CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20997

CHEMISTRY REVIEW(S)

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA # 20-997 (1 S) 25 Added Dog.

REVIEW # 2 **DATE REVIEWED:** 1.22.99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	12-2-98	12-2-98	

Partial response to FDA concerns of October 16, 1998, Chemistry concerns.

NAME & ADDRESS OF APPLICANT:

Darwin Discovery Ltd, 283 Cambridge Science Park, Milton Road, Cambridge, CB4 4WE, England

DRUG PRODUCT NAME

Proprietary:	CHIROCAINE
Established:	Levobupivacaine Injection
Code Name/#:	CAS# 27262-48-2
Chem.Type/Ther.Class:	1 S

PHARMACOL. CATEGORY:

An anesthetic product intended for epidural/intrathecal administration.

DOSAGE FORM:

An injection product prepared by sterile filtration, aseptic fill and terminally sterilized (SVT).

STRENGTHS: 25 mg/10 ml, 50 mg/ 10 ml, 75 mg/ 10 ml
75 mg/30 ml, 150 mg/30 ml and 225 mg/30 ml, drug products supplied in single use vials, and strength is expressed as Levobupivacaine base.

ROUTE OF ADMINISTRATION: For parental use.
DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Levobupivacaine is chemically described as (S)-1-butyl-2-piperidylformo-2',6'-xylidide hydrochloride. It is a white crystalline powder with a molecular formula of C18 H28 N2 O. HCl, with a molecular weight 324.9.

REMARKS:

Revised US marketing request is for not more than 1.2% w/w R-enantiomer for Levobupivacaine Injection . Chirocaine (Levobupivacaine Injection) is a sterile, non-pyrogenic isotonic aqueous solution containing Levobupivacaine HCl equivalent to 2.5 mg/mL 5.0

mg/mL, and 7.5 mg/mL of Levobupivacaine base. Epidural doses of up to 375 mg Levobupivacaine were administered incrementally to patients during a surgical procedure. To reduce cost of mfg. of Levobupivacaine drug substance, a racemization process step was added and justified in terms of chemical purity consideration only. Racemized process material was not used in Phase III clinical testing.

CONCLUSIONS & RECOMMENDATIONS:

Adequate responses were submitted to 8 questions for CMC to recommend approval.

Q.1. Please provide a linkage table that correlates the following: a) Clinical study numbers, b) Chirocaine drug product lots c) Levobupivacaine drug substance lots.

R.1. Linkage table was submitted as page 4. Clinical materials were compounded from Levobupivacaine HCl lots 22341, 23391, 23553. Clinical materials were prepared at batch sizes 30 or 150 lit, on Nov 94 or Nov 96 at [redacted]

Q.2. Please provide executed batch records for Levobupivacaine drug substance lots used in Phase III clinical studies.

. Executed batch records were submitted as pages 9 to 108. S-Bupivicaine HCl lots 001 (control no 22341), lot 007 (control no 23391), lot 009 (control no 23553) were prepared at batch sizes 1 or 5 kg, on April 94 or June 95 or Aug 95 at [redacted] Clinical lots were released at [redacted]% enantiomeric excess purity. Other purity characteristics were about [redacted] % KF moisture, [redacted] ppm residual isopropyl alcohol, 1 ppm residual isopropyl acetate or [redacted] ppm residual methyl t-butyl ether.

Q.3. Please submit chromatograms at zero and retest points for Levobupivacaine drug substance lots 22341, 23391, B0725, D1249.2/97001.

R.3 Chromatograms and 9 different chromatgraphic conditions used at retest points were submitted as pages 111 to 137. Batch chromatograms were for 2 lots processed at [redacted] and for 2 lots processed at Chirocaine. Area % figures and enantiomeric excess computations were not provided but an increase of R-enantiomer content seems obvious from zero time point and retest point chromatograms (control no 22341-pages 117 and 120, control no 23391-pages 123 and 129).

Q.4. Submit process validation document for selective crystallization of Levobupivacaine D-Tartrate salt, and the preparation of seed crystals of Levobupivacaine D-Tartrate.

R.4 Process performance qualification protocol and results were submitted as pages 161 to 175 for the pivotal intermediate Levobupivacaine D-tratrate. Process performance was qualified at about 60 kg batch size for 10 lots. Process performance evaluation lots had less than % w/w R-Bupivacaine, less than 0.05% w/w related substances, % w/w loss on drying, % w/w residual tert butylmethyl ether.

Source of seed crystals of Levobupivicaine D-tartrate seed crystals to promote crystallization is only a previously manufactured lot starting from a laboratory manufactured lot 1W/434/46/1 (see page 225).

Q.5. Submit DMF numbers and LOA to DMFs for Bupivacaine supplied by [ ]

R.5 Submitted letter of access to DMFs [ ] and DMF [ ] as pages 228 and 229. Racemic Bupivicaine sources were not cited on the executed batch records of [ ]

Q.6. Submit reference standard preparation and purification procedures for Levobupivacaine lots GF 117/207 and 1W/434/102/2.

R.6. Levobupivacaine reference lots were prepared by multiple recrystallization in isopropanol (see page 233). Certificates of analysis were only identified as CA971315 and CA981519 (see page 234).

Q.7. Submit a copy of the use patent US 5,708,011 (2014).

R.7 Use patent was submitted as pages 238 and 239. Transthoracic electrical bioimpedance technique was used to estimate myocardial contractility index and stroke index for Levobupivacaine and racemic Bupivacaine in healthy male subjects. From these measurements, the preferred use of Levobupivicaine is suggested for patients having depressed myocardial contractility.

Q.8. A tightening of specification for R-enantiomer to less than % w/w is suggested based on the levels reported for CLINICAL LOTS 22341 and 22391.

R.8 All results of R-enantiomer were collated and presented as page 243. In view of up to % w/w R-enantiomer content of the injection drug product, the revised US marketing request for not more than % w/w R-enantiomer for Levobupivacaine Injections is reasonable.

/S/

P. Maturu, PhD, Review Chemist

/S/ 11/25/99

A.D'Sa, PhD, Team Leader

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ADEQUATE

HFD 170/MaturuR

SEP 21 1998

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #	20-997 (1S)
REVIEW # 1	REVIEWER: Promoda Maturu
DATE REVIEWED:	9-1-98

SUBMISSION	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N000	4-27-98	4-27-98	5-4-98

NAME & ADDRESS OF APPLICANT: Darwin Discovery Ltd, 283 Cambridge Science Park, Milton Road, Cambridge, CB4 4WE, England

DRUG PRODUCT NAME

Proprietary:	CHIROCAINE
Established:	Levobupivacaine Injection
Code Name/#:	CAS# 27262-48-2
Chem.Type/Ther.Class:	1 S

PHARM CATEGORY: An anesthetic product intended for infiltrative, epidural or intrathecal administration.

DOSAGE FORM: An injection product prepared by sterile filtration, aseptic fill and terminally sterilized (SVT).

STRENGTHS: 25 mg/10 ml, 50 mg/ 10 ml, 75 mg/ 10 ml 75 mg/30 ml, 150 mg/30 ml and 225 mg/30ml, drug products supplied in single use vials, and strength is expressed as Levobupivacaine base.

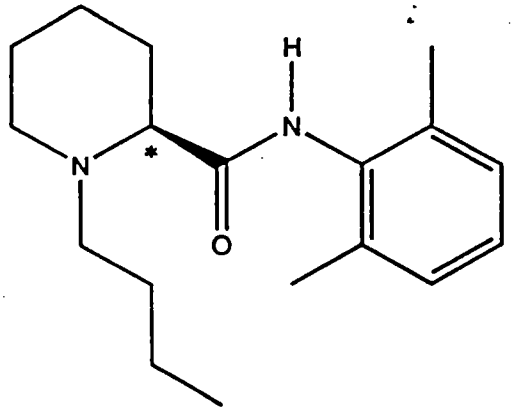
ROUTE OF ADMINISTRATION: For parenteral use.
DISPENSED: X Rx ___ OTC
SPECIAL PRODUCTS: X No ___ Yes

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMFs	Submitted within NDA				

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Levobupivacaine is chemically described as (S)-l-butyl-2-piperidylformo- 2',6'-xylidide hydrochloride. It is a white crystalline powder with a molecular formula of $C_{18}H_{28}N_2O$:HCl, with a molecular weight 324.9, and with the following structural formula:



HCl

* - Indicates the chiral center

RELATED DOCUMENTS (if applicable): IND[ ] HFD-170 division file should be referenced for meetings and telecons.

CONSULTS: Microbiology consulted to Paul Stinavage, review dated 8/98 recommended approval.

REMARKS:

Chirocaine (Levobupivacaine Injection) is a sterile, non-pyrogenic isotonic aqueous solution at pH 4.0-6.5 containing Levobupivacaine HCl equivalent to 2.5 mg/mL 5.0 mg/mL, and 7.5 mg/mL of Levobupivacaine base. Chirocaine is preservative free and it is available in 10 mL and 30 mL single dose vials. Epidural doses of up to 375 mg Levobupivacaine were administered incrementally to patients during a surgical procedure. The maximum dose administered to patients as a single fractionated injection was 300 mg for ancillary brachial plexus block. The maximum dose administered as a post-operative epidural infusion over 24 hours was 570 mg. Bupivacaine cardiotoxicity was supposedly reduced by a switch from Bupivacaine racemic mixture to Levobupivacaine in pregnant women (Press clipping, 51st annual Postgraduate Assembly of NY Society of Anesthesiologist, Speaker Dr. Alan Santos, Assoc Prof of Anesthesiology, OBGY at Albert Einstein College of Medicine, Bronx, NY).

Levobupivacaine drug substance manufacturing site was changed from [redacted] to [redacted] the project moved from Phase III clinical testing to US marketing request. Levobupivacaine injection manufacturing site was also changed from [redacted] to [redacted] as the project progressed. A [redacted] step was added and justified in terms of [redacted] consideration only. [redacted] material was not used in Phase III clinical testing.

US marketing request is for not more than 1.5% w/w R-enantiomer for Levobupivacaine even though clinical LOTS 22341 and 22391 showed 0.12% to 0.23% w/w of R-enantiomer. Based on 9 months data provided according the stability protocol for the drug product in vials, an expiration date of 15 months is recommended.

CONCLUSIONS & RECOMMENDATIONS:

From the CMC standpoint the application is incomplete. At the this point the recommendation is to request the information of the applicant to complete the review.

List of information request:

1. Please provide a linkage table that correlates the following:
a) clinical study numbers, b) Chirocaine drug product lots, c) Levobupivacaine drug substance lots.

2. Please provide executed batch records for Levobupivacaine drug substance lots used in Phase III clinical studies.

3. Please submit chromatograms at zero and retest points for Levobupivacaine drug substance lots 22341, 23391, B0725, D1249.2/97001.

4. Submit process validation document for selective crystallization of Levobupivacaine D-Tartrate salt, and the preparation of seed crystals of Levobupivacaine D-Tartrate.

5. Submit DMF numbers and LOA to DMFs for Bupivacaine supplied by

6. Submit reference standard preparation and purification procedures for Levobupivacaine lots GF 117/207 and 1W/434/102/2.

7. Submit a copy of the use patent US 5,708,011 (2014).

8. A tightening of specification for R-enantiomer to less than 0.2% w/w is suggested based on the levels reported for CLINICAL LOTS 22341 and 22391.

/S/

P. Maturu, PhD, Review Chemist

/S/ 9/21/98

A.D'Sa, PhD, Team Leader Chemistry