CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208791Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
## Cross-Discipline Team Leader Review

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<tr>
<td>From</td>
<td>Leah Crisafi, MD</td>
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<tr>
<td>Subject</td>
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<td>NDA/BLA #</td>
<td>208791</td>
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<td>Supplement#</td>
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<td>Applicant</td>
<td>Sintetica S.A.</td>
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<tr>
<td>Proprietary Name / Established (USAN) names</td>
<td>Clorotekal / chloroprocaine hydrochloride</td>
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<tr>
<td>Dosage forms / Strength</td>
<td>Injection / 10 mg/mL</td>
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<td>Proposed Indication(s)</td>
<td>Single intrathecal injection in adults for the production of subarachnoid block</td>
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<td>Recommended:</td>
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## 1. Introduction

Chloroprocaine is a short-acting local anesthetic approved as Nesacaine and Nesacaine-MPF with indications for the production of local anesthesia by infiltration, peripheral, and central nerve block including lumbar and caudal epidural blocks (NDA 09435). Nesacaine and Nesacaine-MPF Injections are not approved for intrathecal injection.

Clorotekal is a chloroprocaine formulation intended for intrathecal administration that has been marketed in a number of European countries since 2012.

This application for U.S. marketing approval of Clorotekal relies on the Agency’s previous findings of safety and efficacy of Nesacaine. The application is also supported by four clinical studies conducted by the Applicant, European postmarketing data collected by the Applicant, and the published literature.

This review will focus on the post hoc efficacy analyses that supported approval. These post hoc analyses were conducted by the Agency because we did not agree with the endpoints in the pivotal trials, as they did not evaluate the ability of Clorotekal to provide surgical anesthesia. The review also focuses on the safety concern of neurotoxicity, both because neurotoxicity is a primary concern for any product that is administered intrathecally, and because a previous chloroprocaine formulation was associated with neurologic adverse events with intrathecal administration.
2. Background

Nesacaine, the reference, product, is approved in the United States for administration by several routes (infiltration, peripheral nerve block, and epidural block). Nesacaine is not approved for administration via the intrathecal route.

Doses of Nesacaine for epidural administration are much higher than doses proposed for intrathecal administration. A lower dose with intrathecal administration translates to lower systemic exposure than occurs with the higher doses required for an epidural anesthetic. Because of lower systemic exposure with intrathecal administration, and in this case, undetectable plasma levels of chloroprocaine after intrathecal administration, a relative bioavailability study was not performed in order to provide a bridge between Nesacaine and Clorotekal, while reliance upon systemic safety information for Nesacaine was determined to be appropriate.

The potential advantage of intrathecal chloroprocaine is its relatively brief duration of action. Currently, two local anesthetic products are approved for spinal anesthesia. Lidocaine, the shorter acting, is not widely used because it is associated with a relatively high incidence of transient neurologic symptoms. Clorotekal, if approved, could fill the niche left by lidocaine and provide a feasible alternative to general anesthesia for lower body surgeries of brief duration.

The Agency had one meeting with the Applicant under IND 119674 prior to submission of their NDA. The major pertinent issues from that December 17, 2013, meeting, are summarized below.

- Nesacaine is an acceptable reference product for a 505(b)(2) application.
  - Comparative bioavailability data are needed to establish a bridge between Nesacaine and the Sponsor’s drug product
  - Obtaining PK data for the drug product and comparing systemic exposure to Nesacaine may be an acceptable alternative
- “For intrathecal injection for the production of subarachnoid block (spinal anesthesia)” is an appropriate indication.
- Clinical efficacy and safety could be adequately supported by the Phase 3 study, the Phase 2 study, published literature, and reliance on Nesacaine.
- Given a proposed dose of 50 mg, dosing instructions would need to be “as specific as possible for a given clinical situation and patient population” and supported by clinical data.
- Nonclinical study requirements include:
  - Repeat-dose toxicology studies in two species to support an NDA for an acute indication; 28-day studies or a justification for shorter studies was recommended.
  - Toxicology studies to support any intended drug product combination.
  - Qualification of any impurity or degradation product that exceeds ICH thresholds.
Information on potential leachables and extractables from the drug container closure system.
Nonclinical information in the published literature.

The Application included the Phase 3 trial that was conducted by the Applicant in 2006 to support their European marketing application (CHL1/01-2006/M) and data from an underway safety study that was a European postmarketing requirement (PMR) (CHL1/01-2012/M), as well as a Phase 2 study that was conducted after the 2013 PIND meeting (CHL1/02-2014). During the course of the NDA review, it became apparent that another Phase 2 study had been conducted (CHL1/02-2004). The original data from that study were not available, and the available information was incomplete and could not be confirmed. Therefore, the earlier Phase 2 study provided minimal support for the application. During the course of the NDA review, the Applicant also submitted the final data for the European PMR, which was used primarily to support safety.

3. CMC/Device

This NDA contains no unresolved CMC issues and Dr. Julia Pinto, the Application Technical Lead, recommends approval.

General Product Quality Considerations
With regard to the drug substance, the Chemistry Review states the following:

Chloroprocaine, HCl, USP drug substance is supplied by [b](4) and reviewed by Jeff Medwed, Ph.D. The drug substance is adequately supported for use in the preparation of the drug product and has a retest period of [b](4) months.

The drug product is a clear, colorless solution in water, sodium chloride, and pH adjusters. The Chemistry Review states that the excipients are compendial and that given a maximum daily dose of 50 mg chloroprocaine, “no excipient exceeds the FDA inactive ingredient database limit for this route of administration.”

With regard to drug product impurities, three are noted and, according to the Chemistry Review, have been appropriately characterized. The first, [b](4) has been appropriately qualified in nonclinical studies to support the stability specification of up to [b](4)%. The second, [b](4) Because of its significant increase during the study, the chemistry reviewer states that [b](4). The third impurity,

With regard to stability, the Chemistry Review states the following:

There are definite trends in the stability data – [b](4) chloroprocaine assay
results remain within the specifications for 24 months at 25°C.

The Applicant proposes a 24 month expiry with storage at room temperature and protection from light, which Dr. Pinto concludes is appropriate.

Facilities Review/Inspection
Facilities inspections were completed and the facilities determined to be acceptable. The API manufacturing facility is [redacted] that was inspected in [redacted] and classified as NAI. The drug product manufacturer is Sintetica SA in Mendrisio, Switzerland that was inspected in November/December 2017. It was classified as VAI with three items cited [redacted]. All items appear to have been adequately addressed. Finally, the control testing laboratory for finished product release and stability testing is Sintetica-Bioren SA in Couvel, Switzerland that was inspected in November 2014 and classified as NAI.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Imran Khan, has concluded that the nonclinical data submitted by the Applicant are not sufficient to recommend approval. His review states the following:

Prior to submitting the NDA, the Division informed the Applicant that the NDA should include 28-day repeat-dose toxicological studies in both a rodent and non-rodent species using the clinical route of administration in accordance with ICH M3(R2), though a shorter duration may be justified if the toxicological potential of the product was adequately demonstrated. However, in their NDA application, the Applicant submitted single-dose IT toxicity studies with 14-day observation periods, and 7-day repeat-dose studies with 14-day observation periods in both rat and dog species. The Applicant provided explanations for not complying with the ICH M3(R2) guidance with scientific justification suggesting longer term studies were not feasible based on nonclinical studies published by experts in this field and the safety data in humans (with respect to off-label use in humans and the Applicant’s own post-marketing safety reports of their product that has been approved in Europe). The above references to scientific (expert) comments with respect to limitations of indwelling IT catheters in rats and dogs were taken into consideration during the review of the studies. Notably, the Applicant did not explicitly justify the limited duration of their conducted studies or the selection of the top dose tested in the studies which were intended to demonstrate the toxicological potential of their product as we had advised (refer to Pre-IND meeting minutes dated 1/17/2014). As such, they do not appear to have characterized the toxicological potential of the drug product solution.
The Applicant’s seven-day repeat-dose rat study of chloroprocaine 1% and 2% has arguably characterized the toxicological potential of Clorotekal. This is in part because repeat-dosing beyond seven days may not be feasible, as catheters in approximately 80% of males and 50% of females were not patent at seven days. This is also because a female rat administered 40 mcL of chloroprocaine 2% died of respiratory depression on Day 2. Dose reduction to 30 mcL of 2%, or 1.2 times the maximum recommended human dose based on estimated CSF concentration, caused no deaths. Histopathological changes were found in the spinal tissues, however they appeared unrelated to chloroprocaine because they were found with similar incidence and severity in the control animals. Thus, 30 mcL of chloroprocaine 2% is the NOAEL.

The Applicant’s seven-day repeat-dose dog study did not characterize the toxicological potential of Clorotekal. The animals were administered up to 500 mcL of chloroprocaine 2%, with well-tolerated pharmacological effects and no significant histopathological changes observed. There were no catheter patency issues or signs of overt toxicity that would preclude administration of higher doses or longer durations. Additionally, the highest dose tested did not exceed the maximum recommended human dose based on estimated CSF concentration. Specifically, the maximum dose administered to dogs (10 mg) with an estimated lumbar CSF volume of 3 mL yields a CSF concentration of 3.33 mg/mL. This compares to a human CSF concentration of 5 mg/mL (50 mg in a 10 mL CSF volume). Therefore, the dog study does not provide support for the safety of the 50 mg maximum recommended human dose.

With regard to the inadequacy of the repeat-dose toxicology studies, Dr. R. Daniel Mellon, the Pharmacology/Toxicology Supervisor, writes the following in his secondary review:

Under the usual circumstances where the nonclinical studies are conducted to support the safety of the proposed clinical trials, this nonclinical development plan would be deemed inadequate and should not be considered representative of an appropriate model for an intrathecal drug development program. However, the clinical studies for this drug product were completed outside of the U.S. and therefore not supported by an active IND permitted to proceed by the U.S. FDA. As such, in this unusual situation, the nonclinical and clinical data were submitted simultaneously to support this NDA application. The existing nonclinical rat studies do define a NOAEL that largely supports the conclusion that the drug product solution, when administered as labeled, is not likely to result in adverse histopathological changes in the spinal cord. The dog study, although limited, provides supportive data as well. They do not, however, adequately characterize the adverse effects that could occur under the relatively less controlled conditions of clinical practice, if the drug is approved.

No new pharmacology studies were included nor required for this NDA. The reference product labeling describes the pharmacology of chloroprocaine as the following:

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. In general, the progression of anesthesia is related to the
diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Pharmacologic effects observed in the nonclinical studies were consistent with the effects described above, and included respiratory depression and lower limb immobility.

Carcinogenicity studies were not included nor required for this NDA due to its acute use indication.

Genetic toxicology was evaluated via in vitro reverse mutation and chromosome aberration tests. Chloroprocaine was found to be negative in both.

Reproductive and developmental toxicology studies were not conducted for this NDA. To fulfill Pregnancy Lactation and Labeling Rule requirements, the Applicant reviewed the published literature for data about chloroprocaine reproductive and developmental toxicity. The Applicant identified three studies but concluded that they were not pertinent to the proposed indication. Dr. Khan concurs with that conclusion.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacokinetic (ADME) information in the Nesacaine labeling includes the following:

The rate of systemic absorption of local anesthetic drugs is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic injection....

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain...

Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of β-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

To characterize pharmacokinetics of intrathecal chloroprocaine, the Applicant conducted a single Phase 2 dose-ranging, safety and pharmacokinetic study, during which blood and urine samples were collected for analysis of chloroprocaine and its metabolite 2-chloro-4-amino-
benzoic acid (CABA) in subjects administered 30 mg, 40 mg, or 50 mg of chloroprocaine intrathecally for elective lower limb surgery. Chloroprocaine was not detected in the plasma.

Regarding the probability that chloroprocaine is truly undetectable in plasma, the clinical pharmacology reviewer, Dr. Srikanth Nallani, writes that the Applicant used “a fully validated reliable and sensitive LC-MS/MS analytical method” and that “It is quite possible that chloroprocaine absorbed from [cerebrospinal fluid] into the blood circulation may be metabolized rapidly before detection in plasma.”

In the Applicant’s Phase 2 study, they detected CABA in the first blood sample collected at 5 minutes post dose. CABA levels peaked at 30 minutes post-dose, and at 60 minutes were lower than at 30 minutes for most subjects. Therefore, Dr. Nallani concluded that CABA elimination appears to be greater than its formation at the 60 minute post-dose time point.

Dr. Nallani has also concluded that actual relative bioavailability is not needed. The rationale is described in his review as the following:

The sponsor has submitted adequate information to justify that an actual relative bioavailability is not needed. The submitted evidence pertains to the following...

a) Lower dose (50 mg) of proposed product (CLOROTEKAL) by intrathecal route compared to high dose of Nesacaine by epidural route recorded in publications (up to 945 mg).

b) Parent drug, chloroprocaine, could not be detected using validated bioanalytical assay. The observed systemic levels of metabolite of chloroprocaine (ACBA) are several fold low compared to the exposure data reported in the literature for epidural administration for Nesacaine.

Additionally, in an internal clinical pharmacology team meeting (1/31/2017), it was decided that since the sponsor used a validated bioanalytical assay the data would be considered reliable for the sponsor conducted study. In addition, it was noted that, if anything, a more sensitive and specific method developed by the sponsor would only detect the drug and its metabolites more accurately and precisely. Therefore, the systemic levels of chloroprocaine being undetectable with the proposed drug and route of administration would support systemic safety. The scientific “bridge” to Nesacaine was established.

6. Clinical Microbiology

This section is not applicable to this New Drug Application.
7. Clinical/Statistical- Efficacy

This NDA submission included two studies that primarily supported efficacy. The first was a Phase 2 dose-finding, safety and pharmacokinetic study (CHL1/02-2014) that evaluated three doses of chloroprocaine HCl (30, 40, and 50 mg) in adult patients undergoing short duration (<40 minutes) elective surgery of the lower limb. The second was a Phase 3 study (CHL1/02-2006/M) of a non-inferiority design that compared chloroprocaine 50 mg and bupivacaine 10 mg (5 mg/mL) in adult patients undergoing elective short duration (< 40 minutes) lower abdominal surgery.

The primary endpoints for studies CHL1/02-2014 and CHL1/02-2006/M did not evaluate the ability of chloroprocaine to provide adequate anesthesia for performing a surgical procedure. Time to complete regression of spinal block was evaluated in Study CHL1/02-2014, and does not imply that anesthesia was adequate for performing a surgical procedure. Likewise, onset time of sensory block at T10 was evaluated in Study CHL1/02-2006/M, and does not equate to adequate anesthesia for performing a surgical procedure.

Because the primary endpoints in the pivotal studies were incapable of demonstrating adequate anesthesia for performing a surgical procedure, post hoc analyses of these studies were conducted. The statistical reviewer, Dr. Yan Zhou, describes these analyses as follows:

The efficacy of chloroprocaine was evaluated by examining whether or not a patient required rescue medication to complete the surgical procedure. In the phase 2 Study CHL1/02-2014, all patients randomized to 50 mg chloroprocaine were able to complete surgery without the use of rescue medication. In the phase 3 Study CHL1/02-2006/M, 60 out of 66 patients (91%) randomized to chloroprocaine were able to complete the procedure without requiring rescue medication. Based on clinical interpretation and a similar failure rate noted for the control arm, chloroprocaine 50 mg was considered an appropriate dose for inducing spinal anesthesia by the clinical review team.

Two additional studies were conducted by the Applicant, and those were also considered for their possible support of efficacy. The first of those studies, CHL1/02-2004, was a Phase 2 study that the Applicant had originally submitted to the NDA as a literature reference. However, during the course of the NDA review, it became apparent that this study had been conducted by the Applicant but not submitted with the rest of the NDA. Furthermore, it was of interest because it appeared to have a higher incidence of rescue than the more recent Phase 2 study, CHL1/02-2014. However, the Office of Scientific Investigations expressed serious concerns about the reliability of the data from this study, although their final assessment was pending at the time of writing this review. Because of those concerns, the efficacy data will not be further described in this review or considered in support of the Application.

The second additional study that was conducted by the Applicant and considered possibly supportive of efficacy was a prospective, multicenter, open-label, observational study conducted as a post-marketing requirement for their European approval (study CHL1/01-2012/M). The incidence of rescue administration in CHL1/01-2012/M appeared to be higher
than in other studies. However, the protocol did not prohibit any concomitant medications, and it is likely that many medications that we identified as rescue (e.g., midazolam and propofol) were administered as components of routine practice. Ultimately, this study does not refute Clorotekal’s efficacy nor is it highly supportive.

An important consideration with regard to efficacy is the duration of surgical procedures that are appropriate for administration of the 50 mg dose. The Applicant is proposing the 50 mg dose for surgeries

A graphical representation of the Phase 3 study (CHL1/02-2006/M) surgery duration data provided by the Applicant follows, to which I have added stars to identify subjects that required rescue:

Figure 1: Study CHL1/01-2006/M Surgery duration by subject

The breakdown of rescue administration by surgical duration follows:

- With regard to surgeries of at least 60 minutes in duration, the database included only three and two of those subjects (121 and 212) required rescue.
- There appear to be two additional surgeries that were at least 50 minutes in duration and five additional surgeries that were at least 40 minutes in duration; one of the 40 to 50 minute subjects (202) required rescue. This gives a rescue rate of 20 percent for surgeries of at least 40 but less than 50 minutes in duration and 14 percent for surgeries of at least 40 but less than 60 minutes in duration.
- There appear to be only three additional surgeries that were of at least 30 but less than 40 minutes in duration. One of those (211) required rescue, giving a rescue rate of 33 percent.
- Close to 20 subjects had surgeries that were at least 20 but less than 30 minutes in duration, and two (202 and 205) required rescue, giving a rescue rate of roughly ten percent.
- There were no rescues among surgeries less than 20 minutes in duration.
It is also notable that four of the five subjects who required rescue (all except subject 121 whose surgery exceeded 60 minutes in duration) occurred at a single site.

Based on the breakdown of rescue administration, I feel it can be concluded that Clorotekal is not appropriate for surgeries in excess of 60 minutes. However, between 30 and 60 minutes, there is no clear time point beyond which the failure rate becomes unacceptable.

Because analysis of the surgical durations and failures did not clearly delineate a maximum appropriate surgical duration, and time from injection to surgery start is not accounted for by surgical duration, Dr. David Petullo, the statistical team leader, provided descriptive statistics for the times from injection to several time points, as well as surgery times. Those results follow:

<table>
<thead>
<tr>
<th>Table 1: Study CHL1/01-2006/M Duration data in minutes (N = 66)</th>
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<tbody>
<tr>
<td>Time from injection to surgery start</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Time from injection to surgery end</td>
</tr>
<tr>
<td>Time from injection to resolution of motor block</td>
</tr>
<tr>
<td>Time from surgery start to surgery finish</td>
</tr>
</tbody>
</table>

The above data demonstrate a wide range in time from injection to surgery start, which could contribute to the difficulty in delineating a maximum appropriate surgical duration. However, they also demonstrate a strikingly wide range in time from injection to resolution of motor block that supports the notion of inter-subject variability in duration of anesthesia.

For the Phase 2 study CHL1/01-2014, the Applicant was able to provide precise surgical duration data that are presented in the following figure:

**Figure 2: Study CHL1/01-2014 Surgery duration by subject**

![Surgery duration by subject](image)

*Note: Gray = 30 mg; blue = 40 mg; black = 50 mg*
Dr. Zhou’s analysis of the surgery duration data for Study CHL1/01-2014 follows:

Table 2: Study CHL1/02-2014 Surgery duration in minutes (FAS set)

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>≤ 30 mins</th>
<th>≤ 40 mins</th>
<th>≤ 60 mins</th>
</tr>
</thead>
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<tr>
<td>30 mg</td>
<td>25 (16)</td>
<td>22</td>
<td>9</td>
<td>74</td>
<td>87%</td>
<td>87%</td>
<td>93%</td>
</tr>
<tr>
<td>40 mg</td>
<td>20 (10)</td>
<td>17</td>
<td>7</td>
<td>40</td>
<td>87%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>50 mg</td>
<td>20 (8)</td>
<td>20</td>
<td>5</td>
<td>40</td>
<td>93%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: Reviewer’s analyses

While no subject in 50 mg arm of the second Phase 2 study required rescue, the procedures in the Phase 2 trial among subjects administered 50 mg were brief. As depicted above, procedures were of mean and median duration of 20 minutes, and 93% (14 of 15) subjects had procedures of ≤ 30 minutes. These data add little support for efficacy for surgical durations that exceed 30 minutes.

Dr. Petullo’s analysis of time from Clorotekal injection to various time points in Study CHL1/01-2014, which follows, shows variability similar to that observed in the Phase 3 trial:

Table 3: Study CHL1/01-2014 Times from injection for 50 mg subjects in minutes (N = 15)

<table>
<thead>
<tr>
<th>Time from injection to surgery start</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>20</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Time from injection to surgery end</td>
<td>41</td>
<td>40</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Time from injection to resolution of motor block</td>
<td>100</td>
<td>104</td>
<td>56</td>
<td>146</td>
</tr>
</tbody>
</table>

Based on the above data, the duration of procedure for which chloroprocaine is an appropriate anesthetic is not clear. Uncertainties contributing to the difficulty in making this determination are that (1) the majority of procedures were brief (i.e., less than 25 minutes in duration), (2) some of the subjects that we considered to be failures due to midazolam administration for “intraoperative anxiety” may not have actually experienced failure of the spinal anesthetic, (3) I am not sure what an acceptable failure rate for a spinal anesthetic should be, especially given the possibility that with our conservative approach in identifying failures we have overestimated the number of failures, and (4) there is variability in time between chloroprocaine injection and surgery start that is not accounted for by surgery duration.

The other major consideration with regard to efficacy is the adequacy of evidence for the 30 and 40 mg doses. They were evaluated only in the Phase 2 studies, only the latter of which is potentially reliable based on the preliminary assessment of the Office of Scientific Investigations (CHL1/02-2014). The proportion of subjects requiring rescue administration in Study CHL1/02-2014 is presented below and is 20% for both the 30 and 40 mg doses. This
relatively high failure rate and the very small sample size are not adequate to support approval of the 30 and 40 mg doses.

### Table 4: Study CHL1/02-2014 Proportion of subjects requiring rescue administration

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Proportion of Subjects Requiring Rescue Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>3 of 15 (20%)</td>
</tr>
<tr>
<td>40 mg</td>
<td>3 of 15 (20%)</td>
</tr>
<tr>
<td>50 mg</td>
<td>0 of 15 (0%)</td>
</tr>
</tbody>
</table>

**8. Safety**

The safety database consisted of 547 subjects administered intrathecal chloroprocaine in Phase 2, 3, and 4 studies, with 241 (44%) receiving a dose of 50 mg or greater, and another 222 (41%) receiving a dose of 40 to less than 50 mg.\(^1\) The database allows us to rule out with 95% confidence adverse events with a 1.2% or lower incidence with administration of 50 mg. This seems adequate for characterization of the safety profile of intrathecal administration of a drug that has long been approved for use via other routes and for which postmarketing experience in Europe exists.

In the Applicant’s studies there were no major safety signals that would preclude approval. There were no deaths and no serious adverse events among chloroprocaine-administered subjects. The adverse events that occurred were generally similar in type and incidence to adverse events that occur with intrathecal administration of other local anesthetics (e.g., hypotension and bradycardia) and are largely manifestations of sympathetic blockade. The one subject who discontinued due to an adverse event after chloroprocaine administration experienced lack of efficacy and required a rescue anesthetic.

Neurologic adverse events are of particular interest. Transient neurologic symptoms (TNS) is a neurologic adverse event that has been described with all intrathecally administered local anesthetics. It most commonly occurs with lidocaine and seems to be the reason intrathecal lidocaine is not widely used today. The published incidence of TNS with lidocaine is 14%. This compares to a published incidence of TNS with chloroprocaine of 0.6%.

In their clinical study database, the Applicant identified no subjects with TNS. We identified a single subject (05-043) in their Phase 4 study, which was a European postmarketing requirement to evaluate for neurologic adverse events, who experienced an adverse event that could have been TNS. One case in the overall safety database would give an overall incidence of approximately 0.2%, which is acceptable considering the higher incidence of TNS of the other local anesthetics approved for intrathecal administration.

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\(^1\) Forty-four of those subjects were enrolled in the Phase 2 study CHL1/02-2004, with serious concerns about data reliability expressed by the Office of Scientific Investigations but final determination pending.
There were four cases of TNS in the Applicant’s pharmacovigilance database. This small number of reported TNS cases further supports an acceptably low incidence of TNS with the Applicant’s intrathecal chloroprocaine product.

Other neurologic adverse events of interest are the broad category of adverse events associated with neurologic deficits. These are of particular concern with chloroprocaine because in the 1980s, inadvertent intrathecal injection of chloroprocaine reportedly caused serious neurologic injuries (e.g., arachnoiditis, cauda equina syndrome, and paresis). It has been concluded that these adverse events resulted from the preservative, sodium bisulfite, in combination with low pH. Preservative-free formulations have been marketed since 1996 and have been without similar adverse events. Nonetheless, the characterization of any risk of neurologic injuries with intrathecal administration of CLOROTEKAL seems important.

In their clinical study database, the Applicant identified no subjects with neurologic adverse events akin to those seen with chloroprocaine in the 1980s. However, two possible cases of cauda equina syndrome (CES) were included in the NDA.

The first case of possible CES was identified in the Applicant’s pharmacovigilance database. It involved relatively brief symptoms of numbness, urinary retention, and dysesthesia after administration of chloroprocaine 50 mg. Based on the limited information provided in this Application about the case, the diagnosis is unclear, although the French regulatory authority reportedly classified it as “probable cauda equina syndrome.”

The second case was described in the published literature. It involved administration of chloroprocaine 40 mg (20 mg/mL) mixed with 12.5 mcg fentanyl to a subject enrolled in a small clinical trial. The subject developed weakness, numbness, pain, urinary retention, and absence of deep tendon reflexes, and was diagnosed with incomplete CES. The estimated incidence of CES with spinal anesthesia is 0.1 per 10,000 (Brull, McCartney, Chan, & El-Beheiry, 2007), and its occurrence in a small controlled study raises questions about whether there is a potential problem with higher doses or concentrations of chloroprocaine or its combination with fentanyl.

A risk of CES related to higher doses or concentrations of chloroprocaine or its combination with fentanyl was not raised as a specific concern in Dr. Alla Bazini’s clinical review. Administration of doses greater than 50 mg seem improbable with this product because the clinician would have to use two vials, and administration of concentrations greater than one percent are impossible with this product. Therefore, a dose- or concentration-related toxicity is not likely to be observed in the clinical setting. However, it is possible that clinicians will combine Clorotekal with fentanyl in an effort to prolong analgesia without increasing the local anesthetic dose, as is sometimes done with other intrathecally administered local anesthetics. Therefore, a potential problem related to chloroprocaine’s combination with fentanyl might be pertinent to this product, even if it is labeled not to be mixed or diluted with other products.
9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this New Drug Application.

10. Pediatrics

This New Drug Application requires a pediatric assessment. However, pediatric studies were deferred and not included in the submission because the chloroprocaine product was ready for approval for use in adults before pediatric studies could be completed. The Pediatric Review Committee agreed with the deferral of pediatric studies and their conduct as postmarketing requirements under the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

At the time of writing this review, the Office of Scientific Investigations had not finalized its review and was waiting for final reports regarding two of the inspected sites. Based on the available information, Dr. Janice Pohlman, the OSI Clinical Team Leader, expressed various concerns about all four sites, mostly relating to blinding but also related to protocol deviations. Concerns with the 2004 Phase 2 study were numerous and also included adverse event discrepancies and under-reporting. Dr. Pohlman was uncertain if their final conclusion would be that the submitted in the NDA are reliable.

12. Labeling

One primary consideration is the appropriate indication for this product. As described in Section 7 of this memo, the data do not clearly delineate an appropriate maximum duration for labeling. Therefore, I recommend that the product be approved for the general indication of subarachnoid block (spinal anesthesia), as we had discussed at the PIND meeting in 2013. The dose should be limited to 50 mg because the NDA contains data to support efficacy. I recommend that the procedures that were studied and their durations be included in Clinical Studies section in order to inform clinicians about the basis of approval and the limitations of the data.

Also appropriate for inclusion in the Clinical Studies section is the basis of our efficacy conclusions. Our efficacy conclusions are based not on the studies’ primary endpoints, but rather on the post hoc analysis of procedure success without rescue administration.

Another major consideration for labeling is the inclusion of language from the reference product labeling. Much of the language proposed by the Applicant and taken from Nesacaine is pertinent. However, because of the different dosing and route of administration, some of the reference labeling that the Applicant proposed to include in labeling was determined not to be appropriate.
A final consideration is the content of the Adverse Reactions section. In order to be consistent with current best labeling practices, the adverse event incidence table should include only the 50 mg dose, since that is the (b)(4) intend to approve, and only the controlled studies. Furthermore, because of the discrepancies noted in adverse events by OSI, the 2004 Phase 2 study should not be included in the table. A final point regarding the Adverse Reactions section is that CES and transient neurologic symptoms, which have been reported in the Applicant’s pharmacovigilance database, should be included.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
I recommend approval.

Risk Benefit Assessment
In general, the risks of spinal anesthetics, including this product, relate to sympathetic block and neurotoxicity. This product does not appear to have different or greater risks than the other approved products for spinal anesthesia, lidocaine and bupivacaine. The possible exception is the risk of CES.

CES is a devastating complication and ideally its incidence would be known and taken into consideration in the risk-benefit assessment of a product. Based on the Applicant’s clinical study database, which identified no cases of CES, we can conclude with 95% confidence that the incidence with Clorotekal 50 mg is less than 1.2%. There was one possible CES case with Clorotekal that was identified in the Applicant’s pharmacovigilance database, and another case using a higher dose and concentration of chloroprocaine in combination with fentanyl that was identified in the published literature. However, estimating the incidence of CES based on these cases cannot be reliably done. It is possible that the incidence of CES with chloroprocaine is greater than the published estimated incidence of CES after spinal anesthesia of 1 in 100,000. However, determining if the CES incidence with chloroprocaine exceeds 1 in 100,000 would require study of several hundred thousand patients, which is not reasonable. Therefore, in order to approve the product, we must accept that the risk is less than 1.2% but may be higher with chloroprocaine than with other products approved for spinal anesthesia.

Another risk with this Application is the inadequate nonclinical characterization of the product’s toxicological potential. This information is generally used to support initiation of human studies, but in this case, the studies were performed outside the United States and not under an IND. Such characterization would help to inform the adverse events that might be seen in clinical practice, particularly with administration of doses exceeding the labeled dose of 50 mg. This information, while important, should not preclude approval. This is because administration of doses greater than 50 mg seems unlikely because it would require clinicians to use two vials, increasing cost and the important contamination risk for this intrathecally administered product.

The primary benefit of Clorotekal is that it gives clinicians an option for spinal anesthesia of short duration with what appears to be a reasonable side effect profile. Lidocaine, while
approved for spinal anesthesia, has a high incidence of TNS that has limited its use. Clorotekal appears to have a much lower TNS incidence than lidocaine, and otherwise, a similar side effect profile. This alternative might be particularly useful for patients undergoing short procedures on the lower part of the body where avoidance of general anesthesia is desirable, because of patient preference or medical conditions, for example, malignant hyperthermia susceptibility, difficult airway, or severe asthma.

In addition to being a benefit, chloroprocaine’s short duration of action is also a risk, because there will certainly be instances when the product wears off before a surgical procedure is finished. That risk is mitigated by the ability of clinicians to administer rescue medications in the settings where spinal anesthetics are administered. Also mitigating is the anesthesiology community’s decades of experience with chloroprocaine, including its epidural administration for surgical procedures. Furthermore, details regarding the procedure durations to be included in the Clinical Studies section of the Clorotekal labeling plus all that has been published about the duration of intrathecal chloroprocaine are also mitigating. Nonetheless, it will be the clinician’s responsibility to identify appropriate procedures for Clorotekal based on what is known about the drug’s duration of action and what can be anticipated regarding the surgical end time.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
I do not recommend any Risk Evaluation and Management Strategies.

Recommendation for other Postmarketing Requirements and Commitments
I recommend two PMRs. The first is for a pediatric study under PREA. Spinal anesthetics are performed in pediatric patients and the efficacy of this product for surgical procedures in pediatric patients should be evaluated under PREA.

The second PMR is a repeat-dose toxicity study in dogs to better characterize the toxicological profile of intrathecal chloroprocaine. The potential value in a repeat-dose toxicity study in dogs would be understanding the toxicological risk of the drug being administered in doses or concentrations that exceed 50 mg. In the clinical setting, I believe single-dose administration in excess of 50 mg is unlikely given the 50 mg vial content, and administration of concentrations greater than 1% impossible. However, prolonged exposure is possible because spinal catheters may be reemerging in the United States and they are being used in Europe (Forster, Rosenberg, & Niemi, 2006). For that reason it seems prudent to have the applicant conduct a repeat-dose toxicity study as a PMR. Findings from the study could potentially be incorporated into Warnings and Precautions or Nonclinical Toxicology sections of labeling.

CES is a complication that is too rare for its incidence to be reasonably determined via premarket studies, and a PMR to evaluate the risk of CES with intrathecal chloroprocaine was considered. Specifically, we considered the possibility of using enhanced pharmacovigilance to better characterize the risk of CES. However, Drs. Sara Camilli and Allen Brinker of the Office of Surveillance and Epidemiology, Division of Pharmacovigilance felt that enhanced pharmacovigilance would not be useful because CES has already been reported with intrathecal chloroprocaine and because it is not a tool that allows for determination of
incidence. Furthermore, I learned that CDER does not currently have the capability to evaluate inpatient or intraoperative medication data through, for example, Sentinel, such that relationships between CES and chloroprocaine could be explored through database analyses. Because there doesn’t appear to be a reasonable means for characterizing the risk of this rare complication, I do not recommend a PMR for this purpose.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH H CRISAFI  
09/22/2017

RIGOBERTO A ROCA  
09/22/2017
I concur with Dr. Crisafi's assessment and recommendations.