CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209575Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 6, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 209575
Product Name and Strength:	Numbrino (cocaine hydrochloride) nasal solution, 4% (40 mg/mL) and 10% (b) (4))
Applicant/Sponsor Name:	Cody Laboratories
OSE RCM #:	2019-1350-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received via email to Shelly Kapoor on January 3, 2020 for Numbrino. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for Numbrino (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] and some labeling recommendations from the Office of Pharmaceutical Quality (OPQ) that were related to lot number format, expiration date format, and clarification of package type terms. To address the lot number and expiration date format recommendation, the Applicant submitted an example image that is a representation of the product identifier format that will be included on the Numbrino labeling.

[a] Johnson, C. Label and Labeling Review Memo for Numbrino (NDA 209575). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 23. RCM No.: 2019-1350.

2 CONCLUSION

We find the example image that includes the product identifier acceptable from a medication error perspective. Furthermore, the Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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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 23, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209575
Product Name and Strength:	Numbrino (cocaine hydrochloride) topical solution, 4% (40 mg/mL) and 10% ((b) (4))
Applicant/Sponsor Name:	Cody Laboratories
OSE RCM #:	2019-1350
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant resubmitted revised container labels and carton labeling received on August 9, 2019 for Numbrino. The Applicant also submitted the proposed Prescribing Information (PI). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised labels and labeling as well as the PI for Numbrino (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[ab]

2 REGULATORY HISTORY

Cody submitted their original NDA on September 17, 2017. We reviewed the labeling and provided recommendations to Cody. Cody submitted revised labeling on May 30, 2018 and we found the revised labeling acceptable. However, the application received a Complete Response (CR) on July 20, 2018 due to clinical, nonclinical, and regulatory deficiencies. On June 21, 2019, Cody submitted their responses to the deficiencies included in the CR letter as a Class 2

[a] Schlick, J. Label and Labeling Review for Numbrino (NDA 209575). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 19. RCM No.: 2017-1951.

[b] Schlick, J. Label and Labeling Review for Numbrino (NDA 209575). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 25. RCM No.: 2017-1951-1.

Resubmission. While reviewing the labeling, we noted that it was the same labeling that was submitted as part of the original submission on September 21, 2017, which did not include our previous recommendations. We sent an Information Request (IR) to Cody to confirm which proposed labeling (submitted on May 30, 2018 or June 21, 2019) they would like for us to review. In their response, Cody stated that the labeling from the original submission was inadvertently included in the June 21, 2019 resubmission and that the labeling previously submitted on May 30, 2018 is the proposed labeling.[c]

3 CONCLUSION

The PI, container labels and carton labeling are unacceptable from a medication error perspective. We provide our rationale for concern and recommendations to address these concerns in Section 4 and Section 5 below.

4 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information (PI), Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	(b) (4) [redacted]	While this product is indicated for topical use, we note that it is specifically administered into the nostril. We also note that the currently approved cocaine hydrochloride product, Goprelto (NDA 209963), is also indicated for local anesthesia of the nasal mucosa and has the route of administration listed as "nasal solution".	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate dosage form for this product. If OPQ determines the appropriate dosage form is "nasal solution", then the dosage form should be revised in the PI and on the container labels and carton labeling.

[c] Information Amendment Response Document for Numbrino (NDA 209575). Cody (WY): Cody Laboratories, Inc.; 2019 AUG 09. Available from: \\cdsesub1\evsprod\nda209575\0027\m1\us\111-information-amendment\resp-doc.pdf

5 RECOMMENDATIONS FOR CODY LABORATORIES

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

Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	(b) (4)	This statement is inconsistent with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement to read: Recommended Dosage and Administration: See Prescribing Information.

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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA # 209575
Submission Number	# 025
Submission Date	6/21/2019
Date Consult Received	7/2/2019
Clinical Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 02/21/2018 in DARRTS (link);
- Previous QT-IRT review dated 05/31/2018 in DARRTS (link);
- Previous QT-IRT review dated 06/01/2018 in DARRTS (link);
- Sponsor's clinical study report # (SN0025 / SDN025; link)
- Investigator's brochure Ver 3.1 (SN0001 / SDN001; link);
- Sponsor's propose product label (SN0025 / SDN025; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0002 / SDN002; link).

1 SUMMARY

Concentration-dependent QTc prolongation effect of Numbrino® (cocaine hydrochloride solution) was detected in this QT assessment. Large increases in heart rate were also detected, which confounds the estimate of the QTc interval.

The effect of cocaine hydrochloride was evaluated in a randomized, cross-over, positive- and placebo-controlled thorough QT study (Study # COCA-QT-01). The highest dose evaluated was 400 mg (single-dose), which covers the maximum therapeutic dose (section 3.1). The data were analyzed using exposure-response analysis as the primary analysis, which showed that cocaine hydrochloride is associated with significant QTc prolonging effect at the maximum therapeutic dose (cocaine hydrochloride 10% solution; 400 mg single dose), see Table 1 for overall results. Because the peak concentrations of cocaine observed in the present study (mean: 285 ng/mL; range: 162-457 ng/mL) were lower compared to those observed in other study (434 ng/mL; range: 175-1273 ng/mL), the QT effects of cocaine were predicted from the exposure-response model at C_{max} values obtained from Study LNT-P6-733.

Table 1: The Point Estimates and the 90% CIs – Drug Effect (FDA Analysis)

ECG parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (ms)	90% CI (ms)
QTc	Cocaine hydrochloride 4% solution* (160 mg single dose)	127.1	4.1	(2.6, 5.5)
QTc	Cocaine hydrochloride 10% solution* (400 mg single dose)	273.5	9.5	(6.4, 12.5)
QTc	Cocaine hydrochloride 4% solution (160 mg single dose)	142.7	4.7#	(3.0, 6.2)#
QTc	Cocaine hydrochloride 10% solution (400 mg single dose)	433.5	15.4#	(10.6, 20.1)#

**The liquid formulation of cocaine hydrochloride solution (4 mL) was applied to the mucous membranes of nasal cavities using pledgets (1 mL/pledget; 4 pledgets) for 20 min. #The predicted effects at similar dose level based on the Cmax from previous clinical study (Study LNT-P6-733).*

Cocaine caused large increases in heart rate (Table 2). As a result, the estimate of drug-induced QTc prolongation is confounded by the heart rate increases. The sponsor's use of an individual corrected QTc is not appropriate because the baseline data, upon which the correction is based, do not cover at least the heart rate range observed in study drug.

Table 2 The Point Estimates and the 90% CIs for HR (FDA Analysis)

ECG parameter	Treatment	Time (h)	ΔΔHR	90% CI
HR	Cocaine hydrochloride 4% solution (160 mg single dose)	0.5	11.6	(9.8, 13.5)
HR	Cocaine hydrochloride 10% solution (400 mg single dose)	0.5	20.2	(18.3, 22.0)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Although this product will be administered as a single dose in a hospital setting and QTc prolongation is transient, we suggest that the sponsor includes a precautionary statement for QTc prolongation in high risk patients who will use the 10% solution. High risk patients include those patients with a history of risk factors for Torsades de Pointes, including a history of heart failure, hypokalemia, or family history of long QT syndrome or sudden death at young age, or clinically significant ECG abnormalities.

The sponsor could consider a recommendation for checking QTc before initiating treatment with 10% solution and treat only those patients with normal values (i.e., QTc <450 ms). We also recommend the sponsor includes a precautionary statement on the concomitant use with other QT prolonging medications.

2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 from the QT-IRT. Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of cocaine hydrochloride topical solution (4% and 10%) on the QTc interval was evaluated in a randomized, positive- and placebo-controlled four-period crossover thorough QTc study in 32 healthy subjects. [redacted]

Numbrino is associated with concentration-dependent QTc prolongation. Based on the concentration-QTc relationship, the mean placebo corrected change from the baseline QTcF (90% two-sided upper confidence interval) are 4.7 ms (6.2 ms) and 15.4 ms (20.1 ms) at peak concentrations of 143 ng/mL (corresponds to 4% single dose, 160 mg) and 434 ng/mL (corresponds to 10% single dose, 400 mg), respectively. The estimates of the QTcF interval are confounded by increased heart rates.

Numbrino is associated with increases in heart rate. The mean placebo corrected change from baseline heart rate (90% two-sided upper confidence interval) are 12 (14) bpm and 20 (22) bpm for the 4% and 10%, respectively.

The sponsor utilized concentration-QTc model to predict the QT effect at the peak concentrations observed in the present study. However, the peak concentrations of cocaine observed in the present study were lower in comparison to those observed in previous study (Study LNT-P6-733). The QT effects of cocaine were predicted at the peak concentrations of cocaine based on the PK data from previous clinical study.

A large increase in heart rate (i.e. >10 bpm) was observed in 400 mg treatment group. These changes in heart rate can bias the evaluation of QT prolonging effect.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Cody Labs Inc. (Lannett Company, Inc.) is developing topical solution of cocaine hydrochloride for the introduction of local anesthesia during diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. Cocaine hydrochloride is a synthetic tropane alkaloid ester with local anesthetic properties. Previously, cocaine hydrochloride nasal solution (4% Goprelto®; 160 mg/4 mL) is approved for the induction of local anesthesia (NDA-209963 by Genus Lifesciences; Dec-2017) with maximum therapeutic dose of 160 mg. Although no clinically relevant QTc

prolongation was observed at the highest clinically relevant concentrations with a single therapeutic dose of the nasal solution, the peak concentrations were considerably lower (43 ng/mL *vs*. 434 ng/mL) than those observed with the product (400 mg dose; 10% solution).

The topical product is formulated as aqueous solution (Numbrino®) containing cocaine hydrochloride 40 mg/mL (4%: 160 mg/4 mL or 400 mg/10 mL; bottle) or (b) (4) (10%: 400 mg/(b) (4) bottle). This liquid formulation is intended for application to the mucous membranes of nasal cavities using cotton or rayon applicator pledgets (1 mL/pledget; 1 to 2 pledgets per nostril; to be retained for 20 minutes). The maximum recommended dose is 400 mg (4 pledgets × 1 mL × 100 mg) with up to 4 pledgets (2 pledgets per nostril) per procedure. The product is intended for one-time (single dose) use. During the development, the maximum studied dose was 400 mg (single dose/ single use) and maximum tolerated dose was not identified. The peak concentrations of 142.7 (CV:45%) and 433.5 (CV:49%) ng/mL were observed with single administration of 4% and 10% cocaine hydrochloride solution, respectively (Study LNT-P6-733).

Previously, the QT-IRT reviewed the sponsor's substitution request for thorough QT study (Dt: 09/21/2017; SN0001) under NDA-209575. The sponsor submitted ECG data collected in three clinical studies (2 phase 3 studies COCA4vs10-001 & -002 in patients and 1 healthy subject study # LNT-P6-733). However, the submitted data were not found to be adequate as the ECG collection in these studies did not include the time for peak cocaine concentrations (Tmax ~ 0.5 h).

Moreover, no nonclinical in vitro or in vivo QT studies were performed by the Sponsor under the ICH S7B guidance. The sponsor claimed that single dose (single use) regimen is not expected to have any significant QT or QTc interval prolongation. However, considering the available literature data indicate that cocaine can potentially inhibit the hERG potassium channel and prolong the QTc interval (possibly confounded by increase in heart rate; NDA-209963; Haigney et al. 2006), the QT-IRT did not agree with the sponsor's conclusion.

Subsequently, the sponsor submitted the study protocol for their dedicated QT study (Study # COCA-QT-01; LNT-P6-741). In general, the study design was acceptable to the QT-IRT and the response included general advice to the sponsor such as heart-rate increase, exposure-response modeling, and data submission. Subsequently, an addendum was filed due to safety concerns associated with higher dose as well as concerns with interpretability with the supratherapeutic dose (Dt: 06/01/2018). Based on feedback from the review division, it was recommended to change the supratherapeutic dose to the lowest therapeutic dose strength (4%, 160 mg). Thus, it was recommended that the sponsor replaces the supratherapeutic dose with the therapeutic dose (4%, 160 mg) in the study due to the anticipated changes in heart rate.

Recently, the sponsor completed their dedicated QT study in healthy subjects (n=32) using concentration-QT as a primary analysis. This was a randomized, positive- and placebo-controlled, 4-treatment, 4-period, 8-sequence, single-dose, crossover study. Subjects received 1) placebo, 2) moxifloxacin 400 mg tablet, 3) cocaine hydrochloride topical solution, 4 mL of 4% (160 mg dose; therapeutic dose), and 4) cocaine hydrochloride topical solution, 4 mL of 10% (400 mg dose, maximum therapeutic dose) with washout period of ≥ 5 days using a double Williams Latin square design. Replicate 12-lead ECGs were

collected on Days -1 (Study Days -1, 5, 10, 15), 1 (Study Days 1, 6, 11, 16) of each treatment period. PK samples were collected at predose (0.25 h), 0.08, 0.17, 0.25, 0.33 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 h following the start of each treatment administration.

Cocaine is known to increases heart rate and blood pressure and it can produce coronary and peripheral vasospasm. Cocaine has also been reported to prolong the QT interval. Cocaine use has been associated with myocardial ischemia, coronary artery spasm, acute myocardial infarction, acute stroke, congestive heart failure, aortic dissection, supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. The peak concentrations of 127.1 ng/mL and 273.5 ng/mL were observed with single administration of 4% and 10% cocaine hydrochloride solution, respectively (Study # COCA-QT-01). The peak concentrations of cocaine observed in the present study were lower in comparison to those expected (Section 4.5).

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

Sponsor's analysis for both QTcI and QTcF are presented at section 11.5.2 of study report. The corresponding estimates and confidence intervals are listed in Table 14.1.6.1 and Table 14.1.6.1 of expert cardiac safety report. The largest upper limits of 90% CI on ΔQTcF mean differences between cocaine hydrochloride 4% and placebo, and cocaine hydrochloride 10% and placebo are 10.9 ms and 15.9 ms, respectively. The largest upper limits on ΔΔQTcI for 4% and 10% strengths are 10.4 and 13.8 ms, respectively.

The results of the reviewer's analyses are similar to the sponsor's results based on QTcF. The FDA review use QTcF because the difference on ranges of HR observed pre- and post-dose. Please see section 4.1 for details. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin. Please see section 4.5.1 for reviewer's analysis.

3.2.1.1.1 QT bias assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

No subject's QTcF was above 450 ms. No subject's ΔQTcF was above 60 ms.

The results of the reviewer's analyses are similar to the sponsor's results. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

The Safety Population included all 32 randomized subjects.

No SAEs and no deaths were reported during the study. Four subjects (12.5%) were prematurely discontinued, of which 1 subject was prematurely discontinued after

administration of cocaine hydrochloride 10% solution in Period 2 due to a mild AE of elevated ALT.

Five subjects reported cardiac-related AEs in the cocaine treatment arms, and included palpitations (3 subjects), sinus tachycardia (1 subject) and tachycardia (1 subject).

Reviewer's comment: AEs suggestive of proarrhythmic potential based on the ICH E14 Guideline (i.e., seizure, ventricular fibrillation and flutter, torsades de pointes, and AEs consistent with sudden death) were not reported. Two subjects reported mild syncope, 1 subject each in the moxifloxacin and cocaine 4% arms. The AEs occurred during the follow-up period and were not considered related to treatment by the investigator.

3.2.4 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between cocaine plasma concentration and ΔQTcI (change from baseline in QTcI) using a linear mixed-effects approach.

The sponsor's model included ΔQTcI as dependent variable, plasma concentration as a continuous covariate (i.e., 0 for placebo), centered baseline QTcI (i.e., baseline QTcI for individual subject at each post-dose time point subtracting the population mean baseline QTcF for all subjects and all post-dose time points) as an additional covariate, and study treatment (active = 1 or placebo = 0) and time (i.e., time point) as categorical factor, and a random intercept and slope per subject.

The sponsor's model predicted ΔΔQTcI for the cocaine hydrochloride 4% dose at mean Cmax 127 ng/mL was 3.9 ms (90% CI upper: 5.0 ms). The predicted ΔΔQTcI for the cocaine hydrochloride 10% dose at mean Cmax 274 ng/mL was 8.1 ms (90% CI upper: 10.5 ms).

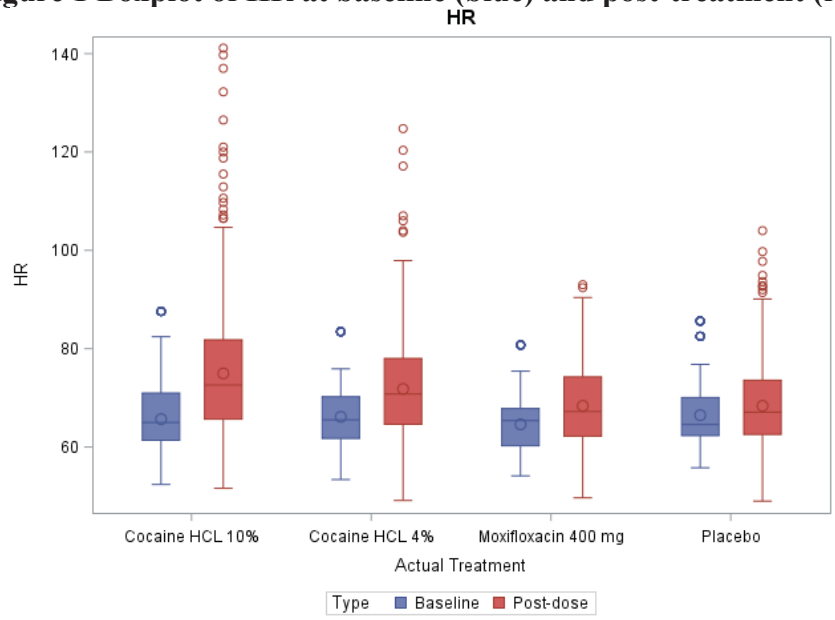
However, the peak concentrations of cocaine observed in the present study are lower in comparison to those observed in previous clinical studies. The FDA reviewers do not agree with the sponsors conclusion as the positive concentration-QTc relationship fails to exclude small effect at the maximum therapeutic dose levels, based on the peak concentrations of cocaine observed in the previous clinical studies. Please see section 4.5 for exposure response analysis performed by the FDA reviewers.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

Considering cocaine's known effects on autonomic tone, the sponsor used QTcI for the primary analysis. As expected the current study showed a rapid and large increase in heart rate (see section 4.3.2). The FDA reviewer used QTcF as the primary endpoint because the range of pre-dose HR does not cover the range of postdose HR as shown in Figure 1.

Figure 1 Boxplot of HR at baseline (blue) and post-treatment (red)



4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not applicable

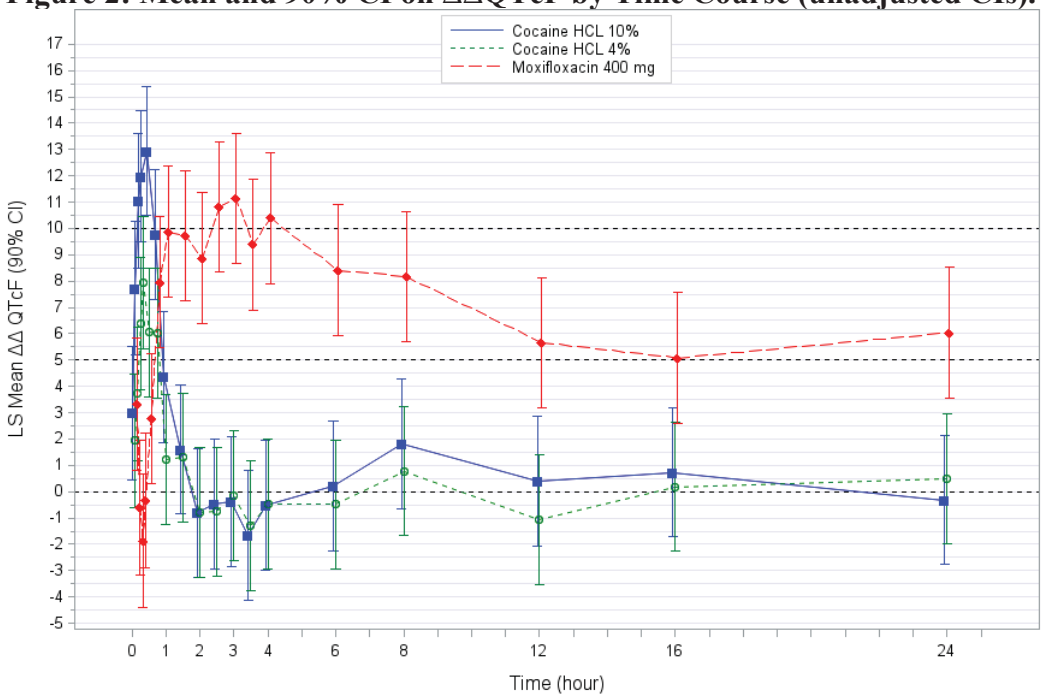
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used linear mixed-effects model to analyze the ΔQTcF effect. The model includes actual treatment, time, time-by-treatment interaction, sequence, and period as fixed effects. Baseline values are also included in the model as a covariate. The largest upper limits of 90% CI on ΔQTcF mean differences between cocaine hydrochloride 4% and placebo, and cocaine hydrochloride 10% and placebo are 10.5 ms and 15.4 ms, respectively.

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 2: Mean and 90% CI on ΔΔQTcF by Time Course (unadjusted CIs).



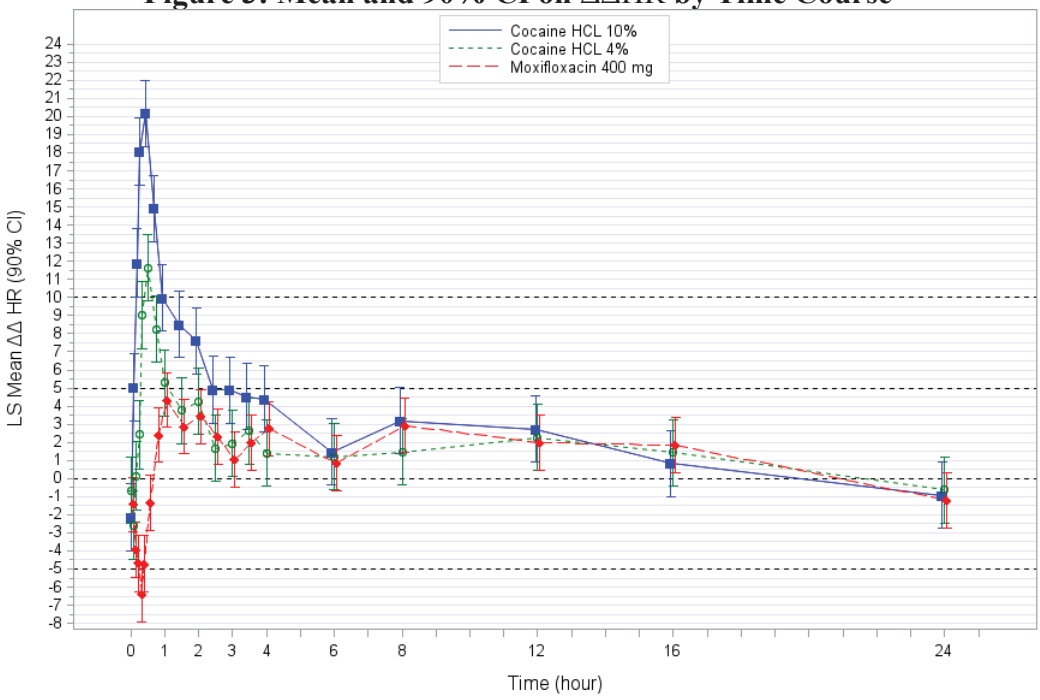
4.3.1.1 Assay sensitivity

Primary method for assay sensitivity was exposure-response analysis. Please see section 4.5.1 for details.

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 3). The largest upper limits of 90% CI on ΔHR mean differences between cocaine hydrochloride 4% and placebo, and cocaine hydrochloride 10% and placebo are 13.5 bpm and 22.0 bpm, respectively.

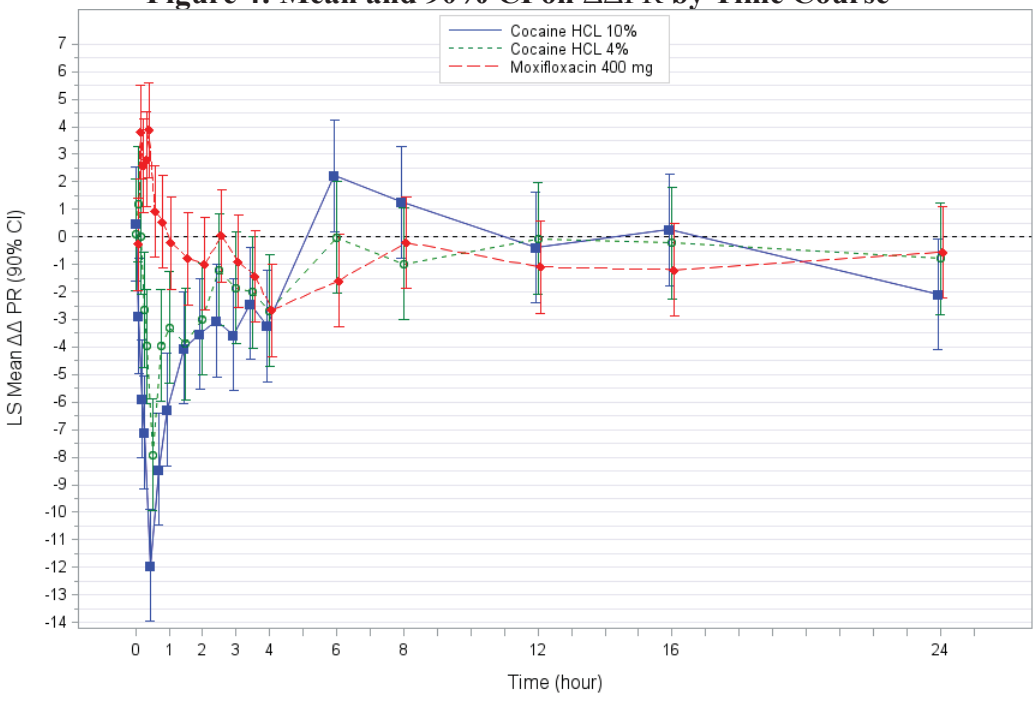
Figure 3: Mean and 90% CI on ΔΔHR by Time Course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 4). The largest upper limits of 90% CI on ΔPR mean differences between cocaine hydrochloride 4% and placebo, and cocaine hydrochloride 10% and placebo are 3.3 ms and 4.3 ms, respectively.

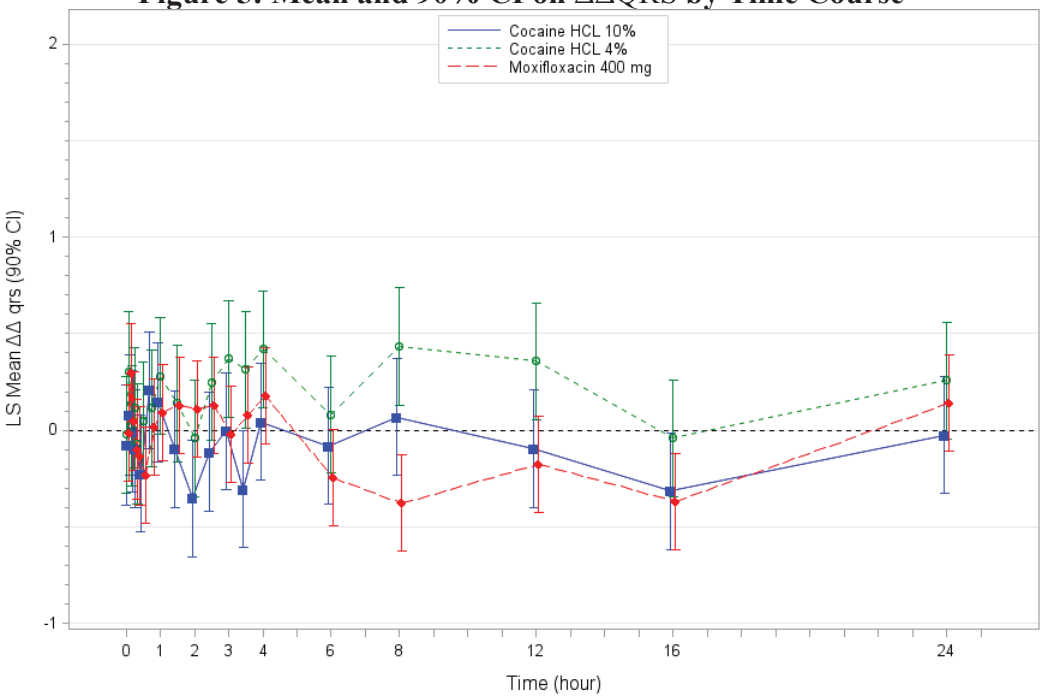
Figure 4: Mean and 90% CI on ΔΔPR by Time Course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 5). The largest upper limits of 90% CI on ΔQRS mean differences between cocaine hydrochloride 4% and placebo, and cocaine hydrochloride 10% and placebo are 0.7 ms and 0.5 ms, respectively.

Figure 5: Mean and 90% CI on ΔΔQRS by Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

No subject's QTcF was above 450 ms. No subject's change from baseline was above 60 ms.

4.4.2 PR

There are no subjects who experienced PR interval greater than 220 ms either in cocaine hydrochloride 4% and placebo, or cocaine hydrochloride 10% groups

4.4.3 QRS

There are no subjects who experienced QRS interval greater than 120 ms with increase from baseline greater than 25% in both cocaine hydrochloride 4% and cocaine hydrochloride 10% groups.

4.4.4 HR

The outlier analysis results for HR are presented in Table 3. There are 9 subjects who experienced HR greater than 100 bpm after receiving cocaine hydrochloride 10%. Three subjects experienced HR greater than 100 bpm after receiving cocaine hydrochloride 4%. All these subjects had baseline HR < 100 bpm.

Table 3: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cocaine HCl 4%	30	535	27 (90.0%)	528 (98.7%)	3 (10.0%)	7 (1.3%)
Cocaine HCl 10%	30	533	21 (70.0%)	508 (95.3%)	9 (30.0%)	25 (4.7%)
Placebo	30	531	29 (96.7%)	530 (99.8%)	1 (3.3%)	1 (0.2%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and concentration of cocaine.

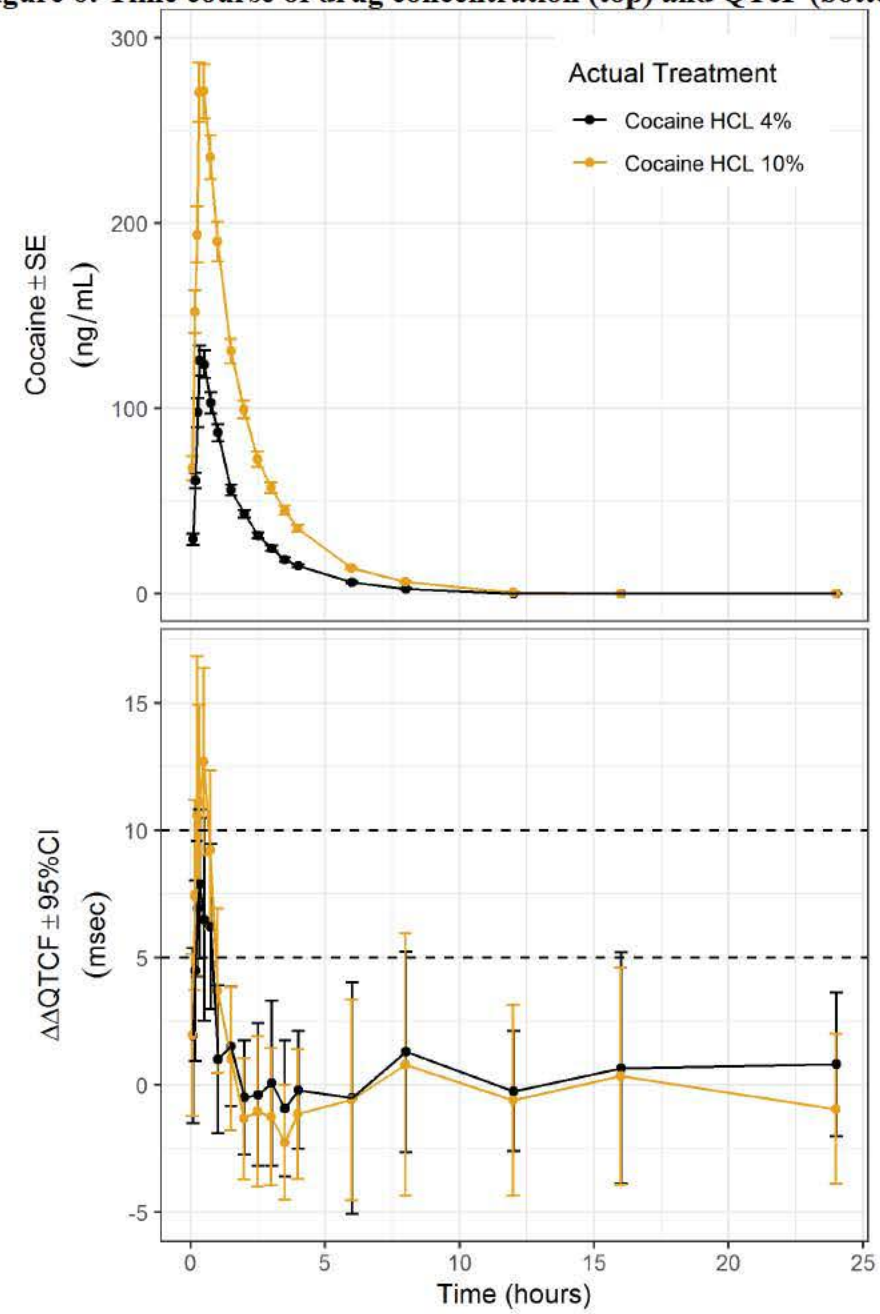
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship.

Significant heart rate increases (>10 bpm) were detected in this thorough QT study for both treatment groups (cocaine hydrochloride 4% solution and cocaine hydrochloride 10% solution) as shown in section 4.3.2. The maximum change in heart rate is above 10 bpm at the therapeutic dose level (i.e. cocaine hydrochloride 4% solution treatment) and above 20 bpm at the maximum therapeutic dose level (i.e. cocaine hydrochloride 10% solution treatment).

The sponsor utilized QTcI for primary analysis which was derived based on supine resting ECGs collected on Day -1. However, the baseline data does not support individual QT correction, because the HR values on treatment is not covered by the baseline data (Figure 1). For this reason, the FDA reviewer used QTcF as the primary endpoint.

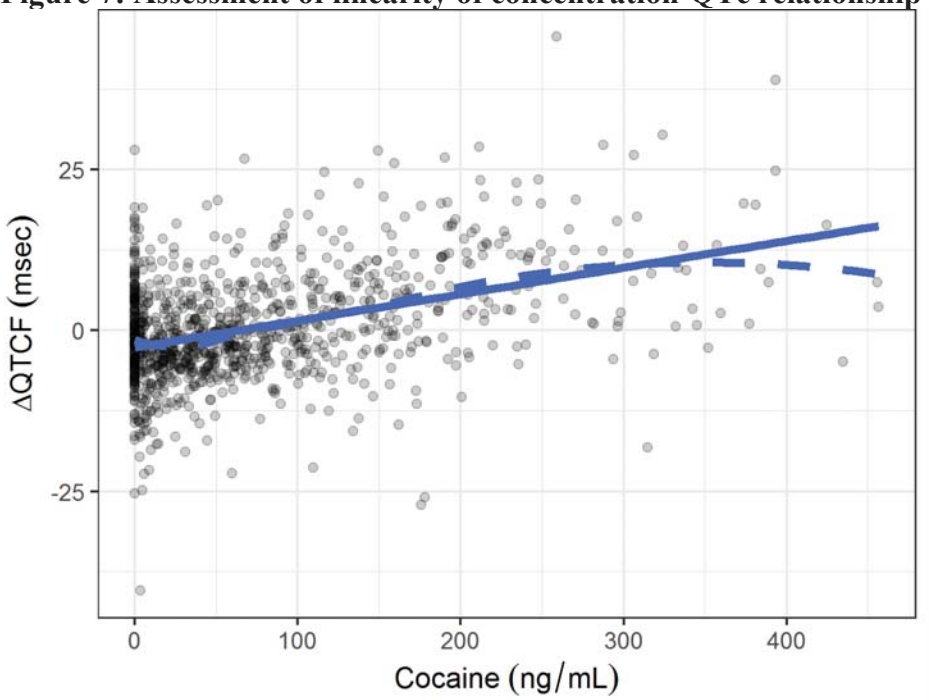
An exploratory evaluation of the time-course of drug concentration and changes in ΔΔQTcF is shown in Figure 6, which do not appear to show significant hysteresis. Moreover, the time at maximum effect on ΔΔQTcF appears to correlate better with Tmax of cocaine.

Figure 6: Time course of drug concentration (top) and QTcF (bottom)



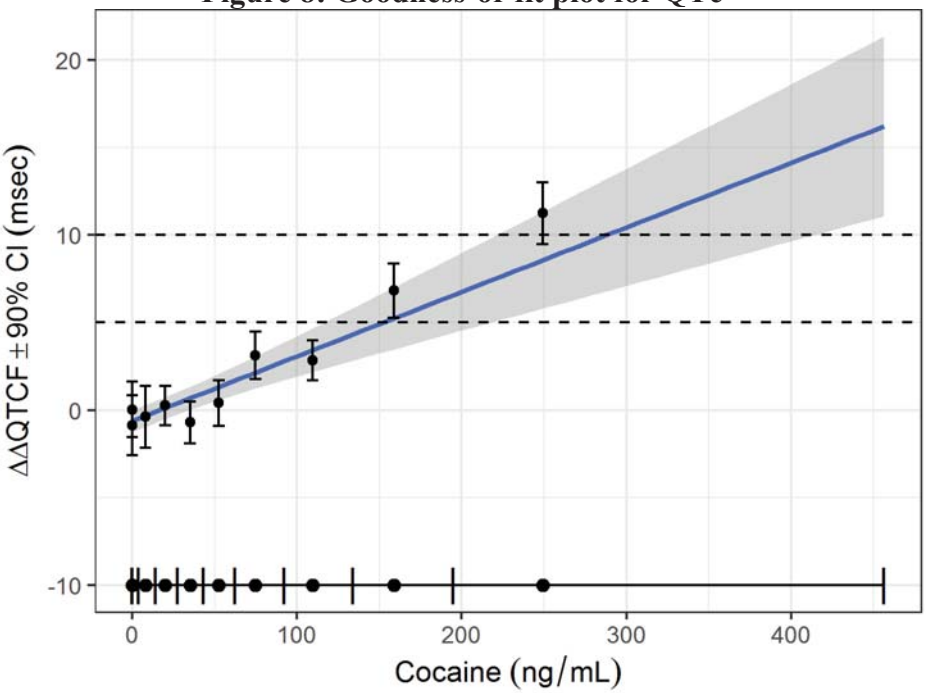
Subsequently, the relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate and it does not suggest the existence of significant nonlinear relationship. Figure 7 shows the relationship between cocaine concentration and ΔQTcF and generally supports the use of a linear model.

Figure 7: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 8.

Figure 8: Goodness-of-fit plot for QTc



In this QT study, the peak concentrations of 127.1 ng/mL and 273.5 ng/mL were observed with single administration of 4% and 10% cocaine hydrochloride solution, respectively (Study # COCA-QT-01). However, these concentrations were lower in comparison to those expected based on the data from previous clinical studies. The peak concentrations of 142.7

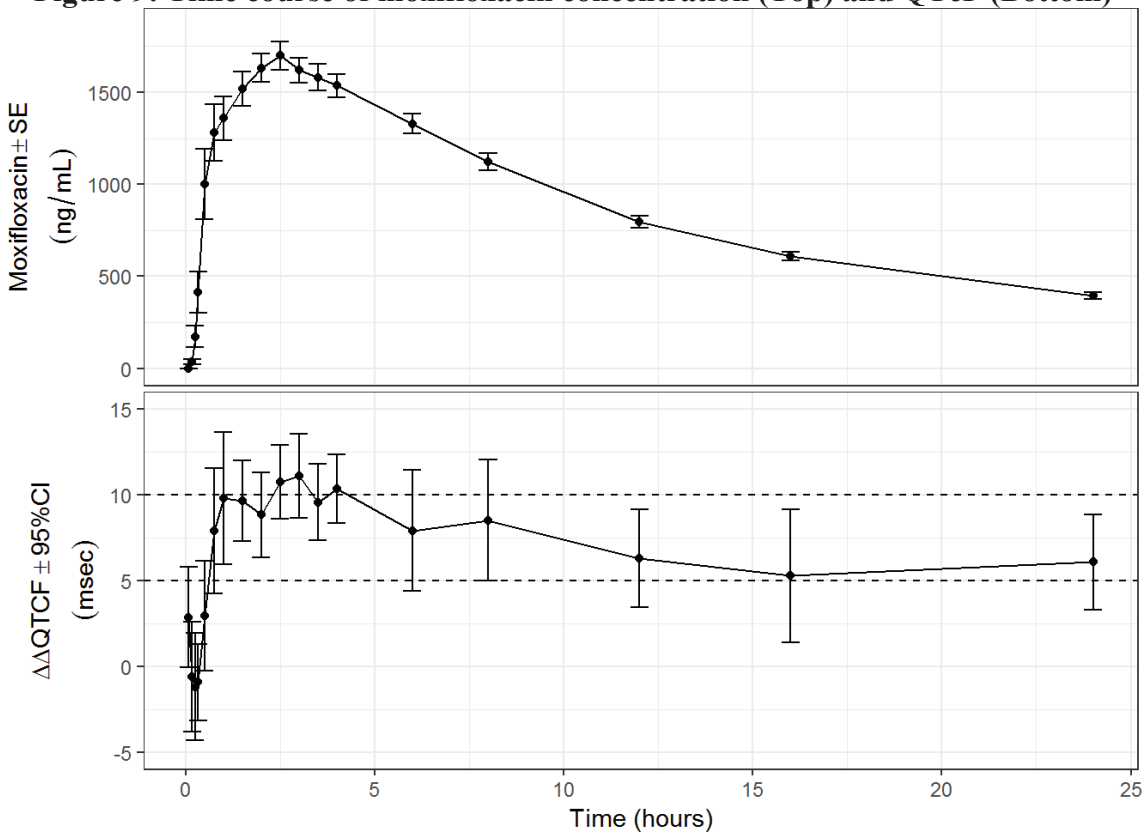
(CV:45%) and 433.5 (CV:49%; Range: 174.8 to 1272.7) ng/mL were observed with single administration of 4% and 10% cocaine hydrochloride solution, respectively (Study LNT-P6-733).

The QT effects of cocaine were predicted at these concentration levels using the linear model. Predictions from the concentration-QTc model are provide in Table 1. However, the exact magnitude of QTc increase at an extrapolated concentration levels may not be predicted with adequate precision as the observed changes in heart rate may confound the interpretation of cocaine concentration-QTc relationship.

4.5.1 Assay sensitivity

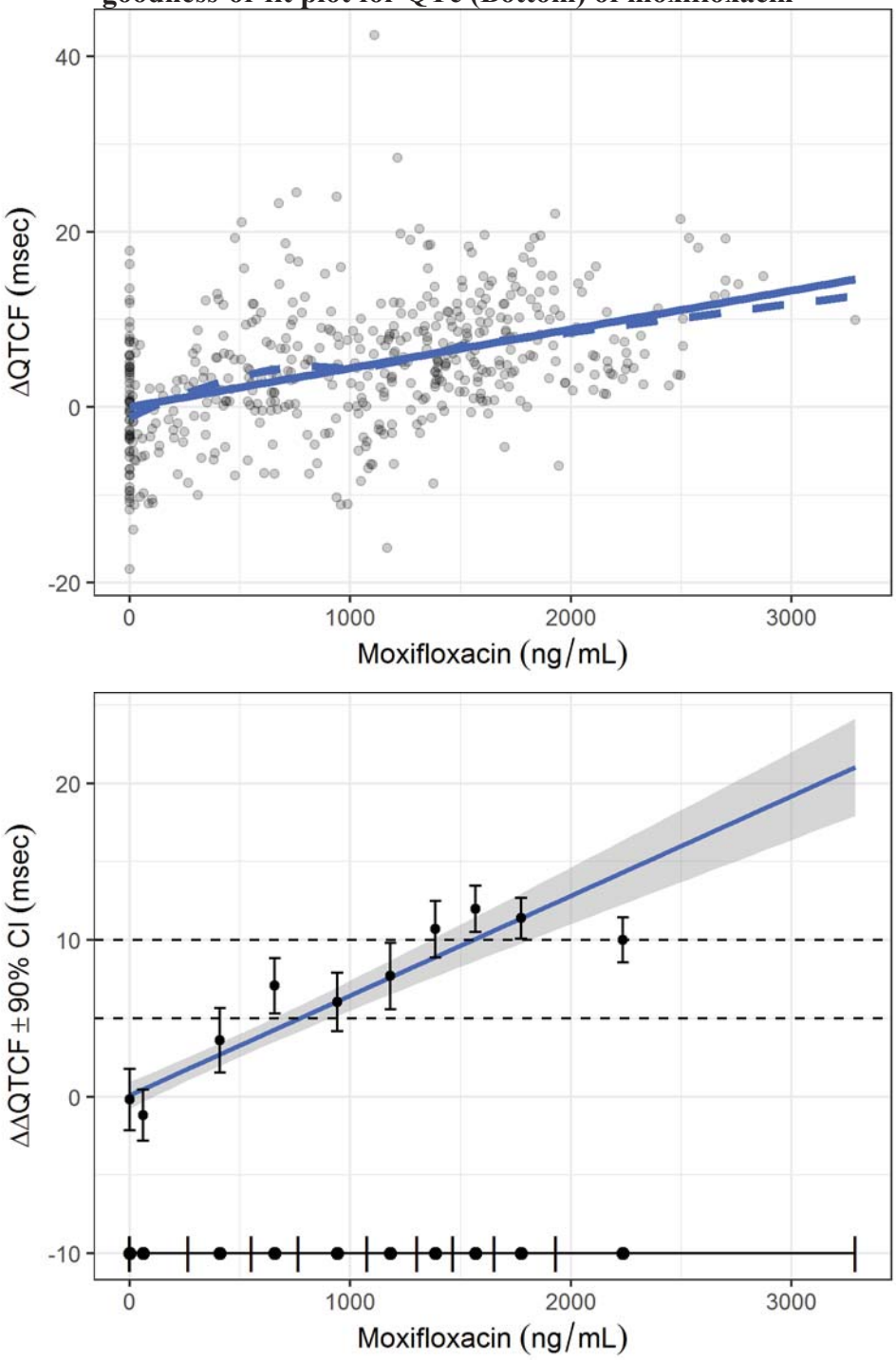
To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control (open-label) to detect small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (Figure 9).

Figure 9: Time course of moxifloxacin concentration (Top) and QTcF (Bottom)



Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Figure 10: Assessment of linearity of concentration-QTc relationship (Top) and goodness-of-fit plot for QTc (Bottom) of moxifloxacin



4.6 SAFETY ASSESSMENTS

See section 3.2.3.

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LARS JOHANNESEN
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CHRISTINE E GARNETT
08/19/2019 08:31:59 PM

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

Date: July 3, 2018

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

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

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

Subject: Cocaine Hydrochloride Nasal Solution (Numbrino)
NDA 209,575 (IND 106,499)
Indication: Induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults.
Dosage: 4% and 10% solution (40 and (b) (4)), for doses ranging from 40 to 400 mg
Sponsor: Lannett Company, Inc.
PDUFA Goal Date: July 21, 2018

Materials reviewed: NDA 209,575 (11/1/17)

Table of Contents

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 Nasal Solution (Numbrino, 4% solution (40 mg/ml) and 10% solution (b) (4) under NDA 209,575. The Sponsor is Lannett Company, Inc. This NDA is submitted as a 505(b) 2 application, so there are no abuse-related nonclinical or clinical studies for CSS to review.

Numbrino is recommended for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults. The recommended dose ranges from 40 mg to 400 mg, depending on the nasal mucosal area to be anesthetized and the procedure to be performed. Each of 4 pledgets absorb one milliliter of the cocaine nasal solution. A maximum of two soaked pledgets may be placed in each nasal cavity, for a total dose of 160 mg for 4 pledgets when using the 4% solution and 400 mg when using the 10% solution.

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

NUMBRINO contains cocaine, a Schedule II controlled substance.

9.2 Abuse

NUMBRINO contains cocaine, a substance with a high potential for abuse. NUMBRINO can be misused and abused, which can lead to addiction. NUMBRINO 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 NUMBRINO 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)]*.

NUMBRINO, 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. NUMBRINO is approved for nasal single use, so physical dependence and withdrawal symptoms are unlikely to develop. Although NUMBRINO is not indicated for chronic therapy, repeated misuse or abuse of this product may lead to physical dependence.

10 OVERDOSAGE

No cases of overdose with NUMBRINO were reported in clinical trials. Reported blood pressure and heart rate increases were greater with NUMBRINO nasal solution 10% than with NUMBRINO nasal solution 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
07/03/2018

SILVIA N CALDERON
07/03/2018

DOMINIC CHIAPPERINO
07/03/2018

Clinical Inspection Summary

Date	June 28, 2018
From	Damon Green, M.D., M.S., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Shelly Kapoor, Regulatory Project Manager Renee Petit-Scott, M.D., Clinical Reviewer Rigoberto Roca, M.D., Deputy Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA #	NDA 209575
Applicant	Cody Laboratories, Inc.
Drug	Numbrino (Cocaine Hydrochloride Topical Solution)
NME	No
Therapeutic Classification	Local anesthetic
Proposed Indication	Introduction of local (topical) anesthesia for procedures on or through the mucous membranes of the nasal cavities.
Consultation Request Date	January 22, 2018
Summary Goal Date	June 30, 2018
Action Goal Date	July 20, 2018
PDUFA Date	July 21, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Major and Armstrong were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The final compliance classification of the inspections of Drs. Major and Armstrong was No Action Indicated (NAI).

II. BACKGROUND

Cody Laboratories, Inc., a subsidiary of Lannett Company, is seeking approval of cocaine hydrochloride topical solution, 4% and 10%, for use in adults for the introduction of local (topical) anesthesia for diagnostic procedures and surgery on or through accessible mucous membranes of the nasal cavities. Inspections were requested for the following protocols in support of this application:

Protocol COCA4vs10-001: "A Phase 3 investigation of topical application of Cocaine HCl 4% and 10% on safety and efficacy in local (topical) anesthesia for diagnostic procedures and surgeries on or through accessible mucous membranes of the nasal cavities"

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the administration of a single anesthetic dose of cocaine hydrochloride (HCl) 4% or 10% topical solution applied to pledgets and delivered to the nasal mucosa in men and women undergoing a single diagnostic or surgical procedure on or through accessible mucous membranes of the nasal cavities.

The study was conducted at 11 sites in the United States beginning May 6, 2014 and ending on November 26, 2014. A total of 156 subjects were randomized.

The primary efficacy endpoints were nasal anesthesia success, defined as immediate analgesia based on a Numeric Pain Rating Scale (NPRS) of 0 (no pain, 0 to 10 scale) 20 minutes post-application of the nasal cavity pledget dose and sustained analgesia based on the lack of need for additional anesthesia or analgesics for the remainder of the diagnostic procedure or surgery.

Protocol COCA4vs10-002: "A Phase 3 investigation of topical application of Cocaine HCl 4% solution on safety and efficacy and Cocaine HCl 4% and 10% solution on safety in local (topical) anesthesia for diagnostic procedures and surgeries on or through accessible mucous membranes of the nasal cavities"

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the administration of a single anesthetic dose of cocaine hydrochloride (HCl) 4% or 10% topical solution applied to pledgets and applied to the nasal mucosa in men and women undergoing a single diagnostic or surgical procedure on or through accessible mucous membranes of the nasal cavities.

The study was conducted at 20 sites in the United States beginning September 17 2015 and ending on July 21, 2016. A total of 646 subjects were randomized.

The primary efficacy endpoints were nasal anesthesia success, defined as immediate analgesia based on a Numeric Pain Rating Scale (NPRS) of 0 (no pain, 0 to 10 scale) 20 minutes post-application of the nasal cavity pledget dose and sustained analgesia based on the lack of need for additional anesthesia or analgesics for the remainder of the diagnostic procedure or surgery.

Rationale for Site Selection

The inspections of Drs. Major and Armstrong were requested due to high enrollment. Neither clinical investigator had a history of previous PDUFA inspections or complaints.

III. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site #1130 **Dr. Michael Major** 5896 S. Ridgeline Drive, Suite A Ogden, UT 84405	COCA4vs10-001 Subjects: 44 COCA4vs10-002 Subjects: 167	09-13 Apr 2018	NAI
Site #1190 **Dr. Michael Armstrong** 8700 Stony Point Pkwy, Suite 110 Richmond, VA 23235	COCA4vs10-001 Subjects: 29 COCA4vs10-002 Subjects: 131	29 May to 01 Jun 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations; Data unreliable.

1. Dr. Michael Major

At this site for Protocol COCA4vs10-001, 61 subjects were screened and 44 subjects were enrolled, all of whom completed the study. For Protocol COCA4vs10-002, 241 subjects were screened and 167 subjects were enrolled, all of whom completed the study.

A total of 102 subject study records were reviewed from both protocols. Study and subject-specific records reviewed included, but were not limited to, informed consent forms (the field investigator reviewed 100% of enrolled subjects from protocol 001 and 30% of enrolled subjects from protocol 002), source documents for data line listing comparison, investigational product reconciliation, inclusion/exclusion criteria, adverse event reporting, financial disclosures, electronic case report forms/EDC, protocol deviations, subject randomization, and concomitant medications.

The primary efficacy endpoint data was verifiable, and there was no evidence of under-reporting of adverse events.

2. Dr. Michael Armstrong

At this site for Protocol COCA4vs10-001, 53 subjects were screened and 29 subjects were enrolled, all of whom completed the study. For Protocol COCA4vs10-002, 240 subjects were screened, 131 subjects were enrolled, and 130 completed the study.

A total of 25 subject study records were reviewed from both protocols. Study and subject-specific records reviewed included, but were not limited to, drug accountability records, laboratory results, adverse events reporting, concomitant medications, monitor and institutional review board (IRB) correspondence, case report forms (CRFs), informed consent forms, protocols, training records, and financial disclosures.

The primary efficacy endpoint data was verifiable, and there was no evidence of under-reporting of adverse events.

Of note, for protocol 001, two non-serious AEs were noted as "resolved" in the eCRF and line listings but as "unresolved" in the source documents. For protocol 002, 16 non-serious AEs (for 16 different subjects) were noted as "resolved" in the line listings but as "unresolved" in the source documents and eCRF. These discrepancies are unlikely to have impacted the safety results of these studies.

{See appended electronic signature page}

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Phillip Kronstein, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D.
Branch Chief
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Office of Scientific Investigations

cc:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Deputy Director/Roca
DAAAP /Project Manager/Kapoor
DAAAP/Medical Officer/Petit-Scott
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Kronstein
OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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/s/

DAMON C GREEN
06/28/2018

PHILLIP D KRONSTEIN
06/28/2018

KASSA AYALEW
06/28/2018

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

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

Memorandum

Date: June 27, 2018

To: Renee Petit-Scott, M.D.
Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Shelly Kapoor, PharmD
Regulatory Project Manager, (DAAAP)

Lisa E. Basham, MS
Associate Director for Labeling, (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 Numbrino (cocaine hydrochloride) nasal solution, CII

NDA: 209575

In response to DAAAP's consult request dated November 9, 2017, OPDP has reviewed the proposed prescribing information (PI), carton and container labeling for the original NDA for Numbrino (cocaine hydrochloride) nasal solution, CII.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on June 22, 2018, 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 May 30, 2018, and we do not have any comments.

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

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KOUNG U LEE
06/27/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	June 25, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209575
Product Name and Strength:	Numbrino (cocaine hydrochloride) Topical Solution 4% and 10%
Applicant/Sponsor Name:	Cody Laboratories
FDA Received Date:	May 30, 2018
OSE RCM #:	2017-1951-1
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

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

2 CONCLUSION

Cody Labs indicated in their May 30, 2018 cover letter that the expiration date format will be expressed as MM/YYYY. We find this presentation acceptable. We also find the revised container labels and carton labeling for Numbrino are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Schlick J. Label and Labeling Review for Numbrino (NDA 209575). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Mar 19. RCM No.: 2017-1951.

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/s/

JAMES H SCHLICK
06/25/2018

OTTO L TOWNSEND
06/25/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

PLLR Labeling Memorandum

Date: June 12, 2018 **Date consulted:** November 9, 2017

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: Numbrino (Cocaine Hydrochloride Topical Solution 4% and 10%)

NDA: 209575

Applicant: Lannett (Cody Labs)

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: Numbrino (cocaine hydrochloride) topical solution is an ester local anesthetic indicated for the introduction of local anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities of adults.

Materials Reviewed

- Sponsor's submitted background package for NDA 209575, submitted on September 21, 2017.

- DPMH consult review of Goprelto (Cocaine Hydrochloride Topical Solution 4%), NDA 209963. Jane Liedtka, M.D. August 18, 2017, DARRTS Reference ID 4139403[1].

Consult Question:
"DAAAP is requesting that PMHS please assist us in reviewing the labeling for the new PLLR format."

INTRODUCTION

On November 9, 2017, DAAAP consulted DPMH to provide input for appropriate labeling of the pregnancy and lactation sections of Numbrino (Cocaine Hydrochloride Topical Solution) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY

- On September 21, 2017, Lannett (Cody Labs) submitted a New Drug Application (NDA) for NDA 209575, Numbrino (Cocaine Hydrochloride Topical Solution)
- Numbrino (Cocaine Hydrochloride Topical Solution) is an ester local anesthetic indicated for the introduction of local anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities of adults.
- This product is currently an unapproved marketed drug.
- Another cocaine hydrochloride topical solution product, Goprelto NDA 209963 was approved in December 2017.
- On November 16, 2017 the Agency requested a review of the published literature to support PLLR labeling. The response was received on December 7, 2017 and was adequate.

BACKGROUND

Cocaine Hydrochloride Topical Solution and Drug Characteristics[2]

- The 4% solution contains 160 mg/4 mL (40 mg/mL= 4%) cocaine hydrochloride, an amino ester local anesthetic and a vasoconstrictor. One mL of the 10% topical solution is equivalent to 100 mg of cocaine hydrochloride.
- Molecular weight is ≈ 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
- Blocks the initiation or conduction of nerve impulses following local application. When applied topically to mucous membranes, the drug produces a reversible loss of sensation and vasoconstriction.

[1] DPMH consult review of Goprelto (Cocaine Hydrochloride Topical Solution 4%), NDA 209963 was part of the materials reviewed, but was not relied upon for the purposes of the recommendations.
[2] NUMBRINO proposed package insert

- The mean systemic absorption of cocaine from a single 160 mg dose (4 mL, 4%) was 23.44% of the topically applied dose. The mean systemic absorption of cocaine from a single 400 mg dose (4 mL, 10%) was 33.34% of the topically applied dose.
- The apparent elimination half-life (mean ± %CV) of cocaine following administration of NUMBRINO (by pledgets) was 1.54 hours (±13.5) for the 4% concentration, and 2.10 hours (±36.8) for the 10% concentration.
- The most common adverse reactions (>1%) occurring in patients treated with Numbrino were hypertension, tachycardia, bradycardia, QT interval prolongation, sinus tachycardia, QRS complex prolongation, increased heart rate, diastolic hypertension, and tachycardia paroxysmal.

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.[3] 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.[4] 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).[5] 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

In published animal reproduction studies, cocaine administered to pregnant females during the gestational period produced cryptorchidism, hydronephrosis, hemorrhage,

[3] http://smarttots.org/wp-content/uploads/2015/10/ConsensusStatementV910.5.2015.pdf
[4] http://smarttots.org/wp-content/uploads/2015/11/CSsupplement11.9.2015.pdf
[5] Per DAAAP meeting 11-30-2016

hydrocephalus, cleft palate, delayed ossification, and limb anomalies in mice XX times the human reference dose (HRD) of XX mg based on body surface area and produced mortality, fetal edema, and microencephaly in rats at greater than XX times the HRD based on body surface area.

Single dose administration of cocaine intravenously during organogenesis in mice produced cryptorchidism, anophthalmia, exencephaly, and delayed ossification at 1.7 times the HRD based on body surface area in mice. In rats, a single dose of cocaine administered by intraperitoneal injection produced edematous fetuses, hemorrhages and limb defects at 6.7 times the HRD based on body surface area.

The PT language was still undergoing revision at the time this review was completed. 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, literature searches were conducted in November 2017 in multiple databases, including PubMed1, CINAHL2, EMBASE3, google.com, and IPA4. Please note that the Cochran database was also reviewed, but no relevant citations were found. The published literature obtained pertained almost exclusively to excessive (sub-chronic, or chronic) cocaine administration associated with misuse, abuse and/or addiction of the illicit drug product. No information addressed the impact of a single-dose administration of cocaine HCl topical solution (4% or 10%) to the nasal mucosa for anesthesia on pregnancy, lactation, or reproductive potential.

See section entitled "DPMH's Review of the Literature" for summaries and discussion of relevant publications.

Applicant Review of Pharmacovigilance Database

The Sponsor's pharmacovigilance database did not report any women having cases related to pregnancy, lactation, or reproduction topics, nor were there any male or female fertility cases (please note, (b) (4) manages the database on behalf of the applicant).

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "Topical Cocaine solution and pregnancy," "Topical Cocaine solution and pregnant women," "Topical Cocaine solution and pregnancy and birth defects," "Topical Cocaine solution and pregnancy and congenital malformations," "Topical Cocaine solution and pregnancy and stillbirth," "Topical Cocaine solution and spontaneous abortion" and "Topical Cocaine solution 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 Micromedex[6] and Briggs and Freeman[7] *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk* was consulted to try to better refine the publications that were relevant.

One of the articles identified as relevant by both the DPMH reviewer and the Applicant was a systematic review of 31 studies regarding maternal antenatal cocaine exposure and adverse perinatal outcomes published by Gouin[8] *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*[8] publication are reproduced as Attachment A.

Another article identified as relevant by both the DPMH reviewer and the Applicant published in 2014 by Cressman[9] *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.[10,11] *Some studies suggested the timing and*

[6] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 6/12/17.
[7] 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.
[8] 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.
[9] Cressman AM, Natekar A, Kim E, Koren G, Bozzo P. Cocaine abuse during pregnancy. J Obstet Gynaecol Can. 2014; 36(7):628-31.
[10] Richardson GA & Day NL: Maternal and neonatal effects of moderate cocaine use during pregnancy. Neurotoxicol Teratol 1991; 13:455-460.
[11] 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.

pattern (binging versus chronic use) of abuse determined the type of adverse developmental outcomes that were seen.[12, 13]

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.

Lactation

Applicant's Review of the Literature

According to the Applicant, literature searches were conducted in November 2017 in multiple databases, including PubMed1, CINAHL2, EMBASE3, google.com, and IPA4. Please note that the Cochran database was also reviewed, but no relevant citations were found. See section entitled "DPMH's Review of the Literature" for summaries and discussion of relevant publications.

DPMH's Review of Literature

DPMH conducted a search of Medications and Mother's Milk[19], the Drugs and Lactation Database (LactMed) [36], Micromedex[28], 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*[14], 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 dangerous and contraindicated[37]…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 clearance[39].

Cocaine is referenced in LactMed[36]. The summary of use states:

[12] Burkett G, Yasin SY, Palow D, et al: Patterns of cocaine binging: effect on pregnancy. Am J Obstet Gynecol 1994; 171:372-379.
[13]Towers CV, Pircon RA, Nageotte MP, et al: Cocaine intoxication presenting as preeclampsia and eclampsia. Obstet Gynecol 1993; 81:545-547.
[14] Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15th edition. HalePublishing, L.P. 2012

> 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 it[15] 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 mother[39].

Under the section "Effects on Lactation and Breastmilk" in LactMed[36] on cocaine it states:

> Long-term cocaine use can result in chronic, low-level hyperprolactinemia. [16, 17, 18]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 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 Numbrino and for 48 hours after administration (6x the half- life) of the solution.

[15] Anderson PO: Drug use during breast-feeding. Clin Pharm 1991; 10:594-624.
[16] Mello NK, Mendelson JH. Cocaine's effects on neuroendocrine systems: clinical and preclinical studies. Pharmacol Biochem Behav. 1997; 57:571-99.
[17] 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.
[18] Patkar AA, Hill KP, Sterling RC et al. Serum prolactin and response to treatment among cocaine-dependent individuals. Addict Biol. 2002; 7:45-53.

Females and Males of Reproductive Potential

Nonclinical Experience
Long term animal studies to evaluate the carcinogenic potential of NUMBRINO have not been conducted.

In published studies, cocaine was genotoxic in the in vitro chromosomal aberration assay, the in vitro sister chromatid exchange assay, the in vitro micronucleus assay, and the in vitro hypoxanthine-guanine phosphoribosyltransferase (hgprt) assay. Cocaine hydrochloride was not mutagenic in the in vitro bacterial reverse mutation assay (Ames assay).

Studies in animals to characterize the effects of cocaine on fertility have not been completed. There are published studies that provide some information on the potential impact of cocaine on fertility. Exposure margins below are based on body surface area comparison to the human reference dose (HRD) of XX mg (estimated amount absorbed from the XX mg cocaine-soaked pledgets).

Acute parenteral administration of cocaine to female rats increased luteinizing hormone and progesterone by approximately X-fold at XX to XX times the HRD. Suppression of estrous/menstrual cyclicity and ovulation was reported in rats at XX times the HRD and in monkeys at XX times the human daily dose.

In a published study, adult (12-week old) male rats treated subcutaneously with 15 mg/kg cocaine (XX times the HRD) daily for at least 28 days prior to mating demonstrated increased apoptosis of germ cells. Studies in younger male rats demonstrated more pronounced effects [see Pediatric Use (8.4)].

The PT language was still undergoing revision at the time this review was completed. 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, literature searches were conducted in November 2017 in multiple databases, including PubMed1, CINAHL2, EMBASE3, google.com, and IPA4. Please note that the Cochran database was also reviewed, but no relevant citations were found. See section entitled “DPMH’s Review of the Literature” for summaries and discussion of relevant publications.

DPMH Review of the Literature
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 (Mueller[19] *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.

[19] 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[20] MB *et al* 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 *et al* 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[21] WW *et al* 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[22] FD *et al* 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[23] M *et al* 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), ecstacy (9), LSD (2), heroin (1) and anabolic steroids for bodybuilding (3), also ↑ history of sexually transmitted diseases and tobacco

[20] Bracken MB *et al*. Association of cocaine use with sperm concentration, motility, and morphology. Fertility and Sterility. 1990; 53(2):315-322.
[21] Hurd WW *et al*. The effect of cocaine on sperm motility characteristics and bovine cervical mucus penetration. Fertil Steril. 1992; 57:178-82.
[22] 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.
[23] 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, 8.3 and 17 in NUMBRINO (cocaine hydrochloride topical solution) labeling for compliance with the PLLR (see below). DPMH discussed these recommendations with the division on June 12, 2018. DPMH refers to the final NDA action for final labeling.

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Breastfeeding not recommended during treatment, but a lactating woman can pump and discard breast milk for 48 hours after treatment. (8 .2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on the use of NUMBRINO in pregnant women to identify a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Adverse maternal and fetal/neonatal outcomes have been seen in women with chronic cocaine abuse during pregnancy *(see Data).*

In published animal reproduction studies, cocaine administered to pregnant females during the gestational period produced cryptorchidism, hydronephrosis, hemorrhage, hydrocephalus, cleft palate, delayed ossification, and limb anomalies in mice at XX times the human reference dose (HRD) of XX mg based on body surface area and produced mortality, fetal edema, and microencephaly in rats at greater than XX times the HRD based on body surface area.

Single dose administration of cocaine intravenously during organogenesis in mice produced cryptorchidism, anophthalmia, exencephaly, and delayed ossification at 1.7 times the HRD based on body surface area in mice. In rats, a single dose of cocaine administered by intraperitoneal injection produced edematous fetuses, hemorrhages and limb defects at 6.7 times the HRD based on body surface area (*see Data*). Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. 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.

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 for major congenital malformations or miscarriage. 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 congenital malformations, prematurity, miscarriage, premature rupture of membranes and gestational hypertension. The applicability of the findings from these studies of chronic abuse in pregnancy to a single topical exposure is limited.

Animal Data

Formal animal reproduction and development studies have not been conducted with intranasal cocaine hydrochloride. However, reproduction and development studies with cocaine have been reported in the published literature. Exposure margins for the following published studies are based on body surface area conversion using a human reference dose (HRD) of XX mg, which is XX% of the maximum recommended human dose of XXX mg that is estimated to be absorbed from the pledgets.

Cerebral hemorrhage, hydrocephalus, limb anomalies, and incomplete ossification of femoral bones were observed when pregnant mice were administered 20 mg/kg/day cocaine intravenously (XX times the HRD) from Gestation Day (GD) 6 to 15. No maternal toxicity was observed.

In another intravenous study, incomplete ossification (sternum and supra-occipital bone), hydrocephalus, hydronephrosis and cryptorchidism were reported when pregnant mice were administered 20 mg/kg/day of cocaine (XX times the HRD) from Gestation Day 9 to 12. No adverse effects were observed following 10 mg/kg/day of cocaine (XX times the HRD). No maternal toxicity was observed.

In different strains of mice, immaturely developed cerebral ventricles, hydronephrosis, dilated or cystic ureters, and cleft lip/palate were noted at doses greater than 40 mg/kg/day (XX times the HRD) when administered from Gestation Day 6 to 10 to pregnant females. These adverse findings were not present at a dose of 20 mg/kg/day (XX times the HRD). No evidence of maternal toxicity was noted.

Following a single subcutaneous injection of cocaine at 60 mg/kg (XX times the HRD) to pregnant mice between Gestation Day 7 to 12, exencephaly, cryptochidism, hydronephrosis, anophthalmia, and delayed ossification were reported. In addition, visceral malformations that included limb anomalies, cerebral and intra-abdominal

hemorrhage were observed at this dose. No significant maternal toxicity was noted at this dose.

In pregnant rats administered cocaine subcutaneously (40-90 mg/kg/day) from Gestation Day 7 to 19, dose-dependent increase in incidences of fetal and maternal mortality and decreased body weight were observed at doses greater than 60 mg/kg/day (XX times the HRD). Fetal edema and hemorrhage were observed in cocaine-treated litters at XX times the HRD and microencephaly at XX times the HRD. No adverse effects were noted following 50 mg/kg/day (XX times the HRD).

In another rat study, fetal and maternal deaths, decreased fetal body weights, edematous fetuses and single incidences of cleft palate and hypertrophic ventricle were observed after intraperitoneal cocaine injection at 60 mg/kg/day (XX times the HRD) from Gestation Day 8 to 12. No adverse effect level for fetal and maternal toxicity was noted at 50 mg/kg/day (XX times the HRD).

Following single injection of cocaine at a dose of 50 mg/kg/day or higher (XX times the HRD) during Gestation Day 9 to 19, hemorrhage and edema was observed when only external malformations were evaluated. Increased resorptions were noted at doses higher than 70 mg/kg/day (XX times the HRD) when administered on Gestation Day 16. No adverse effects were reported at a dose of 40 mg/kg (XX times the HRD).

In published rat studies, prenatal cocaine administration produced hypoactivity in the pups and abnormal open field activity (XX times the HRD) and deficits in associational learning (XX times the HRD) in the absence of maternal toxicity. Decreased birth weights, pup body weight gain (XX to XX times the HRD) and increased still births and postnatal mortality (XX times the HRD) were noted in the presence of maternal toxicity (decreased body weights and mortality).

A published study reported decreased body weights, overall body length and crown circumference of offspring from pregnant Rhesus monkeys treated with escalating doses up to 7.5 mg/kg cocaine three times a day (TID) intramuscularly per day for 5 days per week from prior to conception to term (XX times the HRD).

In other published studies, there were no adverse effects on physical development or cognitive testing of the offspring from pregnant Rhesus monkeys treated with 0.3, 1.0, or escalating doses up to 8.5 mg/kg TID intramuscularly per day cocaine from Gestation Day 28 to term five days per week (XX, XX, or up to XX times the HRD). There was no evidence of maternal toxicity in these studies under the conditions tested.

In another published study, behavioral alterations in primate infants as assessed by a primate neonatal behavioral assessment battery were demonstrated following 10 mg/kg twice a day oral cocaine administration to pregnant Rhesus monkeys from GD 40 to 102 (XX times the HRD).

8.2 Lactation

Risk Summary

Based on 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. No studies have evaluated cocaine concentrations in milk after topical administration of NUMBRINO.

Cocaine is detected in human breastmilk in chronic abuse situations and is expected to be at higher concentrations in milk than in maternal blood based on its physicochemical characteristics. Breastfeeding immediately after administration of NUMBRINO could result in infant plasma concentrations that are approximately half the anticipated maximum maternal plasma concentrations at the clinical dose of 160 mg. The effects of this cocaine plasma concentration in an infant are unknown, but no level of cocaine exposure is considered safe for a breastfed infant.

Comment [LJ1]: Clin pharm will need to verify that this statement is true for NUMBRINO NDA 209575 Jane

Adverse reactions have occurred in infants ingesting cocaine through breastmilk, including vomiting, diarrhea, convulsions, hypertension, tachycardia, agitation and irritability. The long-term effects on infants exposed to cocaine through breast milk are unknown. There are no data on the effects of NUMBRINO on milk production.

Because of the potential for serious adverse reactions in breastfed infants, advise a lactating woman that breastfeeding is not recommended during treatment with NUMBRINO and to pump and discard breastmilk for 48 hours after use of NUMBRINO.

17 Patient Counseling Information

Lactation

Advise a woman that breastfeeding is not recommended during treatment with NUMBRINO and to pump and discard breastmilk for 48 hours after administration of NUMBRINO [*see Use in Specific Populations (8.2)*].

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 et al[4]	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 et al[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 et al[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
Chouteau et al[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 et al[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 et al[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 et al[21]	1986-88	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 et al[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
Gillogley et al[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 et al[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 et al[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 ± 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 ± 750g (C+T) 3423 ± 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 ± 462 (45) for cocaine vs 2824 ± 876 (75) for controls BW/Tobacco –:3051 ± 602 (17) for cocaine vs 3078 ± 853 (167) for controls GA/Tobacco+: 38.4 ± 2.5 (45) for cocaine vs 37.6 ± 4.4 (75) for controls GA/Tobacco-: 39.0 ± 1.6 (16) for cocaine vs 38.4 ± 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)	Multiethnic, 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, PTD, 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 contols	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

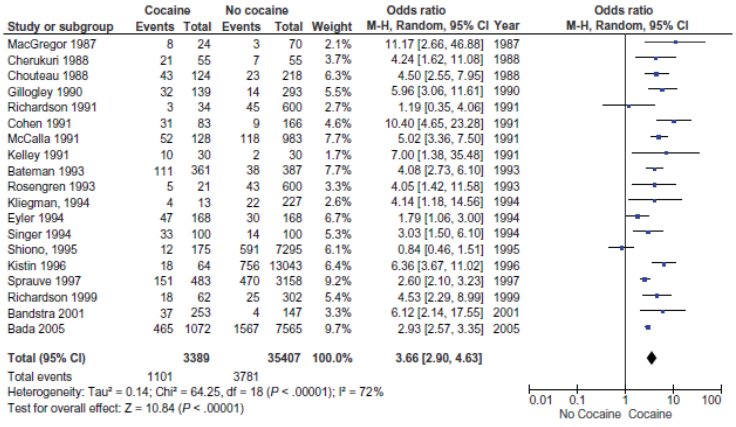
AA, African American; *ANC*, antenatal care; *BW*, birthweight; *exp*, exposure; *GA*, gestational age; *L+D*, labor and delivery suites; *LBW*, low birthweight; *MA*, maternal age; *NS*, not specified; *Ob*, obstetrics; *PNC*, prenatal care; *PP*, postpartum; *PTB*, preterm birth; *PTD*, preterm delivery; *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)

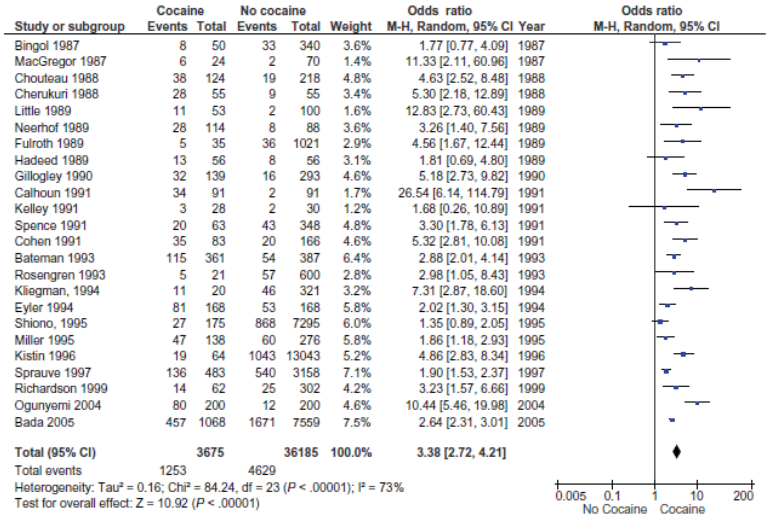


LBW, low birthweight.

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)



Study or subgroup	Cocaine Events	Cocaine Total	No cocaine Events	No cocaine Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Bingol 1987	8	50	33	340	3.6%	1.77 [0.77, 4.09]	1987
MacGregor 1987	6	24	2	70	1.4%	11.33 [2.11, 60.96]	1987
Chouteau 1988	38	124	19	218	4.8%	4.63 [2.52, 8.48]	1988
Cherukuri 1988	28	55	9	55	3.4%	5.30 [2.18, 12.89]	1988
Little 1989	11	53	2	100	1.6%	12.83 [2.73, 60.43]	1989
Neerhof 1989	28	114	8	88	3.6%	3.26 [1.40, 7.56]	1989
Fulroth 1989	5	35	36	1021	2.9%	4.56 [1.67, 12.44]	1989
Hadeed 1989	13	56	8	56	3.1%	1.81 [0.69, 4.80]	1989
Gillogley 1990	32	139	16	293	4.6%	5.18 [2.73, 9.82]	1990
Calhoun 1991	34	91	2	91	1.7%	26.54 [6.14, 114.79]	1991
Kelley 1991	3	28	2	30	1.2%	1.68 [0.26, 10.89]	1991
Spence 1991	20	63	43	348	4.8%	3.30 [1.78, 6.13]	1991
Cohen 1991	35	83	20	166	4.6%	5.32 [2.81, 10.08]	1991
Bateman 1993	115	361	54	387	6.4%	2.88 [2.01, 4.14]	1993
Rosengren 1993	5	21	57	600	2.8%	2.98 [1.05, 8.43]	1993
Kliegman, 1994	11	20	46	321	3.2%	7.31 [2.87, 18.60]	1994
Eyler 1994	81	168	53	168	5.8%	2.02 [1.30, 3.15]	1994
Shiono, 1995	27	175	868	7295	6.0%	1.35 [0.89, 2.05]	1995
Miller 1995	47	138	60	276	5.8%	1.86 [1.18, 2.93]	1995
Kistin 1996	19	64	1043	13043	5.2%	4.86 [2.83, 8.34]	1996
Sprauve 1997	136	483	540	3158	7.1%	1.90 [1.53, 2.37]	1997
Richardson 1999	14	62	25	302	4.2%	3.23 [1.57, 6.66]	1999
Ogunyemi 2004	80	200	12	200	4.6%	10.44 [5.46, 19.98]	2004
Bada 2005	457	1068	1671	7559	7.5%	2.64 [2.31, 3.01]	2005
Total (95% CI)		**3675**		**36185**	**100.0%**	**3.38 [2.72, 4.21]**	
Total events	1253		4629				

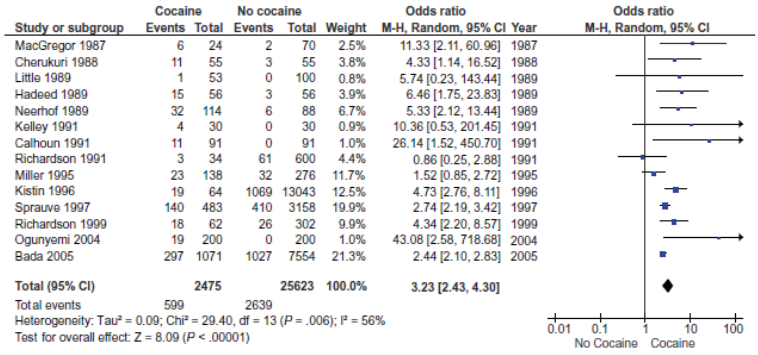
Heterogeneity: Tau² = 0.16; Chi² = 84.24, df = 23 (*P* < .00001); I² = 73%
Test for overall effect: Z = 10.92 (*P* < .00001)

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)



Study or subgroup	Cocaine Events	Cocaine Total	No cocaine Events	No cocaine Total	Weight	Odds ratio M-H, Random, 95% CI	Year
MacGregor 1987	6	24	2	70	2.5%	11.33 [2.11, 60.96]	1987
Cherukuri 1988	11	55	3	55	3.8%	4.33 [1.14, 16.52]	1988
Little 1989	1	53	0	100	0.8%	5.74 [0.23, 143.44]	1989
Hadeed 1989	15	56	3	56	3.9%	6.46 [1.75, 23.83]	1989
Neerhof 1989	32	114	6	88	6.7%	5.33 [2.12, 13.44]	1989
Kelley 1991	4	30	0	30	0.9%	10.36 [0.53, 201.45]	1991
Calhoun 1991	11	91	0	91	1.0%	26.14 [1.52, 450.70]	1991
Richardson 1991	3	34	61	600	4.4%	0.86 [0.25, 2.88]	1991
Miller 1995	23	138	32	276	11.7%	1.52 [0.85, 2.72]	1995
Kistin 1996	19	64	1069	13043	12.5%	4.73 [2.76, 8.11]	1996
Sprauve 1997	140	483	410	3158	19.9%	2.74 [2.19, 3.42]	1997
Richardson 1999	18	62	26	302	9.9%	4.34 [2.20, 8.57]	1999
Ogunyemi 2004	19	200	0	200	1.0%	43.08 [2.58, 718.68]	2004
Bada 2005	297	1071	1027	7554	21.3%	2.44 [2.10, 2.83]	2005
Total (95% CI)		**2475**		**25623**	**100.0%**	**3.23 [2.43, 4.30]**	
Total events	599		2639				

Heterogeneity: Tau² = 0.09; Chi² = 29.40, df = 13 (*P* = .006); I² = 56%
Test for overall effect: Z = 8.09 (*P* < .00001)

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

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

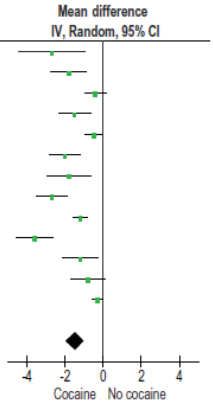
FIGURE 5

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

Study or subgroup	Cocaine Mean	SD	Total	No cocaine Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
MacGregor 1987	36.6	4.2	24	39.3	2	70	4.5%	-2.70 [-4.44, -0.96]	1987
Cherukuri 1988	37.4	3	55	39.2	1.9	55	7.3%	-1.80 [-2.74, -0.86]	1988
Little 1989	38.9	1.4	53	39.3	2.1	100	8.7%	-0.40 [-0.96, 0.16]	1989
Neerhof 1989	37.5	3.7	114	39	2.4	88	7.6%	-1.50 [-2.34, -0.66]	1989
Zuckerman 1989	38.8	2.3	114	39.3	1.9	1010	9.1%	-0.50 [-0.94, -0.06]	1989
Cohen 1991	36.9	3.3	83	38.9	2.4	166	7.8%	-2.00 [-2.80, -1.20]	1991
Kelley 1991	37.9	2.9	30	39.7	1.3	30	6.5%	-1.80 [-2.94, -0.66]	1991
Calhoun 1991	37	3.7	91	39.7	1.4	91	7.8%	-2.70 [-3.51, -1.89]	1991
Bateman 1993	38	2.7	361	39.2	2.1	387	9.3%	-1.20 [-1.55, -0.85]	1993
Singer 1994	34.9	4.1	100	38.5	2.8	100	7.1%	-3.60 [-4.57, -2.63]	1994
Eyler 1994	36.6	5	168	37.8	3.4	168	7.4%	-1.20 [-2.11, -0.29]	1994
Miller 1995	37	4.2	138	37.8	5	276	7.4%	-0.80 [-1.72, 0.12]	1995
Bandstra 2001	39.4	1.4	253	39.7	1.4	147	9.5%	-0.30 [-0.58, -0.02]	2001
Total (95% CI)			**1584**			**2688**	**100.0%**	**-1.47 [-1.97, -0.98]**	

Heterogeneity: Tau² = 0.66; Chi² = 93.93, df = 12 (*P* < .00001); I² = 87%

Test for overall effect: Z = 5.79 (*P* < .00001)



GA, gestational age.

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

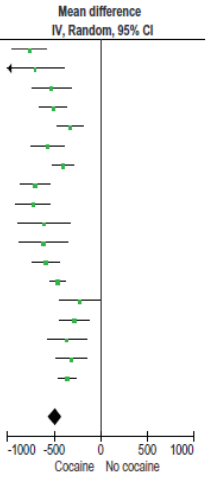
FIGURE 6

Effect of antenatal cocaine exposure on BW (grams)

Study or subgroup	No cocaine Mean	SD	Total	Cocaine Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Bingol 1987	2,464	590	42	3,232	475	307	5.3%	-768.00 [-954.18, -581.82]	1987
MacGregor 1987	2,677	706	24	3,382	551	70	3.2%	-705.00 [-1015.55, -394.45]	1987
Cherukuri 1988	2,528	619	55	3,056	500	55	4.8%	-528.00 [-738.29, -317.71]	1988
Hadeed 1989	2,795	448	56	3,305	345	56	6.2%	-510.00 [-658.10, -361.90]	1989
Little 1989	2,970	415	53	3,295	433	100	6.4%	-325.00 [-465.30, -184.70]	1989
Neerhof 1989	2,644	685	114	3,217	612	88	5.5%	-573.00 [-752.34, -393.66]	1989
Zuckerman 1989	2,847	572	114	3,254	617	1010	7.0%	-407.00 [-518.68, -295.32]	1989
Cohen 1991	2,556	642	83	3,263	558	166	5.9%	-707.00 [-869.12, -544.88]	1991
Calhoun 1991	2,613	757	91	3,340	494	91	5.4%	-727.00 [-912.72, -541.28]	1991
Spence 1991	2,520	1,077	63	3,127	777	348	3.7%	-607.00 [-885.19, -328.81]	1991
Kelley 1991	2,652	540	30	3,268	487	30	3.9%	-616.00 [-876.21, -355.79]	1991
McCalla 1991	2,560	778	128	3,151	699	983	6.3%	-591.00 [-732.69, -449.31]	1991
Bateman 1993	2,713	569	361	3,174	573	387	7.6%	-461.00 [-542.88, -379.12]	1993
Forman 1993	3,162	645	37	3,391	573	563	4.8%	-229.00 [-442.15, -15.85]	1993
Eyler 1994	2,704	742	168	2,988	721	168	6.0%	-284.00 [-440.45, -127.55]	1994
Singer 1994	2,624	769	100	2,989	750	100	4.8%	-365.00 [-575.54, -154.46]	1994
Miller 1995	2,626	721	138	2,943	926	276	5.9%	-317.00 [-479.50, -154.50]	1995
Bandstra 2001	2,971	474	253	3,331	514	147	7.2%	-360.00 [-461.57, -258.43]	2001
Total (95% CI)			**1910**			**4945**	**100.0%**	**-491.52 [-562.18, -420.85]**	

Heterogeneity: Tau² = 15296.60; Chi² = 58.96, df = 17 (*P* < .00001); I² = 71%

Test for overall effect: Z = 13.63 (*P* < .00001)



BW, birthweight.

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

TABLE 2
Sensitivity/subgroup analysis

		PTB		LBW	
Variable	Group	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.

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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.

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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

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/s/

JANE E LIEDTKA
06/12/2018

MIRIAM C DINATALE
06/13/2018

LYNNE P YAO
06/14/2018

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:	March 19, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209575
Product Name and Strength:	Numbrino (cocaine hydrochloride) Topical Solution 4% and 10%
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Cody Laboratories
Submission Date:	September 21, 2017 and December 7, 2017
OSE RCM #:	2017-1951
DMEPA Safety Evaluator:	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 N/A
FDA Adverse Event Reporting System (FAERS)*	E N/A
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 marketed unapproved products, like cocaine topical solution, to seek approval of an NDA for their product. The FDA reviews the data submitted as part of the NDA to assess if the proposed product meets modern safety and efficacy standards. Cody Laboratories submitted their marketed unapproved product via the 505(b)(2) pathway for approval, 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 strength statement does not contain an equivalency statement for the cocaine base and the strength is not expressed as the concentration per milliliter (e.g. 40 mg/mL or (b) (4)) in addition to the percentage (4% or 10%). This aligns with the Office of Pharmaceutical Quality (OPQ) recommendation in NDA 209963, Goprelto (cocaine

hydrochloride) topical solution.[a] We defer to OPQ on the addition of the equivalency statement and strength expression in a concentration per milliliter (mg/mL) format to coincide with the percent (%) strength.

- As currently presented, the format for the expiration date is not defined. Health care professionals 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 professionals misinterpret the statement as an affirmative statement.

- (b) (4) This statement is incorrect.

Prescribing Information

We identified the following in our risk assessment of the Prescribing Information:

- Health care professionals can misinterpret the statement 'Not for injection or Ophthalmic Use' found in the Prescribing Information. 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 professionals misinterpret the statement as an affirmative statement.

- The PI does not indicate that the pledgets are supplied separately. To minimize confusion, this information should be included in the PI.

We provide recommendations in Sections 4.1 and 4.2 to address our findings of the container label, carton labeling, and prescribing information.

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. OPQ Strength and Equivalent Statement

1. The strength statement does not contain an equivalency statement for the cocaine base and the strength is not expressed as concentration per milliliter (40

[a] Schlick J. Label and Labeling Review MEMO for Cocaine Hydrochloride Topical Solution (NDA 209963). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 09. RCM No.: 2016-2721-2.

mg/mL or (b) (4)) in addition to the percentage (4% or 10%). This aligns with the OPQ recommendation in NDA 209963, Goprelto (cocaine hydrochloride) topical solution. We defer to OPQ on the addition of the equivalency statement and strength expression in a concentration per milliliter 'mg/mL' format to coincide with the '%' strength for the container label, carton labeling and Prescribing Information.

B. Prescribing Information

1. Health care professionals can misinterpret the statement 'Not for injection or Ophthalmic Use' found in the Prescribing Information. 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 professionals misinterpret the statement as an affirmative statement. We recommend revising the statement to read 'For Topical Use Only. Not for Injection or Ophthalmic Use' in the Highlights Section of the PI (Warnings and Precautions), before Section 1 (Indications and Usage), and in Section 5 (Warnings and Precautions) in the Full PI.

2. To minimize confusion, we recommend indicating that the pledgets are sold separately in the Full Prescribing Section 2, *Dosage and Administration*.

4.2 RECOMMENDATIONS FOR CODY LABORATORIES

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

A. Container Label and Carton Labeling

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either below:
   - DDMMMYYYY (e.g., 31JAN2013);
   - MMMYYYY (e.g., JAN2013);
   - YYYY-MMM-DD (e.g., 2013-JAN-31); or
   - YYYY-MM-DD (e.g., 2013-01-31)

2. 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 misinterpreted as the opposite of the intended meaning. The reader can overlook the word 'not', and interpret the statement as an affirmative statement.

B. Carton Labeling (also see recommendations above)

1. [redacted] (b) (4) ".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Numbrino that Cody Laboratories submitted on September 21, 2017.

Table 2. Relevant Product Information for Numbrino	
Initial Approval Date	N/A
Active Ingredient	Cocaine Hydrochloride
Indication	Introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities.
Route of Administration	Intranasal
Dosage Form	Topical Solution
Strength	4% (40 mg/mL) and 10% ([(b) (4)])
Dose and Frequency	80 mg to 400 mg per procedure Administration: Apply one or two pledgets to each nostril for 20 minutes. Remove pledgets immediately prior to the procedure.
How Supplied/Container Closure	4% - Single-use 4 mL bottle and Multi-dose 10 mL bottle [(b) (4)] Each bottle is packaged in a carton
Storage	Room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 7, 2017, we searched DMEPA's previous reviews using the terms, cocaine. Our search identified one previous review which we used to inform our current review.

Schlick, J. Label and Labeling Review for Goprelto NDA 209963. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); May 11, 2017. RCM No.: 2017-1951.

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,[b] along with postmarket medication error data, we reviewed the following Numbrino labels and labeling submitted by Cody Laboratories on September 21, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container Labels 200%

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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

/s/

JAMES H SCHLICK
03/19/2018

OTTO L TOWNSEND
03/19/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 21, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to NDA 209575

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 10/20/2017 regarding review of QT information included in a NDA submission. The QT-IRT reviewed the following materials:

- Request for waiver for TQT study submitted to NDA 209575 under sequence 0001 dated 9/21/2017;
- Information request dated 2/15/2018 in DARRTs;
- Response to information requested submitted to NDA 209575 under sequence 0010 dated 02/20/2018;
- Proposed label submitted to NDA 209575 under sequence 0004 dated 12/07/2017;
- Previous QT-IRT review for NDA 209963 dated 04/24/2017;
- Summary of Clinical Safety submitted to NDA 209575 under sequence 0001 dated 09/21/2017; and
- Highlights of clinical pharmacology and cardiac safety submitted to NDA 209757 under sequence #0002 dated 11/14/2017.

1. QT-IRT Responses

Question: DAAAP has received a new NDA for Topical Cocaine. Although the Sponsor did not submit a dedicated QT study, they have conducted a subpopulation analysis of their Phase 3 study to satisfy the TQT requirements. DAAAP is requesting that the QT-IRT review this and provide comments regarding the adequacy of the subpopulation analysis to satisfy the TQT requirements.

QT-IRT's response for DAAAP: ECG data were collected in two phase 3 studies in patients and in one healthy volunteer study, however, the ECG data submitted from these studies are not adequate to satisfy the TQT requirement because two reasons.

1. Patient ECG data: Both phase 3 studies included collection of 12-lead ECGs at screening and after phase 1 recovery (> 90 min post-dose). The timing of the 12-lead ECGs that were collected is not adequate to permit quantification of the effects of cocaine on the QTc interval as the T_{max} of cocaine is ~30 min. In addition, monitoring ECGs were collected, which appears to cover the time of peak cocaine concentration, but no QT data was submitted from these ECGs. An IR was sent to the Applicant (DARRTS 02/20/2018) requesting submission of these data. The Applicant responded to the IR stating that no quantitative ECG measurements were collected from these ECGs per the SPA-approved Case Report Forms (NDA 209575, sequence 0010).

2. Healthy volunteer ECG data: The first post-dose ECG in this study was ~1 h 20 min post-dose and does therefore not capture the time of peak cocaine concentration. Additionally, the study did not include a positive control or sufficiently high exposures to waive the requirement for a positive control.

In addition, we note that the peak plasma concentration of cocaine following the maximum recommended dose (400 mg) exceeds the supratherapeutic dose included in the TQT study for another cocaine containing product GOPRELTO (NUMBRINO: 433 ng/mL; GOPRELTO: 146 ng/mL).

The TQT study for GOPRELTO was previously reviewed by the QT-IRT (DARRTS 04/24/2017). The review notes a concentration-dependent increase in QTc and heart rate (~15 bpm at the supratherapeutic dose), the latter which might confound the interpretation of the QTc changes. However, as the upper bound was <10 ms for both doses and the supratherapeutic dose is expected to be more than the highest clinically relevant exposures, the review concluded minimal risk of clinically relevant QTc prolongation following a single dose.

Because of the limitations of the ECG data included in this NDA and the increased peak plasma concentration of cocaine we recommend that the Applicant conducts a TQT study to characterize the effects of their product on the QTc interval. We defer to the Division whether the study should be conducted pre- or post-approval. If a TQT study is recommended, the Applicant should submit a protocol to the FDA for review, which should include a proposal for how to account for increases in heart rate when characterizing the drug effect on the QTc interval [for design and analysis considerations, see Garnett *et al*. Characterize the QT/Corrected QT Interval in the Presence of Drug-Induced Heart Rate Changes and Other Autonomic Effects. Am Heart J. 2012 Jun;163(6):912-30].

2. BACKGROUND

Product Information

Cocaine HCl Topical Solution, 4% (40 mg) and 10% ([(b) (4)] is indicated for the introduction of topical anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities.

The Applicant is proposing one or two pledgets (containing 1 mL of cocaine HCl solution) to be applied per nostril with a maximum of 2 pledgets per nostril or 4 pledgets per procedure.

Reviewer's Comment: The maximum proposed dose in the label is 4 pledgets (2 per nostril), which equates to up to 400 mg cocaine HCl and is excess of the only other cocaine HCl containing product (GOPRELTO: 160 mg).

Preclinical cardiac safety

No nonclinical in vitro or in vivo QT studies were performed by the Sponsor under the ICH S7B guidance. Single dose, single use regimen was not expected to have any significant QT or QTc interval prolongation, and this was confirmed in the Sponsor's Phase I and Phase III clinical trials.

Reviewer's Comment: The reviewer does not agree with the Applicants conclusion as cocaine is thought to inhibit the hERG potassium channel and prolong the QTc interval as noted in our review of NDA 209963, however, the increase in HR confounds the analysis (DARRTs 04/24/2017). Lastly, there are also literature reports of QTc increase as well as torsade with cocaine (Haigney et al. 2006).

Clinical cardiac safety

ECGs were collected in the three clinical studies included in this NDA and information about study design and ECG is included in Table 1 and summarized below.

The ECG collection in the healthy volunteer study (LNT-P6-733) is not adequate to capture the effects of the product as the first ECG is 1 h after pledget removal or 1 h 20 min after administration of the dose and the time of peak plasma concentration is ~30 min post-dose.

Similarly, the 12-lead ECGs collected in the two patient studies (COCA4vs10-001 and COCA4vs10-002) do not allow for characterizing the QT effects, as they were collected pre-dose and at the end of the procedure. In addition, to the 12-lead ECGs, monitoring ECGs were collected starting pre-dose, every 5 ± 2 min until the end of the procedure. However, QTc measurements for these ECGs were requested (DARRTs 2/15/2018) and the Applicant responded that they are not available.

Overall, none of the studies included in the NDA includes sufficient ECG collection to characterize the QT effect of the drug or allow for detection of delayed effects.

Table 1: Overview of ECG/PK collection across clinical studies in NDA 209575

Study (Population)	Design	Arms	ECG	PK
LNT-P6-733 (Healthy volunteers)	Cross-over, BA study of 4% and 10% solution	4% solution (160 mg) 10% solution (400 mg) Placebo topical solution	Before each period, 1, 2, 4 and 6.5 h after pledget removal (20 min after initiation)	0.08, 0.17, 0.25, 0.33 (after pledget was removed), 0.5, 0.75, 1, 1.5, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 h after placement
COCA4-vs10-001 (Patients)	Placebo-controlled, parallel-group study with two phases. First phase: safety/efficacy of two doses vs placebo. Second phase: safety for the two dose groups.	Phase 1 (n=120): 4% solution 10% solution Placebo Phase 2 (n=476): 4% solution 10% solution	12-lead ECG: - Screening and discharge of phase 1 recovery (≥ 90 min) Monitoring ECG: - Prior to and after administration of drug (every 5 min +- 2 min until discharge from phase 1 recovery)	No PK
COCA4-VS10-002 (Patients)	Placebo-controlled, parallel group study	4% solution (n=259) 10% solution (n=259) Placebo (n=128)	12-lead ECG: - Screening and discharge of phase 1 recovery (≥ 90 min) Monitoring ECG: - Prior to and after administration of drug (every 5 min +- 2 min until discharge from phase 1 recovery)	No PK

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Table 2: Highlights of clinical pharmacology and cardiac safety

Therapeutic dose and exposure	The maximum proposed dosing regimen is a single dose of 160 mg for the Cocaine HCl Topical Solution, 4% or a single dose of 400 mg for the Cocaine HCl Topical Solution, 10% applied topically via pledgets (for 20 minutes) to the accessible mucous membranes of the nasal cavities. Cocaine HCl Topical Solution, 4%, 160 mg dose: Cmax Mean=142.68 ng/mL (44.9%), AUC (0-inf)=286.68 ng ▪ hr/mL (45.6%) Cocaine HCl Topical Solution, 10%, 400 mg dose: Cmax Mean=433.53 ng/mL (49.3%), AUC (0-inf)=960.09 ng ▪ hr/mL (43.1%) There is no steady state exposure; the product is a single (one-time) dose.	
Maximum tolerated dose (MTD)	An MTD was not studied. The maximum dose studied in both Phase III clinical trials was 400 mg applied topically to the mucous membranes of the nasal cavities. A rat NOAEL dose was not determined from the Sponsor's 14-day in-vivo repeat dose study because no toxicities appeared in dosing specified in the protocol and topically applied to the mucous membranes of the nasal cavities for Cocaine HCl 4% solution at 5.4 to 9.6 mg/kg and Cocaine HCl 10% solution at 13.5 to 23.7 mg/kg.	
Principal adverse events	The most common adverse events were reversible hypertension, tachycardia, increased heart rate, QT interval prolongation, sinus tachycardia, diastolic hypertension, bradycardia, QRS complex prolongation, tachycardia paroxysmal, headache and anxiety. A clinically insignificant prolongation of the mean QT interval was observed in the safety population for the Cocaine HCl Topical Solution 4% treatment (5.72 msec), Cocaine HCl Topical Solution 10% treatment (3.51 msec), and placebo (7.51 msec) groups from baseline (ISS, Appendix Table 57).	
Maximum dose tested	Single Dose	The maximum single dose was 400 mg (4 mL of the Cocaine HCl Topical Solution, 10%) applied topically to the accessible mucous membranes of the nasal cavities.
	Multiple Dose	As per its intended use, this is a single-dose/single-use product. No multiple dose studies were conducted in the Sponsor's clinical trials.
Exposures Achieved at Maximum Tested Dose	Single Dose	Cocaine HCl Topical Solution, 4%, 160 mg dose: Cmax Mean=142.68 ng/mL (44.9%), AUC (0-inf)=286.68 ng ▪ hr/mL (45.6%) Cocaine HCl Topical Solution,10%, 400 mg dose:

		Cmax Mean=433.53 ng/mL (49.3%), AUC (0-inf)=960.09 ng ▪ hr/mL (43.1%)
	Multiple Dose	As per its intended use, this is a single-dose/single-use product. No multiple dose studies were conducted in the Sponsor's clinical trials.
Range of linear PK	160 mg to 400 mg, as a single dose.	
Accumulation at steady state	Not applicable. As per its intended use, this is a single-dose, single-use product.	

<table>
<tr><td>Metabolites</td><td colspan="3">• Benzoylecgonine (40-45% of cocaine’s systemic metabolism) - inactive
• Ecgonine Methyl Ester (40-45% of cocaine’s systemic metabolism) - inactive
• Ecgonine (<5% of cocaine’s systemic metabolism) - inactive
• Norcocaine (5-10% of cocaine’s systemic metabolism) - active; only observed at very low serum concentrations or undetectable
Reference is made to the Clinical Pharmacology Summary in Module 2.7.2.</td></tr>
<tr><td rowspan="6">Absorption</td><td>Absolute/Relative Bioavailability</td><td colspan="2">Cocaine HCl Topical Solution, 4%:
Mean 23.44% (SD 8.876%) via pledget administration for 20 minutes to the nasal mucosa.

Cocaine HCl Topical Solution, 10%:
Mean 33.34% (SD 10.710%) via pledget administration for 20 minutes to the nasal mucosa.</td></tr>
<tr><td rowspan="5">Tmax</td><td>Cocaine</td><td>4% product: Median 0.5 hours (0.17-1.00)

10% product: Median 0.5 hours (0.33-1.00)</td></tr>
<tr><td>Benzoylecgonine</td><td>4% product: Median 2.5 hours (1.00-4.03)

10% product: Median 3.00 hours (1.50-4.00)</td></tr>
<tr><td>Ecgonine Methyl Ester</td><td>4% product: Median 2.5 hours (1.00-3.50)

10% product: Median 2.5 hours (1.50-4.00)</td></tr>
<tr><td>Ecgonine</td><td>4% product: Median 8.00 hours (4.00-12.00)

10% product: Median 6.00 hours (4.00-8.07)</td></tr>
<tr><td>Norcocaine</td><td>4% product: Median 1.50 hours (0.75-2.00)

10% product: Median 0.5 hours (1.00-2.50)</td></tr>
</table>

Distribution	Vd/F or Vd	Not studied in the Sponsor's clinical studies. Sponsor provided published literature in Module 2.7.2 indicating volume of distribution of 2 L/kg.	
	% bound	Not studied in the Sponsor's clinical studies. Sponsor provided published literature in Module 2.7.2 indicating cocaine is highly bound to serum proteins (92-96%).	
Elimination	Route	The primary route of cocaine elimination is almost exclusively excretion in the urine as metabolites, with benzoylecgonine and ecgonine methyl ester constituting at least 80% of cocaine's metabolites, detected in the urine for 14-60 hours after cocaine administration, as per Module 2.7.2. Cocaine HCl Topical Solution, 4%: Ae (mg) Mean 0.293 (72.0), fe(%) 0.18 (72.0) Cocaine HCl Topical Solution, 10%: Ae (mg) Mean 0.895 (116.7), fe(%) 0.22 (116.7)	
	Terminal t½	Cocaine	4% product: Mean 1.54 hours (% CV 13.5) 10% product: Mean 2.01 hours (% CV 36.8)
		Benzoylecgonine	4% product: Mean 7.06 hours (% CV 21.3) 10% product: Mean 6.91 hours (% CV 20.6)
		Ecgonine Methyl Ester	4% product: Mean 4.30 hours (% CV 18.2) 10% product: Mean 4.30 hours (% CV 17.4)
		Ecgonine	4% product: Mean 10.11 hours (% CV 11.0) 10 % product: Mean 10.52 hours (% CV 12.6)
		Norcocaine	4% product: Mean 2.26 hours (% CV 11.6) 10% product: Mean 2.69 hours (% CV 61.7)

	CL/F or CL	Not studied in the Sponsor's clinical studies. The Sponsor provided published literature in Module 2.7.2 indicating clearance of 2L/min.
Intrinsic Factors	Age	PK parameters by age (pediatric/adult/elderly) were not evaluated in the Sponsor's clinical studies. All subjects were healthy and between the ages of 20 to 40 years old. However, the individual PK data by subject including age information are available in the PK Clinical Trial Study Report in Module 5.3.3.1. Mean PK parameters by age did not vary significantly from the mean PK parameters overall, and were lower than the %CV overall for AUC(0-inf), AUC(0-t), and Cmax.
	Sex	PK parameters by sex were not evaluated in Sponsor's clinical studies. However, the individual PK data by subject including sex information are available in the PK Clinical Trial Study Report in Module 5.3.3.1. Mean PK parameters by sex did not vary significantly from the mean PK parameters overall, and were lower than the %CV overall for AUC(0-inf), AUC(0-t), and Cmax.
	Race	PK parameters by race were not evaluated in Sponsor's clinical studies. However, the individual PK data by subject including race information are available in the PK Clinical Trial Study Report in Module 5.3.3.1. Mean PK parameters by race did not vary significantly from the mean PK parameters overall, and were lower than the %CV overall for AUC(0-inf), AUC(0-t), and Cmax.
	Hepatic & Renal Impairment	Not studied by the Sponsor's clinical trials in subjects with hepatic or renal impairment
Extrinsic Factors	Drug interactions	Not studied in the Sponsor's clinical trials. The Sponsor provided published literature in Module 2.7.2 indicating interactions with CNS stimulants, cholinesterase inhibitors, sympathomimetics, alpha-modifying agents, monoamine oxidase inhibitors, tricyclic antidepressants, and halothane anesthetic.
	Food Effects	Food effects are not applicable to topical nasal mucosal delivery.
Expected High Clinical Exposure Scenario	(b) (4)	
Preclinical Cardiac Safety	No nonclinical *in vitro* or *in vivo* QT studies were performed by the Sponsor under the ICH S7B guidance. Single dose, single use regimen was not expected to have any significant QT or QTc interval prolongation, and this was confirmed in the Sponsor's Phase I and Phase III clinical trials.	
Clinical Cardiac Safety	There were three clinical studies including two Phase III clinical studies with a total of 805 subjects and one Phase I PK clinical study with 36 subjects. QT	

	and QTc were monitored before and after drug product application in all studies and no significant prolongation was observed. Please see the Sponsor QT/QTc waiver request in Module 1.12.5. There were no adverse events categorized as syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death.

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

/s/

LARS JOHANNESEN
02/21/2018

CHRISTINE E GARNETT
02/21/2018