CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208791Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	208791
Link to EDR	\\CDSESUB1\evsprod\NDA208791\0001
Submission Date	8/26/2016
Submission Type	*[Standard review]*
Brand Name	CLOROTEKAL Injection
Generic Name	Chloroprocaine Injection
Dosage Form and Strength	Parenteral Injection
Route of Administration	Intrathecal Injection
Proposed Indication	Intrathecal Injection for regional anesthesia
Applicant	SINTETICA
Associated IND	*[PIND 119674]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D.]*
OCP Final Signatory	*[Yun Xu, Ph.D.]*

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The submission is acceptable from a clinical pharmacology perspective and labeling recommendations are noted below.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Overview of the Product and Regulatory Background

Sintetica submitted a 505(b)(2) NDA for use of chloroprocaine HCl injection, a local anesthetic, indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia). The sponsor is relying on Agency's previous findings of safety and efficacy for Nesacaine (Chloroprocaine HCl Injection) NDA 009435. Nesacaine is approved for epidural anesthesia, which is a different space or route of administration in spinal cord compared to the proposed route of CLOROTEKAL use. In addition to relying on Nesacaine NDA/label, the sponsor conducted a Phase 2 dose ranging, safety and pharmacokinetic study CHL1/02-2014 (EudraCT 2014-003778-17). Title of the study was 'Spinal anesthesia with Chloroprocaine HCl 1% for elective lower limb procedures of short duration: A Prospective, Randomized, Observer-blind study in Adult Patients'. In addition, the sponsor also submitted a Phase 3 efficacy and safety study CHL1/02-2006/M. The phase 3 clinical study was conducted between September 2007 and November 2008 in Germany, Switzerland and Italy. The study was aimed at determining the non-inferiority of Chloroprocaine 1% (50 mg) versus Bupivacaine 0.5%. Additional clinical studies submitted in support of the NDA are reviewed by Dr. Alla Bazini.

2.2 General Pharmacology and Pharmacokinetic Characteristics

Limited clinical pharmacology information is described in the Nesacaine product label regarding chloroprocaine pharmacokinetics and pharmacodynamics.

> "*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.*

The onset of action with chloroprocaine is rapid (usually within 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.

The in vitro plasma half-life of chloroprocaine in adults is 21 ± 2 seconds for males and 25 ± 1 seconds for females. The in vitro plasma half-life in neonates is 43 ± 2 seconds. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-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."

Systemic absorption of Nesacaine following epidural administration is not described in the product label. However, several publications describe systemic levels of chloroprocaine following labeled use of Nesacaine (See Appendix 4.3). The use of Nesacaine for intrathecal or spinal anesthesia is not recommended due to the additives (antimicrobial agents) in the injection. (b) (4) Sintetica is not seeking use of the CLOROTEKAL by epidural injection. Therefore, a relative bioavailability assessment comparing Nesacaine with CLOROTEKAL following the same route of administration is not possible.

In order to support the use of CLOROTEKAL, the sponsor conducted a Phase 2 dose ranging study CHL1/02-2014 in addition to different clinical studies. The objective of this study was to evaluate the effect of the 3 doses of Chloroprocaine HCl 1% solution for injection (30 mg, D1, 40 mg, D2, and 50 mg, D3) for spinal anesthesia in adult patients undergoing short duration elective surgery of the lower limb (n=15, per dose group). In this study, blood and urine samples were collected for analysis of chloroprocaine and its known metabolite CABA (2-chloro-4-amino-benzoic acid, or 4-amino-2-chloro-benzoic acid, also referred to as ACBA in publications). The details of the study are described in the attached synopsis. The pharmacokinetic variables of the study are described as:

- Plasma concentrations of chloroprocaine at pre-dose and at 5, 10, 30 and 60 minutes after spinal puncture for the three dose levels (30, 40 or 50mg).
- Plasma concentrations of ACBA at pre-dose and at 5, 10, 30 and 60 min after spinal puncture for the three dose levels (30, 40 or 50mg).
- Urinary excretion of ACBA, as percentage of administered chloroprocaine dose for the three dose levels (30, 40 or 50mg).

The concentration of chloroprocaine and its metabolite ACBA (CABA) in plasma and of ACBA in urine has been determined (b) (4) using a fully validated reliable and sensitive LC-MS/MS analytical method (See attached bioanalytical method validation summary). As shown in the table below, plasma levels of chloroprocaine following spinal injection of CLOROTEKAL were not detected up to 1 hour after administration. The metabolite (ACBA/CABA) levels were noticed with the first sample of blood collected 5 minutes post-dose. It is noteworthy that the pseudochlolinesterases are ubiquitously present in the body and may degrade chloroprocaine, including in plasma rapidly. The blood sample was collected in the presence of pseudocholinesterase inhibitors to allow for detection of chloroprocaine without

degradation/metabolism after collection. It is quite possible that chloroprocaine absorbed from CSF into the blood circulation may be metabolized rapidly before detection in plasma.

Table: Plasma concentrations (ng/mL) of chloroprocaine and CABA (or ACBA) following CLOROTEKAL administration via intrathecal route in patients.

Analyte	Chloroprocaine			CABA		
Dose group	30 mg	40 mg	50 mg	30 mg	40 mg	50 mg
	N=15	N=15	N=15	N=15	N=15	N=15
Pre-dose (0)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
5 min post-dose	BLQ	BLQ	BLQ	16.127±20.108	20.411±23.037	24.887±20.340
10 min post-dose	BLQ	BLQ	BLQ	41.440±31.778	38.851±25.492	75.833±67.635
30 min post-dose	BLQ	BLQ	BLQ	57.459±43.773	67.180±36.899	97.647±61.704
60 min post-dose	BLQ	BLQ	BLQ	47.020±41.381	53.093±31.803	78.380±48.403

mean±SD is shown; BLQ: below the quantification limit (4.0 ng/mL)
source: Table 14.2.3.1

The sponsor has submitted adequate information to justify that an actual relative bioavailability is not needed. The submitted evidence pertains to the following (See Appendix 4.3):

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.

2.3 Summary of Labeling Recommendations

The sponsor is primarily relying on the product label for Nesacaine. The section 12.3 Clinical Pharmacology, Pharmacokinetics; describes results of Phase 2 dose ranging study CHL1/02-2014. The sponsor proposed labeling is in regular font, additions and deletions are marked as bold and strikethrough text.

(b) (4)

(b) (4)

Reviewer's comment: The above paragraph was added by the sponsor without any reference to a publication or study conducted by the sponsor. (b) (4)

Pharmacokinetics after intrathecal administration

Plasma concentrations of chloroprocaine and 2-chloro-4-aminobenzoic acid (ACBA) after intrathecal administration of (b) (4) 50 mg dose of CLOROTEKAL reported in Table 3.

Table 3 - PK variables: plasma concentrations (ng/mL) of chloroprocaine and ACBA.

Analyte	Chloroprocaine (b) (4)	ACBA (b) (4)
Dose group	50 mg N=15	50 mg N=15
Pre-dose (0)	BLQL	BLQL
5 min post-dose	BLQL	24.887±20.340
10 min post-dose	BLQL	75.833±67.635
30 min post-dose	BLQL	97.647±61.704
60 min post-dose	BLQL	78.380±48.403

mean±SD is shown; BLQL: below the quantification limit (4.0 ng/mL)

Specific Populations

(b) (4)

Renal Impairment

(b) (4) chloroprocaine is known to be substantially excreted by the kidney (b) (4) [See Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].

Reviewer's comment: The above statements are described in Nesacaine label and can be applied to this product.

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

Plasma Analysis Validation: Concentrations of chloroprocaine and its metabolite CABA (2-chloro-4-amino-benzoic acid, or 4-amino-2-chloro-benzoic acid, also referred to as ACBA in publications) were determined in human plasma containing neostigmine methylsulphate and bis (p-nitrophenyl) phosphate by LC-MS/MS following protein precipitation.

During the conduct of the clinical study CHL1/02-2014, six (6) mL of blood were either directly collected or transferred from the catheter with a syringe into heparinized tubes (Na-heparin) containing a mix of esterase inhibitors. Chloroprocaine demonstrated adequate stability in human plasma with neostigmine methylsulphate and bis (p-nitrophenyl)phosphate added and stored on ice bath. The use of esterase inhibitors and "on-ice" sample processing prevented degradation of chloroprocaine for at least one hour. Bis-(p-nitrophenyl)phosphate is a common esterase inhibitor for *in vitro* use, while neostigmine methylsulphate is a cholinesterase inhibitor that prolongs the *in vivo* effect of local anesthetics.

The tubes were gently inverted for 4-5 times and then placed in a bath of water and ice. Then, within 15 min from collection, the samples were centrifuged at 4° C for 10 min at 2000xg to obtain plasma. Each plasma sample was immediately divided into two aliquots of about 0.5-1 mL each, P1 and P2, in pre-labeled polypropylene tubes and immediately placed in a bath of water and ice. Then, within 15 min of the division into aliquots, the tubes were stored frozen at ≤-70° C until analyses.

At the time of analysis, the appropriate samples were thawed on-ice, vortex mixed and processed. Aliquots of 20 µL of human plasma, containing neostigmine methylsulphate and bis(p-nitrophenyl)phosphate, were added with 200 µL of the internal standard solution (50 ng/mL of (b) (4) and 500 ng/mL of (b) (4)) in a 96-well polypropylene plate. The plate was then capped, vortex mixed and centrifuged at about 2010 g for 10 minutes at 4°C. A volume of 150 µL was transferred by Microlab Starlet liquid handling workstation to a new plate and dried down under mild nitrogen stream at 30°C. The residue was reconstituted with 150 µL of a mixture solution of water: acetonitrile: formic acid (50:48:2, v/v/v). After vortex mixing and centrifugation at 2010 g for 2 minutes, an aliquot of 5 µL was injected into the LC-MS/MS system.

An Ascentis Express C18 column (2.1*50 mm, 2.7 µm, Supelco) was used to perform the chromatographic analysis under gradient conditions. Mobile phase A was 10 mM ammonium formate pH 3.5 and mobile phase B was methanol. The flow rate was 0.3 mL/min. The retention times of chloroprocaine and CABA were 4.2 and 4.3 minutes, respectively. Total run time was 8 minutes.

MS detection was performed on a SCIEX API 4000 with TurboIonSpray interface and MRM (271.5→100.1 m/z for chloroprocaine, 172.5→153.9 m/z for CABA, 235.3→86.2 m/z for (b) (4) 138.5→94.0 m/z for (b) (4)) operated in positive ion mode.

Calibration curves were constructed by plotting the peak area ratio of the analyte to internal standard (y) against the analyte concentration (x). (b) (4) were used as internal standards for the quantification of chloroprocaine and CABA, respectively. A weighted quadratic regression function ($1/x^2$) was used to fit the calibration curves and

consequently to calculate chloroprocaine and CABA concentrations. The lower and upper limits of quantification were 4.0 and 1000 ng/mL, respectively, for both analytes.

Summary of Validation Results for Chloroprocaine	
Sample Matrix	Human Plasma
Matrix Vendor(s)	CTLS
Method Type	LC-MS/MS
Sample Preparation	Protein Precipitation
Sample Volume	20 µL
Carry-over	About 30% of LLOQ
Lower Limit of Quantification	4.0 ng/mL
Upper Limit of Quantification	1000 ng/mL
Intra-assay precision	From 3.8 to 6.5 % CV
Intra-assay accuracy	From - 5.8 to 3.6% of the nominal value
Inter-assay precision	From 4.9 to 6.8% CV
Inter-assay accuracy	From -5.8 to 3.3% of the nominal value
Dilution Integrity	10000 ng/mL - over range VS, dilution factor of 10
Extraction Recovery	From 90.3 to 106.6%
Matrix Stability on-ice	1 hour
Injection Viability at +10°C	70 hours
Freeze/Thaw Stability at -80°C	3 freeze/thaw cycles
Stock Solution Stability at Room Temperature	At least 6 hours [5]
Stock Solution Stability at +4°C	At least 28 days [5]
Working Solution Stability at +4°C	At least 4 days [5]
# of lots used for assay specificity testing	6

Summary of Validation Results for the Internal Standard (b) (4)	
Carry-over	<5% of IS response
Extraction recovery	83.4%
Stock Solution Stability at Room Temperature	At least 6 hours [5]
Stock Solution Stability at +4°C	At least 29 days [5]
Working Solution Stability at Room Temperature	At least 6 hours [5]
Working Solution Stability at +4°C	At least 1 week [5]
# of lots used for assay specificity testing	6

Summary of Validation Results for CABA	
Sample Matrix	Human Plasma
Matrix Vendor(s)	CTLS
Method Type	LC-MS/MS
Sample Preparation	Protein Precipitation
Sample Volume	20 µL
Carry-over	<20 % of LLOQ
Lower Limit of Quantification	4.0 ng/mL
Upper Limit of Quantification	1000 ng/mL
Intra-assay precision	From 4.7 to 8.3% CV
Intra-assay accuracy	From 2.3 to 11.3 % of the nominal value
Inter-assay precision	From 5.8 to 14.6% CV
Inter-assay accuracy	From -2.8 to 7.0% of the nominal value
Dilution Integrity	10000 ng/mL - over range VS, dilution factor of 10
Extraction Recovery	From 66.1 to 69.9%
Matrix Stability on-ice	1 hour
Injection Viability at +10°C	70 hours
Freeze/Thaw Stability at -80°C	3 freeze/thaw cycles
Stock Solution Stability at Room Temperature	At least 6 hours [5]
Stock Solution Stability at +4°C	At least 29 days [5]
Working Solution Stability at +4°C	At least 4 days [5]
# of lots used for assay specificity testing	6

Summary of Validation Results for the Internal Standard (b) (4)	
Carry-over	<5% of IS response
Extraction recovery	76.0%
Stock Solution Stability at Room Temperature	At least 6 hours
Stock Solution Stability at +4°C	At least 32 days
Working Solution Stability at Room Temperature	At least 6 hours
Working Solution Stability at +4°C	At least 1 week
# of lots used for assay specificity testing	6

Urine Analysis Validation: Concentrations of CABA were determined in human urine by LC-MS/MS following direct injection of diluted samples in the 96 well plate format. Aliquots of 100 µL of human urine were added with 20 µL of 20% formic acid in water and 100 µL of methanol in a 96-well polypropylene plate. After vortex mixing and centrifugation at 2060 g for 10 minutes at +4°C, aliquots of 50 µL were transferred to a new plate by Microlab Starlet liquid handling workstation (Hamilton) and added with 500 µL of a mixture solution of water: methanol: formic acid (75: 23: 2, v/v/v). After vortex mixing and centrifugation at 2060 g for 2 minutes, a volume of 5 µL was injected into the LC- MS/MS system. An Ascentis Express C18 column (2.1*50 mm, 2.7 µm, Supelco) was used to perform the chromatographic analysis under gradient conditions. Mobile phase A was 10 mM ammonium formate pH 3.5 and mobile phase B was methanol. The flow rate was 0.3 mL/min. The retention time of CABA was about 4.9 minutes. Total run time was 8 minutes. MS detection was performed on a SCIEX API 4000 with TurboIonSpray interface and MRM (172.5→153.9 m/z) operated in positive ion mode. Calibration curves were constructed by plotting the peak area of the analyte (y) against the analyte concentration (x). A weighted quadratic regression function ($1/x^2$) was used to fit the calibration curve and consequently to calculate CABA concentrations. The lower and upper limits of quantification were 50 and 10000 ng/mL, respectively.

Summary of Validation Results for CABA	
Sample Matrix	Human Urine
Anticoagulant	Not applicable
Matrix Vendor(s)	(b) (4)
Method Type	LC-MS/MS
Extraction Procedure	Direct injection of diluted samples
Sample Volume	100 µL
Carry-over	<20 % of LLOQ response
Lower Limit of Quantification	50.0 ng/mL
Upper Limit of Quantification	10000 ng/mL
Intra-Assay Precision	2.4 – 5.6% CV
Intra-Assay Accuracy	-7.8 – 18.2% of the nominal value
Inter-Assay Precision	6.0 – 8.3% CV
Inter-assay Accuracy	-5.3 – 13.2% of the nominal value
Dilution Integrity	20000 ng/mL - over range VS, dilution factor 10
Matrix Stability at Room Temperature	2 hours
Viability of the Analytical Batch at +4°C	At least 48 hours
Freeze/Thaw Stability at -20°C	3 freeze/thaw cycles
Stock Solution Stability at Room Temperature	At least 6 hours [5]
Stock Solution Stability at +4°C	At least 29 days [5]
Working Solution Stability at +4°C	At least 4 days [5]
# of Lots used for Assay Specificity Testing	6

3.2 Clinical PK Assessments from Study CHL1/02-2014.

A Prospective, single center, randomized, parallel-group, observer-blind, three doses, efficacy and pharmacokinetic study.
Objectives:

The objective of this study was to evaluate the effect of the 3 doses of Chloroprocaine HCl 1% solution for injection (30 mg, D1, 40 mg, D2, and 50 mg, D3) for spinal anaesthesia in adult patients undergoing short duration elective surgery of the lower limb.
Primary end-point:

To evaluate the efficacy of the 3 Chloroprocaine HCl 1% doses (D1, D2 and D3) in terms of time to complete regression of spinal block, T_{ea} (i.e. end of anaesthesia);
Secondary end-points:
To evaluate the efficacy of the 3 Chloroprocaine HCl 1% doses (D1, D2 and D3) in terms of:

- Time to onset of sensory block (T_{sb}),
- Time to onset of motor block (T_{mb}),
- Time to readiness for surgery (T_{rs}),
- Time to resolution of motor block (T_{rmb}),
- Time to unassisted ambulation (T_{ua}),
- Time to resolution of sensory block to S1 (T_{S1}) (where S1 is the 1st sacral dermatomal level),
- Sensory block metameric levels during the block,
- Maximum level of sensory block, (SB_{max})
- Time to regression of two dermatomers with respect to the maximum level of sensory block (T_{rd}),
- Time to first spontaneous urine voiding (T_{uv}),
- Time to administration of rescue anaesthesia or rescue analgesia (T_{ra}),
- Time to first post-operative analgesia (T_{pa}),
- Time to eligibility for home discharge (T_{hd}),
- Proportion of patients achieving an effective anaesthesia,
- Quality of spinal block

- To assess the concentration of chloroprocaine and its metabolite 2-chloro-4-aminobenzoic acid (CABA) in plasma after administration of D1, D2 and D3;
- To assess the excretion of CABA in urine (as % of the chloroprocaine administered dose)
- To investigate the safety and tolerability of the administered Chloroprocaine HCl 1% doses on the basis of the incidence of treatment-emergent adverse events, in particular transient neurological symptoms (TNS); vital signs and ECG.

Number of subjects (planned and analyzed):

- 45 male/female patients (15 patients per dose group), aged 18-65 years, scheduled for elective lower limb surgery (less than 40 min) under spinal anaesthesia were planned to be included and treated in the study. The investigator included in the study and randomized 46 patients. Forty-five (45) patients were treated and completed the study. All of them were considered in the full analysis. One patient was randomized but was not treated due to lack of compliance. The discontinued subject was not included in the analysis.

Diagnosis and criteria for inclusion
Inclusion criteria:

- *Sex, age and surgery*: male/female patients, 18-65 year old, scheduled for short duration (less than 40 min)
  lower limb surgery requiring ≥ T12 metameric level of sensory block
- *Body Mass Index*: 18 - 32 kg/m^2 inclusive
- *American Society of Anesthesiologists (ASA) physical status*: I-II
- *Informed consent*: signed written informed consent before inclusion in the study
- *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study.

Exclusion criteria

- *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study. Contraindications to spinal anaesthesia. History of neuromuscular diseases to the lower extremities
- *ASA physical status*: III-V
- *Further anaesthesia*: patients expected to require further anaesthesia
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients; ascertained or presumptive hypersensitivity to the ester type and major anaesthetics
- *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine or neurological diseases that could interfere with the aim of the study; ascertained psychiatric and neurological diseases, sepsis, blood coagulation disorders, severe cardiopulmonary disease, thyroid disease, diabetes or other neuropathies.
- *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study, calculated from the first day of the month following the last visit of the previous study
- *Drug, alcohol*: history of drug or alcohol abuse
- *Blood donation*: blood donations in the 3 months before this study
- *Pregnancy and lactation*: missing or positive pregnancy test at screening, pregnant or lactating women
- *Chronic pain syndromes*: patients with chronic pain syndromes (taking opioids, antidepressants, anticonvulsant agents or chronic analgesic therapy)
- *Medications*: medication known to interfere with the extent of spinal blocks for 2 weeks before the start of the study. Hormonal contraceptives for females were allowed.

Test product, dose, mode of administration, batch N

Chloroprocaine HCl 1% (10 mg/mL), injectable solution, Sintetica S.A., Switzerland. Batch: 14223; expiry: SEP16.

Three dose levels of the investigational medicinal product were investigated:

- D1: 30 mg chloroprocaine HCl (3 mL)
- D2: 40 mg chloroprocaine HCl (4 mL)
- D3: 50 mg chloroprocaine HCl (5 mL)

Patients undergoing elective short-duration lower limb surgery were randomized into 3 treatment groups (15 patients per group) to receive one of the 3 single doses of Chloroprocaine HCl 1%, i.e. either D1, D2 or D3, via intrathecal injection.

Clinical Review by Dr. Alla Bazini will document the efficacy and safety endpoints of the study.

Statistical methodology

Statistical analysis was done using SAS® version 9.3 (TS1M1) for Windows.

Definition of analysis sets:

Enrolled set: all enrolled subjects. This analysis set was used for demographic, baseline and background characteristics.

Full Analysis Set (FAS): all randomized patients who fulfilled the study protocol requirements in terms of study anaesthetic administration. Missing values of time to complete spinal block regression (T_{ea}) were replaced with the highest T_{ea} detected in the corresponding treatment group. This analysis set was used for sensitivity analysis.

Per Protocol set (PP): all randomized patients who fulfilled the study protocol requirements in terms of anaesthetic administration and primary efficacy evaluation, with no major deviations that could affect the primary efficacy results. This analysis set was used for the primary efficacy analysis.

Pharmacokinetic (PK) Set 1 (PK 1): the PK set 1 included all randomized patients who fulfilled the study protocol requirements in terms of anaesthetic administration and had at least one post-dose blood PK sample collected. *PK Set 2 (PK 2)*: the PK set 2 included all randomized patients who fulfilled the study protocol requirements in terms of anaesthetic administration and had the urine for PK analysis collected.

Safety set: all patients who received at least one dose of the investigational medicinal product. This analysis set was used for the safety analyses.

All study data were listed by patient and were summarized using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.

Pharmacokinetic analysis:

Data were listed and summarized by descriptive statistics. PK analysis was performed using Phoenix WinNonlin® version 6.3 (Pharsight Corporation) and SAS or Windows.

Results:

Pharmacokinetics

- Chloroprocaine was not quantifiable in any plasma sample of any patient.
- CABA was quantifiable in most plasma samples. Plasma CABA concentrations increased in plasma after the spinal injection of the parent compound and reached a peak 30 min post-dose.
- Plasma CABA concentrations showed proportionality to the increase in chloroprocaine dose.
- The percent amount of excretion of CABA was close to 1.70% with all 3 doses.

See additional description of results in the summary of clinical pharmacology findings above.

3.3 Rationale for clinical pharmacology recommendation to waive relative bioavailability requirement to fulfill 505(b)(2).

Clinical Pharmacology recommendation: 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 of proposed product by intrathecal route compared to high dose of Nesacaine by epidural route recorded in publications.

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.

Summary of sponsor's Conclusion - Study CHL.1/02-2014 vs. literature data (copied from below):

In the study (CHL.1/02-2014), no chloroprocaine was detected in any of the intrathecally treated patients at any time point. As expected, systemic exposure to chloroprocaine was negligible after intrathecal injection of 30, 40 and 50 mg Chloroprocaine HCl 1% (10 mg/mL) Injection, USP, as opposed to the findings of the published studies where chloroprocaine was administered epidurally. It is important to keep in mind that intrathecal doses are at least 4-10 times lower than the doses commonly administered epidurally (Nesacaine NDA #009435 – Product Information) and chloroprocaine systemic levels for the epidural route are considered safe for the clinical use. For this reason it can be assumed that the risk of adverse events due to the systemic exposure of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP administered intrathecally cannot be higher than after epidural administration of the listed references.

ACBA was detected in most samples in the 30, 40 and 50 mg chloroprocaine dose groups of study CHL.1/02-2014, particularly at 10, 30 and 60 min after intrathecal injection. Plasma ACBA concentrations increased in plasma after the spinal injection of the parent compound and appeared to reach a peak at 30 min post-dose. At 60 min post-dose ACBA levels were lower than at 30 min for most subjects, suggesting that at that time ACBA elimination was already greater than its formation. Although ACBA was detectable in most plasma samples in study CHL.1/02-2014, these levels were 20-500 times lower than those reported in the literature for epidural administration.

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.

Detailed submission from sponsor jusitifying use literature in place of a relative BA study is below. Reviewer notes on team discussion are in bold and underline text below.

"Bioanalytical methodology employed in Gao et al. 2006 and 2007 and correlation with bioanalytical method employed by the Applicant in study CHL.1/02-2014 in terms of sensitivity, specificity, accuracy and precision

In the publications of Gao et al., 2006 and 2007, the authors do not provide details on which chloroprocaine was used in their studies. Indeed, data in the two articles of Gao et al. were not used for the final descriptive comparison with Sintetica's chloroprocaine pharmacokinetics data.
We would like to clarify that Table 2.1 'List of published studies evaluated for data comparison with study CHL.1/02-2014 data' reported in module 2.7.1 'Summary of Biopharmaceutic Studies and Associated Analytical Methods' shows the exhaustive list of all published studies reporting pharmacokinetics analysis after epidural administration of chloroprocaine. After an evaluation according to FDA requirements (i.e. studies conducted with listed drug(s), analytical method, limit of quantification or detection, number of patients), some papers has been discarded because not enough details were reported. Specifically the work of: O' Brien et al., 1979; Khrog et al., 1981; Kuhnert, 1986; Gao Xm et al., 2006; Gao Xm et al., 2007, were not considered for data comparison with study CHL.1/02-2014 data (as a matter of fact these publications have been reported only in Table 2.1 but not in other sections of module 2.7.1).
Please see below a list reporting only the studies fully or partially meeting the FDA requirements used for the comparative bioavailability analysis:

Article	**Administration route**	**Plasma /Urine concentration reported**	**Product Used**	**Bioanalytical Method Described**
Kuhnert et al, 1980	Epidural	Plasma	Nesacaine	Describe in detail Gas Chromatography
Abboud et al, 1982	Epidural	Plasma	Nesacaine	Cite Mather and Tucker
Kuhnert et al, 1983	Epidural	Urine	Nesacaine	Cite Kuhnert 1980
Weiss et al., 1983	Paracervical block	Plasma	NA	NA
Abboud et al, 1984	Epidural	Plasma	Not reported	Cite Kuhnert 1979, 81
Philipson et al, 1985	Epidural	Plasma	Nesacaine	Cite Kuhnert 1980, 1981

Table 1.1 Plasma chloroprocaine concentrations – Comparison between intrathecal injection and epidural administration data

Study	Administration	N subjects	Dose	Sampling time	Chloroprocaine (ng/mL)
1	Intrathecal	15	30 mg	5, 10, 30, 60 min post-dose	BLQ
		15	40 mg		BLQ
		15	50 mg		BLQ
2	Epidural	12 Vaginal delivery	468±284 mg	At delivery	51±13 (range: 0-470)
		18 Caesarean section	948±347 mg		23±80 (range: 0-335)
3	Epidural	10 Acidotic group	855±326 mg	At delivery	3.0±3.7
		34 Nonacidotic group	838±242 mg		3.9±5.1
4	Epidural	50	NA	5 min post-dose	10.0±1.5 (detected in 8/50)
		30		At delivery	12.05±1.7 (detected in 2/30)
5	Epidural	17	852±125 mg	At delivery	2.7±0.7 (detected in 12/17)

1. Study CHL.1/02-2014 (LOQ: 4 ng/mL); BLQ: Below quantification limit
2. Kuhnert et al, 1980 (LOD: 3 ng/mL)
3. Philipson et al, 1985 (LOD: 3 ng/mL)
4. Abboud et al, 1982 (LOD: approx. 3 ng/mL); NA: Not available
5. Abboud et al, 1984 (LOD: approx. 3 ng/mL)

Nevertheless, in order to fulfil the Agency information request we have contacted the authors of the two articles (Gao et al. 2006 and 2007) in order to provide information about the chloroprocaine formulation that was adopted and the bioanalytical methods details in terms of validation [email sent to corresponding author (b) (4) on October 13, 2016 and follow-up requested on October 14, 2016].

All the available published studies (performed in the United States, Norway and China) documenting pharmacokinetics data following the use of chloroprocaine reported in the 'bridge' comparative bioavailability analysis, actually concern the use of Nesacaine. Please refer to the table below:

Article	Drug Product	Comments
O' Brien et al, 1979	Nesacaine	Declared in the article
Kuhnert et al, 1980	Nesacaine	Pennwalt Corporation* cited
Abboud et al, 1982	Nesacaine	Pennwalt Corporation cited
Kuhnert et al, 1983	Nesacaine	Pennwalt Corporation cited
Weiss et al., 1983	Nesacaine	Declared in the article
Abboud et al, 1984	Not reported	Not reported
Philipson et al, 1985	Nesacaine	Pennwalt Corporation cited

Khrog et al, 1981	Nesacaine	Pennwalt Corporation cited
Kuhnert 1986	Nesacaine	Declared in the article
GAO Xm et al, 2006	Not reported	Not reported
GAO Xm et al, 2007	Not reported	Not reported

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

The use of the Listed Drug in the reported articles is also straightforwardly gathered by referring to the year of publication (original approval date for Nesacaine: March 11, 1955).

Anyway, we do not imply that in Gao et al. articles Nesacaine was used because the information is missing in the articles. As said above, the two papers by Gao et al. were reviewed (because they reported chloroprocaine PK) and then discarded because not enough information was present (they were not used for the comparison).

With regards to the chloroprocaine formulation, we would like to offer you a brief overview resuming the rationale of the 'bridge' comparative bioavailability presented in our NDA 208791.

In the loco regional anesthesia field, every local anesthetic has different concentration on purpose of different loco-regional blocks:

- the lowest concentrations are used e.g. for digital, paracervical, infiltration and intrathecal (subarachnoid) administration.
- the intermediate concentration range for peripheral nerve blocks, e.g. mandibular, brachial plexus or pudendal ones.
- the highest concentration is used for epidural block; as a matter of fact the spinal cord has to be reached by the anesthetic to develop spinal anesthesia and a huge amount of drug needs to be injected in the epidural space, which has also an important vascular drainage.

This assumption holds true for Nesacaine also.

The following table and text, drawn from Nesacaine labeling (Nesacaine NDA #009435 – Product Information, please refer to section 1.14. of Module 1), show the concentrations used for each block:

Anesthetic procedure	Solution concentration %	Volume (mL)	Total Dose (mg)
Mandibular	2	2 to 3	40 to 60
Infraorbital	2	0.5 to 1	10 to 20
Brachial plexus	2	30 to 40	600 to 800
Digital (without epinephrine)	1	3 to 4	30 to 40
Pudendal	2	10 each side	400
Paracervical (see also Precautions)	1	3 per each of 4 sites	Up to 120

'Caudal and Lumbar Epidural Block: NESACAINE-MPF INJECTION.

For caudal anesthesia, the initial dose is 15 to 25 mL of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals.

For lumbar epidural anesthesia, 2 to 2.5 mL per segment of a 2% or 3% solution can be used. The usual total volume of Nesacaine-MPF Injection is from 15 to 25 mL. Repeated doses 2 to 6 mL less than the original dose may be given at 40 to 50 minute intervals'

Chloroprocaine HCl 1% (10 mg/ml) Injection USP has the lowest concentration because is used for intrathecal (subarachnoid) route. The anesthetic solution is injected inside the spinal cord, at lumbar level, and the drug is readily available for the nerve absorption. No connective or parenchymal structures separate the injected solution from the nerves.

For this reason low doses (in volume) and low concentrations are suitable to obtain an efficient spinal block and avoid neurotoxicity.

The use of Chloroprocaine HCl 1% (10 mg/ml) Injection USP for intrathecal (subarachnoid) administration is new, the listed drug Nesacaine is not authorized for this administration and the labeling clearly report '*NESACAINE (chloroprocaine HCl Injection, USP) contains methylparaben and should not be used for lumbar or caudal epidural anesthesia because safety of this antimicrobial preservative has not been established with regard to intrathecal injection, either intentional or unintentional'*.

Nesacaine formulations are different for the excipients, as reported in the following table drawn from the Listed Drug labeling.

Formula (mg/mL)				
Product Identification	**Chloroprocaine HCl**	**Sodium Chloride**	**Disodium EDTA dihydrate**	**Methylparaben**
Nesacaine 1 %	10	6.7	0.111	1
Nesacaine 2 %	20	4.7	0.111	1
Nesacaine-MPF 2 %	20	4.7	-	-
Nesacaine-MPF 3 %	30	3.3	-	-

Sintetica's Product:

The product is an injectable solution containing 10 mg/mL (1.0%) of Chloroprocaine HCl.
If needed, hydrochloric acid may be used in the formulation as a pH adjustor.

Composition of the dosage form

Ingredients	Functions	Quantity mg/mL	Quantity mg/5 mL ampoule	Reference to Standard
Cloroprocaine HCl	Drug substance	10.00	50.00	USP current ed.
Sodium Chloride			(b) (4)	USP current ed
Hydrochloric Acid 1N	pH adiustor		(b) (4)	USP current ed.
Water for Injections	(b) (4,			USP current ed.
				(b) (4)

1% Nesacaine contains Disodium EDTA as antioxidant, and methyl paraben as preservative. Both excipients are not recommended for subdural use because of possible neurotoxicity development.

Instead, Chloroprocaine HCl 1% (10 mg/mL) Injection, USP is an antioxidant and preservative free solution, suitable for subarachnoid injection, containing sodium chloride (b) (4)

Therefore, in order to perform the 'bridge' comparative bioavailability, the pharmacokinetics results obtained in study CHL.1/02-2014 with intrathecal administration of Chloroprocaine HCl

1% (10 mg/mL) Injection, USP, have been compared with the results of previous studies which investigated chloroprocaine levels (Nesacaine) after epidural administration, the closest route of administration to subdural injection, among the authorized routes for the reference drug.
This approach is consistent with the Minutes Meeting PIND #119674 dated January 17, 2014, where FDA reports '*It may be impractical to conduct a comparative or relative bioavailability study between your product and NDA 009435 using a cross-over design. You can consider conducting a study to obtain PK information of your product, and then compare its systemic exposure to NDA 009435. The systemic exposure information of NDA 009435 can be obtained from your own study, or a reliable source*.'
'*…you will need to provide data (e.g., via comparative bioavailability data) to demonstrate that the systemic drug exposure of your proposed product is comparable or lower compared to NDA 009435*.'
All the available published studies after epidural administration of chloroprocaine were reviewed and verified according to FDA requirements (i.e. studies conducted with listed drug(s), analytical method, limit of quantification or detection, number of patients). After the evaluation, only the studies fully or partially meeting the requirements were used for the comparison (for the comprehensive analysis please refer to module 2.7.1). (The sponsor is referring to the Table 1.1 included above).
In particular, the plasma levels of chloroprocaine reveal that, in order to obtain an anesthetic epidural block lasting about 50 minutes (50 ± 25 minutes for cesarean section), the administered dose corresponds to 948 ± 347 mg, in 1 to 5 injections (Khunert et al. 1980).
50 mg of 1% chloroprocaine subdurally injected produce a similar duration of the block, but very low levels of its metabolite only.
Analogue results were obtained for instance in the trial of 1986 by Kunhert: after injection of 750 mg of chloroprocaine, the chloroprocaine plasma levels after 5 and 10 minutes were approximately more than 100 and 5 ng/ml respectively (extrapolated data), well beyond the level determined in case of 50 mg chloroprocaine subarachnoid injection (below the limit of detection 4 ng/ml).
It's unpractical to calculate an area under the curve of the plasma chloroprocaine concentration after epidural administration, because the half-life of the drug is very rapid (the apparent half-life *in vivo* after epidural anesthesia is 3.1 ±1.6 min and ranges from 1.5 to 6.4 min) and the maintenance of an effective spinal block requires in many cases more than one injection (Kunhert 1980). As a matter of fact the curves have an up and down profile.
Nonetheless it is possible to evaluate the plasma concentration of the drug in term of ng/ml. A subarachnoid injection of 50 mg (data from 15 patients) does not show any presence of the drug and very low levels of the metabolite, as previously reported."

Sponsor's Conclusion - Study CHL.1/02-2014 vs. literature data

In our study, no chloroprocaine was detected in any of the intrathecally treated patients at any time point. As expected, systemic exposure to chloroprocaine was negligible after intrathecal injection of 30, 40 and 50 mg Chloroprocaine HCl 1% (10 mg/mL) Injection, USP, as opposed to the findings of the published studies where chloroprocaine was administered epidurally. It is important to keep in mind that intrathecal doses are at least 4-10 times lower than the doses commonly administered epidurally (Nesacaine NDA #009435 – Product Information) and chloroprocaine systemic levels for the epidural route are considered safe for the clinical use. For this reason it can be assumed that the risk of adverse events due to the systemic exposure of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP administered intrathecally cannot be higher than after epidural administration of the listed references.

ACBA was detected in most samples in the 30, 40 and 50 mg chloroprocaine dose groups of study CHL.1/02-2014, particularly at 10, 30 and 60 min after intrathecal injection. Plasma ACBA concentrations increased in plasma after the spinal injection of the parent compound and appeared to reach a peak at 30 min post-dose. At 60 min post-dose ACBA levels were lower than at 30 min for most subjects, suggesting that at that time ACBA elimination was already greater than its formation. Although ACBA was detectable in most plasma samples in study CHL.1/02-2014, these levels were 20-500 times lower than those reported in the literature for epidural administration.

See Table 1.4 from summary of biopharm in the next page.

Table 1.4 Plasma ACBA concentrations – Comparison between intrathecal injection, epidural administration and paracervical block data

Study	Administration	N subjects	Dose	Sampling time	ACBA (ng/mL) Mean±SD
1	Intrathecal	15	30 mg	5, 10, 30, 60 min post-dose	16.1±20.1 - 57.5±43.8
		15	40 mg		20.4±23.0 – 67.2±36.9
		15	50 mg		24.9±20.3 – 97.6±61.7
2	Epidural	12 Vaginal delivery	468±284 mg	At delivery	2000±3000 (range: 0-8000)
		18 Caesarean section	948±347 mg		8000±12000 (range: 1000-46000)
3	Epidural	7 Term	776±261 mg	At delivery	4650±5590
		7 Preterm	695±247 mg		5510±2510
4	Epidural	10 Acidotic group	855±326 mg	At delivery	5300±4100
		34 Nonacidotic group	838±242 mg		10500±13100
5	Paracervical block	27	20 mg	At delivery	BLQ-Traces (n=21) 3133±1568 (n=6)
		13		5 min post-dose	4050±2250

1. Study CHL.1/02-2014 (LOQ: 4 ng/mL); BLQ: Below quantification limit
2. Kuhnert et al, 1980 (LOD: 300 ng/mL)
3. Kuhnert et al, 1983 (LOD: 80 ng/mL)
4. Philipson et al, 1985 (LOD: 80 ng/mL)
5. Weiss et al, 1983 (LOQ: 100 ng/mL)

The pharmacokinetic data for epidural administration compared to the pharmacokinetics data of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP, finally demonstrated that the systemic drug exposure of our proposed product is lower compared to NDA 009435, Listed Drug.

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 detected 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.

In addition, the team agreed that the metabolite levels were an order of magnitude different between sponsor conducted study CHL.1/02-2014 (Study 1 in above table) and other studies referenced by the sponsor.

The sponsor also submitted urine ACBA concentrations:

Table 1.5 Study CHL.1/02-2014 - Urine ACBA concentrations (ng/mL) and amount of excretion (%) measured at first spontaneous urine voiding

Analyte	ACBA (ng/mL) - Mean±SD		
Dose group	**30 mg N=15**	**40 mg N=14**	**50 mg N=14**
Urine concentration	1217.7±627.8	1827.9±904.1	2103.5±1537.5
Amount of excretion	1.70±0.97	1.76±0.93	1.66±1.29

LQL: 50.0 ng/mL

Urine ACBA concentrations following 30-50 mg chloroprocaine intrathecal injection were on average approximately 140-240 times lower than those observed in Kuhnert et al study following epidural injection of 695±247 mg-776±261 mg chloroprocaine, the only work available for comparison [Kuhnert et al., 1983]. Results are detailed in the table below.

Table 1.6 Urine ACBA concentrations – Comparison between intrathecal injection and epidural administration data

Study	Administration	N subjects	Dose	Sampling time	ACBA (ng/mL) Mean±SD
1	Intrathecal	15	30 mg	First spontaneous voiding	1217.7±627.8
		14	40 mg		1827.9±904.1
		14	50 mg		2103.5±1537.5
2	Epidural	11	776±261 mg	72-hr interval	299000±225000
		11	695±247 mg		38±28%

1. Study CHL.1/02-2014 (LOQ: 50 ng/mL)

2. Kuhnert et al 1983 (LOD: 80 ng/mL)

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.5 Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208791	**SDN**	000
Applicant	SINTETICA	**Submission Date**	08/26/2016
Generic Name	Chloroprocaine HCl	**Brand Name**	(b) (4)
Drug Class	Local Anesthetic		
Indication	Intrathecal Injection for regional anesthesia		
Dosage Regimen	Intrathecal injection		
Dosage Form	Injection	**Route of Administration**	Intrathecal Injection
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	10/25/2016	**74-Day Letter Date**	11/8/2016
Review Due Date	5/22/2017	**PDUFA Goal Date**	6/26/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s)

We have received your response to information requests regarding the bioanalytical methodology used in determining chloroprocaine in pharmacokinetic assessments. We have also received your response to information request indicating use of Nescaine in Gao et al. or other publications. Adequacy of the bioanalytical methodology, and your rationale that the risk of adverse events due to the systemic exposure of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP administered intrathecally cannot be higher than after epidural administration of the listed references, will be a review issue.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose		Plasma concentrations of chloroprocaine and its metabolite ACBA and urinary ACBA excretion were investigated as secondary end-points of the phase 2 study CHL1/02-2014.
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			

☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	Relying on Nesacaine label.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Relying on Nesacaine label.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☑No ☐N/A	Sponsor claims drug levels are non-existent following proposed route. Sponsor proposed dosing and route (intrathecal) is different from approved (epidural). Also see notes below on Page 5.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting	☑Yes ☐No ☐N/A	

studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☑Yes ☐No ☐N/A	Two publications were in Chinese language and the sponsor submitted English translated articles upon sending information request.

Filing Memo

Sintetica submitted a 505(b)(2) NDA for use of chloroprocaine HCl injection, a local anesthetic, indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia). The sponsor is relying on Agency's previous findings of safety and efficacy for Nesacaine (Chloroprocaine HCl Injection) NDA 009435.

During PIND Meeting (IND119674) dated January 17, 2014, sponsor was informed "…*you will need to provide data (e.g., via comparative bioavailability data) to demonstrate that the systemic drug exposure of your proposed product is comparable or lower compared to NDA 009435*.'

A comparative BA study was not conducted by the sponsor because

1) Dose proposed for use is less than previously approved for Nesacaine.

2) Pharmacokinetic assessments in the Phase 2 study CHL1/02-2014 revealed that chloroprocaine levels are not noted in systemic circulation.

Two separate information requests were sent to the sponsor:

IR dated 10/6/2016:

> You have cited epidural use of chloroprocaine HCl and the PK data from publications by Gao et al 2006 and 2007.
>
> Provide full articles for citation The pharmacokinetics and pharmacodynamics of chloroprocaine in epidural blockade. The Journal of Clinical Anesthesiology. 2007 (CNKI:SUN:LCMZ.0.2007-05-009) Pharmacokinetics and pharmacodynamics of chloroprocaine with or without epinephrine for epidural blockade Chinese Journal of Anesthesiology. 2006-05.
>
> If these are foreign language articles, translation has to be provided. In addition, identify the bioanalytical methodology employed in these publications and indicate how they relate bioanalytical methods you have employed in terms of sensitivity, specificity, accuracy and precision.

Follow-up IR dated 10/12/2016:

> We have looked at the English translated articles by Gao et al. We have also noted that the publication does not indicate the bioanalytical methods specificity, accuracy and precision in terms of validation.
>
> Your product may be different from Nesacaine and also the product used by Gao et al.
>
> How do the chloroprocaine formulations and concomitant medications (epinephrine) used in Gao et al. publications relate to Nesacaine, and your own product?
>
> Do you have publications documenting PK data following use of Nesacaine?
>
> If not, how can PK data from a different product used in Gao et al., be implied as Nesacaine."

The sponsor provided justification (NDA208791 (SDN not assigned at the time of filing) submission dated 10/21/16 EDR \\cdsesub1\evsprod\NDA208791\0005) to assume that the risk of adverse events due to the systemic exposure of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP administered intrathecally cannot be higher than after epidural administration of the listed references.

The responses to IR constitute adequate material for filing and review of the NDA. From a clinical pharmacology perspective the adequacy of the bioanalytical method is the main review issue. Comparability of the different formulations used in referenced publications (IR response dated 10/21/16) will require input from CMC discipline. Summary of the sponsor's justification

for the lack of systemic exposure with their product compared to literature is described below:

> **Sponsor's Conclusion - Study CHL.1/02-2014 vs. literature data**
>
> In our study, no chloroprocaine was detected in any of the intrathecally treated patients at any time point. As expected, systemic exposure to chloroprocaine was negligible after intrathecal injection of 30, 40 and 50 mg Chloroprocaine HCl 1% (10 mg/mL) Injection, USP, as opposed to the findings of the published studies where chloroprocaine was administered epidurally. It is important to keep in mind that intrathecal doses are at least 4-10 times lower than the doses commonly administered epidurally (Nesacaine NDA #009435 – Product Information) and chloroprocaine systemic levels for the epidural route are considered safe for the clinical use. For this reason it can be assumed that the risk of adverse events due to the systemic exposure of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP administered intrathecally cannot be higher than after epidural administration of the listed references.
>
> ACBA was detected in most samples in the 30, 40 and 50 mg chloroprocaine dose groups of study CHL.1/02-2014, particularly at 10, 30 and 60 min after intrathecal injection. Plasma ACBA concentrations increased in plasma after the spinal injection of the parent compound and appeared to reach a peak at 30 min post-dose. At 60 min post-dose ACBA levels were lower than at 30 min for most subjects, suggesting that at that time ACBA elimination was already greater than its formation. Although ACBA was detectable in most plasma samples in study CHL.1/02-2014, these levels were 20-500 times lower than those reported in the literature for epidural administration.
> The pharmacokinetic data for epidural administration compared to the pharmacokinetics data of Chloroprocaine HCl 1% (10 mg/mL) Injection, USP, finally demonstrated that the systemic drug exposure of our proposed product is lower compared to NDA 009435, Listed Drug."

Some of the important differences noteworthy for (b) (4) and NESACAINE MPF clinical and clinical pharmacology considerations:

Indication:

PROPOSED DRUG:

(b) (4) is a local anesthetic indicated for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia).

REFERENCE DRUG:

Nesacaine-MPF 2% and 3% Injections, in single dose vials without preservative and without EDTA, are indicated for the production of local anesthesia by infiltration, peripheral and central nerve block, including lumbar and caudal epidural blocks.

Nesacaine and Nesacaine-MPF Injections are not to be used for subarachnoid administration.

Nesacaine (containing preservative) is indicated for production of local anesthesia by infiltration and peripheral nerve block instead of spinal anesthesia, and approved for three concentrations 1%-2%-3% instead of one, 1%.

Dosage and Administration:

PROPOSED DRUG: The indications relating to recommended doses are valid in adults of average height and weight (approximately 70 kg) for obtaining an effective block with one single

administration. There are wide individual variations with regard to extent and duration of action. The experience of the anesthesiologist and knowledge of the patient's general condition are essential for establishing the dose.

With regard to adults posology the following guidelines are applied:

(b) (4)

The maximum recommended dose is 50 mg (= 5 mL) of chloroprocaine hydrochloride.

REFERENCE DRUG:

2. Caudal and Lumbar Epidural Block: NESACAINE-MPF INJECTION. 2% (20 mg/mL) 3% (30 mg/mL)

For caudal anesthesia, the initial dose is 15 to 25 mL of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals. (b) (4)

For lumbar epidural anesthesia, 2 to 2.5 mL per segment of a 2% or 3% solution can be used. The usual total volume of Nesacaine-MPF Injection is from 15 to 25 mL. Repeated doses 2 to 6 mL less than the original dose may be given at 40 to 50 minute intervals. (b) (4)

The above dosages are recommended as a guide for use in the average adult. Maximum dosages of all local anesthetics must be individualized after evaluating the size and physical condition of the patient and the rate of systemic absorption from a particular injection site.

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/s/

SRIKANTH C NALLANI
07/19/2017

YUN XU
07/19/2017