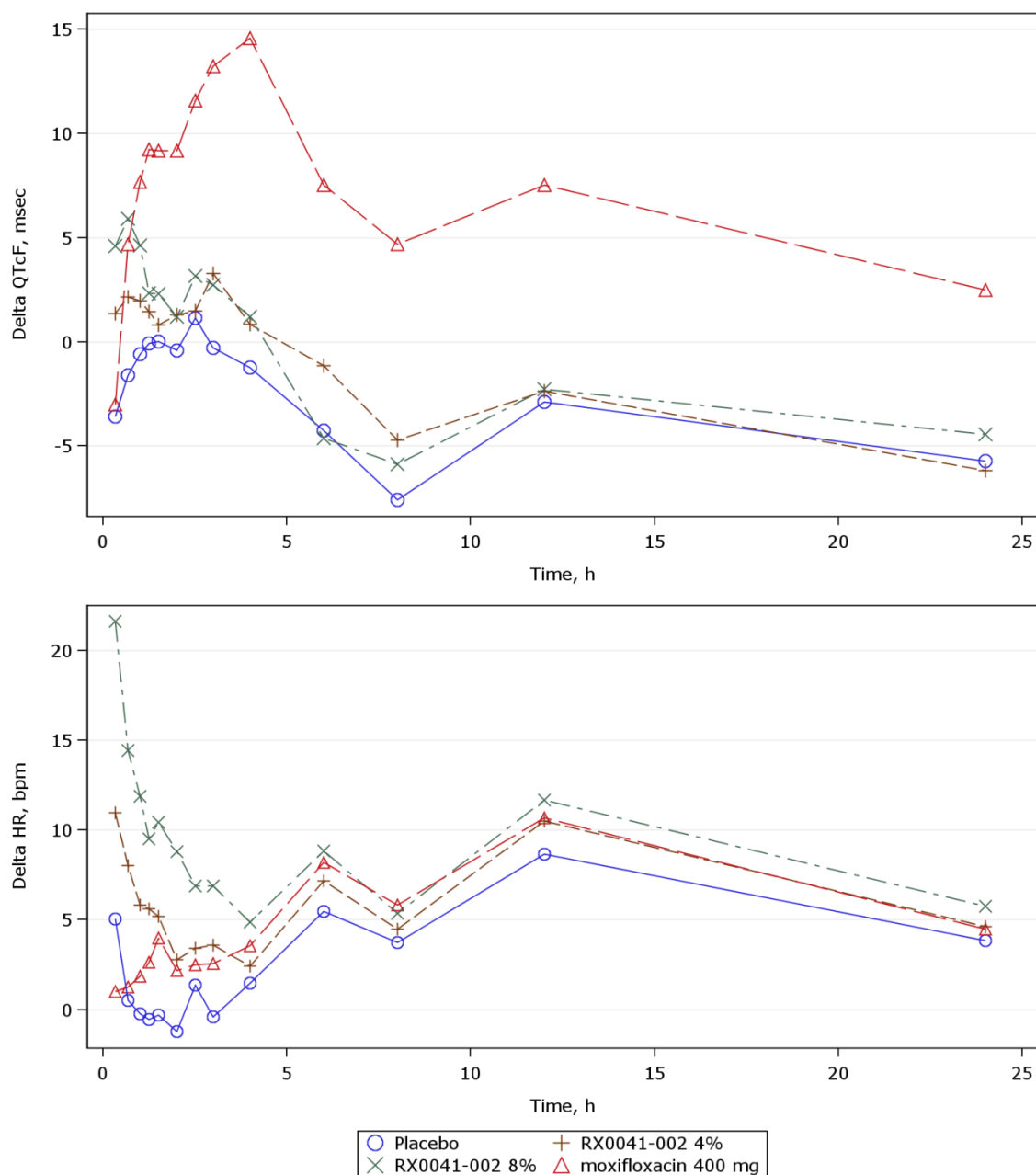


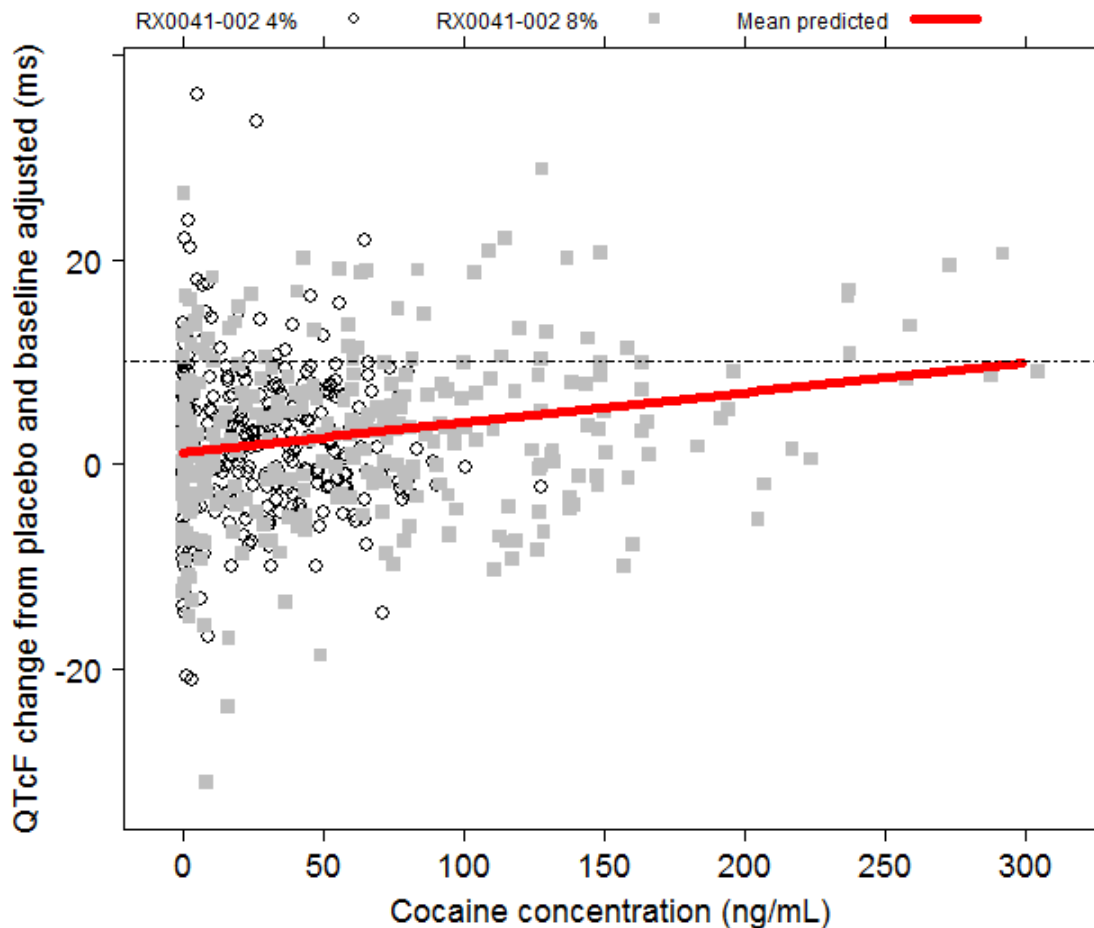
Figure 10 shows the mean delta QTcF and delta HR in subjects with placebo, two dose groups and moxifloxacin. Comparison of Figure 9 and Figure 10 suggests no delay between cocaine concentrations and changes in QTcF and HR.

Figure 10: Mean Δ QTcF-Time and Δ HR-Time Profiles in Subjects with Placebo, Two Dose Groups (4% and 8% Cocaine) and Moxifloxacin



A linear model, similar to that reported by the sponsor, was used to fit the data. The relationship between $\Delta\Delta$ QTcF and cocaine concentrations along with the line based on model fit is visualized in Figure 11.

Figure 11. Relationship Between $\Delta\Delta Q_{TcF}$ and Cocaine Concentrations



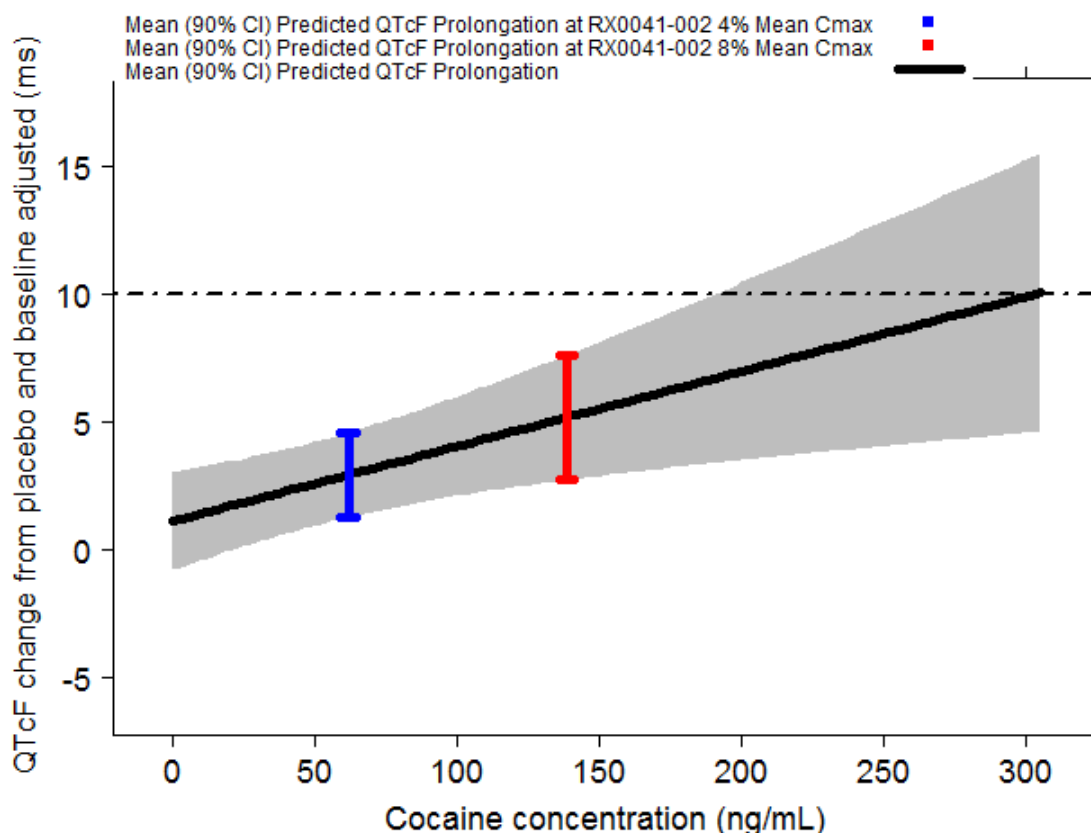
The estimates of final parameters (slope, intercept) are shown in Table 17. The findings are similar to that reported by the sponsor.

Table 17. Exposure-Response Analysis of Cocaine- Associated $\Delta\Delta Q_{TcF}$ Prolongation

Effect	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Intercept	1.1370	1.1181	23.6	1.02	0.3195	0.1	-0.7771	3.0512
CONC	0.02923	0.01171	20.8	2.50	0.0211	0.1	0.009067	0.04940

Based on the linear model used to fit the data, shown in Figure 12 are the predicted $\Delta\Delta Q_{TcF}$ at C_{max} of the two dose groups of cocaine (160 mg equivalent dose using 4% solution and 320 mg equivalent dose using 8% solution).

Figure 12. Mean (90%CI) Predicted $\Delta\Delta$ QTcF Prolongation at Two Dose Levels of Cocaine (4% and 8%)



The predicted mean change in $\Delta\Delta$ QTcF at $C_{\max}$ for the two dose groups is shown in Table 18. The estimates are similar to those reported by the sponsor (Table 4).

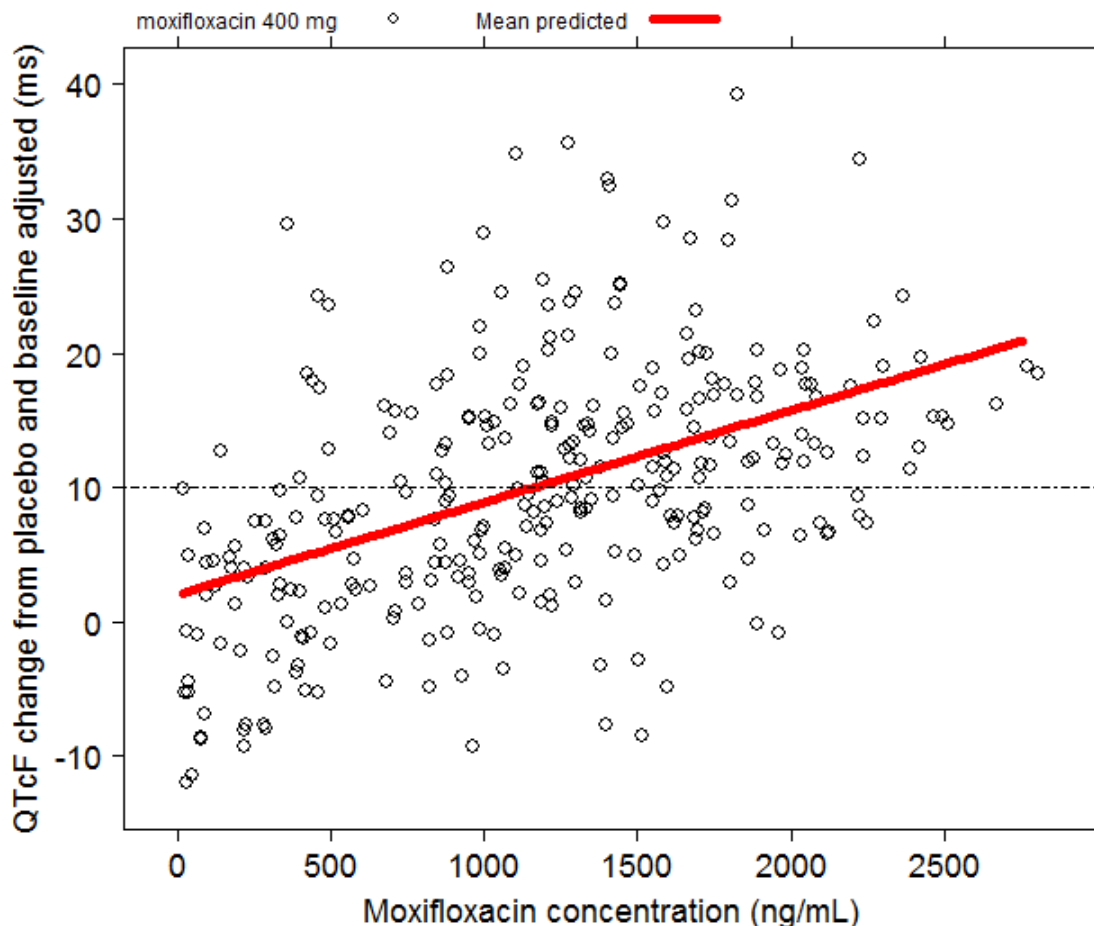
Table 18. Predicted $\Delta\Delta$ QTcF Interval at Geometric Mean Peak Cocaine Concentrations*

Treatment	Conc.	$\Delta\Delta$ QTcF	90% CI
RX0041-002 4%	61.7 ng/mL	2.94	(1.28; 4.6)
RX0041-002 8%	139 ng/mL	5.19	(2.74; 7.64)

The upper bound of the 90% CI for $\Delta\Delta$ QTcF for the two dose groups is less than 10 ms, suggesting that the risk for QT prolongation is low at these exposures.

Figure 13 shows the relationship between $\Delta\Delta$ QTcF and moxifloxacin concentrations.

Figure 13. Relationship Between $\Delta\Delta QTcF$ and Moxifloxacin Concentrations



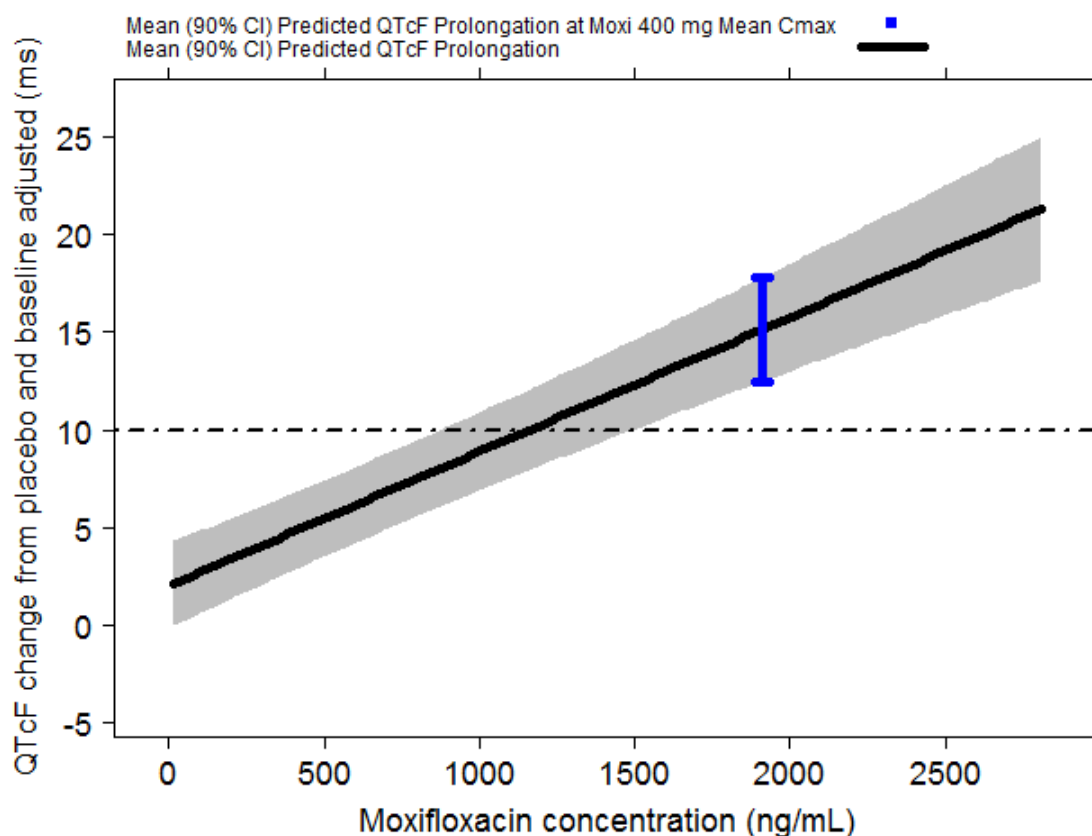
The estimates of final parameters (slope, intercept) are shown in Table 19. The units of slope reported in Table 19 are ms/ μ g/mL. The findings are similar to that reported by the sponsor (Table 5).

Table 19. Exposure-Response Analysis of Moxifloxacin- Associated $\Delta\Delta QTcF$ Prolongation

Solution for Fixed Effects								
Effect	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Intercept	2.0395	1.2701	22.2	1.61	0.1224	0.1	-0.1405	4.2195
CONC	6.8477	0.8507	22.3	8.05	<.0001	0.1	5.3878	8.3077

Based on the linear model used to fit the data, shown in Figure 14 are the predicted $\Delta\Delta QTcF$ at C_{max} of the moxifloxacin group.

Figure 14. Mean (90%CI) Predicted $\Delta\Delta$ QTcF Prolongation in Moxifloxacin Group



The predicted mean change in $\Delta\Delta$ QTcF at $C_{\max}$ for moxifloxacin 400 mg group is shown in Table 20. The estimates are similar to those reported by the sponsor (Table 6)

Table 20. Predicted $\Delta\Delta$ QTcF Interval at Geometric Mean Peak Cocaine Concentrations*

Treatment	Conc.	$\Delta\Delta$ QTcF	90% CI
Moxi 400 mg	1910 ng/mL	15.1	(12.5; 17.8)

The lower bound of the 90% CI for $\Delta\Delta$ QTcF at geometric mean $C_{\max}$ of moxifloxacin is greater than 5 ms indicating that the study has adequate assay sensitivity.

Reviewer's Comments: Overall, the reviewer's findings are similar to those reported by the sponsor. At the two dose levels studied, the risk for QT prolongation is low.

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines, *i.e.*, syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no effect on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	4 mL of 4% cocaine topical solution (160 mg cocaine HCl); administered intranasally via cotton pledgets applied for 20 minutes	
Maximum tolerated dose	> 320 mg [4 mL of 8% cocaine topical solution (320 mg cocaine HCl) was very well tolerated in an efficacy trial]	
Principal adverse events	- Headache, epistaxis, and anxiety were the only AEs reported by more than 1 subject in the 4% RX0041-002 group. - Headache was reported by 3.0% of the 4% RX0041-002 group and 1.1% of the placebo group, epistaxis by 1.0% of the 4% RX0041-002 group and no subjects in the placebo group; - Headache was the only AE that occurred with a $\geq 2\%$ higher incidence in the 4% RX0041-002 group compared to the placebo group. - In the 8% RX0041-002 group, headache (3.0%) and epistaxis (1.0%) were the only AEs reported by more than 1 subject. - No cardiovascular AEs occurred. - In addition to headache, nervous system disorders were limited to dizziness (0%, 0.3%, and 0.4% in the placebo, 4%, and 8% RX0041-002 groups, respectively) and migraine (0%, 0.3%, and 0% in the placebo, 4%, and 8% RX0041-002 groups, respectively).	
Maximum dose tested	Single Dose	4 mL of 4% cocaine topical solution (160 mg cocaine HCl)
	Multiple Dose	Not applicable (single dose regimen)
Exposures Achieved at Maximum Tested Dose	Single Dose	C _{max} : 37.0 ng/mL (CV 46.7%) AUC _{0-inf} : 54.9 ng·hr/mL (CV 43.8%)
	Multiple Dose	Not applicable (single dose regimen)
Range of linear PK	Not tested	
Accumulation at steady state	Not applicable (single dose regimen)	
Metabolites	Benzoylecgonine (BE; inactive), ecgonine methyl ester (EME; inactive), norcocaine (minor, active)	
Absorption	Absolute/Relative Bioavailability	Not known [based on comparison to IV data in literature, absolute BA $\leq 4\%$ (intranasal)]
	T _{max}	0.33 (0.25-1.75) hr for parent - Metabolites were BLQ; no plasma data
Distribution	V _d /F or V _d	V _d /F = 3877 L (CV 32.6%)
	% bound	84-92% at therapeutically relevant concentrations (Edwards and Bowles, 1988; Parker et al., 1995)
Elimination	Route	- Primary route – metabolism (ester cleavage) to BE and EME; 0.07% of intranasal dose recovered unchanged in urine (> 0.53% and > 0.26% of intranasal dose recovered in urine as BE and EME, respectively) - Other routes not known
	Terminal t _{1/2}	1.04 hr for parent (CV 33.7%) - Metabolites were BLQ; no plasma data
	CL/F or CL	CL/F = 3096 L/hr (CV 41.2%)

Intrinsic Factors	Age	No effect of age (22-79 yr)
	Sex	F vs M: C _{max} +16%; AUC _{0-inf} +28% (attributable to differences in body weight between M 82.6 kg and F 61.8 kg)
	Race	Insufficient data to determine
	Hepatic & Renal Impairment	Not known; currently being evaluated in 2 clinical pharmacology studies
Extrinsic Factors	Drug interactions	• Oral alcohol on intranasal cocaine: C _{max} +8%; AUC +6%
	Food Effects	Not applicable; intranasal administration
Expected High Clinical Exposure Scenario	Cocaine HCl Topical Solution, 8% (total dose 320 mg).	
Preclinical Cardiac Safety	Nonclinical cardiac safety studies were not conducted by the Sponsor. Relevant findings from the literature are provided. <i>In Vitro</i> Cocaine blocked human ether-a-go-go-related gene (hERG) potassium channels in HEK 293 cells with a mean IC₅₀ of 4.4 μM (Ferreira et al., 2001). Ecgonine methyl ester (EME) and benzoylecgonine (BE) produced only a minimal block with a mean IC₅₀ of > 1 mM. In humans administered RX0041-002 by intranasal application, the observed plasma C_{max} was 37 ng/mL. Based on a conservative estimate of cocaine free fraction in human serum (0.16; Parker et al., 1995), this equates to an unbound cocaine C_{max} of 5.92 ng/mL. As the hERG study was conducted in the absence of plasma proteins, unbound C_{max} is the more relevant comparator to the observed hERG IC₅₀. Therefore, there is a substantial safety margin for the effects of cocaine on hERG potassium channels; the cocaine IC₅₀ of 4.4 μM (1.33 μg/mL) is 36-fold and 225-fold higher than total and free cocaine C_{max} values, respectively, in humans after administration of RX0041-002. <i>In Vivo</i> The acute effects of cocaine on ECG study parameters were evaluated in dogs (Mehta et al., 2003). A low (1 mg/kg), medium (2 mg/kg) or high (5-7 mg/kg) dose was administered by IV bolus and ECGs were analyzed against a control ECG at 1 through 30 min post-injection. Plasma cocaine levels were assessed within 5-15 min post-injection. Multiple experiments were performed, and ECG changes were seen in some, but not all, experiments at each dose. At 1 mg/kg cocaine, sinus bradychardia, sinus arrhythmia, atrial ectopic, wandering pacemaker, and unifocal ventricular premature complexes were observed. The 2 mg/kg dose generated moderately severe arrhythmias that were of ventricular and supraventricular origin, and atrial flutter and atrial fibrillation were observed in two experiments. In addition to changes seen at lower doses, the dose of 5-7 mg/kg increased electrographic intervals and caused ST-segment elevation (7/10 dogs) as well as serious life-threatening arrhythmias. Three of the dogs developed sustained ventricular tachycardia followed by ventricular flutter-fibrillation and death, whereas in 4 dogs the QT segment reverted to control levels. Blood pressure was not changed at the low dose, increased at the mid dose and decreased at the high dose. The plasma levels of cocaine varied from 220 to 960 ng/mL depending on dose, and mean concentrations are shown in the following Table. Cocaine Dose Plasma Cocaine Concentration Following Intravenous Bolus Injection in Dogs	

	Dose	Dose Effects	Mean Plasma Cocaine Concentration (ng/mL)	Safety Margin to Clinical C_{max} ¹
	Low (1 mg/kg) ²	No effect on blood pressure. Sinus bradychardia, sinus arrhythmia, atrial ectopic, wandering pacemaker, and unifocal ventricular premature complexes	248	6.7
	Medium (2 mg/kg) ³	Blood pressure increased by 17 mmHg; moderately severe arrhythmias that were of ventricular and supraventricular origin, and atrial flutter and atrial fibrillation were observed in two experiments	430	11.6
	High (5-7 mg/kg) ⁴	Blood pressure decreased. At 7mg/kg BP was < 60 mmg (hypotension). Moderately severe ventricular arrhythmias; bigeminy, trigeminy, couplets, salvos. Increased electrographic intervals, ST-segment elevation; life-threatening arrhythmias	840	2.7

¹ mean C_{max} of 37 ng/mL observed after intranasal topical application of RX0041-002

² Low dose: bioequivalent to blood levels attained by sniffing 16-32 mg cocaine

³ Medium dose: bioequivalent to blood levels attained by intranasal sniffing of 32-64 mg cocaine

⁴ High dose: bioequivalent to blood levels attained by intranasal sniffing of 96 mg cocaine

Data Source: [Mehta et al., 2003](#)

Cocaine has a very rapid initial decline and distribution phase across species, which suggests that peak plasma cocaine levels immediately after IV bolus administration in this dog study were likely to have been much higher than those observed at 5-15 minutes post injection. Therefore, the large calculated safety margins (table above) are likely to be significantly underestimated, including that at the low dose (1 mg/kg), which was associated with early, transient, and in most instances, reversible, cardiac responses to cocaine.

Another study ([Beckman et al., 1991](#)) was conducted in anesthetized dogs to evaluate the hemodynamic and electrophysiological effects of cocaine administered as a series of 5 mg/kg IV bolus doses coupled with a continuous infusion of cocaine at 0.2 mg/kg/min for 30-45 min. Hemodynamics and ECG were continuously monitored. Arterial blood was obtained for analysis of cocaine serum levels at baseline and during cocaine infusion, immediately before and at 5 min after each subsequent bolus. All of the animals survived the high-dose infusion period. Cocaine significantly decreased blood pressure.

coronary blood flow and cardiac output; increased PR, QRS, QT and QTc intervals and sinus cycle length as shown in the following table.

Effects of High Repeat-Dose Cocaine on Cardiovascular Parameters

Cardiovascular Parameter	Bolus 1 (5 mg/kg)		Bolus 2 (5 mg/kg)		Bolus 3 (5 mg/kg)	
	Baseline	After	Before	After	Before	After
Mean Arterial Pressure (mm Hg)	103 ± 23	88 ± 30	87 ± 24*	69 ± 21**	65 ± 26**	57 ± 22**
Cardiac Output (L/min)	4.24 ± 1.29	3.06 ± 1.07*	3.03 ± 0.89*	1.98 ± 0.59**	NA	NA
Coronary Blood Flow (mL/min)	16.6 ± 14.1	9.4 ± 7.2*	10.2 ± 8*	6.7 ± 4.2*	7.8 ± 6.1*	3.4 ± 1**
QT (msec)	256 ± 22	317 ± 41*	324 ± 47*	341 ± 42*	346 ± 48*	358 ± 48*
QRS (msec)	57 ± 4	82 ± 11*	69 ± 8**	92 ± 18**	87 ± 19*	98 ± 14*
Cocaine Concentration (µg/mL)	0	4.8 ± 2.2 ^a	4.2 ± 1.8	8.8 ± 3.2 ^a	NA	9.8 ± 2.9 ^a

Data are mean ± SD; NA: not available; *P<0.0001 vs baseline; ** P<0.0001 vs baseline and after bolus

^a 5 minutes post-injection

Data Source: Beckman et al., 1991

Serum cocaine levels increased with successive IV bolus doses, ranging from 4.8 to 9.8 µg/mL from the first through the third bolus injections. Those levels were associated with progressively decreased mean arterial pressure, decreased cardiac output and decreased coronary blood flow, and were associated with ECG changes. These cocaine serum levels provide a safety margin of 130- to 265-fold between high, repeat-dose IV administration and the single, intended clinical dose intranasal drug product (C_{max} 37 ng/mL).

No nonclinical studies were found in an extensive literature search in which cardiovascular (CV) effects of cocaine were evaluated following intranasal administration. However, a large number of additional studies have evaluated cardiac cocaine effects in different species with different routes of administration. Systemic exposures were reported in only a few studies, and based on the review of these studies, it was observed that the onset of CV toxicities occurred at dose levels far in excess of that associated with the RX0041-002 single dose intranasal drug product. Therefore, these studies were not considered relevant to evaluating clinical CV risk with RX0041-002.

Clinical Cardiac Safety	Two clinical studies were conducted as part of the development program for RX0041-002. • Study 2013011, a Phase 3, randomized, double-blind, dose-controlled study of the efficacy and safety of a single topical intranasal dose of either 4% or 8% RX0041-002 or placebo in subjects undergoing a diagnostic procedure or surgery on or through the nasal mucous membranes of either one or both nostrils. The proposed dose of RX0041-002 for labeling is 4% (40 mg/mL); the 8% (80 mg/mL) RX0041-002 dose was included in this study to explore the dosing range, but is not proposed for labeling. • Study 2015016, a Phase 1, open-label study of the systemic PK and safety of a topical solution of 4% RX0041-002 following a single topical intranasal dose to healthy subjects. No cardiac adverse events occurred in either study. Continuous holter monitoring was conducted in the randomized, double-blind study (2013011). Analysis of the heart rate changes from baseline data revealed only minor increases in the active groups versus placebo. These changes did not constitute clinical significance and could be explained by the exposure to study drug and the procedures performed in the active groups. Analysis of the Holter monitor data capturing supraventricular ectopic beats and ventricular ectopic beats change from baseline revealed no differences among the three treatment groups. Intranasal application of a single dose of RX0041-002 modestly increased both blood pressure and heart rate. Mean changes from baseline in systolic and diastolic blood pressure and heart rate were larger in the 4% and 8% RX0041-002 groups compared to the placebo group starting at 7 to 12 minutes postdose through 72 minutes postdose. The largest mean change from baseline for systolic and diastolic blood pressure occurred at 25 to 30 minutes postdose. At 25 to 30 minutes postdose, mean change from baseline for systolic/diastolic blood pressure was 4.5/4.2 mmHg in the placebo group, 9.6/8.4 mmHg in the 4% RX0041-002 group, and 7.1/7.3 mmHg in the 8% RX0041-002 group. The largest mean increase in heart rate was -0.2 bpm in the placebo group, 4.9 bpm in the 4% RX0041-002 group, and 2.1 bpm in the 8% RX0041-002 group at 19 to 24 minutes' post dose.
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/s/

VENKATESH A BHATTARAM
04/20/2017

DHANANJAY D MARATHE
04/20/2017

JANELLE E CHEN
04/20/2017

QIANYU DANG
04/20/2017

MICHAEL Y LI
04/20/2017

DEVI KOZELI on behalf of CHRISTINE E GARNETT
04/24/2017
Signing for Christine as she is on leave

Controlled Substance Staff (CSS) Filing Checklist for NDA

NDA Number: 209,963

Applicant: (b) (4)

Date: Feb 6, 2017

Drug Name: Cocaine 4% solution **IND Number:** 118,527

Checklist	Yes	No	NA	Comment
Did CSS participate in previous review of this drug?	x			CSS had no concerns about a Phase 3 study (July 2013)
Abuse potential assessment is required if any of the following are true for a drug¹²:				
It affects the CNS	x			
It is chemically or pharmacologically similar to other drugs with known abuse potential	x			
It produces psychoactive effects such as sedation, euphoria, and mood changes	x			
Is the drug a new molecular entity?		x		Cocaine has been a Sch. II drug since 1970
Is this a new or novel drug formulation?³	x			4% solution (40 mg/ml) for local anesthesia via nasal cavities
Content of NDA abuse potential section:⁴				
<i>Module 1: Administrative Information and Prescribing Information</i> 1.11.4 Multiple Module Information Amendment contains:				
• A summary, interpretation, and discussion of abuse potential data provided in the NDA.		x		
• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.		x		
• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA		x		Sponsor states product is Sch. II in proposed drug label
<i>Module 2: Summaries</i> 2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.				
<i>Module 3: Quality</i> 3.2.P.1 Description and Composition of the Drug Product - extraction of the drug substance (solvents, pH, or mechanical manipulation).	x			
Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?		x		
3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.				
Is this an extended release or abuse-deterrent formulation?		x		
<i>Module 4: Nonclinical Study Reports</i> 4.2.1 Pharmacology		x		

1 21 CFR 314.50(d)(5)(vii1): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdose is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21USC811(f) Abuse potential: If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

Controlled Substance Staff (CSS) Filing Checklist for NDA

Checklist	Yes	No	NA	Comment
4.2.1.1 Primary Pharmacodynamics - binding profile		X		
Are in vitro receptor binding studies included?		X		
Are functional assays included?		X		
Animal Behavioral and Dependence Pharmacology				
Was a self administration study conducted?		X		
Was a conditioned place preference study conducted?		X		
Was a drug discrimination study conducted?		X		
Was a physical dependence study conducted?		X		
<i>Module 5: Clinical Study Reports</i>				
5.3.5.4 Other Study Reports				
Human abuse potential study:				
Was a human abuse potential study conducted?		X		
Are all the primary data included in the NDA?			X	
Is a Statistics consult necessary?			X	
Preparation of study drug treatments			X	
Other Clinical trials:				
Are all abuse/misuse Case Report Forms submitted?			X	
Labeling				
Section 9.0 text proposed?	X			
Postmarketing activities [PMRs, PMCs, REMS]			X	
Scheduling activities				
Is the drug already scheduled?	X			Schedule II

Is NDA FILEABLE from a CSS perspective?

Yes. This is a 505(b)2 application and does not contain abuse potential studies.

CSS Reviewer: Katherine Bonson, Ph.D. Date: February 6, 2017

CSS Reviewer:: Silvia Calderon, Ph.D. Date: February 6, 2017

CSS Director: Michael Klein, Ph.D. Date: February 6, 2017

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/s/

KATHERINE R BONSON
02/06/2017

SILVIA N CALDERON
02/06/2017

MICHAEL KLEIN
02/07/2017

Controlled Substance Staff (CSS) Filing Checklist for NDA

NDA Number: 209,963

Applicant: (b) (4)

Date: Jan 25, 2017

Drug Name: Cocaine 4% solution **IND Number:** 118,527

Checklist	Yes	No	NA	Comment
Did CSS participate in previous review of this drug?	x			CSS had no concerns about a Phase 3 study (July 2013)
Abuse potential assessment is required if any of the following are true for a drug¹²:				
It affects the CNS	x			
It is chemically or pharmacologically similar to other drugs with known abuse potential	x			
It produces psychoactive effects such as sedation, euphoria, and mood changes	x			
Is the drug a new molecular entity?		x		Cocaine has been a Sch. II drug since 1970
Is this a new or novel drug formulation?³	x			4% solution (40 mg/ml) for local anesthesia via nasal cavities
Content of NDA abuse potential section:⁴				
<i>Module 1: Administrative Information and Prescribing Information</i> 1.11.4 Multiple Module Information Amendment contains:				
• A summary, interpretation, and discussion of abuse potential data provided in the NDA.		x		
• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.		x		
• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA		x		Sponsor states product is Sch. II in proposed drug label
<i>Module 2: Summaries</i> 2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.				
<i>Module 3: Quality</i> 3.2.P.1 Description and Composition of the Drug Product - extraction of the drug substance (solvents, pH, or mechanical manipulation).	x			
Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?		x		
3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.				
Is this an extended release or abuse-deterrent formulation?		x		
<i>Module 4: Nonclinical Study Reports</i> 4.2.1 Pharmacology		x		

1 21 CFR 314.50(d)(5)(vii1): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdose is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21USC811(f) Abuse potential: If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

Controlled Substance Staff (CSS) Filing Checklist for NDA

Checklist	Yes	No	NA	Comment
4.2.1.1 Primary Pharmacodynamics - binding profile		X		
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Animal Behavioral and Dependence Pharmacology				
Was a self administration study conducted?		X		
Was a conditioned place preference study conducted?		X		
Was a drug discrimination study conducted?		X		
Was a physical dependence study conducted?		X		
Module 5: Clinical Study Reports				
5.3.5.4 Other Study Reports				
Human abuse potential study:				
Was a human abuse potential study conducted?		X		
Are all the primary data included in the NDA?			X	
Is a Statistics consult necessary?			X	
Preparation of study drug treatments			X	
Other Clinical trials:				
Are all abuse/misuse Case Report Forms submitted?			X	
Labeling				
Section 9.0 text proposed?	X			
Postmarketing activities [PMRs, PMCs, REMS]			X	
Scheduling activities				
Is the drug already scheduled?	X			Schedule II

Is NDA FILEABLE from a CSS perspective?

Yes. This is a 505(b)2 application and does not contain abuse potential studies.

CSS Reviewer: Katherine Bonson, Ph.D. Date: January 25, 2017

CSS Reviewer:: Silvia Calderon, Ph.D. Date: January 25, 2017

CSS Director: Michael Klein, Ph.D. Date: January 25, 2017

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/s/

KATHERINE R BONSON
01/25/2017

SILVIA N CALDERON
01/25/2017

MICHAEL KLEIN
01/26/2017

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 # 209963 BLA#	NDA Supplement #: S- BLA 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: (b) (4) (proposed) Established/Proper Name: Topical Cocaine, 4% Dosage Form: Solution Strengths: 4%, 40 mg/mL Route of Administration: Topical		
Applicant: (b) (4) Agent for Applicant (if applicable): Melissa Goodhead, (b) (4)		
Date of Application: November 23, 2016 Date of Receipt: November 23, 2016 Date clock started after Unacceptable for Filing (UN): n/a		
PDUFA Goal Date: September 23, 2017		Action Goal Date (if different): September 20, 2017
Filing Date: January 22, 2017		Date of Filing Meeting: January 12, 2017
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 ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication: Induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team		☐ 351(a) ☐ 351(k)

Review Classification: <i>The application will be a priority review if:</i> - 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? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ 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 <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ 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: 118527				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
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?	☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	☒	☐		This is a 505(b)(2) to literature.
• 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)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☒																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> <i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☒		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If no, include template language in the 74-day letter. Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)] Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.	☐	☐		N/A																

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)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ 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 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐	☐	☒	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> 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)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

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)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☒	☐		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒	☐		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	

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)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i> December 5, 2016	☐	☐	☐	Although already Schedule II, the Sponsor was informed at pre-NDA that the NDA submission must include a proposal for the scheduling of the drug product under the Controlled Substances Act. Other data in the NDA should include abuse & diversion information collected from the clinical studies.
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage 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.</i>	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i>	☐	☒		

2

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

3

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

Version: 12/05/2016

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	Submitted in a separate submission, and under review by OSE.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☐	☒	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in Physician Labeling Rule (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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	MHT consulted to review December 5, 2016.
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? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☐	☒	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	December 5, 2016
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	December 5, 2016
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	QT-IRT consulted January 4, 2017.
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date: July 14, 2015	☒	☐		Minutes dated 8/14/2105
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 12, 2017

BACKGROUND: This is an application for Topical Cocaine, a marketed, unapproved drug.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Leah Crisafi		Y
Division Director/Deputy	Sharon Hertz		Y
	Rigoberto Roca		Y
Office Director/Deputy	n/a		N
Clinical	Reviewer:	Renee Petit-Scott	Y
	TL:	Leah Crisafi	Y
Clinical Pharmacology	Reviewer:	Deep Kwatra Wei Qiu (Filing Only)	Y Y
	TL:	Yun Xu	Y
• Pharmacometrics	Reviewer:	n/a	N
Biostatistics	Reviewer:	Feng Li	Y
	TL:	David Petullo	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Belinda Hayes	Y
	TL:	Newton Woo Daniel Mellon	Y Y
Product Quality (CMC) Review Team:	ATL:	Ciby Abraham	Y
	RBPM:	Steven Kinsley	Y
• Drug Substance	Reviewer:	Sam Bain Donna Christner	N N
• Drug Product	Reviewer:	Valerie Amspacher	Y
• Process	Reviewer:	Tarun Mehta Ubrani Venkataram	N N
• Microbiology	Reviewer:	Denise Miller	N
• Facility	Reviewer:	Whenzheng Zhang Derek Smith	N N
• Biopharmaceutics	Reviewer:	n/a	N
• Other (e.g., Branch Chiefs, EA Reviewer)	Julia Pinto (Branch Chief)		N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Koung Lee	Y
	TL:	n/a	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	James Schlick	Y
	TL:	Vicky Borders-Hemphill	N
OSE/DRISK (REMS)	Reviewer:	Kimberly Lehrfeld	N
	TL:	n/a	N

Bioresearch Monitoring (OSI)	Reviewer:	John Lee	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	Kit Bonson	Y
	TL:	n/a	N
Other reviewers/disciplines			
Maternal Health Team	Reviewer:	Jane Liedtka	N
	TL:	Miriam Dinatale	N
Other attendees	Astrid Lopez-Goldberg		Y
	Sally Loewke		Y
	Kerri-Ann Jennings		Y
	David Tyler Coyle		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? 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 applicant is relying on information in the published literature for nonclinical pharmacology, reproductive toxicology, and carcinogenicity studies.
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:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined 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: IR to be sent after the filing meeting. Clinical pharmacology study site(s) inspections(s) needed?	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter ☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: IRs for microbiology and other OPQ disciplines will be sent at a future date by the CMC RPM.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> 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

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ 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, Director, DAAAP Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): April 18, 2017 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Wrap-Up – August 17, 2017 Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ 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 ADRAAs completed: April 2016

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

/s/

DIANA L WALKER
01/25/2017

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

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

Application: NDA 209963

Application Type: New NDA

Proprietary Name: (b) (4) (proposed)

Established/Proper Name: Topical Cocaine, 4%

Dosage Form: Solution

Strengths: 4%, 40 mg/mL

Route of Administration: Topical

Applicant: (b) (4)

Receipt Date: November 23, 2016

Goal Date: PDUFA = September 23, 2017, **Goal Action Date** – September 20, 2017

1. Regulatory History and Applicant's Main Proposals

(b) (4) has submitted a new NDA for Topical Cocaine 4%, 40 mg/mL solution, indicated for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

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

In addition, the following labeling issues were identified:

(b) (4)

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in via email with other labeling revisions from the review team.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

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 for HL format.

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. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• 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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

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

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS**”

Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015."

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. 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 (or will have)** 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** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. 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:
- YES** 26. The same title 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** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. 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 (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. 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)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 35. All text in the BW should be **bolded**.

Comment:

- YES** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“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:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

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

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

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 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

DIANA L WALKER
01/19/2017