



NDA 208791

NDA APPROVAL

Sintetica SA
C/O VPCI, Inc
5640 W. Maple Road, Suite 312
West Bloomfield, MI 48322

Attention: Craig Kruman
US Agent

Dear Mr. Kruman:

Please refer to your New Drug Application (NDA) dated and received August, 26, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CLOROTEKAL (chlorprocaine HCl) 1% (10 mg/mL) Injection.

We acknowledge receipt of your major amendment dated March 17, 2017, which extended the goal date by three months.

This new drug application is indicated for the use of CLOROTEKAL for intrathecal injection for the production of subarachnoid block (spinal anesthesia) in adults undergoing surgical procedures. Indicated procedures include those suitable for CLOROTEKAL's short duration of action.

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 text.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208791.**” 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, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages birth to less than 17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by Section 505B(a) of the FDCA are required postmarketing studies. The status of the postmarketing studies must be reported annually according to 21 CFR 314.81 and Section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

3242-1 Conduct a multicenter, randomized, double-blind, sequential age-group, dose-response study to evaluate the safety and efficacy profile of a single intrathecal chloroprocaine injection for subarachnoid block (spinal anesthesia) in pediatric subjects birth to less than 17 years old undergoing surgical procedures.

Draft protocol Submission:	11/2017
Final Protocol Submission:	04/2018
Final Report Submission:	03/2022

3242-2 Conduct an intrathecal juvenile animal toxicology study to characterize the impact of chloroprocaine on neuronal development.

Final Protocol Submission:	11/2017
Study Completion:	08/2018
Final Report Submission:	03/2019

Submit the protocol to your IND 119674, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as new drug applications (NDAs) or as supplements 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:

- 1) Identify potential toxicity that could occur with higher than recommended dosage of CLOROTEKAL (chlorprocaine HCl) injection and to establish the no-observed-adverse-effect-level (NOAEL).

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 study:

- 3242-3 Conduct an adequate intrathecal toxicity study in a non-rodent species up to 28-days duration that not only defines a no-adverse-effect level, but also characterizes the toxicological potential of the drug product formulation. Submit justification for the study design prior to initiation of the study in order to obtain Division concurrence with the study design.

Draft protocol Submission:	11/2017
Final Protocol Submission:	05/2018
Study Completion:	12/2018
Final Report Submission:	10/2019

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o)**.

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 package insert, Medication Guide, and patient PI (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 (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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 Selma Kraft, Regulatory Project Manager, at (240) 402-9700.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RIGOBERTO A ROCA
09/26/2017