CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-496

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-496	Efficacy Supplement Type SE-	Supplement Number
Drug: **Duocaine**	Applicant: **Amphastar Pharmaceuticals, Inc.**	
RPM: Raphael R. Rodriguez	HFD- 550	Phone # 827-2090
Application Type: **505(b)(2)**	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	~~1/6/2003~~ 5/27/03
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) Literature Review ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) (X) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of	( ) Verified

notice).	
Exclusivity Summary (approvals only)	
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE – January 3, 2003
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	4/29/03
• Most recent applicant-proposed labeling	4/30/03
• Original applicant-proposed labeling	2/28/02
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	6/10/02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	2/27/03; 4/29/03
• Applicant proposed	2/28/02; 4/30/03
• Reviews	12/31/02; 5/2/03
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Pre-IND
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	12/31/02 , 5/2/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	8/22/02
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	8/9/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	7/23/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	9/16/02; 11/8/02; 3/17/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	9/16/02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	9/16/02
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5/24/02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

EXCLUSIVITY SUMMARY for NDA # 21-496 SUPPL # __

Trade Name Duocaine
Generic Name lidocaine HCl-bupivacaine HCl injection 1%/0.375%
Applicant Name Amphastar HFD-550
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_X_/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

   d) Did the applicant request exclusivity?

   YES /__/ NO /_X__/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /__/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 6-488 Xylocaine

NDA # 18-304 Sensorcaine

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness

of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Reference #7 [Oji E, et. al]

Investigation #2, Reference #59 [Bendi E, et. al]

Investigation #3, Reference #85 [Sarvela PJ, et. al]

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Reference #7 [Oji E, et. al]

Investigation # 2 , Reference #59 [Bendi E, et. al]

Investigation # 3 , Reference #85 [Sarvela PJ, et. al]

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /_X_/ Explain _____
_____	Amphastar Pharmaceutical, Inc. submitted NDA 21-496 for Duocaine as a 505(b)2 application. No new clinical studies were performed to support this application. Amphastar relied on the published literature to support the use of a mixture of lidocaine and bupivacaine as a local anesthetic in ophthalmologic surgery.

Investigation #2	
YES /___/ Explain _____	NO /_X_/ Explain _____
_____	Amphastar Pharmaceutical, Inc. submitted NDA 21-496 for Duocaine as a 505(b)2 application. No new clinical studies were performed to support this application. Amphastar relied on the published literature to support the use of a mixture of lidocaine and bupivacaine as a local anesthetic in ophthalmologic surgery.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____ _____
Signature of Preparer Date

Title: **Clinical Team Leader**

_____ _____
Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-496 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 2/28/02 Action Date: _____

HFD 550 Trade and generic names/dosage form: Duocaine (lidocaineHCl-bupivacaine HCl injection) 1%/0.375%

Applicant: Amphastar Pharmaceuticals, Inc. Therapeutic Class: Amide-type local anesthesia combination

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Indicated for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as parabulbar, retrobulbar and facial blocks.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

XX No: Please check all that apply: XX Partial Waiver ___Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

Other: ___

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age range being partially waived:

Min ____	kg ____	mo. ____	yr. 0	Tanner Stage ____
Max ____	kg ____	mo. ____	yr. 12	Tanner Stage ____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

☐ XX Other: **General anesthesia is the method of choice for invasive ophthalmologic procedures in infants and children.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS

tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

William Boyd, Clinical Reviewer **Raphael Rodriguez, PM**

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

'udies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see achment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
5/23/03 04:41:14 PM

APPEARS THIS WAY
ON ORIGINAL

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7410, FAX: (301) 443-7068

MEMORANDUM

TO:	WILEY CHAMBERS, MD, DEPUTY DIVISION DIRECTOR, HFD-550
	WILLIAM BOYD, MD, MEDICAL OFFICER, HFD-550
THROUGH:	CYNTHIA MCCORMICK, MD, DIVISION DIRECTOR, (HFD-170)
	NANCY CHANG, MD (HFD-170)
FROM:	ARTHUR SIMONE, MD, PHD (HFD-170)
SUBJECT:	DUOCAINE CONSULTATION
CONSULTATION DATE:	04-11-2002
cc:	BOB RAPPORT, MD, DEPUTY DIVISION DIRECTOR, (HFD-170),
	ALETA CRANE, PROGRAM SPECIALIST
	PARINDA JANI, SUPERVISORY CONSUMER SAFETY OFFICER

On 21 March 2002, we received a Request for Consultation regarding possible concerns with the mixture of lidocaine and bupivicaine as used in Duocaine (NDA: 21-496). Duocaine is a mixture of 1% lidocaine with 0.375% bupivicaine for the proposed indications of peribulbar and facial nerve blocks at doses up to 0.18 ml/kg. It was noted that the sponsor performed no clinical studies, but rather relies on the published literature to support the safety and efficacy claims of its product.

The combination of lidocaine and bupivicaine in concentrations and volumes found in the formulation of Duocaine have been studied extensively and used widely in clinical practice. In this regard, the purported efficacy and safety of the two local anesthetics used together has been well documented in the literature. The claim that this combination of local anesthetics produces a faster onset and longer lasting block than would be obtained with either agent alone is also evaluated in the literature. While there have been some anecdotal claims that combinations of local anesthetics produce weaker blocks compared to single agents, there are no studies to support this in the literature; nor have there been claims that this was a problem in ophthalmic surgery. When used for peribulbar and facial nerve blocks as indicated on the proposed product label, the major risks, from an anesthetic perspective, are those related to neurological and cardiovascular toxicity due to systemic exposure to toxic doses. Local neural toxicity can also be a concern in this class of drugs. The toxicity profiles of these local anesthetics have been established for their use individually and described in the literature for their use in combination. The systemic toxicity of local anesthetics is thought to be additive. As such, the proposed recommended doses are consistent with doses predicted to be safe based on individual toxicity profiles.

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)

DATE RECEIVED: March 28, 2002	**DUE DATE:** May 28, 2002	**ODS CONSULT #:** 02-0063

TO: Lee Simon, M.D.
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Raphael Rodriduez
Regulatory Health Project Manager
HFD-550

PRODUCT NAME:	**NDA SPONSOR:**
Duocaine Injection) **NDA #:** 21-496	Amphastar Pharmaceuticals, Inc.

SAFETY EVALUATOR: Scott Dallas, R. Ph.

SUMMARY:
In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, HFD-550, DMETS conducted a review of the proposed proprietary name "Duocaine" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objection to the use of the proprietary name, "Duocaine". This name, along with its associated labels and labeling, must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 6, 2002

NDA NUMBER: 21-496

NAME OF DRUG: Duocaine

NDA SPONSOR: Amphastar Pharmaceuticals, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) for an assessment of the proposed proprietary name, Duocaine. This proposed tradename is submitted with NDA 21-496. DMETS also reviewed the container label, multiunit carton labeling and package insert labeling.

PRODUCT INFORMATION

Duocaine contains the two active ingredients lidocaine hydrochloride 1% and bupivacaine hydrochloride 0.375%. This drug is being evaluated by the sponsor to produce local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as parabulbar, retrobulbar and facial blocks. The product is only available as a 1% lidocaine hydrochloride and 0.375% bupivacaine hydrochloride in 10 mL single dose vials.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Duocaine" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[4]. The Saegis[5]

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[1] MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).

[2] Facts and Comparisons, 2002. Facts and Comparisons, St. Louis, MO.

[3] The Drug Product Reference File [DPR], Established Evaluation System [EES], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.

[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Duocaine". Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified four proprietary or established names that were thought to have the potential for confusion with Duocaine. These products are listed in Table 1, along with the dosage forms available and usual dosage. DDMAC did not have any concerns with the promotional aspects of the name Duocaine.

TABLE 1

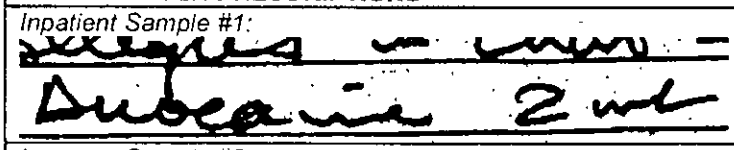
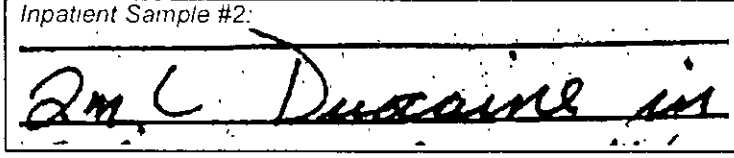
Product Name	Generic name, Dosage form(s)	Usual adult dose*	Other**
Duocaine	Injection 10 mL single dose vials	Varies with anesthetic procedure; Retrobulbar anesthesia: Inject 2-5 mL of solution, a portion injected retrobulbarly and the remainder used to block the facial nerve.	
Procaine	Procaine Hydrochloride, Injection 2 mL Uni-Amps, 6 mL single dose amps, and 30 mL multidose vials	Varies with anesthetic procedure.	S/A and L/A per DMETS
Danocrine	Danocrine, Capsules 50 mg, 100 mg, and 200 mg	Treatment of Endometriosis: Take 100 mg or 200 mg orally twice a day.	L/A per DMETS
Dibucaine	Dibucaine, 1% ointment in 30 g and 60 g 0 5% cream in 42.5 g	Treatment of hemorrhoid pain: Apply thin layer to affected area up to 3-4 times a day.	S/A and L/A per DMETS
Dobutamine	Dobutamine Hydrochloride, Injection 12.5 mg/ml in 20 ml vials	Treatment of cardiac decompensation: 2.5 to 10 mcg/kg/min by intravenous infusion.	S/A and L/A per DMETS

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

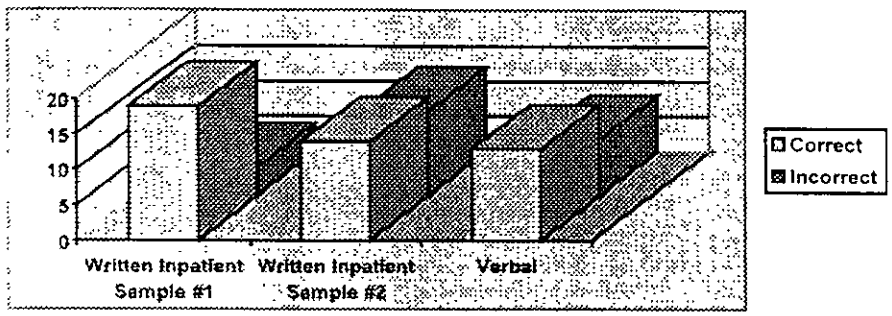
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Duocaine with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote two inpatient prescription orders, each consisting of a combination of marketed and unapproved drug products and prescriptions for Duocaine. These written prescriptions were optically scanned and one prescription was delivered via email to a group of study participants. In addition, one DMETS staff member recorded a verbal inpatient prescription order that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Sample #1: 	*Inpatient:* Duocaine 2 mL In AM clinic
Inpatient Sample #2: 	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Duocaine" response	Other response
Written: Inpatient Sample #1	39	23 (59%)	19 (83%)	4 (17%)
Inpatient Sample #2	36	26 (72%)	14 (54%)	12 (46%)
Verbal: Inpatient	33	21 (64%)	13 (62%)	8 (38%)
Total:	108	70 (65%)	46 (66%)	24 (34%)



Among participants in the written inpatient prescription study sample #1, 19 (83%) of 23 respondents interpreted the name correctly. Incorrect interpretations included Procachine (1), Dubucain (1), Avocaine (1) and Dibucaine (1).

Among participants in the written inpatient prescription study sample #2, 14 (54%) of 26 respondents interpreted the name correctly. Incorrect interpretations included Ducaine (7), Duscaine (3), Duracaine (1) and Diocaine (1).

Among participants in the verbal inpatient prescription study, 13 (62%) of the 21 respondents interpreted the name correctly. Incorrect interpretations included Duocane (3), Duocain (2), Decocaine (1), Duacaine (1) and Duracaine (1).

One of the misinterpreted names, Dibucaine is a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

The FDA Adverse Event Reporting System (AERS) database was searched to evaluate any name confusion among the ophthalmologic anesthetic agents available in the US marketplace. The concern was due to the fact there are seven established names and five tradenames that end with the suffix, "caine". A search of the AERS database did not reveal medication errors with respect to name confusion within the ophthalmologic anesthetic agents.

In reviewing the proprietary name, Duocaine, the primary concerns raised by the DMETS expert panel were related to four potential sound-alike and/or look-alike names that already exist in the US marketplace, Procaine, Danocrine, Dibucaine and Dobutamine.

Procaine Hydrochloride is an established name and is indicated for various anesthesia procedures. Procaine can be used as a regional anesthetic in ophthalmic surgery. It is available as an 1%, 2%, and 10% injection. Procaine and Duocaine can sound similar when spoken and look similar when written. Both names contain exactly the same number of letters, and end with the same six letters, "ocaine". If enunciated clearly when spoken the names can be differentiated by their prefix and a slightly different rhyming quality. The difference in rhyming quality is because, Procaine contains 2 syllables and Duocaine contains 3 syllables. When written, their

prefixes "pro" and "duo" look different. Also, there are other important characteristics to aid in differentiating between the two medications. Procaine and Duocaine have different strengths (1%, 2% and 10% vs. 1%/0.375%). Procaine is available in 2 mL Uni-Amps, 6 mL single dose amps and 30 mL multidose vials, whereas Duocaine is available in only 10 mL single dose vials. These medications would not be dispensed to the general population. Procaine and Duocaine would only be available to either an anesthesiologist trained in ophthalmologic procedures or an ophthalmologist. The same physician administering the anesthetic would generally script a written order. However, if an error did occur the potential for harm should be low, since both agents may be used for ophthalmologic anesthesia. The main concern would be that Procaine has a shorter duration of action, than Duocaine. These characteristics along with the limited distribution to trained professionals in ophthalmologic anesthesia would decrease the potential risk for a medication error and harm between these two drug products.

Danocrine is the proprietary name for Danazol. Danocrine is indicated for the treatment of endometriosis, fibrocystic breast disease and hereditary angioedema. It is available in 50 mg, 100 mg and 200 mg capsules. Danocrine and Duocaine can look similar when scripted. Both names start with the letter "D" and contain 3 syllables. When scripted the letters "ocrine" and "ocaine" can look similar. Also when scripted the initial vowel "a" in Danocrine can also look like the vowel "u" in Duocaine. The only feature in the name to help distinguish the two names when scripted is the letter "n" in Danocrine. However, there are other characteristics to help differentiate the two medications. Danocrine and Duocaine have different strengths (50 mg, 100 mg and 200 mg vs. 1%/0.375%), dosage formulation (capsule vs. injection), package size (60, 100, and 500 capsules vs. 10 mL), indications for use (various vs. ophthalmic surgery anesthesia), frequency of administration (twice or three times a day vs. during a ophthalmologic procedure), route of administration (oral vs. varies with procedure, but not oral). Danocrine could be self administered by the patient, whereas Duocaine should only be administered by a trained professional. Although these names do look alike when scripted, there are many characteristics that should decrease the potential for a medication error between these two medications.

Dibucaine is the established name for Nupercainal. Dibucaine is a topical local anesthetic and is indicated for sunburn pain, pruritus, minor burns, cuts and hemorrhoid pain. It is available as a 1% ointment and a 0.5% cream. Dibucaine and Duocaine can look similar when scripted and sound similar when spoken. Both names start with the letter "D", end with the letters "caine" and contain 3 syllables. The letter "b" in Dibucaine helps to distinguish the names when scripted. There are also other characteristics to help differentiate the two medications. Dibucaine and Duocaine have different package sizes (30 g, 60 g or 42.5 g vs. 10 mL), indications for use (topical local anesthetic vs. ophthalmic surgery anesthesia), frequency of administration (three or four times a day vs. during an ophthalmologic procedure), route of administration (topical vs. varies with procedure), and patient population (general vs. eye surgery patients). These characteristics would decrease the potential for a medication error between these two medications.

Dobutamine Hydrochloride is the established name for Dobutrex. It is indicated for cardiac decompensation. It is formulated as a 12.5 mg/mL injection and available in 20 mL vials. Dibutamine and Duocaine can look similar when scripted and sound

similar when spoken. Both names start with the letter "D", and contain 3 syllables. When scripted the last syllable of each name "amine" and "caine" can look similar. When spoken and scripted the second syllable, "but" in Dobutamine helps to distinguish the names. There are also other characteristics to help differentiate the two medications Dobutamine and Duocaine have different strengths (12.5mg/mL vs. 1%/0.375%), package size (20 mL vs. 10 mL), indication for use (cardiac decompensation vs. ophthalmic surgery anesthesia), frequency of administration (continuous intravenous infusion vs intermittent injections during an ophthalmologic procedure), and route of administration (intravenous vs. varies with procedure, but not intravenous). The prescribing population should be specialists to treat either cardiac or ophthalmic patients. Dobutamine and Duocaine could be physically located in close proximity to each other in a general storage area of a pharmacy. However, the medications should encounter an additional name verification during distribution of the product. Dobutamine could be sent to the intravenous preparation area of a pharmacy or to specialized floor units caring for cardiac patients. While, Duocaine could be sent to anesthesiologists or areas specializing in ophthalmic surgical procedures. The distinctive second syllable of Dobutamine and the other characteristics would decrease the potential for a medication error between these two medications.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS has reviewed the container label, multiunit carton labeling and package insert labeling. We have identified areas of improvement, in the interest of minimizing potential user error and patient safety.

A. Container Label

1. Increase the prominence of the established name along with the strengths.

2. Decrease the prominence of the net quantity statement by moving the statement further away from the product strength.

3. Decrease the size of the star logo.

B. Carton Labeling

1. See comments A 1-3.

2. The back panel includes bupivacaine as a hyphenated word, which appears on two lines of text. At another location on the panel, the drug concentration and established name appear on two lines of text. Please revise to include the drug concentration and established name without hyphenation and on the same line.

3. On the main principal display panel, please include the statement "single dose" in conjunction with the net quantity statement.

C. Package Insert Labeling

1. The "Description" section should include the statement " Each mL contains 3.75 mg bupivacaine and 10 mg lidocaine HCl, with 7 mg NaCl for tonicity, in Water for Injection. pH adjusted with NaOH or HCl."

2. In the "Dosage and Administration" section, DMETS recommends:

   a Inclusion of the word "ophthalmic" several places in the section, for example: "ophthalmic" anesthetic procedure, "ophthalmic" operation, and "ophthalmic" surgical procedure.

   b. The fourth paragraph reads, ".... painful facial never block." Please correct the spelling of the word "never" to "nerve".

   c In the subsection titled "Adults", the last sentence reads, "These dosages should be reduced for young, elderly or debilitated patients." Please consider the appropriateness of including "and patients with cardiac and/or liver disease."

   d. In the subsection titled "Children", the second sentence reads, [redacted] Please revise accordingly to specify whether children 12 years of age can be treated with Duocaine, for example: "for children 12 years of age and over".

3. In the "How Supplied" section, DMETS recommends increasing the prominence of the information "not for spinal anesthesia".

IV. RECOMMENDATIONS

DMETS has no objection to the use of the proprietary name, "Duocaine".

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Scott Dallas
6/10/02 09:57:25 AM
PHARMACIST

Carol Holquist
6/10/02 03:23:31 PM
PHARMACIST

Jerry Phillips
6/10/02 03:43:33 PM
DIRECTOR

Section XIII Patent Information On Any Patent Which Claims The Drug

A patent search was performed to locate any drug substance, drug product or method of use patents regarding Duocaine^{TM} Injection.

Amphastar Pharmaceuticals Inc. intends to certify that in our opinion and to the best of our knowledge, there are no patents, active or valid, that claim the proposed drug in this application, Duocaine^{TM} Injection. We further intend to certify that there are no patents that claim use of a combination of an injectable solution of Lidocaine HCl and Bupivacaine HCl Injection USP have been filed, or that such patents have expired.

Section XIV Patent Certification

Paragraph I Certification

In the opinion and to the best knowledge of Amphastar Pharmaceuticals Inc., there are no patents that claim the listed drug referred to in this application or that claim a use of the proposed drug, Duocaine™ Injection(, 10 mL).

Furthermore, according to the above-mentioned published information, the proposed drug is not entitled to a period of marketed exclusivity under Section 505 (j)(4)(D) of the Food, Drug and Cosmetic Act.

APPEARS THIS WAY
ON ORIGINAL

Diane G. Gerst
Vice President, Regulatory Affairs
Amphastar Pharmaceuticals Inc.

2-28-02
Date

Section XVI Debarment Certification

Debarment Certification

Amphastar Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Amphastar Pharmaceuticals Inc. further certifies that neither the applicant nor any affiliated persons responsible for the development or submission of this application have been convicted as described in subsection (a) and (b) [sections 306(a) and 306(b)] within the previous 5 years.

Diane G. Gerst
Vice President, Regulatory Affairs
Amphastar Pharmaceuticals Inc.

2-28-02
Date

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga CA 91730
Tel. (909) 980-9484 • Fax (909) 980-8296

February 28, 2002

Department of Health and Human Services
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Blvd.
Rockville, MD 20850

Gentlemen:

At this time Amphastar Pharmaceuticals Inc. (Amphastar) is submitting an original New Drug Application in accordance with 21CFR §314.54. The enclosed NDA provides for Duocaine™ Injection), 10 mL, for the production of local or regional anesthesia in ophthalmic surgery. Duocaine™ Injection contains the same individual active and inactive ingredients as the listed drugs, AstraZeneca's Xylocaine® brand of Lidocaine HCl Injection (NDA 6-488) and AstraZeneca's Sensorcaine® Bupivacaine HCl Injection (NDA 18-304)

Reference is made to the meeting held on October 10, 2001, between Agency and Amphastar representatives to discuss the appropriateness of submitting Duocaine™ as a 505(b)(2) application. Amphastar's presentation covered a description of the proposed product, an overview of the types of literature studies that have been determined to support the safety, efficacy and superiority of the proposed fixed combination over the individual actives, as well as the regulatory rationale for both the 505(b)(2) submission and a full waiver for an assessment of the pediatric use of Duocaine™ . The presentation also covered the toxicity profile for the combination and data demonstrating that the combination was less toxic than the individual actives and that no new impurities are formed. A copy of the meeting minutes are attached to this cover letter as well as provided in the Clinical Section of the application.

There have been no new clinical studies performed to support this application. Amphastar is relying on the published literature to support the use of a mixture of lidocaine and bupivacaine as an anesthetic in ophthalmic surgery.

This submission contains twelve (12) volumes. It contains the information requested under 21CFR §314.54, Procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug.

Duocaine™ is an aseptically filled, sterile product, manufactured at Amphastar's newly constructed facility in Rancho Cucamonga, California. We are currently awaiting an establishment number to be assigned to this facility as we have one other drug product currently under review at the Agency. Duocaine™ will be supplied premixed and ready to use. It will provide an important value to the medical community in terms of convenience and safety. The sterile, premixed dosage form will obviate the need for additional pharmacy compounding in the hospital.

Please direct all correspondence regarding this application to the undersigned at the following address:

Diane G. Gerst
Associate Vice President, Regulatory
Amphastar Pharmaceuticals Inc.
11570 Sixth Street
Rancho Cucamonga, CA 91730

We trust the information contained in this application meets with your requirements. Any questions regarding this application should be directed to the undersigned at (626) 459-5253.

Sincerely,

Diane G. Gerst
Vice President
Regulatory Affairs
Amphastar Pharmaceuticals

Cc: Los Angeles District Office
Irvine, CA

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

April 1, 2002

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NEW CORRESP

Department of Health and Human Services
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Blvd.
Rockville, MD 20850

DUPLICATE

RE: NDA 21-496 Duocaine™ (Injection)

Gentlemen:

This letter is written in response to the conversation between Raphael Rodriguez of the Agency and Maria Wagner of Amphastar Pharmaceuticals Inc., (Amphastar) on March 29, 2002. Mr. Rodriguez requested additional copies of the Clinical Data Section, a comprehensive Table of Content for the referenced clinical data, and a diskette for the proposed labeling with respect to the above application.

At this time Amphastar is submitting additional copies of volumes 1.9, 1.10, 1.11, and part of 1.12 of the original application. The content of these volumes are Section VII, Clinical Microbiology and Section VIII, Clinical Data Section. We are also providing a comprehensive Table of Content for the referenced Clinical Data Section and a diskette in PDF format of the labeling for our Duocaine submission. Please note that we are omitting reference to reference #100, *Dipenylhydantoin concentrations in saliva*. By Bochner F, Hooper WD, Sutherland JM, Eadie MJ and Tyrer JH.; Arch Neurol 1974; 31:57-9. Although the study was not included in the original application it was inadvertently included in the reference list, therefore we have deleted it from the list.

We trust the information contained in this application meets with your requirements. Any questions regarding this application should be directed to the undersigned at (626) 459-5253.

Sincerely,

Maria E. Wagner/gn

Diane G. Gerst
Vice President
Regulatory Affairs
Amphastar Pharmaceuticals

/mew

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

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April 5, 2002
Via Fax (301) 827-2531

NC
NEW CORRESP

Attn: Raphael Rodriquez
Food and Drug Administration

The following 7 pages are the Table of Contents (TOC) you requested for our NDA 21-496, Duocaine™ (Injection) submission. The TOC is for **Section VIII, Clinical Data Section** of our submission, which is found in volume 9.

An original Table of Content will be filled to the application with the additional information you requested from Diane Gerst.

Should you have any questions, please call me at (626) 459-5279.
Thank you.

Maria E. Wagner
Regulatory Affairs
Amphastar Pharmaceuticals Inc.

APPEARS THIS WAY
ON ORIGINAL

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

April 8, 2002

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Department of Health and Human Services
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Blvd.
Rockville, MD 20850

DUPLICATE

2C
NEW CORRESP

Re: NDA 21-496
Duocaine™ (——— **Injection)**

Gentlemen.

Reference is made to the Amphastar Pharmaceuticals Inc. (Amphastar) New Drug Application for Duocaine™ (1% Lidocaine HCl and 0.375% Bupivacaine HCl Injection), 10 mL, NDA 21-496 dated February 28, 2002. Further reference is made to the telephone conversation held between Agency representative Raphael Rodriguez and Amphastar representative Maria Wagner in which Mr. Rodriguez requested additional information in support of Amphastar's filing. At this time we are amending the application providing our response to the issues raised. The Agency's requests are provided below in italics, followed by Amphastar's response.

1. Authorization to reference information on the listed drugs.

Section 505(b)(2) of the Federal Food Drug and Cosmetic Act, was established by the Waxman-Hatch Amendments of 1984 to specifically allow approval of a new drug application based on full reports of investigations establishing a drug's safety and efficacy where such investigations "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference for use from the person by or for whom the investigations were conducted". It thereby makes the Agency's conclusions that would support the approval of a 505(j) application available to an applicant who develops a modification of a drug. 21CFR §314.54 codifies the requirements for a 505(b)(2) application, essentially permitting an applicant to rely on the Agency's finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j), codified in 21CFR §314.94.

This concept is confirmed in the Agency's Draft Guidance Document, "Applications Covered by Section 505(b)(2)". In that document, the following is stated:

> "A 505(b)(2) application should include the following:
>
> Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).
>
> If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs, identification of any and all listed drugs by established name, proprietary name (if any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number [(21 CFR 314.54(a)(1)(iii)]."

The draft guidance makes no mention of a requirement to provide an authorization to reference the listed drug's information. Additionally, according to §314.54(g)(3), if an applicant obtains "right of reference or use" to any investigation, the application becomes essentially a 505(b)(1) application. Therefore, since Amphastar is relying on the Agency's finding of safety and effectiveness for the listed drugs AstraZeneca's Xylocaine® brand of Lidocaine HCl Injection (NDA 6-488) and AstraZeneca's Sensorcaine® Bupivacaine HCl Injection (NDA 18-304), we feel such an authorization is inappropriate for this application.

2. *Financial Disclosure Information (Form FDA-3455).*

The basis for the determination of safety and effectiveness for this drug product, Duocaine™, is based on a review of the available literature and the Agency's findings regarding approved applications, not on actual human clinical trials sponsored by Amphastar. Since, no IND was opened and no Form FDA-1572 has been generated, we feel it is inappropriate to include a financial disclosure form (FDA-3455) with this application.

This was confirmed by Ms. Mary Gross (currently HFD-400), the Agency contact person for the final rule on Financial Disclosure published in the Federal Register (Feb. 2, 1998), in a conversation held between her and Diane Gerst on April 2, 2002.

3. *Additional Patent Information.*

At this time we are providing replacement pages for Sections 13 and Section 14 (pages 3686 and 3688) for Patent Information and Certification. Please see Attachment 1. A general patent search for drug substance, drug product, or method of use patents regarding the combination product has been performed. No reference to our particular formulation and combination and method of use has been found.

Additionally, we have provided information from the Approved Prescription Drug Products with Therapeutics Equivalence Evaluations (The Orange Book), taken from the current Edition as well as obsolete editions. It also demonstrates that there are no relevant patents that claim the use of our combination product. A certification in accordance with 21CFR §314.50(i)(1)(ii) has been made.

4. *Studies performed that were excluded from the evaluation of safety and effectiveness.*

At this time we are providing copies of two articles that were not included in the patient totals for evaluation, however they were used in obtaining other references. These articles are provided in Attachment 2. Their titles are as follows:

"Efficacy and complication rate of 16,224 consecutive peribulbar blocks" by: David B. Davis II, M.D., Mark Richard Mandel, M.D.

And

"Regional anesthesia for intraocular surgery" by: David H.W. Wong MB BS FRCPC.

These two articles are review articles that evaluate retrospectively the use of mixtures of lidocaine and bupivacaine in ophthalmic surgeries.

5. *Table 3 and 4 omitted from original application.*

At this time we are providing copies of the Tables, Efficacy Evaluation of the Proposed Fixed Combination Product. Table 3: Summary of the Clinical Studies Using the Same Formulation as the Proposed Fixed Combination Product, Duocaine™ ([redacted] ; Injection); and Table 4: Summary of the Clinical Studies Using Mixture of Lidocaine and Bupivacaine (Various Concentrations other than 1% Lidocaine – 0.375% Bupivacaine). These Tables are provided under Attachment 3.

6. The drug substance manufactures CF number for ——

The CF number for —— Please also note we have provided the active drug substance manufacturer CF numbers on the Form 356(h).

7. A comprehensive Table of Contents for Section VIII, Clinical Data Section (Volume 9).

We are providing a Table of Contents (TOC) for Section VIII, Clinical Data Section of our submission found in volume 9 of our original application. This TOC was previously faxed to Mr. Rodriquez on April 5, 2002. This is provided under Attachment 4.

We trust the information contained in this application meets with your requirements. Any questions regarding this application should be directed to the undersigned at (626) 459-5253.

Sincerely,

Maria E. Wagner /for

Diane G. Gerst
Vice President
Regulatory Affairs
Amphastar Pharmaceuticals

cc: Los Angeles District Office
Irvine, CA

Desk copy: Raphael Rodriguez, HFD-550

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone: (909) 980-9484 • Fax (909) 980-8296

July 22, 2002

ORIGINAL

RECEIVED
JUL 2 4 2002
MEGA/CDER

Department of Health and Human Services
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Blvd.
Rockville, MD 20850

ORIGINAL

RE: NDA 21-496 Duocaine™ (~~~ ~ Injection)

BC
ORIG AMENDMENT

Gentlemen:

Reference is made to Amphastar Pharmaceuticals' (Amphastar's) NDA 21-496 for Duocaine™ (~~~~~~~~~~) Injection, originally submitted March 5, 2002. Further reference is made to the Agency's fax correspondence dated April 30, 2002 and June 14, 2002, regarding CMC comments pertaining to the above stated pending NDA. At this time, Amphastar is submitting an Amendment to NDA 21-496 in response to the comments raised in the Agency's faxes. As a convenience, a copy of each fax is attached to our response.

The following data and associated attachments provide Amphastar's response to those items raised by the Agency regarding NDA 21-496, specifically, items related to the CMC comments. For the convenience of the reviewer our response to each specific item follows the same sequence as those cited in the Agency's faxes.

Amphastar hereby certifies that a complete copy of this Amendment has been forwarded to the Los Angeles District Office of the Food and Drug Administration.

We trust that the information provided is satisfactory to the Agency. If I may be of further assistance, please contact me at (626) 459-5253.

Sincerely,

Diane G. Gerst
Vice President
Regulatory Affairs
Amphastar Pharmaceuticals

Cc: Alonza Cruse, FDA Los Angeles District Office

Desk copy: Dr. Hossein Khorshidi, HFD-550

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone: (909) 980-9484 • Fax: (909) 980-8296

August 1, 2002

NDA 21-496 AMENDMENT
BC

Department of Health and Human Services
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-496 Duocaine™ (——— Injection)

Gentlemen:

Reference is made to Amphastar Pharmaceuticals' (Amphastar's) NDA 21-496 for Duocaine™ (1% Lidocaine HCl and 0.375% Bupivacaine HCl) Injection, originally submitted March 5, 2002. Further reference is made to the Agency's fax correspondence dated July 29, 2002, regarding CMC comments pertaining to the above stated pending NDA. At this time, Amphastar is submitting an Amendment to NDA 21-496 in response to the comments raised in the Agency's fax. As a convenience, a copy the fax is attached to our response.

The following data and associated attachments provide Amphastar's response to the items raised by the Agency regarding NDA 21-496, specifically, items related to the CMC comments. For the convenience of the reviewer our response to each specific item follows the same sequence as cited in the Agency's fax.

Amphastar hereby certifies that a complete copy of this Amendment has been forwarded to the Los Angeles District Office of the Food and Drug Administration.

We trust that the information provided is satisfactory to the Agency. If I may be of further assistance, please contact me at (626) 459-5253.

Sincerely,

Maria E. Waggoner

Diane G. Gerst
Vice President
Regulatory Affairs
Amphastar Pharmaceuticals

Cc: Alonza Cruse, FDA Los Angeles District Office

Desk copy: Dr. Hossein Khorshidi, HFD-550

ORIGINAL

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone: (909) 980-9484 • Fax: (909) 980-8296

August 19, 2002

DUPLICATE

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AUG 2 1 2002
MEGA/CDER

Department of Health and Human Services
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Blvd.
Rockville, MD 20850

ORIG AMENDMENT

RE: NDA 21-496 Duocaine™ (— Injection)

Gentlemen:

Reference is made to Amphastar Pharmaceuticals' (Amphastar's) NDA 21-496 for Duocaine™ ( ) Injection, originally submitted March 5, 2002. Further reference is made to the Agency's e-mails dated August 12 and August 13, 2002, regarding Medical Review comments pertaining to the above stated pending NDA. At this time, Amphastar is submitting an Amendment to NDA 21-496 in response to the comments raised in the Agency's e-mails. As a convenience, copies of the e-mails are attached to our response.

The following data and associated attachments provide Amphastar's response to the items raised by the Agency regarding NDA 21-496, specifically, items related to the Medical Review comments. For the convenience of the reviewer, our response to each specific item follows the same sequence as cited in the Agency's e-mails.

Amphastar hereby certifies that a complete copy of this Amendment has been forwarded to the Los Angeles District Office of the Food and Drug Administration.

We trust that the information provided is satisfactory to the Agency. If I may be of further assistance, please contact me at (626) 459-5253.

Sincerely,

Stephen Campbell
Vice President
Regulatory Affairs
Amphastar Pharmaceuticals, Inc.

Cc: Alonza Cruse, FDA Los Angeles District Office

Desk copy: Dr. William M. Boyd, HFD-550

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

NC

August 28, 2002

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-496
Duocaine™ (

AMENDMENT

Dear Sir or Madam:

Reference is made to NDA 21-496 for Duocaine™ (

). This amendment is filed to notify FDA that the primary contact person for issues arising in regard to this New Drug Application has changed. Effective immediately, the primary contact is Stephen A. Campbell, Esq., Vice President of Regulatory Affairs for Amphastar Pharmaceuticals, Inc. The telephone numbers and facsimile number remain unchanged.

Very truly yours,

Stephen A. Campbell, Esq.
Vice President of Regulatory Affairs
Amphastar Pharmaceuticals, Inc.

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

NDA ORIG AMENDMENT
BC

RECEIVED
SEP 0 9 2002
MEGA/CDER

August 28, 2002

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-496
Duocaine™ [redacted]

AMENDMENT

Dear Sir or Madam:

Reference is made to NDA 21-496 for Duocaine™ ([redacted]) and to the facsimile transmission dated August 12, 2002 from Shawn H. Khorshidi, Ph.D. Amphastar has reviewed Dr. Khorshidi's comments and hereby files this minor amendment to the CMC section of NDA 21-496. The individual observations are addressed below.

1. [redacted]

2.
3. [redacted]
4. e

5. [redacted]

6.

7. [redacted]

ORIGINAL

8.

9.

10

I certify that a true and complete copy of this minor amendment has been forwarded to the Los Angeles District Office. Please do not hesitate to contact the undersigned should you need any clarification or additional information.

Very truly yours,

Stephen A. Campbell, Esq.
Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District Office
19900 MacArthur Blvd. Suite 300
Irvine, CA 92715

ORIG AMENDMENT
BC

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone. (909) 980-9484 • Fax: (909) 980-8296

RECEIVED
NOV 0 5 2002
MEGA/CDER

November 1, 2002

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-496
Duocaine™ / [redacted]

MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to NDA 21-496 for Duocaine™ ([redacted] and to the facsimile transmission dated October 10, 2002 from Shawn H. Khorshidi, Ph.D. Amphastar has reviewed Dr. Khorshidi's comments and hereby files this minor amendment to the CMC section of NDA 21-496. The individual observations are addressed below.

1. In order to monitor impurity profile in the drug product, the [redacted] run time should be extended. Please submit representative chromatograms of the stability batches (one long term batch and three accelerated batches at the highest time point) with the extended run time (e.g. 25 minutes).

Amphastar Response:

The requested chromatograms are attached hereto as Attachment 1

2. In the certificate of analysis for Bupivicaine HCl, the acceptance criterion for "[redacted]' is not needed.

Amphastar Response:

The acceptance criterion for " [redacted] nas been deleted from the certificate of analysis. A copy of the revised certificate of analysis is attached as Attachment 2.

DUPLICATE

3. For the particulate matter test, please provide the actual results of analysis instead of reporting "Pass or Fail."

Amphastar Response:

Actual test results for the particulate matter tests included in the stability sheets which are attached hereto as Attachment 3.

4. Submit updated specification sheets for both drug substances and drug product. Also submit the revised method validation packages (in three copies) once all specification-related issues are resolved.

Amphastar Response:

Updated specification sheets for both drug substances and the drug product, and revised method validations are attached hereto as Attachment 4.

I certify that a true and complete copy of this minor amendment has been forwarded to the Los Angeles District Office. Please do not hesitate to contact the undersigned should you need any clarification or additional information.

Very truly yours,

Stephen A. Campbell, Esq.
Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

cc: Mr. Alonsa Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District Office
19900 MacArthur Blvd. Suite 300
Irvine, CA 92715

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone (909) 980-9484 • Fax: (909) 980-8296

NDA 21-496

DUPLICATE

RECEIVED
DEC 0 4 2002
MEGA/CDER

November 25, 2002

CDER, FDA
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Boulevard
Rockville, MD 20850

BL
ORIG AMENDMENT

RE: Minor Amendment to NDA 21-496:
Duocaine™ (Injection)

Professional Staff:

At this time, Amphastar Pharmaceuticals, Inc. is submitting a Minor Amendment to NDA 21-496, to provide revised draft labeling. In reviewing the original labeling as submitted, we noted some typographical errors which needed correction.

Amphastar hereby certifies that a complete copy of this Amendment is being forwarded to the Los Angeles District Office of the Food and Drug Administration.

We trust you will find the revised labeling satisfactory. If I may be of further assistance, please contact me at (626) 459-5253.

Sincerely,

Stephen A. Campbell, Esq.
Vice President
Regulatory Affairs

Enclosures

ORIGINAL

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone: (909) 980-9484 • Fax: (909) 980-8296

January 7, 2003

RECEIVED
JAN 0 8 2003
MEGA/CDER

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

RE: NDA 21-496
Duocaine™ [redacted] l)

Dear Sir or Madam:

Reference is made to NDA 21-496 for Duocaine™ (1% lidocaine HCl AND 0.375 % bupivacaine HCl) and to the facsimile transmission dated January 3, 2003 informing Amphastar that, as amended, the above referenced NDA is approvable, pending resolution of issues identified in the pre-approval inspection.

As requested, draft copies of all labeling and planned promotional materials are included in this amendment. In addition, two copies of the draft insert and promotional materials have been forwarded to the Division of Drug Marketing, Advertising and Communications, under separate cover.

As no clinical trials were associated with this NDA, submitted under section 505(b)(2) of the FD&C Act, as amended, no additional safety data are available.

I certify that a true and complete copy of this amendment has been forwarded to the Los Angeles District Office, 19900 MacArthur Blvd. Suite 300, Irvine, CA 92612.

Please do not hesitate to contact the undersigned should you need any clarification or additional information.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

cc: Mr. Alonsa Cruse
Los Angeles District Director
U.S. Food and Drug Administration

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax (909) 980-6233

ORIGINAL

RECEIVED
JAN 2 1 2003
MEGA/CDER

BL
ORIG AMENDMENT

January 10, 2003

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, MD 20857

RE. NDA 21-496
Duocaine™

MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to NDA 21-496 for Duocaine™ (1% lidocaine HCl AND 0.375 % bupivacaine HCl) and to the facsimile transmission dated January 3, 2003 informing Amphastar that, as amended, the above referenced NDA is approvable, pending resolution of issues identified in the pre-approval inspection. Further reference is mad to the telephone conversation between Raphael Rodriguez of the Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products and the undersigned on January 10, 2003.

As requested, draft copies of package insert draft labeling, version A6990710B, revision date 10/02 are attached hereto. These draft copies replace the copies of version A6990710A previously submitted in error by Amphastar. In addition, two copies of this draft insert have been forwarded to the Division of Drug Marketing, Advertising and Communications, under separate cover.

As no clinical trials were associated with this NDA, submitted under section 505(b)(2) of the FD&C Act, as amended, no additional safety data are available.

I certify that a true and complete copy of this amendment has been forwarded to the Los Angeles District Office, 19900 MacArthur Blvd. Suite 300, Irvine, CA 92612.

Please do not hesitate to contact the undersigned should you need any clarification or additional information.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

cc: Mr. Alonsa Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District Office
19900 MacArthur Blvd. Suite 300
Irvine, CA 92715

APPEARS THIS WAY
ON ORIGINAL

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone (909) 980-9484 • Fax (909) 980-8296

N-000/82

ORIG AMENDMENT

RECEIVED
FEB 2 5 2003
MEGA/CDER

February 20, 2003

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
Central Document Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-496
Duocaine™ (

Dear Sir or Madam:

Reference is made to NDA 21-496 for Duocaine™ (
), originally filed February 28, 2002, and for which an "approvable" letter was issued January 3, 2003. Amphastar Pharmaceuticals, Inc., hereby submits an amendment to the above referenced NDA. This amendment provides a replacement design for the twenty-five unit box labeling for this product. Rather than a fully enclosed box, Duocaine will be packaged with 25 10mL vials in a tray, which is subsequently shrink-wrapped. Four copies of the proposed tray are attached hereto for review. Both a review copy and an archival copy are provided.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

DUPLICATE

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

N-000/C

NEW CORRESP

RECEIVED
MAR 2 7 2003
MEGA/CDER

March 26, 2003

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
Central Document Room, N-360
9201 Corporate Blvd.
Rockville, MD 20857

RE: NDA 21-496
Duocaine™ (

Dear Sir or Madam:

Reference is made to Amphastar Pharmaceuticals, Inc. (Amphastar) NDA 21-496 for Duocaine™ (, originally filed February 28, 2002, and for which an "approvable" letter was issued January 3, 2003. The referenced approvable letter also noted that as the result of certain observations made during the September/October 2002 pre-approval inspection of Amphastar's Rancho Cucamonga facility, approval was being withheld, pending completion and verification of corrective actions. Corrective actions were completed in early January 2003, and at the request of Amphastar, a re-inspection of the facility was performed by the Los Angeles District on February 5 and 6, 2003. No negative observations were made and no FDA 483 was issued at the close of the inspection. A follow up letter was forwarded to the lead inspector, Ms. Caryn McNab, CSO, on February 12, 2003, with attachments requested at the close of the inspection. A true copy of that letter, less attachments is attached hereto.

Amphastar was informed by the Los Angeles District acting Director of Compliance, Mr. Robert McNab, that the District had recommended approval of the Duocaine NDA, based on the results of the re-inspection. Amphastar was further informed that the Los Angeles District has forwarded its approval recommendation to the Center for Drug Evaluation and Research, Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products. Therefore, Amphastar hereby submits an amendment to NDA 21-496, formally requesting that the review clock be restarted and that approval of this NDA be completed forthwith.

DUPLICATE

Both a review copy and an archival copy of this amendment are provided. The undersigned hereby certifies that a true copy of this amendment has been forwarded to the Los Angeles District Office.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

cc: Mr. Alonsa Cruse, Director
Los Angeles District Office
Irvine, CA

APPEARS THIS WAY
ON ORIGINAL

NEW CORRESP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Ampahstar Pharmaceuticals, Inc.	March 26, 2003
TELEPHONE NO (Include Area Code) (909) 980-9484, ext. 2019	FACSIMILE (FAX) Number (Include Area Code) (909) 980-8296
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U S. License number if previously issued):* 11570 Sixth Street Rancho Cucamonga, California 91730 Reg. No. pending drug approval	AUTHORIZED U S AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-496

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* —	PROPRIETARY NAME *(trade name)* IF ANY Duocaine Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* 2-(Diethylalmino)-2,6'-acetoxylidide and ( )-1-Butyl-2',6'-pipercoloxylidide monohydrochloride, monohydrate — CODE NAME *(If any)*

DOSAGE FORM: Injection	STRENGTHS: 10 mg/mL Lidocaine HCl and 3.75 mg/mL Bupivacaine HCl	ROUTE OF ADMINISTRATION: Parenteral (Retrobulbar/Peribulbar/Parabulbar)

(PROPOSED) INDICATION(S) FOR USE:
Indicate for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as penbulbar, retrobulbar and parabulbar.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314 94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Xylocaine (Lidocaine HCl Injection) - NDA 6-488 Holder of Approved Application Astra Zeneca
Sensorcaine (Bupivacaine HCl Injection) - NDA 18-304

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Restart review clock

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

C

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MAR 2 7 2003
MEGA/CDER

DUPLICATE

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
  - ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314 50(d)(1); 21 CFR 601.2)
  - ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 C FR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(l)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19 Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Request to re-start review clock and complete review

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314 71, 314.72, 314.97, 314.99, and 601.12
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, ti tle 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Stephen A. Campbell	Stephen A. Campbell, Esq. Sr. Vice President, Regulatory Affairs	3/26/03

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
11570 Sixth Street, Rancho Cucamonga, CA 91730	(626) 459-5253 (909) 980-9484 Extention 2019

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to.

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

February 12, 2003

Mrs. Caryn McNab, CSO
U.S. Food and Drug Administration
19900 MacArthur Blvd. Suite 300
Irvine, CA 92612

RE: Pre-Approval Inspection for NDA 21-496, Duocaine™

Dear Ms. McNab:

Thank you for your recent re-inspection of the Amphastar Pharmaceuticals, Inc. facility in Rancho Cucamonga. We sincerely appreciate the rapid response to our request for re-inspection, as well as the professional courtesy extended by you and Ms. Karsik.

As discussed at the closure of the inspection, Amphastar committed to provide certain updated documents to allow you to formally close this inspection. Those documents are attached hereto for your review. The documents include the following:

1. Addendum to Duocaine Injection Development Summary Report
2. Manufacturing Instruction MPR-9071-F
3. Environmental Monitoring Procedure for the Sterility Suite (SOP-B-2002)
4. Bacterial Endotoxin Procedure (SOP-E-3501)

As we discussed, I will forward an invitation to agency personnel to view our newly designed : once it is complete and operational.

Please do not hesitate to contact the undersigned if I can provide any additional information or clarification.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-6296

ORIGINAL

April 21, 2003

U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
Central Document Room, N-360
9201 Corporate Blvd.
Rockville, MD 20857

RE: NDA 21-496
Duocaine™

Dear Sir or Madam:

Reference is made to Amphastar Pharmaceuticals, Inc. (Amphastar) NDA 21-496 for Duocaine™, originally filed February 28, 2002, and for which an "approvable" letter was issued January 3, 2003. Further reference is made to the facsimile transmission received April 21, 2003, which contained recommended revisions to the package insert for the above referenced NDA.

Amphastar hereby amends NDA 21-496, by accepting, in total, the changes recommended by the agency, and hereby commits to incorporate each change into the package insert. Amphastar will further amend this application upon receipt of final printed labeling which complies with the sample represented by the attached facsimile.

Both a review copy and an archival copy of this amendment are provided. The undersigned hereby certifies that a true copy of this amendment has been forwarded to the Los Angeles District Office.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

ORIG AMENDMENT N-000/BL

AMPHASTAR PHARMACEUTICALS, INC.
11570 6th Street, Rancho Cucamonga, CA 91730 • Telephone: (909) 980-9484 • Fax (909) 980-8296

NDA 21-496

RECEIVED
MAY 0 1 2003
MEGA/CDER

April 30, 2003

CDER, FDA
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
HFD-550, Room N360
9201 Corporate Boulevard
Rockville, MD 20850

Professional Staff,

Reference is made to Amphastar Pharmaceuticals, Inc. NDA 21-496 and to a facsimile transmission from project manager Raphael Rodriguez to the undersigned on this date. Attached is the 356h and copy of the labeling comments received on April 30, 2003. Initials at each paragraph indicate Amphastar's acceptance of the changes.

Please do not hesitate to contact me at (626) 459-5253 if I may provide any additional information.

Sincerely,

Stephen A. Campbell, Esq.
Senior Vice President
Regulatory Affairs

Attachment

DUPLICATE

Amphastar Pharmaceuticals, Inc.

11570 6th Street, Rancho Cucamonga, CA 91730
Tel: (909) 980-9484 • Fax: (909) 980-8296

MAY 22 2003

REC'D BY
DR. SIMON

(PROCESS THIS AS OFFICIAL SUBMISSION

By facsimile and U.S. Mail

May 19, 2003

Lee Simon, M.D., Director,
U. S. Food and Drug Administration
Division of Anti-inflammatory, Analgesic
& Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-496
Duocaine™ (

CONFIDENTIAL COMMUNICATION

Dear Dr. Simon:

Reference is made to the Amphastar Pharmaceuticals, Inc. (Amphastar) NDA 21-496 for Duocaine™ (and to the telephone conversation between the undersigned and Raphael Rodriguez, Project Manager in the Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products on May 9, 2003. During this conversation, Mr. Rodriguez informed the undersigned that as the result of a Citizen's Petition filed by Pfizer and Pharmacia, Amphastar's 505(b)(2) NDA had been placed on a hold status at the request of the Office of the General Counsel of FDA. This letter is in response to that action by the agency, and presents Amphastar's position regarding the subject petition.

Amphastar has reviewed the Citizen's Petition (01P-0323) filed July 21, 2001, and the subsequently filed position statements by Amgen, Inc. (December 17, 2001), Abbott Laboratories (July 15, 2002), Generic Pharmaceuticals Association (December 10, 2001), and Pfizer's response thereto (April 4, 2002). There are three primary issues raised in the petition, alleging:

1) FDA is not properly authorized to rely on an innovator's proprietary data for approval of a similar drug product;
2) Reliance of FDA's prior finding of safety and effectiveness in an innovator's NDA to approve a 505(b)(2) application constitutes an unconstitutional taking under the Fifth Amendment;

3) Assignment of "A" therapeutic equivalence codes for 505(b)(2) application drugs are unsupported by the Act.

The 505(b)(2) NDA for Duocaine is not impacted by these arguments. The safety and effectiveness of Duocaine, a mixture of lidocaine and bupivicaine, is fully supported by literature included and/or referenced in the application, and does not rely on or reference any other innovator's proprietary information. As a 505(b)(2) NDA product, Duocaine is in fact an innovator drug product. Duocaine does not represent a change in an approved drug; rather it is a new drug, based upon the combination of two generic drugs.

"Section 505(l)(5) provides for the disclosure of the safety and effectiveness data in an NDA when "the first application under subsection (j) which refers to such [NDA] drug" is or could be approved."[1] Both active pharmaceutical ingredients contained in Duocaine, that is lidocaine HCl and bupivacaine HCl are the subjects of multiple approved ANDAs. "NDA data properly may be released when an abbreviated NDA ("ANDA") is approved because at that point, the data are subject to third-party use—by the ANDA applicant, in support of its application—and thus no longer commercially sensitive."[2]

Since any data relative to the safety and effectiveness of lidocaine HCl or bupivacaine HCl has previously been released and relied upon, such data can no longer be considered the proprietary data of the innovator.

Amphastar has not requested that a therapeutic equivalence code be assigned to Duocaine. Amphastar is the innovator of Duocaine, and any subsequent generic copy of Duocaine would reference Duocaine as the reference listed drug, and seek a finding of therapeutic equivalence to Duocaine.

For the reasons cited above, Amphastar requests that the FDA find that Citizen's Petition 01P-0323, filed by Pfizer Inc. and Pharmacia Corporation, does not impact NDA 21-496 for Duocaine ™ (lidocaine HCl and bupivacaine HCl, 1% and 0.375%). Amphastar further requests that NDA 21-496 be approved forthwith. Based upon a recent conversation with Mr. Raphael Rodriguez, Project Manager for the Duocaine NDA, the anticipated approval date for this NDA is May 27, 2003. Amphastar requests that approval not be delayed beyond that date.

Amphastar considers this communication to be a confidential communication between Amphastar and the Food and Drug Administration and requests that this document be so treated by the Agency.

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[1] Citizen's Petition 01P-0323
[2] *id.*

RE: 01P-0323
May 13, 2003
CONFIDENTIAL COMMUNICATION

Please do not hesitate to contact the undersigned should you need any clarification or additional information. The fact that Amphastar does not choose to contest the merits of the Petition in this letter should not be construed as otherwise endorsing the Petition and Amphastar reserves the right to contest the merits of the Petition at a later date.

Very truly yours,

Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs,
Amphastar Pharmaceuticals, Inc.

Cc: Daniel E. Troy, Chief Counsel, FDA
Jack Zhang, President/CEO,
Amphastar Pharmaceuticals, Inc.

APPEARS THIS WAY
ON ORIGINAL