CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208791Orig1s000

PRODUCT QUALITY REVIEW(S)
Recommendation:
NDA: Approval

NDA 208791

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>Chloroprocaine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>1% (10mg/ml)</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Injection</td>
</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant</td>
<td>Sintetica, SA</td>
</tr>
<tr>
<td>US agent, if applicable</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUBMISSION(S) REVIEWED</th>
<th>DOCUMENT DATE</th>
<th>DISCIENCE(S) AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original NDA</td>
<td>August 28 2016</td>
<td></td>
</tr>
</tbody>
</table>

**Quality Review Team**

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>REVIEWER</th>
<th>BRANCH/DIVISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Jeffrey Medwid</td>
<td>OPQ/ONDF/DNDP/API/BII</td>
</tr>
<tr>
<td>Drug Product Process</td>
<td>Valerie Amspacher</td>
<td>OPQ/ONDF/DNDPII/BIV</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Jennifer Patro</td>
<td>OPQ/OPF/DMA/BII</td>
</tr>
<tr>
<td>Facility</td>
<td>Karthik Iyer</td>
<td>OPQ/OPF/DIA/BII</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>None</td>
<td>OPQ/ONDF/DB/BII</td>
</tr>
<tr>
<td>Regulatory Business Process Manager</td>
<td>Steve Kinsley</td>
<td>OPQ/OPRO/RBPMI/BI</td>
</tr>
<tr>
<td>Application Technical Lead</td>
<td>Julia Pinto</td>
<td>OPQ/ONDF/DNDPII/BIV</td>
</tr>
<tr>
<td>Laboratory (OTR)</td>
<td>NA</td>
<td>ORA/OGROP/ORA/OO/OMPTO/DMPTPO/M</td>
</tr>
<tr>
<td>ORA Lead</td>
<td>NA</td>
<td>ORA/OGROP/ORA/OO/OMPTO/DMPTPO/M</td>
</tr>
<tr>
<td>Environmental Assessment (EA)</td>
<td>Valerie Amspacher</td>
<td></td>
</tr>
</tbody>
</table>
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of Contents</td>
<td>2</td>
</tr>
<tr>
<td>Quality Review Data Sheet</td>
<td>3</td>
</tr>
<tr>
<td>Executive Summary</td>
<td>4</td>
</tr>
<tr>
<td><strong>Primary Quality Review</strong></td>
<td>5</td>
</tr>
<tr>
<td>ASSESSMENT OF THE DRUG SUBSTANCE</td>
<td>5</td>
</tr>
<tr>
<td>2.3.S DRUG SUBSTANCE</td>
<td>5</td>
</tr>
<tr>
<td>ASSESSMENT OF THE DRUG PRODUCT</td>
<td>19</td>
</tr>
<tr>
<td>2.3.P DRUG PRODUCT</td>
<td>19</td>
</tr>
<tr>
<td>ASSESSMENT OF ENVIRONMENTAL ANALYSIS</td>
<td>50</td>
</tr>
<tr>
<td>Labeling &amp; Package Insert</td>
<td>51</td>
</tr>
<tr>
<td>ASSESSMENT OF THE PROCESS</td>
<td>56</td>
</tr>
<tr>
<td>ASSESSMENT OF THE MICROBIOLOGY</td>
<td>68</td>
</tr>
<tr>
<td>ASSESSMENT OF FACILITIES</td>
<td>84</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>92</td>
</tr>
</tbody>
</table>
Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(8)(4)</td>
<td>II</td>
<td></td>
<td></td>
<td>1</td>
<td>January 11 2017</td>
<td>Reviewed Jeff Medwick; adequate</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
<td></td>
<td>4</td>
<td>N/A</td>
<td>Sufficient information in Application</td>
</tr>
</tbody>
</table>

Action codes for DMF Table:
1 – DMF Reviewed.
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. Other Documents: N/A

2. CONSULTS: None
Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

C. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [Chloroprocaine HCl] Quality Summary

The manufacture and control of the drug substance is referenced to DMF and reviewed by Jeff Medwid, Ph.D. The drug substance is adequately supported for use in the preparation of the drug product and has a retest period of months.

B. Drug Product [Chloroprocaine HCl] Quality Summary

Since the ampules will be stored in cardboard containers, the statement “protect from light” is added to the labels. Satisfactory stability data is provided to support an expiry of 24 months for the drug product, when stored at 25C.
C. Summary of Drug Product Intended Use

<table>
<thead>
<tr>
<th>Proprietary Name of the Drug Product</th>
<th>01(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Proprietary Name of the Drug Product</td>
<td>Chloroprocaine HCl, USP</td>
</tr>
<tr>
<td>Non Proprietary Name of the Drug Substance</td>
<td>Chloroprocaine HCl, USP</td>
</tr>
<tr>
<td>Proposed Indication(s) including Intended Patient Population</td>
<td>Spinal block anesthetic to be used during surgery</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td></td>
</tr>
<tr>
<td>Maximum Daily Dose</td>
<td></td>
</tr>
<tr>
<td>Alternative Methods of Administration</td>
<td></td>
</tr>
</tbody>
</table>

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

This NDA is recommended for approval.

Application Technical Lead Signature:

Julia C. Pinto, Ph.D.
Branch Chief(Acting)
ONDP/Division II/Branch IV

62 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
MICROBIOLOGY

Product Background:

NDA/ANDA/BLA: NDA 208791

Drug Product Name / Strength: Chlorprocaine HCl 1% (10 mg/mL) Injection

Route of Administration: intrathecal

Applicant Name: Sintetica

Manufacturing Site: Sintetica SA
Via Penate 5
CH-6850 Mendrisio
Switzerland

Method of Sterilization: (b) [4]

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed: 8/26/16, 12/22/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: (b) [4]

Remarks Section: N/A

S Drug Substance
N/A

P.1 Description of the Composition of the Drug Product

- Description of drug product – Chlorprocaine HCl 1%
  This is a sterile, clear, colorless solution.
- Drug product composition
  (3.2.P.1 Description and Composition of the drug product.pdf)
**Ingredients**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Function</th>
<th>Quantity mg/mL</th>
<th>Quantity mg/5 mL ampoule</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopropramine HCl</td>
<td>Drug substance</td>
<td>10.00</td>
<td>50.00</td>
<td>USP current ed.</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td></td>
<td>(0)(4)</td>
<td>(0)(4)</td>
<td>USP current ed.</td>
</tr>
<tr>
<td>Hydrochloric Acid 1N</td>
<td>pH adjustor</td>
<td></td>
<td>(0)(5)</td>
<td>USP current ed.</td>
</tr>
<tr>
<td>Water for injections</td>
<td></td>
<td></td>
<td>(0)(4)</td>
<td>USP current ed.</td>
</tr>
</tbody>
</table>

- Description of container closure system – A type I (USP) 5 mL score break glass ampoule.

**Reviewer’s Assessment:** The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

**P.2.5 Microbiological Attributes**

**Container/Closure and Package Integrity**

(See 3.2P.3.5 Process Validation and/or Evaluation.pdf, p. 38)

**Test method:** All ampoules are checked for leaks. The production ampoules and production conditions are used in this test.
was also included. This testing method shows a

This same microbial immersion study from July 2011 was reviewed by Scott Steffen on 7/14/2011 in (b)(4).doc and found adequate.

Information Request (November 8, 2016): Please provide a methods description to explain the validation of container closure

Response (December 22, 2016): The ampoules used in validation

Reviewer’s Assessment: The container closure integrity test is adequate for this product.

ACCEPTABLE

Antimicrobial Effectiveness Testing- N/A
P.3 Manufacture
P.3.1 Manufacturers
Drug product
    Sintetica SA
    Via Penate 5
    CH-6850 Mendrisio
    Switzerland
    Manufacturing, release and stability testing are performed here

P. 3.3 Description of the Manufacturing Process and Process Controls
Overall Manufacturing Operation

Reviewer’s Assessment:
Reviewer’s Assessment: The described for a sterilized product are adequately ACCEPTABLE.
- Environmental monitoring including product bioburden

**Information Request (November 8, 2016):** No environmental monitoring was found in the submission. Please include environmental monitoring information including:
  - A description of the environmental classification of the formulation and filling areas,
  - A description of types of monitoring performed in these areas (active, passive, surface, etc.) and monitoring methods,
  - Acceptance criteria for environmental monitoring
  - Methods, schedule, and acceptance criteria for WFI monitoring.

**Response (December 22, 2016):**

**Acceptance Criteria:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Total Bacterial Load (CFU/m³)</th>
<th>Yeast and Molds (CFU/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alert</td>
<td>Limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Surface monitoring is performed with

**Acceptance Criteria:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Surface Type</th>
<th>Total Bacterial Load (CFU/m³)</th>
<th>Yeast and Molds (CFU/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alert</td>
<td>Limit</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>NMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioburden</td>
<td>Alert: 10³ CFU/100 mL Limit: 10⁶ CFU/100 mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reviewer’s Assessment:** The environmental monitoring are adequately described.
ACCEPTABLE

- **Product Bioburden**
  (3.2.P.3.4 Description of Manufacturing Process and Process Controls.p df. p 6)
  Bioburden is monitored for every batch using methods found in USP <61>.

**Acceptance Criteria:**

<table>
<thead>
<tr>
<th>Bulk Solution Sample</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMT ((6)) CFU/mL</td>
</tr>
<tr>
<td></td>
<td>NMT ((6)) CFU/10 mL</td>
</tr>
</tbody>
</table>

**Reviewer’s Assessment:** Bioburden limits are found acceptable for a sterilized product.

**ACCEPTABLE**

**P. 3.5 Process Validation and/or Evaluation**
BI information
specified pop: (b)(4) CFU; confirmed pop: (b)(4) CFU

Reviewer’s Assessment: BI utilized comparison study completed in 2015

The submission includes a
This validation study was reviewed by Steven P. Donald on March 12, 2010 in doc and found adequate.

**Information Request (November 8, 2016):** It is acknowledged that validation of the 5 mL ampoule load sterilization was performed; however, more information is needed. Please provide:

- acceptance criteria for the study
- status of the positive control BIs used in the studies
- results

**Response (December 22, 2016):** Acceptance criteria for HP.BI studies are provided.

- The temperature read by each TC should be
- No growth of BIs after day incubation.
- Positive control should have growth.

All results meet these acceptance criteria.

The status of BIs is provided in the response and all BIs are negative for growth in all runs while the positive control displays positive growth in all runs. Therefore, all BIs meet acceptance criteria.

**Reviewer’s Assessment:** The applicant has provided and did not provide additional data when requested. However, this data was found adequate in pdf by Maria Cruz-Fisher, Ph.D. on November 8, 2016 so no additional information will be requested.

**ACCEPTABLE**

- **Thermal monitors**
  (Process Validation and/or Evaluation.pdf, p. 20)

- **Effects of loading**
  (Process Validation and/or Evaluation.pdf, p. 20)
- Microbiological efficacy of the cycle
  - Identification and characterization of bioburden
    (Process Validation and/or Evaluation.pdf, p.10)

- Characterization of biological indicators
  See loaded chamber HP/BI studies above.

**Reviewer’s Assessment:** The bioburden are all adequate. **ACCEPTABLE**

**Holding Periods**
(3.2.P.3.5 Process Validation and/or Evaluation.pdf, p.47)
Endotoxin Information:

- **E. coli** Lot number: GL1457; Expiry: Nov 2011; Potency: EU/vial; Recovery: EU/vial

**Reviewer’s Assessment:** A mathematical model is used

The total exposure time for a 5mL ampoule is seconds.

Therefore, no further information will be requested

**Requalification**

Information Request (November 8, 2016): *It is acknowledged that the 5 mL ampoules are*

Response (from December 22, 2016): The ampoules received are

**Reviewer’s Assessment:** the ampoules are adequately described. **ACCEPTABLE**

P.5 Control of Drug Product

P. 5.1 Specification

(3.2.P.5.1 Specifications.pdf; batch analyses.pdf)

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Method</th>
<th>Acceptance Criteria</th>
<th>Exhibit Batch Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Endotoxins</td>
<td>USP &lt;85&gt;</td>
<td>&lt; (b)(4) EU/mL</td>
<td>Complies</td>
</tr>
<tr>
<td>Sterility</td>
<td>USP &lt;71&gt;</td>
<td>No growth after (b)(4) days</td>
<td>Sterile</td>
</tr>
</tbody>
</table>

**Reviewer’s Assessment:** Specifications provided in the submission are acceptable.

P.5.2 Analytical Procedures- See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

**Endotoxins**

(3.2.P.5.3 validation analytical procedure-3-endotoxin.pdf; p.1-3)
QUALITY ASSESSMENT

Test Method: kinetic-chromogenic test that follows USP <85>, used for release and shelf life testing.

Endotoxins Specification: blank EU/mL.

Information provided in the submission:

Linear regression curve built on 3 concentration points has a correlation coefficient of blank and no reaction times are recorded for solution D (blank). These two results meet the acceptance criteria listed in USP <85>:

1. Absolute value of the correlation coefficient is greater than the required 0.980
2. Solution D results do not exceed the limit of the blank value required in the description of the lysate reaction or is less than the endotoxin detection limit of the lysate reagent.

Acceptance Criteria (according to USP <85>):

The mean recovery of endotoxin must be within blank % (according to USP <85>).

Results for Interfering Factors Test:

<table>
<thead>
<tr>
<th>Batch #</th>
<th>Dilution</th>
<th>Series (from USP &lt;85&gt;)</th>
<th>Reaction Time (s)</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>15007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reviewer’s Assessment: The test results meet the acceptance criteria determined by USP <85> and has no interfering factors between the dilution factors of blank. The MVD used for validation is blank. The batch used for validation of endotoxin testing is not one of the executed batches.

Validation

Correlation coefficient: blank concentration points (complies with USP <85>).

Acceptance Criteria (from USP <85>):

Endotoxin recovery should be within range blank %.

Results (results are an average of three analyses):

<table>
<thead>
<tr>
<th>Batch</th>
<th>Series (from USP &lt;85&gt;)</th>
<th>Reaction Time (s)</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>15007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1404901</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results meet acceptance criteria from USP <85>.
Endotoxin Dosage:
Maximum recommended dosing for a 70 kg person is 50 mg (5 mL) over 60 minute surgery

$$\frac{\text{EU/mL} \times 5 \text{ mL}}{70 \text{ kg/hr}} = \frac{(0)(4)}{\text{EU/kg/hr}}$$

**Reviewer’s Assessment:** This is with USP requirements of $^{(0)(4)}$ EU/kg/hr for an intrathecal product.

**ACCEPTABLE**

**Sterility**

(3.2.P.5.3 Validation Analytical Procedure-4-sterility.pdf, p.1-2)

Test Method: Plate count method as described in USP <71>
Protocol Number: VSTR15038-01
Bacteriostasis/fungistasis testing was performed and was used for both release and shelf life testing.
The subject drug product was tested using a battery of organisms:

Results: Batches 03088, 05022, and 05043 were tested and growth of all organisms was measured by $^{(0)}$ days incubation time. This meets USP <71> acceptance criteria of growth within $^{(0)}$ days.

**Reviewer’s Assessment:** Sterility tests meets USP <71> criteria. The batches used for sterility testing are not the same as the executed batches in the submission.

**ACCEPTABLE**

P.7 Container Closure See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability Summary and conclusion.pdf, p1-9)
Proposed Expiry: Two Years Store at 20-25°C

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Stability Summary and conclusion.pdf, p1-9)

The product stability specification includes the following microbiological tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Method</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Endotoxins</td>
<td>USP &lt;85&gt;</td>
<td>$^{(0)(4)}$ EU/mL</td>
</tr>
<tr>
<td>Sterility</td>
<td>USP &lt;71&gt;</td>
<td>No growth</td>
</tr>
</tbody>
</table>
The testing schedule in the post-approval protocol is as follows:

**Stability storage conditions:** 25°C ± 2°C at 60 % ± 5% R.H

<table>
<thead>
<tr>
<th>Test</th>
<th>Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bacterial Endotoxins</td>
<td>X</td>
</tr>
<tr>
<td>Sterility</td>
<td>X</td>
</tr>
</tbody>
</table>

**Post Approval Stability Commitment**

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

**Reviewer’s Assessment:** The drug product expiration is 24 months and therefore does not require annual stability testing. Testing at 0 months and 24 months is adequate for this case.

**P.8.3 Stability Data**

Stability data is included for product at 1, 2, 3, and 6 months under storage conditions of 40°C±2°C for accelerated conditions, plus 9 and 12 months at 30 °C±2°C for intermediate conditions and plus 18 and 24 months at 25 °C±2°C for long-term stability studies. Batch # used for these studies is same as the test batches (12101, 12102 and 12103).

**Reviewer’s Assessment:**

Stability data is adequate for this drug product.

**ACCEPTABLE**

**R Regional Information**

**Comparability Protocols- N/A**

**2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1**

**2.A. Package Insert**

Storage temperature: 20-25°C, excursions permitted between 15°C to 30° C; Route of administration: intrathecal;

Container: Single dose/ discard unused portion

Product should be used immediately upon opening.

**Reviewer’s Assessment:** The drug product is supplied directly to the patient with no additional storage or dilution. The smallest dose possible should be supplied to the patient.

**ACCEPTABLE**

Primary Microbiology Reviewer Name and Date: Jennifer N. Patro 1/13/2017
Secondary Reviewer Name and Date: Erika Pfeiler, PhD.
12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page