CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-496

CHEMISTRY REVIEW(S)

NDA 21-496

Duocaine

Amphastar Pharmaceuticals

Hossein S. Khorshidi
Division of Anti-Inflammatory/Analgesics & Ophthalmic
Drug Products

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA # **21-496**

2. REVIEW # 1

3. REVIEW DATE: 9/16/02

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	2/28/02
Amendment #1	4/9/02
Amendment #2	7/22/02
Amendment #3	8/1/02

7. NAME & ADDRESS OF APPLICANT:

Name: Amphastar Pharmaceuticals

Address: 11570 6th Street, Rancho Cucamonga, CA, 91730

Representative: Stephen Campbell

Telephone: 909-980-9484

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Duocaine ® (proposed)
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anaesthetic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1% Lidocaine HCl and 0.375% Bupivacaine HCl

13. ROUTE OF ADMINISTRATION: Parenteral

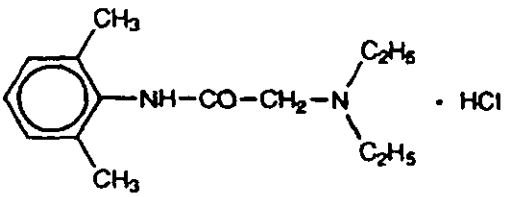
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

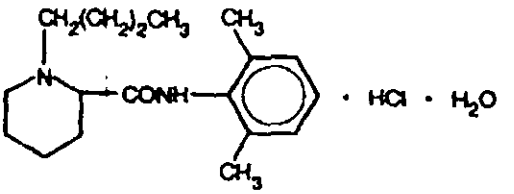
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Lidocaine HCl ($C_{14}H_{22}N_2O$·HCl)

acetamide, 2-(Diethylamino)-N-(2, 6-dimethylphenyl)-monohydrochloride

Molecular Wt. 270.8



Bupivacaine HCl ($C_{18}H_{28}N_2O$·HCL·H_2O)

2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate

Molecular Wt. 342.9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	II			1	Inadequate	4/18/02 Chem Rev #1 8/14/02 Chem Rev #2	Deficiency letter forwarded
	II			1	Adequate	4/19/02	
	II			1	Adequate	7/3/02	
	III			3	Adequate	9/24/ 01	
	II			3	Adequate	2/11/02	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	6-488	Xylocaine®(Lidocaine HCl Injection)
NDA	18-304	Sensorcaine®(Bupivacaine HCl Injection)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending	9/16/02	Hossein Khorshidi
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending, issues to be resolved	9/16/02	Hossein Khorshidi
OPDRA			
EA	Exclusion Acceptable	9/16/02	Hossein Khorshidi
Microbiology	Recommend for approval	9/9/02	Bryan Riley

The Chemistry Review for NDA # 21-496

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommended for Non-Approval at this time.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not at this time

II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(2) application and request for a full waiver for assessment of the pediatric use of [redacted]. Amphastar Pharmaceuticals has not performed any clinical trials for this product. The company has relied on the Agency's previous finding of safety and efficacy for the listed drugs as well as published clinical studies performed using 1% Lidocaine HCl and 0.375% Bupivacaine HCl.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substances:
Amphastar Pharmaceuticals will prepare Duocaine®injection using Lidocaine HCl, USP (CAS No. 137-58-6) and Bupivacaine HCl, USP (CAS No. 14252-80-3). [redacted], are the manufacturers and suppliers of Lidocaine HCl and Bupivacaine HCl respectively [redacted] was found inadequate to support NDA 21-496.

Both Lidocaine HCl and Bupivacaine HCl are USP listed monographs and are manufactured as individual approved drug products. However, and due to administrative route of this drug product (injection in ophthalmic surgery), the drug substance specification is needed to be revised with respect to OVI and the residual solvents (refer to FDA's IR facsimile dated 8/13/02).

Drug product:
Duocaine®injection contains the same individual active and inactive ingredients as listed approved drug products, Xylocaine® brand of lidocaine HCl injection (NDA 6-488) and Sensorcaine® (Bupivacaine HCl injection), NDA 18-304 (both manufactured by Astra

Zeneca).

The bulk solution for the stability batches was compounded at —— :. The commercial batches will be produced at —— in one run). Applicant has committed to submit a complete master batch record for the — batch size before marketing the product. Manufacturing process includes a —— Appropriate in-process tests/controls for color, clarity, pH, assay and bioburden (prior to —— are included.

Adequate drug product specification is submitted. Certain revisions were implemented with respect to the proposed acceptance criteria (tightening of the acceptance criteria for the pH, impurities and osmolality). Refer to the Agency's IR facsimiles dated 4/19/02 and 6/14/02. Analytical methods and the related validation data are described in details. In case of the "impurity study", the application did not provide adequate presentation or interpretation to correlate the observed data, for e.g., no impurity chromatograms are submitted. Adequate stability protocols and data package is submitted, however, occasional discrepancies have been noted in reporting the stability data, especially, impurity data. Applicant has proposed 18 months of expiry for this product based on 12 month of long-term and 12 month of accelerated stability data on three stability batches.

The drug product is aseptically filled into 10 cc clear glass with a gray rubber stoppers —— and a flip off seal —— . Three) have been referenced for the —— . All DMFs were reviewed and found to be adequate in support of NDA 21-496. The container/closure extractable test was done by the applicant according to USP <381> with two vehicles, water and isopropyl alcohol. Similar extractable data were reviewed and found to be adequate by Dr. Richard Lostritto and his DMF task force in case of —— Therefore, the submitted extractable data (by the applicant which is very similar to the original DMF data) can be considered acceptable.

B. Description of How the Drug Product is Intended to be Used

Duocaine®(') injection, 10 ml, will be used as a local or regional anesthetic agent intended for administration by parenteral injection in ophthalmic surgery. See package insert for further details.

Duocaine®injection will be supplied premixed and ready to use. Premixed dosage form will obviate the need for additional pharmacy compounding in the hospital, or extemporaneously mixing at the time of administration.

The product will be packaged and supplied in a carton of 10 singles dose vials and recommended to be stored at controlled room temperature 15° to 30° C (59° to 86° F). Unused portion should be discard after initial use.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission has provided inadequate information on the chemistry, manufacturing and controls for the production of Duocaine®injection.

As far as the drug substances are concerned, the [redacted] was found inadequate in support of NDA 21-496. In addition, the drug substance specification is needed to be revised with respect to QVI and the residual solvents (refer to FDA's IR facsimile dated 8/13/02).

For the drug product, the following deficiencies have been identified:

a)- [redacted]

b)- [redacted]

c) [redacted]

FDA's IR facsimile covering the outstanding issues has been sent on 8/13/02.

III Administrative

A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

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

/s/

Hossein Khorshidih
10/18/02 02:17:40 PM
CHEMIST

Linda Ng
10/18/02 02:38:36 PM
CHEMIST
No action needed by PM. Comments already sent to applicant.

CHEMISTRY REVIEW

NDA 21-496

Duocaine

Amphastar Pharmaceuticals

Hossein S. Khorshidi
Division of Anti-Inflammatory/Analgesics & Ophthalmic
Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA # **21-496**

2. REVIEW # 2

3. REVIEW DATE: 11/8/02

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	2/28/02
Amendment #1	4/9/02
Amendment #2	7/22/02
Amendment #3	8/1/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #4	8/28/02
Amendment #5	11/1/02

7. **NAME & ADDRESS OF APPLICANT:**

Name: Amphastar Pharmaceuticals
Address: 11570 6th Street, Rancho Cucamonga, CA 91730
Representative: Stephen Campbell, Esq
Telephone: (909) 980-9484

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Duocaine ® (proposed)
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anaesthetic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1% Lidocaine HCl and 0.375% Bupivacaine HCl

13. ROUTE OF ADMINISTRATION: Parenteral

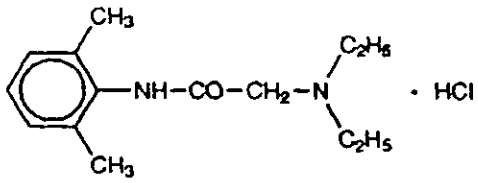
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

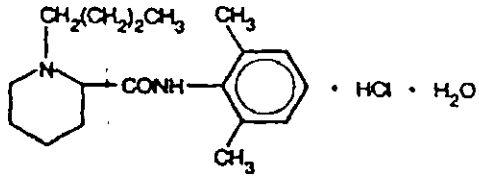
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Lidocaine HCl ($C_{14}H_{22}N_2O$·HCl)

acetamide, 2-(Diethylamino)-N-(2, 6-dimethylphenyl)-monohydrochloride

Molecular Wt. 270.8



Bupivacaine HCl ($C_{18}H_{28}N_2O$·HCL·H_2O)

2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate

Molecular Wt. 342.9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	10/10/02	
	II			1	Adequate Adequate	4/19/02 11/19/02	
	II			1	Adequate	7/3/02	
	III			3	Adequate	9/24/ 01	
	II			3	Adequate	2/11/02	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	6-488	Xylocaine®(Lidocaine HCl Injection)
NDA	18-304	Sensorcaine®(Bupivacaine HCl Injection)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	11/18/02	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Method will be sent for validation	11/18/02	
OPDRA			
EA	Exclusion Acceptable		
Microbiology	Recommend for approval	8/22/02	

The Chemistry Review for NDA # 21-496

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommended for Non Approval at this time

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not at this time

II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(2) application and request for a full waiver for assessment of the pediatric use of [redacted]®. Amphastar Pharmaceuticals has not performed any clinical trials for this product. The company has relied on the Agency's previous finding of safety and efficacy for the listed drugs as well as published clinical studies performed using 1% Lidocaine HCl and 0.375% Bupivacaine HCl.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substances:
Amphastar Pharmaceuticals will prepare Duocaine®injection using Lidocaine HCl, USP (CAS No. 137-58-6) and Bupivacaine HCl, USP (CAS No. 14252-80-3). [redacted] are the manufacturers and suppliers of Lidocaine HCl and Bupivacaine HCl respectively. All DMFs were found to be adequate in support NDA 21-496.

Both Lidocaine HCl and Bupivacaine HCl are USP listed monographs and are manufactured as individual approved drug products. However, and due to administrative route of this drug product (injection in ophthalmic surgery), the drug substance specification were revised with respect to OVI and the residual solvents (refer to FDA's IR facsimile dated 8/13/02).

Drug product:
Duocaine®injection contains the same individual active and inactive ingredients as listed approved drug products, Xylocaine® brand of lidocaine HCl injection (NDA 6-488) and Sensorcaine® (Bupivacaine HCl injection), NDA 18-304 (both manufactured by Astra

Zeneca).

The bulk solution for the stability batches was compounded at [redacted] The commercial batches will be produced at [redacted]
Applicant has committed to submit a complete master batch record for the [redacted] batch size before marketing the product. Manufacturing process includes a [redacted]
Appropriate in-process tests/controls for color, clarity, pH, assay and bioburden (prior to [redacted] are included.

Reference is made to FDA's IR letters dated 4/30/02, 6/14/02, 7/29/02, 8/13/02 and 10/10/02 respectively. Adequate drug product specification and impurity data is submitted. Certain revisions were implemented with respect to the proposed acceptance criteria (tightening of the acceptance criteria for the pH, impurities and osmolality). Analytical methods and the related validation data are described in details.

Adequate stability protocols and data package is submitted. Applicant has proposed 18 months of expiry for this product based on 12 month of long-term and 12 month of accelerated stability data on three stability batches. Stability data indicated that the drug product is quite stable and less likely would show any trend over the proposed expiry. Therefore, the proposed expiration dating period of 18 months can be granted.

The drug product is aseptically filled into 10 cc clear glass with a gray rubber stoppers ([redacted]) and a flip off seal ([redacted]). Three DMFs ([redacted]) have been referenced for the [redacted] . All DMFs were reviewed and found to be adequate in support of NDA 21-496. The container/closure extractable test was done by the applicant according to USP <381> with two vehicles, water and isopropyl alcohol. Similar extractable data were reviewed and found to be adequate by Dr. Richard Lostritto and his DMF task force in case of [redacted] Therefore, the submitted extractable data (by the applicant which is very similar to the original DMF data) can be considered acceptable.

B. Description of How the Drug Product is Intended to be Used

Duocaine®([redacted]) injection, 10 ml, will be used as a local or regional anesthetic agent intended for administration by parenteral injection in ophthalmic surgery. See package insert for further details.

Duocaine®injection will be supplied premixed and ready to use. Premixed dosage form will obviate the need for additional pharmacy compounding in the hospital, or extemporaneously mixing at the time of administration.

The product will be packaged and supplied in a carton of 10 singles dose vials and recommended to be stored at controlled room temperature 15° to 30° C (59° to 86° F). Unused portion should be discard after initial use.

C. Basis for Approvability or Not-Approval Recommendation

The overall compliance recommendation for Amphastar Pharmaceutical is withhold on 11/18/02. A form 483 has been issued to the firm on 10/9/02. It should be mentioned that Amphastar pharmaceutical is the manufacturer of the drug product. The drug substance sites are acceptable.

Additional labeling comment also forwarded to the applicant.

III Administrative

A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

16

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

/s/

Hossein Khorshidih
12/2/02 11:24:13 AM
CHEMIST

Linda Ng
12/2/02 12:17:12 PM
CHEMIST

NDA 21-496

Duocaine®
(Lidocaine HCl-Bupivacaine HCl Injection) 1%/0.375%

Amphastar Pharmaceuticals

Hossein S. Khorshidi, Ph.D.
Division of Anti-inflammatory, Analgesics and Ophthalmic
Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA # **21-496**

2. REVIEW # 3

3. REVIEW DATE: 3/17/2003

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	2/28/02
Amendment #1	4/9/02
Amendment #2	7/22/02
Amendment #3	8/1/02
Amendment #4	8/28/02
Amendment #5	11/1/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #6	2/20/03

7. **NAME & ADDRESS OF APPLICANT:**

Name: Amphastar Pharmaceuticals
Address: 11570 6th Street, Rancho Cucamonga, CA 91730
Representative: Stephen Campbell, Esq
Telephone: (909) 980-9484

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Duocaine ® (proposed)
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anaesthetic

11. DOSAGE FORM: Injection (10 ml vial)

12. STRENGTH/POTENCY: 1% Lidocaine HCl and 0 375% Bupivacaine HCl

13. ROUTE OF ADMINISTRATION: Parenteral

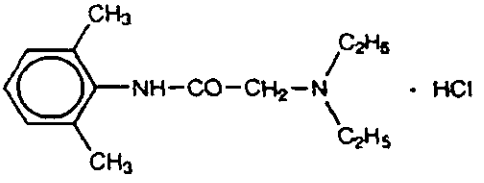
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

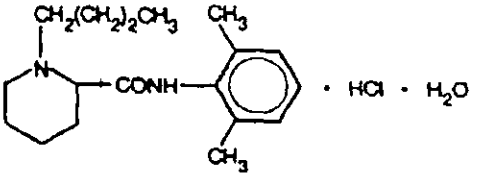
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Lidocaine HCl ($C_{14}H_{22}N_2O$·HCl)

acetamide, 2-(Diethylamino)-N-(2, 6-dimethylphenyl)-monohydrochloride

Molecular Wt. 270.8



Bupivacaine HCl ($C_{18}H_{28}N_2O$·HCL·H_2O)

2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate

Molecular Wt. 342.9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	10/10/02	
	II			1	Adequate Adequate	4/19/02 11/19/02	
	II			1	Adequate	7/3/02	
	III			3	Adequate	9/24/ 01	
	II			3	Adequate	2/11/02	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	6-488	Xylocaine®(Lidocaine HCl Injection)
NDA	18-304	Sensorcaine®(Bupivacaine HCl Injection)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	All sites acceptable	3/12/03	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Submitted to FDA labs. Results pending	3/21/03	
OPDRA			
EA	Exclusion Acceptable		
Microbiology	Recommend for approval	8/22/02	Dr. Bryan Riley

The Chemistry Review for NDA # 21-496

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, this NDA application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not at this time

II. Summary of Chemistry Assessments

This application has been filed as a 505(b)(2) application and request for a full waiver for assessment of the pediatric use of [redacted]. Amphastar Pharmaceuticals has not performed any clinical trials for this product. The company has relied on the Agency's previous finding of safety and efficacy for the listed drugs as well as published clinical studies performed using 1% Lidocaine HCl and 0.375% Bupivacaine HCl.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substances:
Amphastar Pharmaceuticals will prepare Duocaine®injection using Lidocaine HCl, USP (CAS No. 137-58-6) and Bupivacaine HCl, USP (CAS No. 14252-80-3). [redacted] are the manufacturers and suppliers of Lidocaine HCl and Bupivacaine HCl respectively. All DMFs were found to be adequate in support NDA 21-496.

Both Lidocaine HCl and Bupivacaine HCl are USP listed monographs and are manufactured as individual approved drug products. However, and due to administrative route of this drug product (injection in ophthalmic surgery), the drug substance specification were revised with respect to OVI and the residual solvents (refer to FDA's IR facsimile dated 8/13/02).

Drug product:
Duocaine®injection contains the same individual active and inactive ingredients as listed approved drug products, Xylocaine® brand of lidocaine HCl injection (NDA 6-488) and Sensorcaine® (Bupivacaine HCl injection), NDA 18-304 (both manufactured by Astra Zeneca).

The bulk solution for the stability batches was compounded at [redacted]. The commercial batches will be produced at [redacted]
Applicant has committed to submit a complete master batch record for the [redacted] size before marketing the product. Manufacturing process includes a [redacted] Appropriate in-process tests/controls for color, clarity, pH, assay and bioburden (prior to [redacted]; are included.

Reference is made to FDA's IR letters dated 4/30/02, 6/14/02, 7/29/02, 8/13/02 and 10/10/02 respectively. Adequate drug product specification and impurity data is submitted. Certain revisions were implemented with respect to the proposed acceptance criteria (tightening of the acceptance criteria for the pH, impurities and osmolality). Analytical methods and the related validation data are described in details.

Adequate stability protocols and data package is submitted. Applicant has proposed 18 months of expiry for this product based on 12 month of long-term and 12 month of accelerated stability data on three stability batches. Stability data indicated that the drug product is quite stable and less likely would show any trend over the proposed expiry. Therefore, the proposed expiration dating period of 18 months can be granted.

The drug product is aseptically filled into 10 cc clear glass with a gray rubber stoppers (13 mm) and a flip off seal (13 mm). Three [redacted]) have been referenced for the container/closure system. All DMFs were reviewed and found to be adequate in support of NDA 21-496. The container/closure extractable test was done by the applicant according to USP <381> with two vehicles, water and isopropyl alcohol. Similar extractable data were reviewed and found to be adequate by Dr. Richard Lostritto and his DMF task force in case of [redacted] Therefore, the submitted extractable data (by the applicant which is very similar to the original DMF data) can be considered acceptable.

B. Description of How the Drug Product is Intended to be Used

Duocaine®(1% Lidocaine US and 0.375% Bupivacaine HCl, USP) injection, 10 ml, will be used as a local or regional anesthetic agent intended for administration by parenteral injection in ophthalmic surgery. For normal healthy adults, the individual maximum recommended dose of Duocaine should not exceed 12 ml (without epinephrine) and 20 ml (when used with epinephrine).

Duocaine®injection will be supplied premixed and ready to use. Premixed dosage form will obviate the need for additional pharmacy compounding in the hospital, or extemporaneously mixing at the time of administration.

The product will be packaged and supplied in a carton of 10 singles dose vials. Applicant has initially proposed the labeled storage temperature of [redacted] for this product, however, and based on FDA's recommendation, they have changed it to 15° to 25°C (59° to 77° F). Unused portion should be discard after initial use.

C. Basis for Approvability or Not-Approval Recommendation

Amphastar Pharmaceutical has successfully addressed all CMC's related questions. In the following section, a brief summary of the important issues are discussed:

In review # 1, the major issues were encountered around inadequate DMFs and also incomplete specification for the drug substance. Recommendation was made to revise the drug substance specification with respect to the residual solvents.
As far as the drug product was concerned, the NDA submission was deficient in providing adequate information to explain and correlate the impurity profile (e.g., lack of impurity chromatograms). Occasional discrepancies were observed in reporting stability data (e.g., impurity data). Also, the proposed storage temperature [redacted] was not justified by adequate supporting data.

In reviews #2 and #3, the following key issues were resolved.
In general, there were some discrepancies between the COA (submitted by the DMF holders) and those of NDA's specification. Applicant revised and tightened the acceptance criteria for the residual solvents. For the drug product impurities, the representative [redacted] were provided. Also, and part of system suitability test for the assay and the impurity, a standard of Bupivacaine HCl at the limit of quantitation [redacted] was included to insure the detection of peaks at that level.

Applicant has agreed to report the actual results of analysis instead of reporting "Pass or/Fail" (e.g. Particulate Matter). For the labeling, the proposed storage temperature was recommended to be revised from [redacted] 15-25°.

As far as the inspection issues were concerned, the original inspection of Amphastar pharmaceuticals by the office of compliance (on September 2002) was not satisfactory. Applicant has resolved all outstanding 483 issues with the office of compliance and as a result, all manufacturing sites have been found acceptable by the office of compliance.

III Administrative

A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

8

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

/s/

Hossein Khorshidih
4/18/03 01:03:49 PM
CHEMIST

Linda Ng
4/18/03 01:13:51 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL