

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20997

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-997

OCT 16 1998

PAREXEL
Rose Tree Corporate Center
1400 North Providence Road, Suite 2000
Media, Pennsylvania 19063

Attention: **Mark Szewczak, Ph.D.**
Regulatory Consultant
U.S. Agent for Darwin Discovery Ltd.

Dear Dr. Szewczak:

Please refer to your pending April 27, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Chirocaine (levobupivacaine) injection.

We are reviewing the chemistry and clinical sections of your submission and have the following eight (8) chemistry and three (3) clinical information requests:

Chemistry Information Requests:

Please provide the following:

1. A linkage table that correlates the following: a) clinical study numbers, b) Chirocaine drug product lots, and c) Levobupivacaine drug substance lots.
2. Executed batch records for Levobupivacaine drug substance lots used in Phase III clinical studies.
3. Chromatograms at zero and retest points for Levobupivacaine drug substance lots 22341, 23391, B0725, and D1249.2/97001.
4. Process validation document for selective crystallization of Levobupivacaine D-Tartrate salt, and the preparation of seed crystals of Levobupivacaine D-Tartrate.
5. DMF numbers and LOA to DMFs for Bupivacaine supplied by
6. Reference standard preparation and purification procedures for Levobupivacaine lots GF 117/207 and 1W/434/102/2.
7. 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.

Clinical Information Requests:

1. Upon review of Study # 030632, "A Double-blind Randomized Controlled Trial of 0.5% Levobupivacaine Compared to 0.5% Bupivacaine for Extradural Anaesthesia in Patients Undergoing Elective Caesarean Section", please review the following flow chart for accuracy and provide the missing information in the table below regarding patient withdrawals.

Flow Chart

69 Subjects Randomized To Receive Study Drug

MINUS

2 subjects who did not receive study drug (patient # 007,018)



67 Subjects who received study drug

MINUS

3 Protocol Violators (*Patient ID ?*) and

2 Patients Who Received Prohibited Pre-dose (*Patient ID ?*)



62 "Per Protocol" Patients

MINUS

5 Patients Who Did Not Achieve Bilateral T5 Block (*Patient ID ?*)



57 Evaluable Primary Efficacy Patients

Table 1.0

Patient	Center	Treatment	Number of Injections	Age (yrs)	Height	Weight	Reason For Withdrawal
007							Dural Tap
018							Consent Withdrawn
							Protocol Violation PLEASE SPECIFY
							Protocol Violation PLEASE SPECIFY
047							Prohibited Pre-Dose PLEASE SPECIFY
054							Prohibited Pre-Dose PLEASE SPECIFY
							Did Not Achieve Bilateral T5 Block
							Did Not Achieve Bilateral T5 Block
							Did Not Achieve Bilateral T5 Block
							Did Not Achieve Bilateral T5 Block
							Did Not Achieve Bilateral T5 Block

2. Study # 030276 - Please provide: (1) the races of the patients described as "other", (2) the definition of the abbreviation "LUSC" (3) Page 35, "Withdrawals", reads as follows: " All 169 patients received study medication although seven patients were considered to be technical failures (please provide the patient numbers and reason for technical failure)..." (4) please provide a similar description, i.e., patient number and reason for withdrawal, in the "Results" as well as in the "Summary Tables and Figures" sections for this study.

This information, i.e., patient number and reason for withdrawal will be needed for all studies submitted for review. An example of the format in which to submit this information is found in Study # 006175, "Table L1.1 Efficacy Evaluation Population", p. L3 (p. 354) as seen below:

TABLE L1.2
Efficacy Evaluation Populations
Patients Excluded from Per-Protocol Analysis

Patient	Treatment	Patients withdrawn prior to dosing
025	3	Did not meet inclusion criteria - no adequate contraception
056	1	Patient withdrew consent
061	2	Failed epidural - drug not given
068	2	Did not meet inclusion criteria - first degree heart block
072	3	Operation postponed for surgical reasons
085	2	Dural tap <u>is</u> failed epidural technique
094	1	Operation cancelled due to intercurrent illness - hypertension
104	1	List over-ran, operation cancelled by surgeons
Patients eliminated from the per-protocol analysis		
026	1	Nitrous oxide general anaesthetic
039	2	Nitrous oxide general anaesthetic
043	3	Bupivacaine infiltration into wound
044	2	Nitrous oxide general anaesthetic
058	1	Nitrous oxide general anaesthetic
070	2	Nitrous oxide general anaesthetic
078	2	Nitrous oxide general anaesthetic

Key for Treatment

1 = 0.5% Levobupivacaine
2 = 0.75% Levobupivacaine
3 = 0.5% Bupivacaine

3. Study # 030433 - (1) Please explain what is meant by, "failed to reach outcome". (2) Please explain why the following patients were not withdrawn despite being classified as protocol violators: Patients A01, 012, 014, 045, 008, 056 and 038.

NDA 20-997

Page 5

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Ken Nolan, Project Manager, at 301-443-3741.

Sincerely,

/s/

Cythia G. McCormick, M.D.

Director

Division of Anesthetic, Critical Care, and

Addiction Drug Products, HFD-170

Office of Drug Evaluation III

Center for Drug Evaluation and Research

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

February 24, 1999

Cynthia McCormick, MD
Director
Division of Anesthetics and Critical Care and Addiction Drug Products (HFD-170)
Center for Drug Evaluation and Research
Food and Drug Administration
Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-997**
CHIROCAINE™ (levobupivacaine injection)
Agreement to Phase 4 Commitments

Dear Dr. McCormick:

PAREXEL International Corporation, on behalf of Darwin Discovery Limited (a wholly owned subsidiary of Chiroscience Group plc), hereby amends NDA 20-997.

In follow up to our February 23, 1999 teleconference with the Division, during which we discussed Phase 4 Commitments, Darwin Discovery Limited, is hereby agreeing to the following Phase 4 Commitments:

Preclinical Studies

- Direct carotid artery infusion of levobupivacaine with cardiovascular function maintained performed in large mammals (sheep) to evaluate the indirect effect of levobupivacaine on the heart via the CNS.

- Direct coronary artery infusion of levobupivacaine with CNS function maintained performed in large mammals (sheep) to evaluate the direct effect of levobupivacaine on the heart.
- Timely completion of a final study report of a cardiovascular resuscitation study in the dog given a convulsive dose of levobupivacaine.
- Consider the feasibility of performing a developmental toxicity study in a newborn animal model (e.g. neonatal pig or newborn beagle)

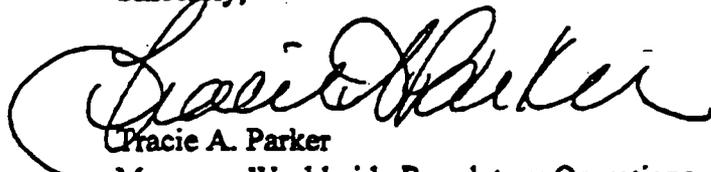
Clinical Studies

Pediatric development program to evaluate levobupivacaine in pediatric patients from birth to 16 years of age for anesthesia and pain management. This development plan should primarily include pharmacokinetics and safety data, and efficacy data designed to determine appropriate dosing regimens (including continuous infusions). Please note that this does not constitute a "Written Request" under Section 111 of FDAMA.

We are, however, interested in pursuing activities described in Section 111 of FDAMA. This will be addressed in a separate amendment to the NDA.

Thank you for your attention. Please contact me at (610) 565-2622, ext. 2244 if you have any questions.

Sincerely,


Pracie A. Parker
Manager, Worldwide Regulatory Operations

PAREXEL

Rose Tree Corporate Center
1400 N. Providence Road, Suite 2000, Media, PA 19063
Telephone: (610) 565-9400
Fax: (610) 565-5223

July 22, 1998

Cynthia McCormick, MD
Director

Division of Anesthetics and Critical Care and Addiction Drug Products (HFD-170)
Center for Drug Evaluation and Research
Food and Drug Administration
Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

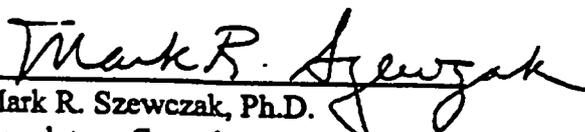
Re: NDA 20-997; levobupivacaine injection
Amendment to the NDA: Partial Response to FDA Questions (6/28/98)

Dear Dr. McCormick:

PAREXEL International Corporation, on behalf of Darwin Discovery Ltd., is hereby submitting 2 copies of a partial response to the series of concerns expressed in the fax memo of June 28, 1998. The response is not complete because we did not want to delay the review of the NDA where answers were available; a further complete response is anticipated in the near future.

This submission is in accordance with the responsibilities transferred to PAREXEL International Corporation which were outlined in IND _____ submitted on October 31, 1996. Should you have any questions or concerns, please do not hesitate to contact me at (610) 565-2622-9201 ext.2222.

Sincerely,


Mark R. Szewczak, Ph.D.
Regulatory Consultant