CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-665

CHEMISTRY REVIEW(S)

NDA 21-665

AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-665

2. REVIEW #: 4

3. REVIEW DATE: 08-OCT-2004

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003
BC	13-JAN-2004
BC	05-FEB-2004
BC	15-JUN-2004
BC	21-JUL-2004
BC	30-JUL-2004
BC	12-AUG-2004
DMETZ Review	29-AUG-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC	17-SEP-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticals Inc.
Address:	11570 6th Street Rancho Cucamonga, CA 91730
Representative:	Stephen A. Campbell, Esq.
Telephone:	(909) 980-9484 Ext. 2019

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AMPHADASE™
b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: P

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.

10. PHARMACOL. CATEGORY: Proteolytic enzyme

11. DOSAGE FORM: Hyaluronidase injection

12. STRENGTH/POTENCY: 150 USP Units/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous, 150 USP units/injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__SPOTS product – Form Completed

_____Not a SPOTS product

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

Hyaluronidase is a protein — composed of — with apparent molecular weights of — respectively. Based on the aminoacid sequence, the applicant reports the molecular weight of the enzyme at —

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	/	/	4	N/A	N/A	This product has an NF monograph
—	III	—	/	4	N/A	N/A	
—	III	/	/	4	N/A	N/A	

[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	6343	Wydase referenced through Section 505(b)(2) of the FDA Food , Drug and Cosmetic Act

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	JUL-20-2004	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Sent	SEP-15-2004	
OPDRA			
EA	Acceptable (Categorical Exclusion)	Review #1 11-DEC-2003	L. Rodriguez
Microbiology	Approval	18-Nov-2003	Dr. B. Riley

The Chemistry Review for NDA 21-665

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended as **approval.**

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

None

II. Summary of Chemistry Assessments

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

The drug product AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL — glass — vial, with a — — rubber stopper and a flip off — aluminum cap. This product was formulated to be the equivalent of the presently discontinued Wydase®. It contains the enzyme hyaluronidase, 150 USP Units/mL, sodium chloride, edetate disodium — ,alcium chloride — .thimerosal, monobasic sodium phosphate — — oatches of Amphadase. — . each, were manufactured for stability studies in support of this application. The components of the drug product are — —

The drug substance (bovine hyaluronidase) is extracted from — bovine testes. The testes are obtained from herds — . Crude hyaluronidase is obtained within ten days of collection of the testes and shipped for refinement to the — The crude material arrives to — accompanied by a — CERTIFICATE" issued by the — — The certificate states that 1) the hyaluronidase comes from healthy cattle from non-infected areas 2) the cattle is — and 3) that the processing facility does not receive, store or process any ruminate material from BSE countries. Each animal is examined by a veterinarian before slaughter.

The drug substance (bovine hyaluronidase) is a mixture composed approximately of — proteins — and — impurities. The — impurities are: —

— . The molecular weight, as claimed in the application, is — , as determined from the aminoacid sequence(s). However, further characterization conducted during the review cycle indicates that the protein mixture is composed of the drug substance, — , and approximately impurities. The apparent molecular weights of the — — are — — The — impurities do not interfere with the hyaluronidaze activity as demonstrated by —

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

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic C_{1-4} bond of the glucosamine moiety.

Amphadase™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial with a grey rubber stopper and an aluminum flip off seal. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical dose of 150 USP units. Other than aseptical removal the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated by mixing with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is 5°C ± 3°C. Based on the long term stability submitted in this amendment, the expiration time recommended for this drug product is 18 months. The recommended retest period for the drug substance remains at — . Amphastar should be able to extend retest and expiry periods based on updated stability data, via annual report.

C. Basis for Approvability or Not-Approval Recommendation

A variety of issues and deficiencies raised during the review cycle were resolved satisfactorily by the applicant. Amphastar intends to submit Freeze thaw cycles data for the drug product in the future, with the purpose of removing the "DO NOT FREEZE" warning from all the labeling. Updated stability data will also be submitted for the purpose of extending retest and shelf life expiry.

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez Ph.D., Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Ph.D., Review Chemist/08-OCT-2004
Linda Ng ,Ph.D., ChemistryTeamLeader/08-OCT-2004
Mike Puglisi, ProjectManager/08-OCT-2004

C. CC Block

HFD-550/division file/NDA 21665
Wiley Chambers, M.D./DD/HFD-550

7 Page(s) Withheld

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/s/

Libaniel Rodriguez
10/8/04 12:39:16 PM
CHEMIST
AP, amendment to extend expiry to 18 months for DP

Linda Ng
10/8/04 01:52:13 PM
CHEMIST
Complements chem review #3

CHEMISTRY REVIEW

Chemistry Review Data Sheet

NDA 21-665

AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-665

2. REVIEW #: 3

3. REVIEW DATE: 15-SEP-2004

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003
BC	13-JAN-2004
BC	05-FEB-2004
BC	15-JUN-2004
BC	21-JUL-2004
BC	30-JUL-2004
BC	12-AUG-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
DMETS Review	August 29, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticals Inc.
Address:	11570 6th Street Rancho Cucamonga, CA 91730
Representative:	Stephen A. Campbell, Esq.
Telephone:	(909) 980-9484 Ext. 2019

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AMPHADASE™

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: P

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.

10. PHARMACOL. CATEGORY: Proteolytic enzyme

11. DOSAGE FORM: Hyaluronidase injection

12. STRENGTH/POTENCY: 150 USP Units/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous, 150 USP units/injection

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__ SPOTS product – Form Completed

_____ Not a SPOTS product

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

Hyaluronidase is a protein — composed of — with apparent molecular weights of — respectively. Based on the aminoacid sequence, the applicant reports the molecular weight of the enzyme a—

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	/	/	4	N/A	N/A	This product has an NF monograph
—	III	—	/	4	N/A	N/A	
—	III	/	/	4	N/A	N/A	

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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	6343	Wydase referenced through Section 505(b)(2) of the FDA Food , Drug and Cosmetic Act

18. STATUS:

CONSULTS/ CMC	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

RELATED REVIEWS			
Biometrics			
EES	Acceptable	JUL-20-2004	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Sent	SEP-15-2004	
OPDRA			
EA	Acceptable (Categorical Exclusion)	Review #1 11-DEC-2003	L. Rodriguez
Microbiology	Approval	18-Nov-2003	Dr. B. Riley

The Chemistry Review for NDA 21-665

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended as **approval.**

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

None

II. Summary of Chemistry Assessments

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

The drug product AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL — glass — vial, with a — — rubber stopper and a flip off — aluminum cap. This product was formulated to be the equivalent of the presently discontinued Wydase®. It contains the enzyme hyaluronidase, 150 USP Units/mL, sodium chloride, edetate disodium — ,calcium chloride — ,thimerosal, monobasic sodium phosphate — — batches of Amphadase — each, were manufactured for stability studies in support of this application. The components of the drug product are — —

The drug substance (bovine hyaluronidase) is extracted from — oovine testes. The testes are obtained from herds — . Crude hyaluronidase is obtained within ten days of collection of the testes and shipped for refinement to the — The crude material arrives to — accompanied by a — CERTIFICATE" issued by the — The certificate states that 1) the hyaluronidase comes from healthy cattle from non-infected areas 2) the cattle is of chinese origin only and 3) that the processing facility does not receive, store or process any ruminate material from BSE countries. Each animal is examined by a veterinarian before slaughter.

The drug substance (bovine hyaluronidase) is a mixture composed approximately of — proteins — impurities. The — impurities are: —

The molecular weight, as claimed in the application, is , as determined from the aminoacid sequence(s). However, further characterization conducted during the review cycle indicates that the protein mixture is composed of the drug substance , and approximately impurities. The apparent molecular weights of the are, The impurities do not interfere with the hyaluronidaze activity as demonstrated by

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

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic C_{1-4} bond of the glucosamine moiety.

Amphadase™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial with a grey rubber stopper and an aluminum flip off seal. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical dose of 150 USP units. Other than aseptical removal the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated by mixing with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is 5°C ± 3°C. Based on the stability data submitted, the retest period for the drug substance is recommended to be twelve months. For the drug product the recommended expiry is twelve months. The retest and expiry periods are less than requested for each by the firm.

C. Basis for Approvability or Not-Approval Recommendation

A variety of issues and deficiencies raised during the review cycle were resolved satisfactorily by the applicant.

Updated stability data will also be submitted for the purpose of extending retest and shelf life expiry.

This addendum (review # 3) deals with the recommendation issued by DMETS and DDMAC about trade name and labeling.

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez Ph.D., Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Ph.D., Review Chemist/14-SEP-2004
Linda Ng ,Ph.D., ChemistryTeamLeader/14-SEP-2004
Mike Puglisi, ProjectManager/14-SEP-2004

C. CC Block

HFD-550/division file/NDA 21665
Wiley Chambers, M.D./DD/HFD-550

3 Page(s) Withheld

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/s/

Libaniel Rodriguez
9/15/04 11:40:28 AM
CHEMIST
adendum, labeling consult from DMETS

Linda Ng
9/20/04 03:04:48 PM
CHEMIST

NDA 21-665

AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-665

2. REVIEW #: 2

3. REVIEW DATE: 20-AUG-2004

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC	13-JAN-2004
BC	05-FEB-2004
BC	15-JUN-2004
BC	21-JUL-2004
BC	30-JUL-2004
BC	12-AUG-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticals Inc.
Address:	11570 6th Street Rancho Cucamonga, CA 91730
Representative:	Stephen A. Campbell, Esq.
Telephone:	(909) 980-9484 Ext. 2019

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AMPHADASE™
b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: P

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.

10. PHARMACOL. CATEGORY: Proteolytic enzyme

11. DOSAGE FORM: Hyaluronidase injection

12. STRENGTH/POTENCY: 150 USP Units/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous, 150 USP units/injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__SPOTS product – Form Completed

_____Not a SPOTS product

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

Hyaluronidase is a protein — composed of — with apparent molecular weights of — respectively. Based on the aminoacid sequence, the applicant reports the molecular weight of the enzyme at —

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III			4	N/A	N/A	This product has an NF monograph
—	III	—		4	N/A	N/A	
—	III			4	N/A	N/A	

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[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	6343	Wydase referenced through Section 505(b)(2) of the FDA Food , Drug and Cosmetic Act

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	JUL-20-2004	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Ready to be sent to the FDA laboratory.		
OPDRA			
EA	Acceptable (Categorical Exclusion)	Review #1 11-DEC-2003	L. Rodriguez
Microbiology	Approval	18-Nov-2003	Dr. B. Riley

The Chemistry Review for NDA 21-665

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended as **approval.**

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

None

II. Summary of Chemistry Assessments

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

The drug product AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL — glass. — vial, with a — — rubber stopper and a flip off — aluminum cap. This product was formulated to be the equivalent of the presently discontinued Wydase®. It contains the enzyme hyaluronidase, 150 USP Units/mL, sodium chloride, edetate disodium — ,calcium chloride — ,thimerosal, monobasic sodium phosphate — — — batches of Amphadase. — each, were manufactured for stability studies in support of this application. The components of the drug product are — —

The drug substance (bovine hyaluronidase) is extracted from — bovine testes. The testes are obtained from herds — Crude hyaluronidase is obtained within ten days of collection of the testes and shipped for refinement to the — The crude material arrives to — accompanied by a — CERTIFICATE" issued by the — — The certificate states that 1) the hyaluronidase comes from healthy cattle from non-infected areas 2) the cattle is of chinese origin only and 3) that the processing facility does not receive, store or process any ruminate material from BSE countries. Each animal is examined by a veterinarian before slaughter.

The drug substance (bovine hyaluronidase) is a mixture composed approximately of — proteins — , and — impurities. The — impurities are: —

— The molecular weight, as claimed in the application, is — , as determined from the aminoacid sequence(s). However, further characterization conducted during the review cycle indicates that the protein mixture is composed of the drug substance, — ,, and approximately — impurities. The apparent molecular weights of the of — , are. — The — impurities do not interfere with the hyaluronidaze activity as demonstrated by —

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

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic C_{1-4} bond of the glucosamine moiety.

Amphadase™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial with a grey rubber stopper and an aluminum flip off seal. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical dose of 150 USP units. Other than aseptical removal the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated by mixing with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is 5°C ± 3°C. Based on the stability data submitted, the retest period for the drug substance is recommended to be — s. For the drug product the recommended expiry is twelve months. The retest and expiry periods are less than — requested for each by the firm.

C. Basis for Approvability or Not-Approval Recommendation

A variety of issues and deficiencies raised during the review cycle were resolved satisfactorily by the applicant. Amphastar intends to submit Freeze thaw cycles data for the drug product in the future, with the purpose of removing the "DO NOT FREEZE" warning from all the labeling. Updated stability data will also be submitted for the purpose of extending retest and shelf life expiry.

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez Ph.D., Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Ph.D., Review Chemist/20-AUG-2004
Linda Ng ,Ph.D., ChemistryTeamLeader/20-AUG-2004
Mike Puglisi, ProjectManager/20-AUG-2004

C. CC Block

HFD-550/division file/NDA 21665
Wiley Chambers, M.D./DD/HFD-550

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/s/

Libaniel Rodriguez
8/20/04 11:06:34 AM
CHEMIST
Amphadase 150 USP units/mL. AP

Linda Ng
8/20/04 11:43:44 AM
CHEMIST

NDA 21-665

Amphadase™ (hyaluronidase injection, USP)
Bovine

Amphastar Pharmaceuticals, Inc.

Stephen Moore, Ph.D.
Division of Metabolic and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-665

2. REVIEW #: 2

3. REVIEW DATE: July 19, 2004

4. REVIEWER: Stephen Moore, Ph.D., Chemistry Team Leader, ONDC/DNDCII, DMEDP (HFD-510)

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED: Viral clearance studies only

Submission(s) Reviewed	Document Date
Original Submission	06-JUN-2003
Amendments	28-OCT-2003
	07-NOV-2003
	18-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticald, Inc.
Address:	11570 6th Street Rancho Cucamonga CA 91730

CHEMISTRY REVIEW

REVIEW NOTE

Representative: Contact: Stephen A. Campbell, Esq.
Senior Vice President Regulatory Affairs

Telephone: 909-980-8296

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Amphadase™
b) Non-Proprietary Name (USAN): Hyaluronidase Injection, USP, Bovine
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- **Chem. Type: 1 (New Molecular Entity)**
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Adjuvant to increase absorption and dispersion of other injected drugs and other indications (see primary chemistry review)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/1 ml

13. ROUTE OF ADMINISTRATION: S.C.

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___X___SPOTS product – Form Completed

_____Not a SPOTS product

REVIEW NOTE

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See primary chemistry review.

17. RELATED/SUPPORTING DOCUMENTS: See primary chemistry review.

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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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")

REVIEW NOTE

[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

18. STATUS: See primary chemistry review.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

REVIEW NOTE

The Chemistry Review for NDA 21-665

Consultative Review for Viral Clearance Studies

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From this consultative CMC reviewer's viewpoint.this application can be APPROVED (AP) with respect to the information provided for the viral clearance studies. See primary chemist's review for overall CMC recommendation.

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

II. Summary of Chemistry Assessments

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

See primary chemist's review.

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

See primary chemist's review.

C. Basis for Approvability or Not-Approval Recommendation

This consultative reviewer's recommendation is based on the finding of satisfactory CMC information regarding the viral clearance studies provided by the Applicant. See primary chemist's review for basis of overall CMC recommendation.

REVIEW NOTE

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Stephen Moore, Ph.D., Chemistry Team Leader, ONDC/DNDCII DMEDP (HFD-510)
ChemistryTeamLeaderName/Date:
ProjectManagerName/Date:

C. CC Block

Linda Ng, Ph.D., Chemistry Team Leader, ONDC/DNDCIII, DAAOPD (HFD-550)
Libaniel Rodriguez, Ph.D., Primary Chemistry Reviewer, ONDC/DNDCIII, DAAOPD (HFD-550)
Michael Puglisi, Project Manager, DAAOPD (HFD-550)

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/s/

Stephen Moore
7/19/04 06:56:59 PM
CHEMIST

NDA 21-665

Amphadase™ (hyaluronidase injection, USP)
Bovine

Amphastar Pharmaceuticals, Inc.

Stephen Moore, Ph.D.
Division of Metabolic and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-665

2. REVIEW #: 1

3. REVIEW DATE: December 19, 2003

4. REVIEWER: Stephen Moore, Ph.D., Chemistry Team Leader, ONDC/DNDCII, DMEDP (HFD-510)

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED: Viral clearance studies only

Submission(s) Reviewed	Document Date
Original Submission	06-JUN-2003
Amendments	28-OCT-2003
	07-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticald, Inc.
Address:	11570 6th Street Rancho Cucamonga CA 91730

CHEMISTRY REVIEW

REVIEW NOTE

Representative: Contact: Stephen A. Campbell, Esq.
Senior Vice President Regulatory Affairs

Telephone: 909-980-8296

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Amphadase™
b) Non-Proprietary Name (USAN): Hyaluronidase Injection, USP, Bovine
c) Code Name/# (ONDC only)
d) Chem. Type/Submission Priority (ONDC only):

- **Chem. Type: 1 (New Molecular Entity)**
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Adjuvant to increase absorption and dispersion of other injected drugs and other indications (see primary chemistry review)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/1 ml

13. ROUTE OF ADMINISTRATION: S.C.

14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__ SPOTS product – Form Completed

_____ Not a SPOTS product

REVIEW NOTE

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See primary chemistry review.

17. RELATED/SUPPORTING DOCUMENTS: See primary chemistry review.

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[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")

REVIEW NOTE

[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

18. STATUS: See primary chemistry review.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

REVIEW NOTE

The Chemistry Review for NDA 21-665

Consultative Review for Viral Clearance Studies

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From this consultative CMC reviewer's viewpoint.this application is APPROVABLE (AE) with respect to the information provided for the viral clearance studies. See primary chemist's review for overall CMC recommendation.

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

II. Summary of Chemistry Assessments

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

See primary chemist's review.

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

See primary chemist's review.

C. Basis for Approvability or Not-Approval Recommendation

This consultative reviewer's recommendation is based on the finding of unsatisfactory CMC information regarding the viral clearance studies provided by the Applicant. See Draft Deficiency Letter. See primary chemist's review for basis of overall CMC recommendation.

REVIEW NOTE

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Stephen Moore, Ph.D., Chemistry Team Leader, ONDC/DNDCII DMEDP (HFD-510)
ChemistryTeamLeaderName/Date:
ProjectManagerName/Date:

C. CC Block

Linda Ng, Ph.D., Chemistry Team Leader, ONDC/DNDCIII, DAAOPD (HFD-550)
Libaniel Rodriguez, Ph.D., Primary Chemistry Reviewer, ONDC/DNDCIII, DAAOPD (HFD-550)
Michael Puglisi, Project Manager, DAAOPD (HFD-550)

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/s/

Stephen Moore
12/19/03 04:53:13 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-665

AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-665

2. REVIEW #:1

3. REVIEW DATE: 11-Dec-2003

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Amphastar Pharmaceuticals Inc.
Address:	11570 6th Street Rancho Cucamonga, CA 91730
Representative:	Stephen A. Campbell, Esq.
Telephone:	(909) 980-9484 Ext. 2019

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AMPHADASE™
b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.

10. PHARMACOL. CATEGORY: Proteolytic enzyme

11. DOSAGE FORM: Hyaluronidase injection

12. STRENGTH/POTENCY: 150 USP Units/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous; 150 USP units/injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__SPOTS product – Form Completed

_____Not a SPOTS product

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

Hyaluronidase is a protein — composed of — with apparent molecular weights of . Based on the aminoacid sequence, the applicant reports the molecular weight of the enzyme at —

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	/	/	4	N/A	N/A	This product has an NF monograph
—	III	/	/	4	N/A	N/A	
—	III	/	/	4	N/A	N/A	

[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	6343	Wydase referenced through Section 505(b)(2) of the FDA Food , Drug and Cosmetic Act

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending		
OPDRA			
EA			
Microbiology	Approval	18-Nov-2003	Dr. B. Riley

The Chemistry Review for NDA 21-665

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended as **approvable** upon satisfactory resolution of CMC issues.

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

None

II. Summary of Chemistry Assessments

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

The drug product AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL — glass — vial, with a — — rubber stopper and a flip off — aluminum cap. This product was formulated to be the equivalent of the presently discontinued Wydase®. It contains the enzyme hyaluronidase, 150 USP Units/mL, sodium chloride, edetate disodium — ,calcium chloride — ,thimerosal, monobasic sodium phosphate — — — batches of Amphadase, — each, were manufactured for stability studies in support of this application. The components of the drug product are —

—

The drug substance (bovine hyaluronidase) is extracted from — bovine testes. The testes are obtained from herds — .. Crude hyaluronidase is obtained within ten days of collection of the testes and shipped for refinement to the — The crude material arrives to accompanied by a "CERTIFICATE" Issued by the The certificate states that 1) the hyaluronidase comes from healthy cattle from non-infected areas 2) the cattle is — and 3) that the processing facility does not receive store or process any ruminate material from BSE countries.

The drug substance (bovine hyaluronidase) is a mixture composed approximately of — proteins — The molecular weight, as claimed in

the application, is — as determined from the aminoacid sequence(s). However, further characterization conducted during the review cycle indicates that the protein mixture is composed of the drug substance — and approximately — impurities. The apparent molecular weights of the — are, — The — impurities do not interfere with the hyaluronidaze activity as demonstrated by —

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic C_{1-4} bond of the glucosamine moiety.

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

Amphadase, ™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical 150 USP units. Other than aseptically remove the flip off cap and withdrawing of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated mixed with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is 5°C ± 3°C. Based on the stability data submitted, the retest period for the drug substance is recommended to be —. For the drug product the recommended expiry is —. The retest and expiry periods are less than the firm requested.

C. Basis for Approvability or Not-Approval Recommendation

Many information requests were sent to the applicant and some issues were resolved and summarized in this review. Some issues remain outstanding, for example, drug substance composition, drug substance specification, drug substance stability, drug product specification and stability.

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Review Chemist/11-DEC-2003
Linda Ng, ChemistryTeamLeader/11-DEC-2003
Mike Puglisi, ProjectManager/11-DEC-2003

C. CC Block

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/s/

Libaniel Rodriguez
12/16/03 02:23:08 PM
CHEMIST
approvable

Linda Ng
12/16/03 04:26:00 PM
CHEMIST