APPLICATION NUMBER:

208791Orig1s000

OTHER REVIEW(S)
### Application Information

<table>
<thead>
<tr>
<th>NDA # 208791</th>
<th>NDA Supplement #: S-</th>
<th>Efficacy Supplement Type SE-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name:</td>
<td>Established/Proper Name: Chloroprocaine HCl</td>
<td></td>
</tr>
<tr>
<td>Dosage Form: Injection</td>
<td>Strengths: 1%</td>
<td></td>
</tr>
<tr>
<td>Applicant: Sintetica SA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date of Receipt: August 26, 2016

PDUFA Goal Date: September 26, 2017

Action Goal Date (if different): September 7, 2017

RPM: Selma Kraft

Proposed Indication(s): Intrathecal Injection in adults for the production of subarachnoid block (Spinal Anesthesia)

### GENERAL INFORMATION

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

   YES [ ] NO [x]

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

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

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

<table>
<thead>
<tr>
<th>Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)</th>
<th>Information relied-upon (e.g., specific sections of the application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 009435- Nesacaine 1% Injection</td>
<td>FDA’s previous finding of safety and effectiveness</td>
</tr>
<tr>
<td>Published Literature</td>
<td>ClinPharm Data</td>
</tr>
<tr>
<td>Published Literature</td>
<td>Literature references were provided to justify the safety of extractables and leachables from the drug product container closure. A literature review</td>
</tr>
</tbody>
</table>
For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s).

For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

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

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

**Nonclinical information used for bridging to Nesacaine**

The systemic safety of the proposed product is covered by the Agency’s previous determination of safety of the reference product Nesacaine (chloroprocaine HCl Injection, USP; NDA 009435) because there is lower exposure with the proposed drug product. This justifies the reliance on the nonclinical reproduction and mutagenicity information from the Nesacaine label that will be used for Sections 8 and 13 of the proposed drug product labeling.

Reference to the published literature to support the safety of the extractables from the manufacturing equipment is scientifically justified. The published literature cited extractables that were demonstrated to come out of the tubing and filters (of the manufacturing equipment) under conditions of use and which presumably are exposed spinally to the patient. The data on these specific chemicals are scientifically relevant because the safety of the specific chemical in question and the toxicological profile of that chemical was compared to the worst-case exposures to the chemical following use of the drug product.

Reference to published studies about reproductive and developmental data or other toxicology data relevant to the safety profile of the chloroprocaine hydrochloride was required by the Agency as part of the standard review process; however, none of the data in the published studies were determined to alter the safety profile of the drug or impact labeling at this time. The published studies we reviewed did not test the drug product, as most toxicology studies do not test the drug product. However, the published studies did test the drug substance which is in the drug product and which is what the fetus (for reproductive and developmental effects) or person would be exposed to and therefore, the data are directly scientifically relevant to the risk assessment for the drug substance. The drug doses and/or exposures obtained in the published studies were compared to the exposures that would be obtained in humans via the drug product in order to put these findings into perspective.

**Clinical pharmacology Information used for bridging to Nesacaine**

The applicant did not conduct a relative bioavailability study between the proposed product, and the listed drug, Nesacaine. The bridge between the proposed product and the listed product is established by means of a scientific rationale which utilizes published literature. The scientific rationale compares data from a PK study where intrathecal...
administration of (8/9) did not result in any plasma levels, to published literature on higher doses of Nesacaine epidural infusion known to produce significantly high plasma levels of chloroprocaine. As such Nesacaine labeling does not include plasma level information on chloroprocaine following the indicated epidural route of administration. Therefore, the applicant used publications that directly cited Nesacaine or indicated the chloroprocaine product was obtained from Pennwalt Corporation the approved manufacturer of Nesacaine in 1980’s (See table below).

<table>
<thead>
<tr>
<th>Article</th>
<th>Drug Product</th>
<th>Information Derived</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’ Brien et al, 1979</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Declared in the article</td>
</tr>
<tr>
<td>Kuhnert et al, 1980</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Pennwalt Corporation* cited</td>
</tr>
<tr>
<td>Abboud et al, 1982</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Pennwalt Corporation cited</td>
</tr>
<tr>
<td>Kuhnert et al, 1983</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Pennwalt Corporation cited</td>
</tr>
<tr>
<td>Weiss et al., 1983</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Declared in the article</td>
</tr>
<tr>
<td>Philipson et al, 1985</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Pennwalt Corporation cited</td>
</tr>
<tr>
<td>Khrog et al, 1981</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Pennwalt Corporation cited</td>
</tr>
<tr>
<td>Kuhnert 1986</td>
<td>Nesacaine</td>
<td>Chloroprocaine and metabolite levels</td>
<td>Declared in the article</td>
</tr>
</tbody>
</table>

*first Marketing Authorization Holder of Nesacaine (currently Fresenius Kabi USA)

Since this is a local anesthesia, systemic exposure will provide information on systemic safety. The sponsor demonstrated that the systemic exposure of the new product is comparable or lower than the listed drug so they can rely on previous findings of systemic safety of the listed drug. The sponsor conducted their own clinical trial to demonstrate clinical efficacy of the new product. Hope this may answer the clinical bridge question.

**RELIANCE ON PUBLISHED LITERATURE**

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

If **NO**, “proceed to question #5.

---

Reference ID: 4158628  Version: January 2015
(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) listed drug product?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
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<tbody>
<tr>
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</tbody>
</table>

If “NO”, proceed to question #5.

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

Cicloproca HCl Injection (Nesacaine)

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

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
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<tbody>
<tr>
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</table>
RELIANCE ON LISTED DRUG(S)

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

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

   YES ☒ NO ☐

If “NO,” proceed to question #10.

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

<table>
<thead>
<tr>
<th>Name of Listed Drug</th>
<th>NDA #</th>
<th>Did applicant specify reliance on the product? (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NESACAIN (Chloroprocaine HCl Injection)</td>
<td>009435</td>
<td>Y</td>
</tr>
</tbody>
</table>

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

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

   N/A ☒ YES ☐ NO ☐

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

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

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

      YES ☐ NO ☒

If “YES”, please list which drug(s).

   b) Approved by the DESI process?

      YES ☐ NO ☒

If “YES”, please list which drug(s).

   c) Described in a final OTC drug monograph?

      YES ☐ NO ☒

If “YES”, please list which drug(s).
Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES □  NO ☒  
If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES □  NO ☒  
(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

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

This application provides for a new route of administration for the dosage strength.

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

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

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

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

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

YES □  NO ☒  

[Reference ID: 4158628]
If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.

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

YES ☐ NO ☐

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

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

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

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

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

YES ☒ NO ☐

If “NO”, proceed to question #12.

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

YES ☐ NO ☒

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

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in
the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Nesacaine (chloroprocaine HCl 10 mg/mL) 1% Injection, USP

**PATENT CERTIFICATION/STATEMENTS**

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

Listed drug/Patent number(s):

No patents listed ☒ proceed to question #14

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

YES ☐ NO ☐

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

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

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


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

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

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

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
   YES ☐ NO ☐  
   *If “NO”, please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
   YES ☐ NO ☐  
   *If “NO”, please contact the applicant and request the documentation.*

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

   Date(s):

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

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

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

   YES ☐ NO ☐  
   Patent owner(s) consent(s) to an immediate effective date of approval  ☐
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------------------
SELMA S KRAFT
09/26/2017
Clinical Inspection Summary

<table>
<thead>
<tr>
<th>Date</th>
<th>Thursday, September 15, 2017</th>
</tr>
</thead>
</table>
| From                  | John Lee, M.D., Medical Officer  
Janice Pohlman, M.D., M.P.H., Team Leader  
Kassa Ayalew, M.D., M.P.H., Branch Chief  
Good Clinical Practice Assessment Branch (GCPAB)  
Division of Clinical Compliance Evaluation (DCCE)  
Office of Scientific Investigations (OSI) |
| To                    | Selma Kraft, Pharm.D., Regulatory Project Manager  
Alla Bazini, M.D., Medical Officer  
Leah Crisafi, M.D., Medical Team Leader  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| Application           | NDA 208791                     |
| Applicant             | Sintetica SA                   |
| Drug                  | Chloroprocaine 1% Injection (Clorotekal®) |
| New Molecular Entity  | No                            |
| Review Priority       | Standard                      |
| Proposed Indication   | Subarachnoid block (intrathecal spinal anesthesia) in adults |
| Consultation Date     | January 26, 2017               |
| CIS Goal Date         | 5-19-2017 (original), 8-10-2017 (amended), 8-18-2017 (extended) |
| Action Goal Date      | September 26, 2017             |
| PDUFA Due Date        | September 26, 2017             |

I. OVERALL ASSESSMENT OF FINDINGS

Sintetica submitted this 505(b)(2) NDA to support the intrathecal use of chloroprocaine hydrochloride 1% (CH-1, Clorotekal®) in adults as a spinal anesthetic (subarachnoid block). The NDA relies on Nesacaine® (chloroprocaine, NDA 009435) as the reference product and is supported by the literature and four applicant-sponsored studies, three blinded randomized controlled trials (BRCTs, two Phase 2 and one Phase 3) and an uncontrolled (Phase 4, open-label, single-arm) observational safety study.

The three applicant-sponsored BRCTs of CH-1 were audited at good clinical practice (GCP) inspections of four clinical investigator (CI) sites. The two dose-finding (Phase 2) studies were each audited at the only participating CI site, Study CHL1/02-2004 conducted entirely by Guido Fanelli (Parma, Italy) and Study CHL1/02-2014 conducted entirely by Stefano Bonarelli (Bologna, Italy). The Phase 3 Study CHL1/02-2006/M was audited at two CI sites, at Site 02 (F. W. Hinnerk Wulf; Marburg, Germany) and at Site 03 (Claudio Camponovo; Lugano, Switzerland). Of the five total study-sites in the three BRCTs (one for each Phase 2 study, three for Phase 3 study), four were inspected (all except one site in Phase 3 study), and data reliability was examined for 190 of the 220 subjects (86%) in the three studies combined (applicant-sponsored BRCTs). These studies were not conducted under the IND. Data submitted in support of this marketing application were solely based on foreign data from non-IND sites.
For all four CI inspections, a Form FDA 483, Inspectional Observations was issued as summarized below.

- Dr. Guido Fanelli: For the earlier (2004) Phase 2 dose-finding (and dose-blinded assessor) Study CHL1/02-2004: the lack of source records makes it difficult to establish the reliability of the data reported by this site, particularly with many GCP non-compliant data corrections.

- Dr. Stefano Bonarelli: For the later (2014) Phase 2 dose-finding (and dose-blinded assessor) Study CHL1/02-2014: based upon the CI’s 483 response, the explanation of the role of the unblinded anesthesiologist in continuing care in the OR is concerning for potential introduction of bias in terms of any ancillary care administered and assessment of safety by the unblinded anesthesiologist. The review division will need to determine whether the continued care and decisions by the unblinded anesthesiologist in the OR could substantially bias the results of the dose finding, including the review division’s planned post hoc efficacy assessment of the product.

- Dr. Claudio Camponovo (Site #3): There were no clear delineations in staff participating in study designated as blinded versus unblinded for each subject. For 7 of 13 subjects (over half of the 16.5% of study subjects’ records reviewed at this site, the unblinded investigator participated in post-operative assessments (i.e. discharge assessment or 24 hour and 7 day follow-up for TNS symptoms). The review division seriously needs to consider whether the uncertainty in blinding and potential introduction of bias that could be introduced in the analyses for investigators unblinded to treatment assignment performing continued activities in the OR and conducting 24 hour and 7 day follow-up TNS assessments. There were also a number of protocol violations and inaccurate case histories reported from this site.

- Dr. Friedrich Wulf (Site #2): There were record keeping related protocol violations noted at this site. Although regulatory violations were noted, they are unlikely to significantly impact primary safety and efficacy analyses.

Based upon significant inspectional findings such as lack of original study source documents, inconsistencies between medical records provided by the site and copies of the case report forms provided by the sponsor as well as lack of adequate blinded assessments and documentation as to who completed the blinded assessments at Drs. Guido Fanelli, Stefano Bonarelli and Claudio Camponovo clinical sites, we concluded that the study was not conducted according to the Good Clinical Practice standards at these CI sites.

Because of issues related to unblinding, it is recommended the review division evaluates the data from the above three sites as if they were obtained from an open label study.

II. BACKGROUND

As a short-acting local anesthetic, lidocaine is widely used for (intrathecal) spinal anesthesia despite transient neurological symptoms (TNS) often seen following its use. Chloroprocaine is similar to lidocaine in latency and duration (half-life < 60 seconds) and
appears to be as effective but with less frequent TNS. Based on the literature and two BRCTs sponsored by Sintetica (CHL1/02-2004 and CHL1/02-2006/M), CH-1 (50 mg) was first approved in Germany in 2012 for spinal anesthesia in adult surgery not exceeding 40 minutes. Since, CH-1 (50 mg) has been approved in 8 other countries in Europe (Austria, Belgium, France, Ireland, Italy, Poland, Spain, and United Kingdom) for the same indication. The two applicant-sponsored studies (apparently) were not originally intended to support a regulatory submission in the United States and were not conducted under an IND. This NDA is supported by the literature and four applicant-sponsored studies: (1) the two earlier BRCTs, CHL1/02-2004 and CHL1/02-2006 (2) a more recent Phase 2 BRCT CHL1/02-2014 conducted (also not under an IND) to re-examine CH-1 dose response, and (3) an uncontrolled Phase 4 observational TNS safety study. Of the four applicant-sponsored studies, the three BRCTs were audited to support this NDA review.

**Study CHL1/02-2004 (Phase 2)**

*Spinal Anesthesia with 2-Chloroprocaine 1% for Lower Limb Procedures of Short Duration: A Prospective, Randomized, Blind, Dose-Finding Study*

This randomized dose-finding study was conducted between 2004 and 2005 at a single CI site in Italy, in 45 subjects scheduled for elective lower limb surgery. The primary study objective was to evaluate and compare three intrathecal doses of CH-1 (30, 40, and 50 mg) for efficacy in inducing spinal anesthesia.

- **Primary endpoint (Sponsor's):** time to end of anesthesia (Tea) from end of anesthetic injection, determined based on resolution of sensory and motor blocks, unassisted ambulation, and spontaneous voluntary urine voiding.

- **Sponsor-reported study outcome:** CH-1 at doses of 40 or 50 mg (but not 30 mg) appeared to provide adequate spinal anesthesia for up to 60 minutes, sufficient to complete lower limb procedures as outpatients.

**Study CHL1/02-2014 (Phase 2)**

*Spinal anesthesia with Chloroprocaine HCl 1% for elective lower limb procedures of short duration: a prospective, randomised, observer-blind study in adult patients*

This repeat dose-finding study was conducted at a single site in Italy (different from the site in the 2004 study) in 2014 (10 years after original study) to: (1) revisit the efficacy of 30 mg (deemed ineffective in the 2004 study), (2) evaluate CH-1 pharmacokinetics (PK), and (3) confirm previous findings with greater attention to GCP.

- **Primary Endpoint (Sponsor’s):** time to end of anesthesia (Tea)

- **Sponsor-reported study outcome:** For anesthesia efficacy, 40 and 50 mg were effective in all subjects (not significantly different) and 30 mg was effective in most subjects (83%). Rescue analgesia was not required with 50 mg. When required with 30 or 40 mg, timing (Tra) was not significantly different for the two dose levels. No treatment-emergent adverse events were reported through 7 days after surgery.
Study CHL1/02-2006/M (Phase 3)

Prospective, blind-observer, randomised clinical study to investigate and compare the efficacy of intrathecal plain solutions containing Chloroprocaine 1% (50 mg) versus Bupivacaine 0.5% (10 mg)

This Phase 3 randomized controlled study was conducted between 2007 and 2008, in between the two Phase 2 dose-finding studies (2004 and 2014), at three CI sites in Europe (Italy, Germany, and Switzerland) in 120 subjects scheduled for elective lower abdominal (gynecology or urology) surgery of short-duration (expected to take no longer than 40 minutes) requiring no more than T-10 sensory block. The primary study objective was to show that intrathecal CH-1 (50 mg) is not inferior to intrathecal bupivacaine 0.5% (10 mg) for spinal anesthesia.

For this Phase 3 study, two (of three) CI sites were selected for inspection, based on: (1) large subject enrollment (80 of 130) at Site 03, and (2) an NDA review concern, high rates of rescue medication use for anxiety and/or analgesia for both test and control arms at Site 02. The CI at Site 01 in Italy was the same as the CI for the 2004 study (Guido Fanelli).

Study Assessment

- Primary efficacy endpoint: Time to sensory block (Tsb) at T-10 (different from Tea in Phase 2 studies CHL1/02-2004 and CHL1/02-2014)
- Major secondary efficacy endpoints: similar as in Phase 2 studies, including Time to motor block (Tmb), Time to readiness for surgery (Trs), Time to surgery start (Tss), Time to surgery end (Tes) Time to resolution of motor block (Tmr)
- Sponsor-reported study outcome: Intrathecal CH-1 (50 mg) was adequate as a spinal anesthetic for urological or gynecological lower abdominal surgery lasting < 40 minutes. Surgical anesthesia, recovery from anesthesia, and home discharge were significantly quicker with CH-1 than with bupivacaine 0.5% (10 mg), with a more favorable safety profile.
- Study blind: unblinded investigator administers known study medication (CH-1 50 mg or bupivacaine 10 mg) and a different unblinded (co)investigator assesses efficacy and safety
- Assessment of adequacy of spinal block and resolution: evolution of nerve block evaluated by blinded observer, serial assessment: every one minute until ready for surgery, every 5 minutes until maximum (3 consecutive observations for same sensory level), and every 30 minutes until sensory regression to S-1 (ready for home discharge)
- TNS assessment using prepared questionnaire: to be evaluated at 24 hours and 7 days after surgery by blinded (co)investigator including general health, fatigue, nausea, vomiting, dizziness, any difficulty in elimination (voiding or stool), and pain (intensity and location, including injection site and anesthetized areas)
### III. RESULTS (by Site)

<table>
<thead>
<tr>
<th>Clinical Investigator/Address/Site#</th>
<th>Study Enrollment</th>
<th>Inspection Date</th>
<th>Compliance Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guido Fanelli Azienda Ospedaliera di Parma Via Gramsci, 14-43126 Parma, Italy (single site)</td>
<td>CHL1/02-2004 45 subjects</td>
<td>May 8 – 12, 2017</td>
<td>VAI</td>
</tr>
<tr>
<td>Stefano Bonarelli Istituto Ortopedico Rizzoli Struttura Complessa per Anestesia Bologna, Italy (single site)</td>
<td>CHL1/02-2014 45 subjects</td>
<td>May 15 – 19, 2017</td>
<td>Pending: Preliminary VAI</td>
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<td>Claudio Camponovo Ospedale Regionale di Lugano Via Tesserete 46 CH-6903 Lugano, Switzerland Site 03</td>
<td>CHL1/02-2006/M 80 subjects</td>
<td>May 2 – 5, 2017</td>
<td>VAI</td>
</tr>
<tr>
<td>Friedrich W. Hinnerk Wulf Univ Hosp Giessen &amp; Marburg Baldingerstrasse 1-D 35033 Marburg, Germany Site 02</td>
<td>CHL1/02-2006/M 20 subjects</td>
<td>June 12 – 16, 2017</td>
<td>VAI</td>
</tr>
</tbody>
</table>

**Key to Compliance Classification of Inspection**

NAI = No Action Indicated, no significant deviations from regulations  
VAI = Voluntary Action Indicated, minor deviations from regulations  
OAI = Official Action Indicated, major deviations from regulations

For three CI sites, the establishment inspection report (EIR) has been received from the field office (Fanelli, Wulf, Camponovo) and reviewed by OSI. The classification will be finalized once correspondence is issued to the inspected entity.

The EIR for the inspection of Dr. Bonarelli has not been received from the field office. Preliminary classification is based upon communication with the field, the Form FDA 483 issued, and the CI’s response to the 483. An addendum to this clinical inspection summary (CIS) may be forwarded to the review division if new significant findings are discovered at EIR review; otherwise, OSI’s written post-inspection correspondence to the CI (to be copied to review division) indicates completion of EIR review and confirmation of the inspectional findings as reported in this CIS.

1. **Guido Fanelli, M.D.**

   **Study CHL1/02-2004:** This early Phase 2 dose-finding study was conducted over 10 years ago entirely at this single CI site in Italy (not under US IND). The original CIs were not available on-site and who was not involved with the conduct of the
study, assisted with the inspection. Much of the original (source) study records were apparently no longer available for inspectional review. The only documents remaining on site were the original signed informed consent documents for the participating subjects. Copies of pre-anesthesia screening, operative notes (anesthesia records), and other medical information from around the time of surgery were provided by the hospital administrator. Some summary-level study records (paper case report forms) and clinical site regulatory documents (such as Ethics Committee approval, monitoring records, copy of screening log) were provided by the sponsor.

At this CI site, 45 subjects were screened, 44 subjects enrolled, and 43 subjects completed the study (based on copy of screening log provided by the sponsor). Case records were reviewed for all subjects, including detailed review for 12 subjects completing the study. A Form FDA 483 was issued for the following deficiencies:

- **Recordkeeping, inadequate documentation or record retention:**
  - Failure to maintain study records including regulatory and pharmacy documents (such as EC review and approval of the protocol and informed consent, sponsor monitoring records, investigational product accountability records, and screening and enrollment documents) and study worksheets used to document efficacy and AE assessments. The sponsor-provided copies of the case report form corresponded to these study worksheets.
  
  **OSI Reviewer Comment:** This study was performed in 2004 and was not under IND. The study was submitted to the NDA initially as a literature publication with no raw data. The sponsor was able to confirm that at the time of site close-out in 2005, those records existed. Copies of the documents were provided by the sponsor to the site for the inspection.

  - Sponsor provided copies of case report forms for randomization and unblinded study medication administration and subsequent operative and post-operative assessments by a blinded anesthesiologist were not always signed and dated.

  - For Subject #26, Dr. Berti signed the randomization form and was the unblinded anesthesiologist. The CRF however does not indicate who completed the blinded assessment of anesthesia for this subject.

  - For Subject #29, the randomization form was not signed and the operative report does not indicate who administered the study medication (unblinded anesthesiologist not documented). The blinded assessment report does not have a signature, although one of the designated blinded co-investigators appears to have made a correction to the form indicating that this subject received 50 mg of fentanyl during the operative procedure; since much of the source operative report is illegible, it is not clear if this change made to the CRF reflects the source report.

  - For Subject #44, Dr. Berti signed the randomization record and the subject's informed consent, however the anesthesia record does not contain his name as anesthesiologist administering the medication. Blinded assessments in the case report form are not signed and it appears that
initials of two different (blinded) co-investigators made corrections to that form.

- There is no documentation that the standardized checklist for transient neurologic symptoms (pain, headache, and paresthesia) was used for the 24 hour and 7 day follow-up assessments. Only a single yes or no checkbox was available for experiencing symptoms.

- Withdrawal of Subject 045 was not documented until 15 days later with CI note to file. However, the anesthesia record indicates that 30 mg chloroprocaine was administered to the subject.

- There is no explanation of why subject screening dates and numbers, do not correlate logically (sequentially). Sponsor-provided copies of monitoring reports showing fluctuation (decrease) in total number of subjects screened overtime bringing into question the reliability of this document.

- Study records edited without an adequate audit trail (dates/times, recorder signatures/initials, supporting comments)

- Protocol training, task delegation, and task performance not consistently documented for some participating hospital staff (surgery/operative care)

- There was no documentation of a negative pregnancy testing result, an inclusion criterion for Subject #29

- Hospital (institutional) medical records copies for one subject included an outdated version of the case report form (CRF), which differed in format from the in-date version copies provided by sponsor from the Trial Master File and contained discrepant data (BP and sensory evaluations at 120 and 150 minutes) without documentation to reconcile the two CRFs.

- The hospital medical record "copy" for Subject #44 contained original ink marks (post-operative time/care) that were not present in the study binder provided by sponsor.

- For three subjects, source records did not provide documentation of many AEs recorded on CRFs (and reported in NDA).

- **Failure to follow the investigational plan (protocol-specified procedures):**

  - Bromage evaluation for surgery readiness was assessed using binary code (0 = not ready, 1 = ready) in lieu of the 4-point scale per protocol (0 or 1 = not ready; 2 = ready, hip/knee blocked; or 3 = ready, hip/knee/ankle blocked)

  - Readiness for surgery assessment based on motor block only (sensory block as assessed by loss of pinprick sensation to T10 not always met). For example, Subject #44 only had a sensory level of T11 recorded and Subject #22 L2.

  - Use of midazolam (pre-medication) or Ringer’s lactate (for managing hypotension) not always documented
**OSI review Comment:** Midazolam administration times were not always adequately documented on surgery records, whether administered before or during surgery (administration times sometimes consistent with intra-operative use).

- Concomitant medication use: documentation of tramadol use limited to immediate post-operative recovery period (and not for 24 hours after surgery, per protocol)
- Study medication administration (3 subjects): by non-study staff, not identified as part of the study staff and not otherwise delegated to perform this study task
- Time to home discharge, secondary efficacy endpoint: not consistently captured on CRF, apparently due to use of inadequate CRF form

**Adverse Events (AE) under-reporting (or discrepancies in AE reporting):**

- Subject 009: pre-operative sweating, nausea, and paleness attributed to vasovagal reaction prior to anesthesia recorded on CRF treated with atropine, included in the “intraoperative” AE listing, although review of hospital medical record document doesn’t include exact time relative to administration of anesthesia
- Subject 033: intra-operative hypotension recorded (no recorded bradycardia) on hospital anesthesia record, however CRF and data listing indicates bradycardia treated with atropine
- Subject 038: hypertension following surgery requiring admission to the hospital overnight not listed on CRF or data listing
- Subject 039: surgery site pain, fainting, and “feeling ill” in the general section of the hospital record (overnight in-hospital stay), nausea treated with Zofran in CRF AE listing following the procedure (although NDA data listing includes AE of nausea during the procedure.
- For Subjects 20 and 33, NDA Intraoperative AE data listing report episode of bradycardia treated with atropine during the surgical procedure. For Subject #20, hospital anesthesia record and CRF AE page indicate that atropine and event occurred pre-anesthesia, pre-operatively. For Subject #30, the NDA Intraoperative AE listing and CRF AE page record bradycardia event occurring during the surgical procedure, the hospital anesthesia record does not provide any evidence that this event occurred.

This Phase 2 dose-finding (dose-blinded) study was conducted over 10 years ago in Italy, not under an IND. The NDA was originally supported only with the medical literature. When requested to provide primary data, the sponsor submitted the study report with CRFs and surgery records (some of which were illegible) but were unable to provide datasets. The many deficiency observations included those that raise residual concerns about the integrity of the study blind and potential AE under-reporting.

The lack of original study source documents at the CI site and numerous inconsistencies between medical records provided by the site and copies of the case report forms provided by the sponsor, as well as lack of documentation as to who completed the
blinded assessments reported in the case report forms renders it impossible to establish reliability of data as reported to the NDA.

2. Stefano Bonarelli, M.D.

Study CHL1/02-2014: In this repeat Phase 2 dose-finding study, 47 subjects were screened, 46 were enrolled, and 45 completed the study. Case records were reviewed for all subjects, including detailed review for 12 subjects completing the study. A Form FDA 483 was issued for the following deficiency observations.

Recordkeeping:

- Maximum sensory block level (SBmax) was not documented by two successive observations for five subjects, two for 30 mg (Subjects 05 and 06) and three for 40 mg (Subjects 27, 39, and 45).
- Serial monitoring of BP, HR, and OS during anesthesia induction was not adequately documented for Subjects 33 and 14.
- For the 24-hour and 7-day follow up evaluations, monitoring for any interim AE (including TNS), surgery-related pain, or medication use appeared inadequate and/or lacked adequate documentation (typically without timeframes and treatment details for events).

Protocol deviations:

- For Subjects 12 and 18, readiness for surgery was determined based on the surgeon’s judgment that included L-1 sensory block and Bromage 3 motor block, close to but not entirely within the protocol-specified range (sensory ≥ T-12 and Bromage ≥ 2).
- Unblinded anesthesiologist performed post-operative assessment (including vitals, OS, Aldrete consciousness score, and motor activity), and unblinded CI participated in data review, correction, and query resolution.
- Protocol-inconsistent peri-operative use of sedatives (concomitant medications) was not reported as protocol deviations: Subject 12 received additional midazolam during surgery, and Subject 02 received bromazepam (instead of midazolam) for sedation.
- Storage temperature was not continuously monitored to detect and prevent temperature excursions: (1) > 25 °C for the study medication, and (2) > -70 °C for PK samples (documented excursion to -57.6 °C, not at risk for thawing).

OSI Review Comment: Dr. Bonarelli responded to the Form FDA 483 with a written correspondence dated June 8, 2017. Dr. Bonarelli states that the purpose of the blinding in this study was to prevent any possible introduction of bias on the study evaluation parameters (for example, block evaluations and safety), not to exclude the doctor from duty after the injection. Therefore, evaluation of the modified Aldrete score (eligibility to leave the OR) is not a measure included in the CRF, is not part of the study assessment, and does not influence any of the later assessments. He also states that according to hospital practice, only one anesthesiologist was present during the surgery, his exclusion from any other duties would not have been possible legally and would have compromised patient safety.
Dr. Bonarelli also states in his response that Dr. Ghisis (one of the unblinded investigators) addressed 201 data queries. For 138 of these queries, she was the unblinded anesthesiologist. Of these only 58 queries that could be potentially biased by knowledge of treatment assignment (such as, AEs, events during or post-surgery, modified Aldrete events, pain and TNS assessments, and assessment of motor or sensory block), most were derived from and clarifications of items already recorded in source documents. Only six queries (involving three subjects), only two queries involving a single subject (#007) had the possibility of introducing bias and were related to reporting of a somewhat anomalous regression and subsequent brief ascension of sensory block in which she used the more conservative time point of the second regression of the block to L1.

With the exception of the CI’s explanation of the unblinded anesthesiologist role in patient care described above, the deficiency observations otherwise appear to be GCP violations unlikely to affect efficacy and safety analyses and unlikely to be significant to the study/analysis outcome.

Based upon Dr. Bonarelli’s explanation and while awaiting the inspection report, the review division will need to make a determination of how critical the role of blinding is in their planned post hoc assessment of efficacy of the product. Based upon Dr. Bonarelli’s explanation described above, the anesthesiologist, although not directly involved with assessment of time and level of the block could potentially have influenced outcome by actions or treatment of the patient in the OR.

3. Claudio Camponovo, M.D.

Study CHL1/02-2006/M, Site 03: 80 subjects were screened, all were enrolled, and 79 completed the study. Case records were reviewed for all subjects, including detailed review for 13 subjects (16.5%) completing the study. Dr. Camponovo relocated from the study sites referenced for this study (Mendriso and Lugano, Switzerland to Gravesano, Switzerland in 2011). Records from the study had been transferred to Dr. Camponovo’s site in Gravesano, Switzerland in 2011. A Form FDA 483 was issued for the following deficiency observations:

Recordkeeping:

- There was an investigator and sub-investigator staff list outlining duties that could be performed (same for all individuals with the exception of Dr. Camponovo serving as study coordinator). There was no designation of blinded vs unblinded participants.
- Protocol training, task delegation, and task performance were not consistently documented for some participating hospital staff (surgery/operative care).
- Screening evaluations were sometimes performed prior to IC; date of CI’s signature on IC document (ICD) different from (typically preceding) date of subject’s signature; post-operative evaluations were not always performed by staff documented as blinded.
- Available study records did not consistently include all in-hospital progress notes, and some ECGs retrieved from hospital records were not included in subject case records.
Documentation of sponsor authorization to destroy drug accountability records was not consistently available for review for all destroyed records.

Protocol deviations:

- **Post-operative assessments at 24 hours and at 7 days were:** (1) performed by CIs not documented as blinded; (2) not performed by the same CI as for the screening visit; and (3) not performed to consistently track accurately the use of all concomitant medications [See OSI review comment below]

- **Pre-surgery assessment:** performed up to several days before screening visit, reported inaccurately on CRFs as performed at screening visit (4 subjects)

- **Screening ECG:** often not obtained at screening visit, but obtained either before (up to 2 days) or after screening visit (at Visit 2, recorded on CRFs as screening visit)

- **Subject randomization:** not consecutive in numbering to correspond with study medication kit number/availability, Subject 339 randomized before Subject 338 and transfer of kits 306-320 from satellite location (Mendriso) to primary location (Lugano), both locations under same CI

- **Concomitant medication use:** when not relevant to efficacy assessment, not consistently tracked to include active review of all in-hospital progress notes

For 8 subjects (0301, 0303, 0304, 0319, 0326, 0327, 0335, and 0339), the use of 14 medications (typically late post-operative, none intra-operative) was not consistently recorded on CRFs. Medications relevant to pain management included: non-steroidal anti-inflammatory agents (acetaminophen, diclofenac, and tramadol), opioids, and sedatives (escitalopram and lorazepam). Other medications (apparently not relevant to pain management) included: allopurinol, atenolol, cefuroxime, cephazolin, ephedrine, metronidazole, nadroparin, pantoprazole, and paraffin.

**OSI Review Comment:** Review of subjects’ study records (13 of 79 subjects (16.5%) who completed study) was made difficult due to lack of designation of blinded vs unblinded investigators, hospital personnel (including anesthesiologists in training and other non-study participating physicians or ancillary personnel) not listed on the study staff delegation list (along with representative initials or signature), multiple anesthesiologists being listed on a single subject’s anesthesia record, illegible handwriting, quality of copies, incomplete availability of hospital records for subjects admitted to the hospital, and failure of investigators to follow the protocol.

The protocol stated that the investigator who did preoperative screening (V1) should be the blinded investigator responsible for post-anesthesia administration evaluations (spinal block “time to” assessments of nerve block) at V2 during and following surgery, and transient neurologic symptom assessment at (TNS 24 hour and TNS 7 day) follow-up. This was not consistently followed. Although this was considered to be a protocol violation, the primary concern considered by the OSI reviewer (given variation of subject source documents included as evidence in the inspection report and multiple individuals listed as designated participating study staff) was whether the (unblinded) anesthesiologist documented on the source anesthesia record was also documented on a “blinded” anesthesia assessment (OR “nerve block evaluation”,
post-surgical criteria for discharge, or 24 hour and 7 day post-surgery TNS). For 7 of the 13 subject records reviewed at this site (16.5% of subjects completing study reviewed), problems were evident.

- **Subject #301:** Anesthesiology record (assuming administering medication and unblinded) is . Assessment of nerve block and post-op anesthesiology assessment for discharge was performed by and 24 hour and 7 day TNS assessments had no specified personnel attribution.

- **Subject #303:** Anesthesiology record (assuming administering medication and unblinded) is . Nerve block assessment is by and 24 hour and 7 day TNS assessment is by (although initials or signature difficult to discern).

- **Subject #305:** Anesthesiology record (assuming administering medication and unblinded) is . Nerve block assessment and anesthesiology assessment for discharge is by The 24 hour and 7 day assessment by (although cosigned by).

- **Subject #323:** Anesthesiology record (assuming administering medication and unblinded) is listed as , and unidentified person is underlined, significance not clear. Nerve block assessment by discharge assessment by , and 24 hour and 7 day TNS symptom assessment by .

- **Subject #327:** Anesthesiology record (assuming administering medication and unblinded) is listed as , and unidentified person. Nerve block assessment does not have initials and discharge assessment by The 24 hour and 7 day TNS assessment is by.

- **Subject #338:** Anesthesiology record (assuming administering medication and unblinded) is listed as (officially listed in formal surgical note as anesthesiologist), unidentified person, and . The nerve block and discharge assessment is done by The 24 hour and 7 day TNS assessment is by .

- **Subject #339:** Anesthesiology record (assuming administering medication and unblinded) is listed as (officially listed in formal surgical note as anesthesiologist), , and unidentified person. The discharge assessment is done by . The 24 hour and 7 day TNS assessment was done by.

**OSI Review Comment:** Although there were many observations related to failure to follow the protocol, it appears that individuals assessing the spinal block (i.e. nerve block) were not the same individuals who administered the block. However, 24 hr. and 7 day post-procedure follow-up assessments for TNS may have been conducted by the same individual for up to 5 of the 7 subjects. Additionally, it is unclear based upon the study records who was responsible for completion of the official anesthesia record (potentially similar concern as the 2014 dose-ranging study), since anesthesiologist of record was assumed person performing the block, determining disposition of patient and whether intervention was warranted.
In addition to record keeping deficiencies, the review division seriously needs to consider whether the uncertainty in blinding and potential introduction of bias that could be introduced in the analyses for investigators unblinded to treatment assignment performing continued activities in the OR and conducting 24 hour and 7 day follow-up TNS assessments.

4. Friedrich W. Hinnerk Wulf

Study CHL1/02-2006/M, Site 02: 21 subjects were screened, 20 were enrolled, 5 were discontinued (inadequate nerve block), and 15 completed the study. Case records were reviewed in detail for all 20 enrolled subjects. This foreign clinical study was not performed under IND.

A Form FDA 483 was issued for data discrepancies between CRFs and corresponding source records. Specifically, Visit 2 (Day 1) CRF data for 10 subjects did not exactly match the values recorded on source records.

- 15 data (value pairs) for secondary endpoints were discrepant between source record and CRF for the following five endpoints (number of value pairs): Time to motor block (Tmb) (8), Time of surgery end (Tes) (4), Time to sensory block (Tsb) (2), Time of end of anesthesia (Tea) (1), and Time of surgery end (Tss) (1). The CRF-reported time is reflected in the NDA data listings.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment</th>
<th>Value</th>
<th>Source</th>
<th>Case Report Form</th>
<th>Difference (in minutes)</th>
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<tbody>
<tr>
<td>202</td>
<td>CH-1</td>
<td>Tsb</td>
<td>13:34</td>
<td>13:33</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tmb</td>
<td>13:33</td>
<td>13:34</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tmr</td>
<td>15:14</td>
<td>15:10</td>
<td>(-) 4</td>
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<td>8:17</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Tes</td>
<td>8:40</td>
<td>8:47</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td>10:07</td>
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<tr>
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<td>9:05</td>
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<td>14:33</td>
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<tr>
<td></td>
<td></td>
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<td>7:54</td>
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<td>(+) 28</td>
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</table>

Tsb = time to onset of sensory block at T-10; Tmb = time to onset of motor block; Tss = time of surgery start; Tes = time of surgery end; Tmr = time to motor block resolution; Tea = time to end of anesthesia (resolution of motor and sensory block)

**OSI reviewer comment:** During previous discussions with the review division, it was noted that the review division would not be relying on the sponsor’s predefined efficacy endpoints, but was concerned with times of study drug (anesthesia) administration, duration (start and stop time) of surgery, resolution of motor block, and administration of any rescue anesthesia, analgesia, or anxiolytics administered to the subjects. Although there are a number of data points that appear to have undergone revision on the CRF (and reflected in the NDA data listings), most are considered to be minor and of unclear significance. Focusing on points of concern to review division (appear in the shaded lines of the table), the specific findings are sporadic among multiple parameters and appear to be distributed across both treatment groups. See following text on CI response to Form FDA 483 observations.

Other (minor) deficiency observations appeared to reflect inadequate recordkeeping and were verbally discussed with the investigator at the close of the inspection:

- Isolated recording of study medication doses on the source records (Subject #s 205, 206, 213, and 215) reported to have been completed by the (blinded) CI were noted to be handwritten by another individual on the case report form (potential unblinding, although no clear attribution of staff responsible for adding information).
- Internally inconsistent study medication administration dates (discrepant by one day)
- Use of midazolam pre-medication inconsistent with protocol-specified time window
- Incomplete study medication storage temperature records
- Obscured, obliterated, or other unacceptable error correction
The discussion with the site management about good recordkeeping practice included the need for: immediate error correction when recognized with an adequate audit trail to assure transparency and internal consistency, and an adequate explanation of any protocol non-adherence, including rationale and sponsor authorization when intentional.

Dr. Wulf responded adequately to the Form FDA 483 observations in a letter dated April 21, 2017. The data point discrepancy observations were primarily attributed to transcription errors introduced by duplicative reporting of times on the site-supplied work sheet and then on to the CRF. In the written response, he stated that the times on the CRF were correct (based upon protocol definitions) with the exception of an isolated erroneous record time for resolution of motor block for Subject #213 (subject treated with chloroprocaine), source indicated time of 16:10 and CRF (NDA data listing) of 16:34. Upon recheck by Dr. Wulf, he notes that this error in time to resolution on motor block resolution for Subject #213 should have been 16:10 as recorded in the source documents.

All deficiency observations were considered to be minor and unlikely to be significant. However, the source documents (site worksheets) reportedly completed by the blinded investigator contained study and comparator medication dosing information in addition to recorded efficacy. The medication dose information appeared to be written in a different style handwriting from an unidentified individual. Including this information on the worksheet containing efficacy information could (potentially) indicate that the investigator may not have been blinded to treatment.

{See appended electronic signature page}
John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
CC:

DAAAP / Division Director / Sharon Hertz
DAAAP / Clinical Team Leader / Leah Crisafi
DAAAP / Medical Officer / Alla Bazini
DAAAP / Regulatory Project Manager / Selma Kraft

OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters
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/s/

JONG HOON LEE
09/15/2017

KASSA AYALEW
09/15/2017
Memorandum

Date: August 4, 2017

To: Selma Kraft, PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Koung Lee, RPh, MSHS
Regulatory Review Officer
Division of Advertising & Promotion Review 1 (DAPR1)
Office of Prescription Drug Promotion (OPDP)

CC: Olga Salis, Senior Regulatory Project Manager
OPDP

Subject: NDA 208791
CLOROTEKAL® (chloroprocaine HCl) injection for intrathecal use
Professional Labeling Review

As requested in DAAAP’s consult dated September 16, 2016, OPDP has reviewed the draft prescribing information for CLOROTEKAL® (chloroprocaine HCL) injection for intrathecal use. The draft prescribing information (substantially complete prescribing information) was provided to OPDP on July 27, 2017, via email by Selma Kraft with the file name “NDA 208791 SCL to OPDP 07.27.2017.docx”.

OPDP has provided comments on the substantially complete prescribing information in the attached document below.

OPDP has no comments on the container and carton labeling submitted on April 14, 2017.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

Reference ID: 4135489
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/s/

KOUNG U LEE
08/04/2017
Division of Pediatric and Maternal Health Memorandum

Date: June 26, 2017  Date Consulted: October 3, 2016

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

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

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

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

Drug: CLOROTEKAL (Chloroprocaine HCl) 1% (10 mg/ml) injection

NDA: NDA 208791

Indication: CLOROTEKAL is a local anesthetic indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia).

Applicant: Sintetica SA

Subject: Pregnancy and Lactation labeling

Materials Reviewed:
- Applicant’s background package for NDA 208791 submitted on August 26, 2016.
- Applicant’s revised label, literature review and summary of pharmacovigilance database submitted as SD#5 on October 6, 2016.
Consult Question: PLLR updated labeling

INTRODUCTION

On August 26, 2016, DAAAP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of CLOROTEKAL (Chloroprocaine HCl) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On August 26, 2016, Sintetica SA submitted a new NDA 209279 via the 505 (b) (2) pathway for CLOROTEKAL (Chloroprocaine HCl).
- Sintetica SA is relying on the FDA-approved drug product Nesacaine (Chloroprocaine HCl injection; NDA # 009435) as reference listed drug (RLD).
- CLOROTEKAL is a local anesthetic indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia).
- Chloroprocaine HCl indicated for spinal anesthesia has been approved for use in Europe (sponsored by Sintetica) for this indication since 2012.
- On October 6, 2016, the Agency sent the Applicant an information request (IR) via email requesting that they submit a review and summary of the available published literature and a summary of the Applicant’s pharmacovigilance database regarding chloroprocaine use in pregnant and lactating women.
- On November 3, 2016, the Applicant submitted the revised labeling and the requested supporting information which was adequate.
- A clock extension based on a major amendment was received on April 17, 2017.

BACKGROUND

Chloroprocaine and Drug Characteristics

- Chloroprocaine is a sterile non-pyrogenic local anesthetic.
- A 1 mL of solution for injection contains 10 mg of chloroprocaine hydrochloride.
- Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse and by reducing the rate of rise of the action potential.
- The onset of action with chloroprocaine is rapid (usually 6 to 12 minutes), and the duration of anesthesia, depending upon the amount used and the route of administration, may be up to 60 minutes.
- Chloroprocaine plasma half-life in vitro is about 25 seconds, whereas the apparent half-life in vivo was found to be 3.1±1.6 min (range 1.5 – 6.4 min) in maternal plasma after intrapartum epidural anesthesia.

1 proposed package insert
• Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The products of hydrolysis, 2-chloroaminobenzoic acid (CABA) and 2-diethylaminoethanol, can be both considered pharmacologically inactive.
• The protein binding capacity of chloroprocaine has not been reliably determined.
• Chloroprocaine has a molecular weight of $\approx 271 \text{ g/mol}$.
• Common adverse reactions (an incidence $\geq 1 \%$) observed in CLOROTEKAL clinical trials were procedural pain, injection site pain, hypotension and nausea.

Anesthesia during Pregnancy and Lactation

In obstetric patients, regional anesthesia (neuraxial block) refers to partial or complete loss of pain sensation below the T8 to T10 spinal level. In addition, a varying degree of motor block may be present, depending on the agents used. Epidural and spinal (subarachnoid block) anesthesia are two types of regional analgesia used to diminish labor pain in women, where analgesia refers to the relief of pain without the loss of consciousness.

• Spinal anesthesia is given by injecting anesthesia into and around the nerves of the spinal column. This gives a rapid and complete numbing sensation. Surgery can be started soon after the anesthesia is given because the effect begins quickly. Treatment for hypotension is more likely to be needed if spinal anesthesia (versus epidural) is used.
• Epidural anesthesia requires a little more time and is given by inserting a small catheter into the space around the spinal column. The epidural catheter is used to keep constant levels of anesthetic medication in the space. The extent of numbing in the legs and abdomen and the length of time you are numbed can be controlled and adjusted as needed to prevent pain. Approximately ten times the volume of anesthetic is required for an epidural technique compared to spinal anesthesia.
• Combined spinal/epidural anesthesia is called a CSE. A CSE provides both the immediate pain relief of the spinal anesthesia and longer acting pain relief with fine tuning, if needed, associated with the epidural technique.

Potential adverse effects common to both spinal and epidural anesthetic techniques include: failure to provide adequate anesthesia, maternal hypotension, post dural puncture headache (PDPH), itching and transient backache over the injection site. Rare serious complications include meningitis, compression of the spinal cord from a blood clot or abscess and damage to nerve roots causing paresthesia or weakness.

Both spinal and epidural anesthesia can be used in any stage of labor, in vaginal delivery and in cesarean section (C-section). Obstetrical anesthesia guidelines recommend that the decision to use a particular anesthetic technique for delivery should be individualized, based on anesthetic, obstetric, or fetal risk factors (e.g., elective vs. emergency), the preferences of the patient, and the judgment of the anesthesiologist.

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Chloroprocaine is one of the local anesthetics used as analgesic in the pain management during labor or as anesthetic during delivery or C-section.

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. 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. 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). 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.

On December 14, 2016 the Agency issued a Drug Safety Communication (DSC) and Safety Labeling Changes (SLC) notification that require labeling changes to include a warning in all general anesthetic and sedative drugs. The DSC and labeling changes also include pregnant women in the third trimester, as this time period is important in brain development. Key messages of the DSC and labeling changes include the following:

- Repeated or lengthy (greater than 3 hours) use of general anesthetic and sedation drugs in pregnant women and young children during surgery or other procedures may affect the child’s developing brain.
- Parents, pregnant women, care providers, obstetricians, surgeons, and anesthesiologists should be aware of the potential risks that anesthetics and sedation drugs pose to the developing brain and carefully decide on the appropriate timing for potentially elective surgery, particularly for pregnant women in their third trimester and children under three years of age.

According to the division clinical team, both epidural and spinal anesthesia with chloroprocaine is considered “local anesthesia” and is not expected to affect the fetal or neonatal brain. Therefore, the above warnings, DSC and SLC do not apply to this product for this indication.

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7 Per DAAAP meeting 11-30-2016
Current State of the Labeling

- Current labeling for Nesacaine (chloroprocaine HCl), NDA 9435, the RLD for this submission, was originally approved in 1955. The currently approved labeling is from February 19, 2010.
- Nesacaine is not in the Physician Labeling Rule (PLR) format nor does it comply with PLLR requirements.
- There are no boxed warnings.
- There are Warnings and Precautions for use only by clinicians “well versed” in the diagnosis and management of dose-related toxicities of anesthetics and with resuscitative equipment available, chondrolysis with intra-articular infusions and increased toxicity with anesthetic mixtures.
- Significant interactions with hormonal contraceptives are not noted in the label.
- Section 8.1 Pregnancy states:
  Category C
  Animal reproduction studies have not been conducted with chloroprocaine. It is also not known whether chloroprocaine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Chloroprocaine should be given to a pregnant woman only if clearly needed. This does not preclude the use of chloroprocaine at term for the production of obstetrical anesthesia.
  Labor and Delivery
  Local anesthetics rapidly cross the placenta, and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (see Clinical Pharmacology and Pharmacokinetics).
- Section 8.3 Nursing Mothers states
  It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when chloroprocaine is administered to a nursing woman.

Pregnancy and Lactation Labeling

On June 30, 2015, the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

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9 Approved Nesacaine (chloroprocaine HCl) PI
10 Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).
11 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).
REVIEW

Pregnancy

Nonclinical Experience

Animal reproduction studies have not been conducted with chloroprocaine.

Applicant’s Review of Literature

The Applicant reviewed the literature on chloroprocaine use in pregnancy covering the period up to October 18, 2016 using the search terms ‘chloroprocaine’; ‘pregnancy’; obstetric”; epidural/spinal anesthesia”. Publications cited by the applicant as relevant and specific to the use of chloroprocaine during pregnancy include twelve articles regarding chloroprocaine use in epidural administration and 2 in spinal administration. See Tables 3 and 4 in Attachment A for details of these 14 relevant articles. This reviewer’s summary of the key information in these 14 publications is provided below:

- Ten of the fourteen articles were published in the 1980’s.
- No maternal outcomes (MO) were reported in 8 out of 14 publications.
- No fetal outcomes (FO) were reported in 6 out of the 14 publications.
- Where MO were provided, hypotension was reported in 6/6 publications, nausea and vomiting in 3/6, and need for additional anesthesia, hypoxia and motor weakness in 1/6.
- Where FO were provided, Apgars were reported in 8/8 publications and umbilical vein blood gases in 6/8.

In addition to the publications summarized in Tables 3 and 4, one additional trial by Annsens12 S et al (2015) was identified and is summarized below:

- Annsens S et al.12 reported on a prospective trial of 18 parturients, with a pregnancy duration of 36 to 41 weeks, requesting analgesia, who were given a combined spinal-epidural analgesia and received a predetermined dose of chloroprocaine 1% intrathecally, according to an up-down sequential allocation. The initial dose of chloroprocaine was chosen to be 20mg and the testing interval was set at 2mg. Using the Dixon and Mood method, the median effective dose of intrathecal chloroprocaine in the spinal component of a CSE for labour was calculated to be 15 mg (95% CI:11.7-18.3 mg). No maternal or fetal outcomes (except for effectiveness of anesthesia) were reported.

In addition, the Applicant cited 3 case reports from the published literature, details are provided in Table 1 below:

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Maternal Age (yrs.)</th>
<th>Fetal Age at Exposure</th>
<th>Dose/% of Chloroprocaine</th>
<th>Condition/ Diagnosis (Dx)</th>
<th>Maternal/Fetal Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhnert et al 1982</td>
<td>31</td>
<td>Not Applicable (N/A)</td>
<td>5 ml of 3% test dose then 20 ml of 3%, then 5ml of 3%</td>
<td>Tubal ligation one day post-partum after vaginal delivery</td>
<td>Head felt numb, patient somnolent, laparotomy revealed a hemoperitoneum and an active bleeding site. Following completion of the operative procedure, the patient was unable to breathe spontaneously or respond to stimuli for a period of three hours. Low pseudocholinesterase levels were suspected. The dibucaine number and cholinesterase activity at six weeks postpartum confirmed the presence of atypical pseudocholinesterase.</td>
</tr>
<tr>
<td>Monedero P and Hess P 2001</td>
<td>29</td>
<td>term</td>
<td>15 ml of 3% via the epidural catheter and, 20 min later, an additional 12 ml of 2% lidocaine</td>
<td>Emergency C-section due to fetal bradycardia</td>
<td>Thirty minutes after delivery, the patient complained of shortness of breath and, within five minutes, she was unresponsive to command. Patient recovered 3 hours and 45 min after the intubation. After delivery, plasma cholinesterase activity was low and seven weeks later, pseudocholinesterase activity had returned to normal.</td>
</tr>
<tr>
<td>Goudra BG et al 2016</td>
<td>23</td>
<td>term</td>
<td>10 cc of 3% chloroprocaine was administered as a single bolus while the patient was still in 4 point position</td>
<td>Emergency C-section due to non-reassuring fetal heart sounds with chorioamnionitis</td>
<td>As soon as the patient was placed on the operating table, it was observed that her ventilation was inadequate with an inability to move the legs. Weak hand grip raised the suspicion of high epidural. Positive pressure ventilation was commenced immediately, phenylephrine infusion was started to support BP, and baby was delivered. After the delivery, surgical anesthesia was induced with propofol and endotracheal intubation was performed. Accidental subarachnoid migration during the 4 point positioning was postulated as leading to a high dermatomal block requiring respiratory assistance. The fetal outcome was not reported beyond the Apgars of eight and nine at one and five minutes.</td>
</tr>
</tbody>
</table>

Source: Reviewer’s Table

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “chloroprocaine and pregnancy,” “chloroprocaine and pregnant women,” “chloroprocaine and pregnancy and birth defects,” “chloroprocaine and pregnancy and congenital malformations,” “chloroprocaine and pregnancy and stillbirth,” “chloroprocaine and spontaneous abortion” and “chloroprocaine and pregnancy and miscarriage.”

Several general reviews of regional anesthesia for labor and delivery were identified. These were previously referenced in the section of this review entitled “Anesthesia during Pregnancy and Lactation”. A publication by Burm, AGL16 (1989), discussed concerns that arose in the 1980s regarding

…reports of several cases of persistent neurological damage and prolonged sensory or motor deficits following epidural or accidental subarachnoid injection of large volumes (doses between 360 and 840mg) of chloroprocaine solutions.17,18,19 Recent investigations suggest that these effects may have been due to the low pH and high sodium bisulphite concentrations in the solutions rather than to a neurotoxic action of chloroprocaine.20,21

The notation regarding chloroprocaine in Micromedex was as follows:

Local anesthetics appear to cross the placenta by passive diffusion22. However, this does not prevent the use of chloroprocaine at term for the production of obstetrical anesthesia. Local anesthetics, in general, are well-tolerated throughout pregnancy. No teratogenic effects have been reported in humans following local anesthetic treatment during pregnancy.23

Pharmacovigilance Database Summary

According to the Applicant, there are four cases of intrathecal chloroprocaine use during pregnancy coming from European post-marketing experience which are presented in Table 2:

22 Prod Info Nesacaine-MPF(R) Injection, 1997
23 Schaefer, 2001. This reference was not further identified in MicroMedex.
Table 2: Cases of Intrathecal Chlorprocaine (Off-label Treatment) coming from European Post-marking Experience

<table>
<thead>
<tr>
<th>Case Report #</th>
<th>Maternal Age (yrs.)</th>
<th>Fetal Age at Exposure</th>
<th>Dose/% of Chlorprocaine</th>
<th>Condition/ Diagnosis (Dx)</th>
<th>Maternal/Fetal Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE131209AMP005</td>
<td>Not reported</td>
<td>12 weeks</td>
<td>4 ml of 10 mg/ml 1%</td>
<td>Cervical cerclage</td>
<td>ultrasound -no adverse reaction in fetus</td>
</tr>
<tr>
<td>FR140610AMP026</td>
<td>Not reported</td>
<td>term</td>
<td>10 mg/ml/dose and % not reported</td>
<td>Cesarean Section (C-section)</td>
<td>No adverse events reported</td>
</tr>
<tr>
<td>FR150414AMP046</td>
<td>~ 100 patients Ages not reported</td>
<td>term</td>
<td>10 mg/ml/dose and % not reported</td>
<td>Cesarean Sections</td>
<td>No adverse events reported</td>
</tr>
<tr>
<td>BE141220AMP346</td>
<td>Not reported</td>
<td>23 weeks</td>
<td>35 mg total % not reported</td>
<td>Condyloma surgery</td>
<td>Patient developed hypotension leading to cardiac arrest, Rx’d with cardiac massage and injection of atropine (Dx later changed to vasovagal reaction), Healthy baby girl later delivered by C-section</td>
</tr>
</tbody>
</table>

Source: Reviewer’s Table adapted from Applicant’s Response to IR

Summary:

There are limited human pregnancy outcome data available in the published literature and the Applicant’s pharmacovigilance database for the use of chlorprocaine as epidural or spinal anesthesia during pregnancy. There are no animal studies for chlorprocaine use. Since epidural and spinal anesthesia with chlorprocaine are considered “local anesthesia,” chlorprocaine is not expected to affect the fetal or neonatal brain. Therefore, the warnings, DSC and SLC discussed above in the section of this review entitled “Anesthesia during Pregnancy and Lactation” do not apply to chlorprocaine for currently proposed indication. There are risks to the mother and the fetus associated with use of local anesthetics during labor and delivery. The following language has been used in other local anesthetic labels and will be placed under clinical considerations in section 8.1:

Clinical Considerations

Labor or delivery
Local anesthetics rapidly cross the placenta, and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity [see Clinical Pharmacology (12.3)]. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Reference ID: 4116351
Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturients reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life.

**Lactation**

**Applicant’s Review of Literature**

The Applicant did not provide a review of the literature regarding chloroprocaine and lactation.

**DPMH Review of Literature**

DPMH conducted a search of Medications and Mother’s Milk\(^{24}\), the Drugs and Lactation Database (LactMed)\(^ {25}\), Micromedex\(^ {26}\), and of published literature in PubMed and Embase using the search terms “chloroprocaine and lactation” and “chloroprocaine and breastfeeding.” No reports of adequate and well-controlled studies of chloroprocaine use in lactating women were found. No case reports were found.

Chloroprocaine was not referenced in Medications and Mother’s Milk\(^ {22}\). Chloroprocaine is referenced in LactMed\(^ {21}\). The summary of use during lactation states: “No information is available on the use of chloroprocaine during breastfeeding. Based on the low excretion of other local anesthetics into breastmilk and the extremely short half-life of chloroprocaine, it is unlikely to adversely affect the breastfed infant. However, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.


\(^{25}\) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Micromedex notes the following; “Infant risk cannot be ruled out”.

Summary

There are no data on the presence of chloroprocaine in human or animal milk. Based on the very short half-life of chloroprocaine, it is unlikely to cause serious adverse effects in the breastfed infant. Therefore, the following language is recommended for Section 8.2 Lactation:

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CLOROTEKAL and any potential adverse effects on the breastfed infant from CLOROTEKAL or from the underlying maternal condition.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for CLOROTEKAL (chloroprocaine) labeling:

- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of CLOROTEKAL (chloroprocaine) labeling was structured in the PLLR format to include the “Risk Summary” section.\(^{27}\)

• **Lactation, Section 8.2**
  - The “Lactation” subsection of CLOROTEKAL (chloroprocaine) labeling was formatted in the PLLR format to include the “Risk Summary” section.\(^{28}\)

**LABELING RECOMMENDATIONS**

DPMH revised subsections 8.1, and 8.2 of CLOROTEKAL (chloroprocaine) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DAAAP on 7/24/17. DPMH refers to the final NDA action for final labeling.

DPMH Proposed CLOROTEKAL (chloroprocaine) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
The limited available data with chloroprocaine use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are no animal reproduction studies for chloroprocaine. There are risks to the mother and the fetus associated with use of chloroprocaine during labor and delivery (see Clinical Considerations).

The estimated background risk of major birth defects and miscarriage for the indicated population is 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.

Clinical Considerations
Labor or delivery
Local anesthetics rapidly cross the placenta, and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity [see Clinical Pharmacology (12.3)]. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturients reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance. The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.
8.2 Lactation

Risk Summary
There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CLOROTEKAL and any potential adverse effects on the breastfed infant from CLOROTEKAL or from the underlying maternal condition.
# Attachment A

**Table 3:** List of published articles with epidural 2-chloroprocaine in obstetric patients

<table>
<thead>
<tr>
<th>Article</th>
<th>Route</th>
<th>Labor and/or type of delivery</th>
<th>Treatment</th>
<th># of Patients</th>
<th>Dose (mg)</th>
<th>Mother complications</th>
<th>Childbirth Patient Safety Indicators</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 O’Brien&lt;sup&gt;29&lt;/sup&gt; et al. 1979</td>
<td>Epidural</td>
<td>Labor</td>
<td>2% chloroprocaine</td>
<td>2</td>
<td>800</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Chloroprocaine Plasma concentration: BLQ*</td>
</tr>
<tr>
<td>#2 Kuhnert&lt;sup&gt;2&lt;/sup&gt; et al. 1980</td>
<td>Epidural</td>
<td>Vaginal delivery (VD) and caesarean section (CS)</td>
<td>2% + 3% chloroprocaine</td>
<td>VD=12 CS=18</td>
<td>VD=468±284 CS=948±347</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Even though unchanged 2-chloroprocaine can reach the fetus, its low toxicity and inactive metabolites appear to justify its preference over amide-linked drugs for obstetric anesthesia.</td>
</tr>
<tr>
<td>#3 James&lt;sup&gt;30&lt;/sup&gt; et al. 1980</td>
<td>Epidural</td>
<td>Elective CS</td>
<td>3% chloroprocaine</td>
<td>15</td>
<td>600</td>
<td>Hypotension: 33% of patients, Additional nitrous oxide analgesia: 2 patients</td>
<td>Apgar at 1’: &lt; 7 in 2 neonates No significant differences in blood-gas value among the groups.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5% bupivacaine</td>
<td>15</td>
<td>800</td>
<td>Hypotension: 13% of patients, Additional nitrous oxide analgesia: 2 patients</td>
<td>No significant differences in blood-gas value among the groups</td>
<td></td>
</tr>
<tr>
<td>#4 DeCampo&lt;sup&gt;31&lt;/sup&gt; et al. 1980</td>
<td>Epidural</td>
<td>VD or CS</td>
<td>3% chloroprocaine</td>
<td>10</td>
<td>360</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Evaluation of sensory profile of pregnant persons at term</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3% chloroprocaine with epinephrine</td>
<td>10</td>
<td>360</td>
<td></td>
<td></td>
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</table>


Reference ID: 4116351
<table>
<thead>
<tr>
<th>Article</th>
<th>Route</th>
<th>Labor and/or type of delivery</th>
<th>Treatment</th>
<th># of Patients</th>
<th>Dose (mg)</th>
<th>Mother complications</th>
<th>Childbirth Patient Safety Indicators</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>#5 Krohg and Jellum 1981</td>
<td>Epidural</td>
<td>Elective CS</td>
<td>3% chloroprocaine</td>
<td>16</td>
<td>240</td>
<td>Not reported</td>
<td>Not reported</td>
<td>In the mother, the major metabolic route for the elimination of CABA is N-acetylation and subsequent excretion in the urine. The neonate seems quite capable of eliminating the metabolite.</td>
</tr>
<tr>
<td>#6 Abboud et al. 1982</td>
<td>Epidural</td>
<td>Labor and delivery</td>
<td>0.5% bupivacaine</td>
<td>5 min post-dose: 50 Delivery: 42</td>
<td>Not specified</td>
<td>Hypotension: 5</td>
<td>At 1': low Apgar score in 7 neonates At 5': low Apgar score in 1 neonate</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Epidural</td>
<td>Labor and delivery</td>
<td>2% chloroprocaine</td>
<td>5 min post-dose: 50 Delivery: 34</td>
<td>Not specified</td>
<td>Hypotension: 8</td>
<td>At 1': low Apgar score in 9 neonates At 5': low Apgar score in 0 neonate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidural</td>
<td>Labor and delivery</td>
<td>1.5% lidocaine</td>
<td>5 min post-dose: 50 Delivery: 47</td>
<td>Not specified</td>
<td>Hypotension: 3</td>
<td>At 1': low Apgar score in 6 neonates At 5': low Apgar score in 0 neonate</td>
<td></td>
</tr>
<tr>
<td>#7 Kuhnert et al.</td>
<td>Epidural</td>
<td>Labor, VD and elective</td>
<td>Chloroprocaine</td>
<td>21 10=term Term=776±261 Preterm=695±2</td>
<td>Not reported</td>
<td>Term: Apgar at 1': &lt; 7 in 1 neonate</td>
<td>Elimination rate constants for CABA and patterns of</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Article</th>
<th>Route</th>
<th>Labor and/or type of delivery</th>
<th>Treatment</th>
<th># of Patients</th>
<th>Dose (mg)</th>
<th>Mother complications</th>
<th>Childbirth Patient Safety Indicators</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>1983</td>
<td>CS</td>
<td></td>
<td></td>
<td>11=preterm</td>
<td>47</td>
<td></td>
<td>Apgar at 5': &lt; 7 in 1 neonate Preterm: Apgar at 1': &lt; 7 in 4 neonates Apgar at 5': &lt; 7 in 1 neonate</td>
<td>cumulative excretion for mother and neonate.</td>
</tr>
<tr>
<td>#8 Abboud et al. 1984</td>
<td>Epidural Labor and delivery (CS, vacuum extraction, forceps)</td>
<td>0.5% bupivicaine</td>
<td>23</td>
<td>182±36</td>
<td></td>
<td>Hypotension:3</td>
<td>At 1': low Apgar score in 3 neonates At 5': low Apgar score in 0 neonates</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2% chloroprocaine</td>
<td>19</td>
<td>852±125</td>
<td>Hypotension:4 Tachyphylaxis:1 Motor weakness:1</td>
<td>At 1': low Apgar score in 2 neonates At 5': low Apgar score in 0 neonates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.5% lidocaine</td>
<td>19</td>
<td>623±50</td>
<td>Hypotension: 3 Tachyphylaxis: 1 Motor weakness: 2</td>
<td>At 1': low Apgar score in 2 neonates At 5': low Apgar score in 0 neonates</td>
<td></td>
</tr>
<tr>
<td>#9 Philipson et al. 1985</td>
<td>Epidural catheter Elective or repeat CS</td>
<td>2% or 3% chloroprocaine</td>
<td>44</td>
<td>Acidotic group: 855±326 mg</td>
<td>Not reported</td>
<td>Acidotic group: At 1': low Apgar score in 0 neonates At 5': low Apgar score in 0 neonates</td>
<td>2-chloroprocaine may also be the local anesthetic of choice for these types of obstetric anesthesia when fetal acidosis is anticipated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonacidotic group: 838±242 mg</td>
<td>Not reported</td>
<td>Nonacidotic group: At 1': low Apgar score in 0 neonates At 5': low Apgar score in 0 neonates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>Childbirth Patient Safety Indicators</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>#10 Kuhnert 1986</td>
<td>Epidural</td>
<td>VD + repeat CS</td>
<td>2-chloroprocaine</td>
<td>9</td>
<td>643±289 mg</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Apgar at 1': &lt; 7 in 0 neonates</td>
</tr>
<tr>
<td>#11 Ackerman et al. 1989</td>
<td>Epidural</td>
<td>First stage of labor</td>
<td>2% chloroprocaine (sitting)</td>
<td>10</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Neither the pH adjustment nor the position of epidural injection of local anesthetic had any effect on the duration of analgesia of 2-chloroprocaine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pH-adjusted 2% chloroprocaine (sitting)</td>
<td>10</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2% chloroprocaine (supine)</td>
<td>10</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pH-adjusted 2% 2-chloroprocaine (supine)</td>
<td>10</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>#12 Feng et al. 2012</td>
<td>Epidural</td>
<td>Elective CS</td>
<td>3% chloroprocaine</td>
<td>20</td>
<td>360</td>
<td>Hypotension: 10 Bradycardia: 0 Nausea or vomiting: 3 Hypoxia: 0</td>
<td>There were also no statistically significant between-group differences in Apgar scores at 1</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Article</th>
<th>Route</th>
<th>Labor and/or type of delivery</th>
<th>Treatment</th>
<th># of Patients</th>
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<th>Mother complications</th>
<th>Childbirth Patient Safety Indicators</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3% chloroprocaine with epinephrine</td>
<td>20</td>
<td>360</td>
<td>Hypotension: 11 Bradycardia: 1 Nausea or vomiting: 1</td>
<td>There were also no statistically significant between-group differences in Apgar scores at 1 and 5 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2% lidocaine with epinephrine</td>
<td>20</td>
<td>240</td>
<td>Hypotension: 11 Bradycardia: 1 Nausea or vomiting: 2 Hypoxia: 0</td>
<td>There were also no statistically significant between-group differences in Apgar scores at 1 and 5 min</td>
<td></td>
</tr>
</tbody>
</table>

*BLQ=below the limit of quantification

Source: Applicant’s Response to IR (modified) October 6, 2016, pg 6-14.
Table 4: List of published articles with spinal 2-chloroprocaine in obstetric patients

<table>
<thead>
<tr>
<th>Article</th>
<th>Route</th>
<th>Labor and/or type of delivery</th>
<th>Treatment</th>
<th># of Patients</th>
<th>Dose (mg)</th>
<th>Mother complications</th>
<th>Childbirth Patient Safety Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Fu et al. 2006</td>
<td>spinal</td>
<td>CS</td>
<td>2.2 ml chloroprocaine solution (1.2 ml of 2.5% chloroprocaine, 0.5 ml of 10% glucose, 0.5 ml of 3% ephedrine)</td>
<td>40</td>
<td>30</td>
<td>Hypotension: 17 Nausea: 22 Vomiting: 16</td>
<td>Not reported</td>
</tr>
<tr>
<td>#2 Maes et al. 2015</td>
<td>spinal</td>
<td>CS</td>
<td>1% chloroprocaine without sufentanil</td>
<td>19</td>
<td>40</td>
<td>Hypotension 5’: 4 Hypotension 10’: 8 Hypotension 20’: 3 Hypotension 30’: 8 Nausea: 5</td>
<td>APGAR scores and umbilical blood gasses (arterial and venous pH) were measured for all babies and were not significantly different between groups. One newborn was admitted to the neonatal intensive care unit, within 24 h after birth (APGAR 10/10/10), because of respiratory distress, which improved after a small period of CPAP Rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>40 mg (1 μg sufentanil)</td>
<td>Hypotension 5’: 2 Hypotension 10’: 8 Hypotension 20’: 4 Hypotension 30’: 2 Nausea: 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>9 mg (1 μg sufentanil)</td>
<td>Hypotension 5’: 3 Hypotension 10’: 8 Hypotension 20’: 3 Hypotension 30’: 4 Nausea: 3</td>
<td></td>
</tr>
</tbody>
</table>

Source: Applicant’s Response to IR (modified) October 6, 2016, pg 19-20.

---

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/s/

JANE E LIEDTKA
06/26/2017

MIRIAM C DINATALE
06/26/2017

LYNNE P YAO
06/27/2017
1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling for Clorotekal (Chloroprocaine HCl injection, USP) (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. Sinetetica SA submitted two proposals of the revised labels and labeling for our review. Sinetetica SA provided the following rationale for submitting two proposals for our review, “Please note that, due to a lack of space, the introduction of a linear bar code affects the information readability. Therefore to save space and avoid readability issues, we are submitting our second proposal of container label reporting the Data Matrix encoded.”

\[ a \]
Shah M. Label and Labeling Review for Chloroprocaine HCl injection (NDA 208791). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 FEB 21. 8 p. OSE RCM No.: 2016-2082.

\[ b \]
Shah M. Memorandum Review of Revised Label and Labeling for Chloroprocaine HCl injection (NDA 208791). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 APR 06. 3 p. OSE RCM No.: 2016-2082.
code and containing the following information: National Drug Code (NDC) 6805569901 which refers to the manufacturer of the drug product Sintetica SA.” Proposal 1 is not acceptable from a medication error perspective because it does not contain a linear barcode. Proposal 2 contains a linear barcode and is acceptable from a medication error perspective. Thus, we provide comments to Sinetetica SA below.

2 CONCLUSION & COMMENTS TO SINTETICA SA
Proposal 2 of the revised container label and carton labeling for Clorotekal (Chloroprocaine HCl injection, USP) is acceptable from a medication error perspective. Proposal 1 is unacceptable from a medication error perspective because it does not contain a linear barcode. We have no further recommendations at this time.
APPENDIX A. LABEL AND LABELING SUBMITTED ON APRIL 14, 2017 (PROPOSAL 2)

Container labels

Carton labeling
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/s/

MILLIE C BRAHMBHATT  
04/24/2017

OTTO L TOWNSEND  
04/24/2017
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 6, 2017
Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 208791
Product Name and Strength: Clorotekal (Chloroprocaine HCl injection, USP)
50 mg/5 mL (10 mg/mL)
Submission Date: March 17, 2017
Applicant/Sponsor Name: Sintetica SA
OSE RCM #: 2016-2082
DMEPA Primary Reviewer: Millie Shah, PharmD, BCPS
DMEPA Team Leader: Otto Townsend, PharmD

1 PURPOSE OF MEMO
The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling for Clorotekal (Chloroprocaine HCl injection, USP) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.\(^{a}\)

2 CONCLUSION
The revised container label is unacceptable from a medication error perspective. The linear barcode is missing from the revised container label. Additionally, the container label is missing the statement that the contents are per mL, which is present on the carton labeling.

\(^{a}\) Shah M. Label and Labeling Review for Chloroprocaine HCl injection (NDA 208791). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 FEB 21. 8 p. OSE RCM No.: 2016-2082.
3 RECOMMENDATIONS FOR SINETICA SA

We recommend the Applicant implement the following prior to approval of this NDA:

A. Container Label

1. The linear barcode containing the National Drug Code (NDC) is missing on the revised container label. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label. Therefore, we request you add the drug barcode to each individual container label as required per 21CFR 201.25(c)(2). Ensure the drug barcode is surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i). The barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g. perforation). We note the Quick Response Code appears on the revised container label. The presence of multiple barcodes is confusing to healthcare providers. Therefore, we recommend you move the barcode that does not contain the NDC number to the side or the back panel of the container label, away from the barcode containing the NDC number, and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.

2. Add the statement, “Each ml contains: 10 mg Chloroprocaine Hydrochloride Sodium Chloride, Hydrochloric Acid 1N, Water for Injection” to be consistent with the statement present on the carton labeling.

Reference ID: 4080560


APPENDIX A. LABEL AND LABELING SUBMITTED ON MARCH 17, 2017

Container labels

(b) (4)

Carton labeling

(b) (4)
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/s/

----------------------------------------
MILLIE C BRAHMBHATT
04/06/2017

OTTO L TOWNSEND
04/06/2017
RPM FILING REVIEW  
(Including Memo of Filing Meeting)  
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<thead>
<tr>
<th>Application Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA # 208791</td>
<td>NDA Supplement #: S-</td>
</tr>
<tr>
<td>BLA#</td>
<td>BLA Supplement #: S-</td>
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<tr>
<td>Efficacy Supplement Category:</td>
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<tr>
<td>□ New Indication (SE1)</td>
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<tr>
<td>□ New Dosing Regimen (SE2)</td>
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<td>□ New Route Of Administration (SE3)</td>
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<tr>
<td>□ Comparative Efficacy Claim (SE4)</td>
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<tr>
<td>□ New Patient Population (SE5)</td>
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<td>□ Rx To OTC Switch (SE6)</td>
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<tr>
<td>□ Accelerated Approval Confirmatory Study (SE7)</td>
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<tr>
<td>□ Labeling Change With Clinical Data (SE8)</td>
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<tr>
<td>□ Manufacturing Change With Clinical Data (SE9)</td>
<td></td>
</tr>
<tr>
<td>□ Animal Rule Confirmatory Study (SE10)</td>
<td></td>
</tr>
</tbody>
</table>

Proprietary Name: (proposed)  
Established/Proper Name: Chloroprocaine 1%  
Dosage Form: Injection  
Strengths: 10mg/mL  
Applicant: Sintetica SA  
Agent for Applicant (if applicable): VPCI, Inc – Craig Kruman  
Date of Application: August 26, 2016  
Date of Receipt: August 26, 2016  
Date clock started after Unacceptable for Filing (UN):  
PDUFA/BsUFA Goal Date: June 26, 2017  
Action Goal Date (if different):  
Filing Date: October 25, 2016  
Date of Filing Meeting: October 6, 2016  
Chemical Classification (original NDAs only):  
□ Type 1- New Molecular Entity (NME); NME and New Combination  
□ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination  
□ Type 3- New Dosage Form; New Dosage Form and New Combination  
□ Type 4- New Combination  
□ Type 5- New Formulation or New Manufacturer  
□ Type 7- Drug Already Marketed without Approved NDA  
□ Type 8- Partial Rx to OTC Switch  
□ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)  
□ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)  
Proposed indication(s)/Proposed change(s): local anesthetic indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia)  
Type of Original NDA:  
□ AND (if applicable)  
Type of NDA Supplement:  
□ 505(b)(1)  
□ 505(b)(2)  

If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:  
Type of BLA

If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team

Review Classification:

The application will be a priority review if:
- A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)
- The product is a Qualified Infectious Disease Product (QIDP)
- A Tropical Disease Priority Review Voucher was submitted
- A Pediatric Rare Disease Priority Review Voucher was submitted

Resubmission after withdrawal? □ Resubmission after refuse to file? □

Part 3 Combination Product? □

If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

Fast Track Designation □

Breakthrough Therapy Designation (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager) □

Rolling Review □

Orphan Designation □

Rx-to-OTC switch, Full □

Rx-to-OTC switch, Partial □

Direct-to-OTC □

PMC response □

PMR response:
- FDAAA [505(o)]
- PREA deferred pediatric studies (FDCA Section 505B)
- Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
- Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (if OTC product):

List referenced IND Number(s): PIND 119674

Goal Dates/Product Names/Classification Properties

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>PDUFA/BsUFA and Action Goal dates correct in the electronic archive?</td>
<td>❌</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.

Are the established/proper and applicant names correct in electronic archive? ❌

If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name.
to the supporting IND(s) if not already entered into electronic archive.

<table>
<thead>
<tr>
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<th>YES</th>
<th>NO</th>
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<tr>
<td>Application Integrity Policy</td>
<td>☑️</td>
<td>☐️</td>
<td>☐️</td>
<td>Standard Review</td>
</tr>
</tbody>
</table>

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm

If no, ask the document room staff to make the appropriate entries.

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Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm

If yes, explain in comment column.

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</tbody>
</table>

If affected by AIP, has OC been notified of the submission? If yes, date notified:

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<th>YES</th>
<th>NO</th>
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</tr>
</tbody>
</table>

User Fees

Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature? ☑️ ☐️ ☐️ Waiver submitted for small business

User Fee Status

If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.

Payment for this application (check daily email from UserFeeAR@fda.hhs.gov):

☑️ Paid
☐ Exempt (orphan, government)
☒ Waived (e.g., small business, public health)
☐ Not required

If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.

Payment of other user fees:

☒ Not in arrears
☐ In arrears

User Fee Bundling Policy


Has the user fee bundling policy been appropriately applied? If no, or you are not sure, consult the User Fee Staff.

N/A
☐ Yes
☒ No

505(b)(2)
(NDAs/NDA Efficacy Supplements only)

Is the application a 505(b)(2) NDA? (Check the 356h form, ☑️ ☐️ ☐️
cover letter, and annotated labeling). If yes, answer the bulleted questions below:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</td>
<td>☐</td>
<td>☒</td>
<td>No spinal injection formulations for Chloroprocaine 1%</td>
</tr>
<tr>
<td>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
</tbody>
</table>

*If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.*

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
</tbody>
</table>

*Check the Electronic Orange Book at:*
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

*If yes, please list below:*

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.*

**Exclusivity**

<table>
<thead>
<tr>
<th>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at:</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></td>
</tr>
</tbody>
</table>

*If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?*

*If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy*

**NDAs/NDA efficacy supplements only:**

*Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?*

*If yes, # years requested: not indicated*
| Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. |
| NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? |
| If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? |
| If yes, contact the Orange Book Staff (CDER-Orange Book Staff). |
| BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? |
| If yes, notify Marlene Schultz-DePaloo, CDER Purple Book Manager |
| Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. |

### Format and Content

| Do not check mixed submission if the only electronic component is the content of labeling (COL). |
| If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format? |
| Overall Format/Content |
| YES | NO | NA | Comment |
| If electronic submission, does it follow the eCTD guidance? |
| If not, explain (e.g., waiver granted). |
| Index: Does the submission contain an accurate comprehensive index? |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: |

If no, explain.

**BLA only:** Companion application received if a shared or divided manufacturing arrangement?

If yes, BLA #

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### Forms and Certifications

Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

#### Application Form

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].*

Are all establishments and their registration numbers listed on the form/attached to the form?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Patent Information (NDAs/NDA efficacy supplements only)

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?*

#### Financial Disclosure

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?*

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*

*Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

#### Clinical Trials Database

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Is form FDA 3674 included with authorized signature?*

*If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”*
<table>
<thead>
<tr>
<th>Debarment Certification</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Original Debarment certification signed by Applicant ONLY – not US agent – IR sent and US agent signed certification</td>
</tr>
</tbody>
</table>

**Certification is not required for supplements if submitted in the original application. If foreign applicant, both the applicant and the U.S. Agent must sign the certification** [per Guidance for Industry: Submitting Debarment Certifications].

**Note:** Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge…”

<table>
<thead>
<tr>
<th>Field Copy Certification</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(NDAs/NDA efficacy supplements only)</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td>Electronic submission</td>
</tr>
</tbody>
</table>

**For paper submissions only:** Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?

**Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)**

**If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.**

<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
</tbody>
</table>

**If yes, date consult sent to the Controlled Substance Staff:**

**For non-NMEs:**

**Date of consult sent to Controlled Substance Staff:**

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREA</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
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</tbody>
</table>

**If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[^1]**


Version: 4/12/2016

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Reference ID: 4008380
<table>
<thead>
<tr>
<th>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</td>
</tr>
<tr>
<td>If no, may be an RTF issue - contact DPMH for advice.</td>
</tr>
<tr>
<td>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</td>
</tr>
<tr>
<td>If no, may be an RTF issue - contact DPMH for advice.</td>
</tr>
<tr>
<td>BPCA:</td>
</tr>
<tr>
<td>Is this submission a complete response to a pediatric Written Request?</td>
</tr>
<tr>
<td>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</td>
</tr>
<tr>
<td>Proprietary Name</td>
</tr>
<tr>
<td>Is a proposed proprietary name submitted?</td>
</tr>
<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</td>
</tr>
<tr>
<td>REMS</td>
</tr>
<tr>
<td>Is a REMS submitted?</td>
</tr>
<tr>
<td>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMISB via the CDER OSI RMP mailbox</td>
</tr>
<tr>
<td>Prescription Labeling</td>
</tr>
<tr>
<td>Check all types of labeling submitted.</td>
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<td></td>
</tr>
<tr>
<td>Is Electronic Content of Labeling (COL) submitted in SPL format?</td>
</tr>
</tbody>
</table>

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alHealthStaff/ucm027829.htm

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Version: 4/12/2016

Reference ID: 4008380
<table>
<thead>
<tr>
<th><strong>If no, request applicant to submit SPL before the filing date.</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the PI submitted in Physician Labeling Rule (PLR) format?</td>
<td>✗</td>
</tr>
<tr>
<td><strong>If PI not submitted in PLR format</strong>, was a waiver or deferral requested before the application was received or in the submission? <strong>If requested before application was submitted</strong>, what is the status of the request?</td>
<td>☐</td>
</tr>
<tr>
<td><strong>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</strong></td>
<td></td>
</tr>
<tr>
<td>For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLHR) format?</td>
<td>✗</td>
</tr>
<tr>
<td>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?</td>
<td>☐</td>
</tr>
<tr>
<td><strong>For applications submitted on or after June 30, 2015:</strong> <strong>If PI not submitted in PLLHR format</strong>, was a waiver or deferral requested before the application was received or in the submission? <strong>If requested before application was submitted</strong>, what is the status of the request?</td>
<td>☐</td>
</tr>
<tr>
<td><strong>If no waiver or deferral, request applicant to submit labeling in PLLHR format before the filing date.</strong></td>
<td></td>
</tr>
<tr>
<td>Has all labeling [PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling]] been consulted to OPDP?</td>
<td>✗</td>
</tr>
<tr>
<td>Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<em>send WORD version if available</em>)</td>
<td>✗</td>
</tr>
<tr>
<td>Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?</td>
<td>✗</td>
</tr>
<tr>
<td><strong>OTC Labeling</strong></td>
<td>✗</td>
</tr>
<tr>
<td>Check all types of labeling submitted.</td>
<td></td>
</tr>
<tr>
<td>Outer carton label</td>
<td>☑</td>
</tr>
<tr>
<td>Immediate container label</td>
<td></td>
</tr>
<tr>
<td>Blister card</td>
<td></td>
</tr>
<tr>
<td>Blister backing label</td>
<td></td>
</tr>
<tr>
<td>Consumer Information Leaflet (CIL)</td>
<td></td>
</tr>
<tr>
<td>Physician sample</td>
<td></td>
</tr>
<tr>
<td>Consumer sample</td>
<td></td>
</tr>
</tbody>
</table>


Reference ID: 4008380
<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is electronic content of labeling (COL) submitted?</td>
<td>☐</td>
<td>☑</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>If no, request in 74-day letter.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are annotated specifications submitted for all stock keeping units (SKUs)?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td><strong>If no, request in 74-day letter.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If representative labeling is submitted, are all represented SKUs defined?</td>
<td>☐</td>
<td>☑</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>If no, request in 74-day letter.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All labeling/packaging sent to OSE/DMEPA?</td>
<td>☐</td>
<td>☑</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Other Consults</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, specify consult(s) and date(s) sent:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meeting Minutes/SPAs</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>End-of Phase 2 meeting(s)? Date(s):</td>
<td>☐</td>
<td>☑</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):</td>
<td>☐</td>
<td>☑</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Any Special Protocol Assessments (SPAs)? Date(s):</td>
<td>☐</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**ATTACHMENT**

**MEMO OF FILING MEETING**

**DATE:** October 6, 2016

**REVIEW TEAM:**

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Selma Kraft</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Parinda Jani</td>
<td>N</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Leah Crisafi</td>
<td>Y</td>
</tr>
<tr>
<td>Division Director/Deputy</td>
<td>Rigoberto Roca</td>
<td>Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>Curtis Rosebraugh</td>
<td>N</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Alla Bazini</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Leah Crisafi</td>
<td>Y</td>
</tr>
<tr>
<td>Social Scientist Review (<em>for OTC products</em>)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OTC Labeling Review (<em>for OTC products</em>)</td>
<td>Reviewer:</td>
<td></td>
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<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Clinical Microbiology (<em>for antimicrobial products</em>)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Srikanth Nallani</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Yun Xu</td>
<td>Y</td>
</tr>
<tr>
<td>Genomics</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Reviewer: Yan Zhou</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: David Petullo</td>
<td>Y</td>
</tr>
<tr>
<td>Category</td>
<td>Reviewer</td>
<td>TL</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>---------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Imran Khan</td>
<td>Y</td>
</tr>
<tr>
<td>Statistics (carcinogenicity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Quality (CMC) Review Team:</td>
<td>ATL: Julia Pinto</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>RBPM: Steven Kinsley</td>
<td>N</td>
</tr>
<tr>
<td>• Drug Substance</td>
<td>Reviewer: Jeffrey Medwid</td>
<td>Y</td>
</tr>
<tr>
<td>• Drug Product</td>
<td>Reviewer: Valerie Amspacher</td>
<td>Y</td>
</tr>
<tr>
<td>• Process</td>
<td>Reviewer: Karthik Iyer/ Pei-I Chu</td>
<td>Y/N</td>
</tr>
<tr>
<td>• Microbiology</td>
<td>Reviewer: Jennifer Patro</td>
<td>N</td>
</tr>
<tr>
<td>• Facility</td>
<td>Reviewer: Aditi Thakur/Christina Capcei-Daniel</td>
<td>N/N</td>
</tr>
<tr>
<td>• Biopharmaceutics</td>
<td>Reviewer: Suneet Shukla/Haritha Mandula</td>
<td>Y/Y</td>
</tr>
<tr>
<td>• Immunogenicity</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td>• Labeling (BLAs only)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td>• Other (e.g., Branch Chiefs, EA Reviewer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMP/OMPI/DMPP (MedGuide, PPI, IFU)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)</td>
<td>Reviewer: Koungee Lee</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name, carton/container labeling)</td>
<td>Reviewer: Millie Shah</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OC/OSI/DSC/PMSB (REMS)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
</tbody>
</table>
**FILING MEETING DISCUSSION:**

**GENERAL**

- **505 b)(2) filing issues:**
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?  
    - NO
  
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?
    - YES  
    - NO

  Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):

  PK Data from 1 study and literature used to support bridge – adequacy of the data will be a review issue

- Per reviewers, are all parts in English or English translation?
  
  If no, explain:

- Electronic Submission comments

  List comments:
### CLINICAL

#### Comments:

- Clinical study site(s) inspections(s) needed?
  - If no, explain:
    - **YES**
    - **NO**

- Advisory Committee Meeting needed?
  - Comments:
    - **YES**
    - Date if known:
      - **NO**
      - To be determined
    - Reason:

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  - Comments:
    - **Not Applicable**
    - **YES**
    - **NO**

### CONTROLLED SUBSTANCE STAFF

- Abuse Liability/Potential
  - Comments:
    - **Not Applicable**
    - **FILE**
    - **REFUSE TO FILE**

### CLINICAL MICROBIOLOGY

- Comments:
  - **Not Applicable**
  - **FILE**
  - **REFUSE TO FILE**

- Review issues for 74-day letter
<table>
<thead>
<tr>
<th>Category</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL PHARMACOLOGY</strong></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
</tr>
</tbody>
</table>
| • Clinical pharmacology study site(s) inspections(s) needed? | Not Applicable  
☑ FILE  
☒ REFUSE TO FILE  
☒ Review issues for 74-day letter |
| **BIOSTATISTICS**                            |                                                                          |
|  Comments:                                   |                                                                          |
| **NONCLINICAL** (PHARMACOLOGY/TOXICOLOGY)    |                                                                          |
|  Comments:                                   |                                                                          |
| **PRODUCT QUALITY (CMC)**                    |                                                                          |
|  Comments:                                   |                                                                          |
| **New Molecular Entity (NDAs only)**         |                                                                          |
| • Is the product an NME?                    | ☐ YES  
☒ NO |
| **Environmental Assessment**                 |                                                                          |
| • Categorical exclusion for environmental assessment (EA) requested? | ☒ YES  
☒ NO  
☐ YES  
☒ NO |
| If no, was a complete EA submitted?          | ☒ YES  
☒ NO |
|  Comments:                                   |                                                                          |
| **Facility Inspection**                      |                                                                          |
| • Establishment(s) ready for inspection?     | ☒ YES  
☒ NO |
|  Comments:                                   | OPQ has sent requests for inspections already |

Version: 4/12/2016
| **Facility/Microbiology Review (BLAs only)** | ☒ Not Applicable |
| Comments: | ☐ FILE |
| | ☐ REFUSE TO FILE |
| | ☐ Review issues for 74-day letter |

| **CMC Labeling Review (BLAs only)** | ☐ Review issues for 74-day letter |
| Comments: | |

| **APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)** | N/A |
| | ☐ YES |
| | ☐ NO |

- Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?
- If so, were the late submission components all submitted within 30 days?
- What late submission components, if any, arrived after 30 days?
- Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?
- Is a comprehensive and readily located list of all clinical sites included or referenced in the application?
- Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?
REGULATORY PROJECT MANAGEMENT

Signatory Authority: TBD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): Jan 26, 2017

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

<table>
<thead>
<tr>
<th>Primary Reviews Due in DARRTS</th>
<th>May 22, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Reviews Due in DARRTs</td>
<td>May 30, 2017</td>
</tr>
<tr>
<td>CDTL Memo Due</td>
<td>June 5, 2017</td>
</tr>
</tbody>
</table>

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☐ No review issues have been identified for the 74-day letter.
☒ Review issues have been identified for the 74-day letter.

Review Classification:

☒ Standard Review
☐ Priority Review

ACTION ITEMS

☒ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).

☐ If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐ If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☐ If priority review, notify applicant in writing by day 60 (see CST for choices)

☒ Send review issues/no review issues by day 74

☒ Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☐ Update the PDUFA V DARRTS page (for applications in the Program)

☐ Other

Annual review of template by OND ADRAs completed: April 2016

Reference ID: 4008380
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-----------------------------------------
SELMA S KRAFT
11/03/2016

AYANNA S AUGUSTUS on behalf of PARINDA JANI
11/03/2016
on behalf of Parinda Jani
Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208791

Application Type: New NDA

Drug Name(s)/Dosage Form(s): (Proposed name) Chloroprocaine HCl 1% (10mg/mL) Injection, USP

Applicant: Sintetica

Receipt Date: August 26, 2016

Goal Date: June 26, 2017

1. Regulatory History and Applicant’s Main Proposals
   - Chloroprocaine 1% is a local anesthetic indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia).
   - 505(b)(2) application to Nesacaine (chloroprocaine HCl) Injection – NDA 009435 as the reference listed drug
   - Had PIND meeting (PIND 119674) in December 2013
   - Agreed iPSP 4/21/2016

2. Review of the Prescribing Information
   This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements of Prescribing Information (SRPI)” checklist (see Section 4 of this review).

3. Conclusions/Recommendations
   SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information
   The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.
Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: The HL section is longer than 1/2 page

YES 3. A horizontal line must separate:
   - HL from the Table of Contents (TOC), and
   - TOC from the Full Prescribing Information (FPI).

Comment:

NO 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be bolded and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: Headings are not centered on a horizontal line. The line used is dashed and not a solid line

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: There is extra white space between the product name and the initial US approval date

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

<table>
<thead>
<tr>
<th>Heading</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>• Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>• Initial U.S. Approval</td>
<td>Required</td>
</tr>
<tr>
<td>• Boxed Warning</td>
<td>Required if a BOXED WARNING is in the FPI</td>
</tr>
<tr>
<td>• Recent Major Changes</td>
<td>Required for only certain changes to PI*</td>
</tr>
<tr>
<td>• Indications and Usage</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

- Dosage and Administration: Required
- Dosage Forms and Strengths: Required
- Contraindications: Required (if no contraindications must state "None.")
- Warnings and Precautions: Not required by regulation, but should be present
- Adverse Reactions: Required
- Drug Interactions: Optional
- Use in Specific Populations: Optional
- Patient Counseling Information Statement: Required
- Revision Date: Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, “HIGHLIGHTS OF PRESCRIBING INFORMATION” must be bolded and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The bolded HL Limitation Statement must include the following verbatim statement: “These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be bolded.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be bolded, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be bolded.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. Even if there is more than one warning, the term “WARNING” and not “WARNINGS” should be used. For example: “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

Reference ID: 4008374
Selected Requirements of Prescribing Information

14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement must be placed immediately beneath the BW title, and should be centered and appear in italics.

Comment:

15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “See full prescribing information for complete boxed warning.”)

Comment:

Recent Major Changes (RMC) in Highlights

16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: Only 1 dosage form - ampules

Contraindications in Highlights

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment: Missing this bullet point in HL (included in FPI): intravenous regional anesthesia (the anesthetic agent is introduced into the limb and allowed to set in while tourniquets retain the agent within the desired area??
Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

NO 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

*Comment:* verbatim statement is not bolded in HL section

Patient Counseling Information Statement in Highlights

NO 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

*Comment:* Must include statement "See 17 for PATIENT COUNSELING INFORMATION"

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 8/2015”).

*Comment:*
Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS.” This heading should be in all UPPER CASE letters and bolded.

Comment:

NO 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and bolded.

Comment:

YES 27. In the TOC, all section headings must be bolded and should be in UPPER CASE.

Comment:

NO 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: "For" and "And" capitalized in section 5.1 - should not be capitalized

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “FULL PRESCRIBING INFORMATION: CONTENTS*” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:
FULL PRESCRIBING INFORMATION: GENERAL FORMAT

31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in **UPPER CASE** and **title case**, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “Labor and Delivery”)</td>
</tr>
<tr>
<td>8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “Nursing Mothers”)</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSAGE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:**

32. The preferred presentation for cross-references in the FPI is the **section** (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in **italics** and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)].”
33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading “FULL PRESCRIBING INFORMATION” must be bolded, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be bolded.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “WARNING” and not “WARNINGS” should be used.) For example: “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

NO 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: No statement included in this section

N/A 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:
PATIENT COUNSELING INFORMATION Section in the FPI

40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:
Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ...

Limitations of Use: Text (1)

DOSE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSE FORMS AND STRENGTHS
Dosage form(s): strength(s) (3)

- CONTRAINDICATIONS
  - Text (4)
  - Text (4)

- WARNINGS AND PRECAUTIONS
  - Text (5.x)
  - Text (5.x)

- ADVERSE REACTIONS
  Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- DRUG INTERACTIONS
  - Text (7.x)
  - Text (7.x)

- USE IN SPECIFIC POPULATIONS
  - Text (8.x)
  - Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
   2.1 Subsection Title
   2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
   5.1 Subsection Title
   5.2 Subsection Title
6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Immunogenicity
   6.3 or 6.4 Postmarketing Experience
7 DRUG INTERACTIONS
   7.1 Subsection Title
   7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Lactation (If not required to be in PLLR format use Labor and Delivery)
   8.3 Females and Males of Reproductive Potential (If not required to be in PLLR format use Nursing Mothers)
   8.4 Pediatric Use
   8.5 Geriatric Use
   8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.2 Abuse
   9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
   12.4 Microbiology
   12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
   14.1 Subsection Title
   14.2 Subsection Title

15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
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/s/
SELMA S KRAFT
11/03/2016

AYANNA S AUGUSTUS on behalf of PARINDA JANI
11/03/2016
on behalf of Parinda Jani