CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209575Orig1s000

Trade Name:	NUMBRINO nasal solution, 4% (40 mg/mL)
Generic or Proper Name:	cocaine hydrochloride
Sponsor:	Cody Laboratories, Inc.
Approval Date:	January 10, 2020
Indication:	For the introduction of local anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities of adults.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 209575

NDA APPROVAL

Cody Laboratories, Inc.
9000 State Road
Philadelphia, PA 19136

Attention: Kristie Stephens
Vice President, Regulatory Affairs

Dear Ms. Stephens:

Please refer to your new drug application (NDA) dated and received September 21, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NUMBRINO (cocaine hydrochloride) nasal solution, 4% (40 mg/mL).

We acknowledge receipt of your amendment dated June 21, 2019, which constituted a complete response to our July 20, 2018, action letter.

This new drug application provides for the use of NUMBRINO for the introduction of local anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities of adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209575**. Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies according to the timetables listed below, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

3768-1 Conduct a juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing in children 12 years of age to less than 17 years of age.

The timetable you submitted on December 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	3/2020
Final Protocol Submission:	6/2020
Study Completion:	12/2020
Final Report Submission:	6/2021

3768-2 Conduct a multicenter trial to evaluate the pharmacokinetic and safety profiles of a single topical administration of NUMBRINO for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in pediatric subjects 12 years of age to less than 17 years of age.

The timetable you submitted on December 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	2/2020
Final Protocol Submission:	5/2020
Study Completion:	9/2021
Final Report Submission:	3/2022

Submit the protocols to your IND 106499 with a cross-reference letter to this NDA.

Reports of this/these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of fertility, embryo-fetal developmental, or pre-/post-natal developmental adverse events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3768-3 Conduct a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

The timetable you submitted on December 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	3/2021
Study Completion:	6/2021
Final Report Submission:	12/2021

3768-4 Conduct an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

The timetable you submitted on December 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2020
Final Protocol Submission:	1/2021
Study Completion:	2/2021
Final Report Submission:	10/2021

3768-5 Conduct an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

The timetable you submitted on December 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2020
Final Protocol Submission:	1/2021
Study Completion:	2/2021
Final Report Submission:	10/2021

3768-6 Conduct a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional assessments, and reproductive capacity of the offspring.

The timetable you submitted on December 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	1/2021
Final Protocol Submission:	3/2021
Study Completion:	10/2021
Final Report Submission:	4/2022

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

EXPIRATION DATING

NUMBRINO (cocaine hydrochloride) nasal solution, 4% (40 mg/mL) is granted an expiry dating of 14 months when stored at 20°C –25°C (68°F -77°F) with excursions permitted between 15° - 30°C (59° and 86° F).

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

Reference ID: 4563057

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Shelly Kapoor, PharmD, Regulatory Project Manager, at 240-402-2787.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
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