CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-903

CHEMISTRY REVIEW(S)

NDA 21-903

NeoProfen™ (ibuprofen lysine) Injection

Farmacon-IL, LLC

Monica D. Cooper, Ph.D.
Division of Cardiovascular and Renal Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-903

2. REVIEW #: **2**

3. REVIEW DATE: 23-Feb-2006

4. REVIEWER: Monica D. Cooper, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Pre-Submission (M000)	13-Apr-2005
Amendment (M001 BC)	13-Apr-2005
Amendment (M002 C)	27-Apr-2005
Amendment (M004 C)	27-Jun-2005
Amendment (M006 C)	12-Jul-2005
Amendment (M007 C)	15-Jul-2005
Amendment (M008 C)	21-Jul-2005
Amendment (M010 C)	30-Aug-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission (N000) – Labeling	30-Aug-2005
Amendment (N000 BC)	19-Sep-2005
Amendment (N000 BC)	16-Nov-2005
Amendment (N000 BC)	12-Jan-2006
Amendment (N000 C)	17-Jan-2006
Amendment (N000 BC)	18-Jan-2006
Amendment (N000 BC)	30-Jan-2006
Amendment (N000 BC)	09-Feb-2006
Amendment (N000 BC)	13-Feb-2006
Amendment (N000 BC)	14-Feb-2006
Amendment (N000 BC)	21-Feb-2006
Amendment (N000 BC)	23-Feb-2006

7. NAME & ADDRESS OF APPLICANT:

Name	Farmacon-IL, LLC
Address	1071 Post Road East, Westport, CT 06880-5361
Representative	Laszlo L. Darko, Ph.D.
Telephone	203-222-8801

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	NeoProfen™
Non-Proprietary Name (USAN)	Ibuprofen Lysine
Code Name	Ibuprofen L-Lysinate
Chemistry Type	2
Submission Priority	P

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

10. PHARMACOL. CATEGORY: Early Treatment of Patent Ductus Arteriosus (PDA)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg/mL as (±) ibuprofen

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

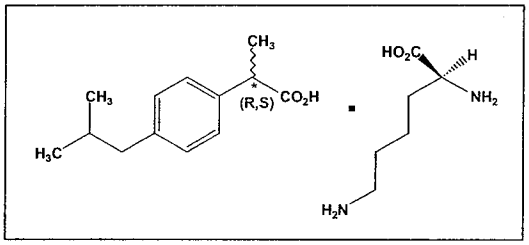
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Chemical Name:

1) L-Lysine, mono[α-methyl-4-(2-methylpropyl)benzeneacetate]
2) Benzeneacetic acid, α-methyl-4-(2-methylpropyl)-, L-lysine (1:1)



Molecular Formula: $C_{19}H_{32}N_2O_4$
MW = 352.48
CAS = 57469-77-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	18-Jun-2005	Reviewed by Y. Amin
	II			3	Adequate	30-Apr-1997	Reviewed by P. Dietze
	III			4	N/A	---	---
	III			3	Adequate	01-Jun-2004 and 10-Jul-2003	Reviewed by R. Madurawe and D. Lewis
	V			1	Adequate	14-Feb-2006	Reviewed for Microbiology by R. Mello

[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
IND Application	IND 59,778 (N000)	Sponsor: Farmacon IL, LLC Stamp Date: 27-Jan-2000

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	17-Jun-2005	S. Adams, J. D'Ambrogio
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	*to be initiated post approval*	----	----
DMETS	Trade Name: NeoProfen™ is Acceptable	06-Jan-2006	C. Holquist (in Meeting Minutes)
EA	Categorical Exclusion Acceptable	14-Feb-2006	M. Cooper
Microbiology	Adequate	14-Feb-2006	R. Mello

The Chemistry Review for NDA 21-903

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (21-903) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All deficiencies identified in the NDA have been resolved.

The action letter should state –

- ***A retest date of*** [redacted] ***is recommended*** for the drug substance when stored at controlled room temperature.
- ***An expiration date of 24 months is granted for the drug product*** when stored at controlled room temperature (20 – 25°C with excursions permitted to 15 – 30°C), ***protected from light.***

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

There are no Phase 4 commitments, agreements, or risk management steps.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug product, NeoProfen™ is a clear, colorless, sterile, aqueous solution for intravenous injection containing 17.1 mg/mL of (±)-ibuprofen-L-lysine (equivalent to 10 mg/mL of (±)-ibuprofen) in Water for Injection, USP. The solution is neutral, non-buffered, [redacted] There are no additional excipients with the exception of [redacted] produced upon pH adjustment to neutrality. The formulation does not contain antimicrobial preservatives. The drug product is packaged in single-use, 2-mL glass vials with gray rubber stopper closures and aluminum seals with flip-off caps. The applicant has proposed supplying NeoProfen™ in a carton containing 3 vials, which is a supply consistent with the recommended first course of treatment. The application provided for a single strength (10 mg/mL ibuprofen) of the drug product. Each vial contains 2 mL of solution with a total of 34.18 mg of ibuprofen lysine salt (20.0 mg ibuprofen). Farmacon-IL proposed storage of the drug product at room temperature. A stability update to support the storage condition and proposed expiration date was submitted mid-review and supports a 24-month expiration

date for the drug product when stored at controlled room temperature, protected from light. The applicant indicated that NeoProfen™ has not been marketed previously, although a similar ibuprofen formulation, Imbun®, is commercially available in Europe. The Imbun® product is also an ibuprofen lysine salt but is distinguished by containing racemic lysine as the amine component in place of L-lysine. The European formulation also contains a weight equivalent of mannitol as an excipient. Ibuprofen as the free acid is marketed widely worldwide and in the US as tablets, oral suspensions, and drops. Ibuprofen potassium is also marketed in the US in liquid-gel capsules.

The drug substance, (±)-ibuprofen-L-lysine (1:1), is a white solid salt which contains [redacted] and has been shown to undergo slight discoloration, from white to pale yellow, upon storage. Data were provided during the review demonstrating the hygroscopicity of the drug substance, which appears to reach a plateau at approximately [redacted] Additional characterization data were also provided during the review; however, the applicant was unable to determine whether the changes observed in differential scanning calorimetry (DSC) were the result of a change in physical form [redacted] The drug substance is prepared by a simple [redacted] The resulting material is isolated as a 1:1 mixture of salt diastereomers. The effect of precipitation rate and time on the diastereomeric ratio has not been studied. The drug substance is chiral and has a measurable optical rotation. A 1:1 mixture of ibuprofen enantiomers in the drug substance has been confirmed by chiral HPLC and is controlled in the drug substance by specification. Notably, the two enantiomers are known to interconvert *in vivo* via their respective CoA thio-esters with the S-isomer being the pharmacologically active form. The drug substance is stored [redacted] A significant increase in impurities has not been detected upon storage. Additional stability data were submitted during the review cycle and the applicant proposed a [redacted] retest date for the bulk drug substance when stored at room temperature. ***A retest date of [redacted] is recommended for the bulk drug substance when stored at controlled room temperature.***

B. Description of Intended Use of Drug Product

NeoProfen™ is indicated for [redacted] The recommended first course treatment regime is defined as three intravenous doses. NeoProfen should be prepared for infusion and infused continuously over a period of 15 minutes. NeoProfen may be diluted with either Normal Saline (NS) or Dextrose (D5W). The diluted drug should be used within 30 minutes of preparation. The doses are patient weight-based with an initial dose of 10 mg/kg and two follow-up doses of 5 mg/kg, each dose separated by a 24 hr period. If the ductus arteriosis significantly closes, a second course of treatment is recommended. The drug product is packaged in single-use, 2-mL glass vials with gray rubber stopper closures and aluminum

seals with flip-off caps. The applicant originally proposed expiration date for the drug product. However, data are not available to support this initial proposal. Additional stability data were submitted during the review cycle and the applicant revised their proposal to a 24-month expiration date. The data will support the revised proposal. ***Thus, a 24-month expiration date is granted for the drug product when stored under controlled room temperature conditions, protected from light.***

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (21-903) is recommended for **APPROVAL**. There are no outstanding issues with regard to chemistry, manufacturing, and controls.

III. Administrative

A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D.

B. Endorsement Block

Chemist Name:	Monica D. Cooper, Ph.D.
Chemistry Team Leader Name:	Kasturi Srinivasachar, Ph.D.
Project Manager Name:	Daryl Allis

C. CC Block

Orig. NDA 21-903
HFD-110/Division File

52 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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/s/

Monica Cooper
2/23/2006 05:18:32 PM
CHEMIST

Kasturi Srinivasachar
2/24/2006 03:25:38 PM
CHEMIST

NDA 21-903

NeoProfen™ (ibuprofen lysine) Injection

Farmacon-IL, LLC

Raj N. Misra, Ph.D.
Division of Cardiovascular and Renal Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-903

2. REVIEW #: **1**

3. REVIEW DATE: 27-Oct-2005 (revised: 03-Feb-2006)

4. REVIEWER: Raj N. Misra (with minor revisions by Monica D. Cooper)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission	Document Date
CMC Pre-Submission (M000)	13-Apr-2005
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Name: Farmacon-IL, LLC

Address: 1071 Post Road East, Westport, CT 06880-5361

Representative: Laszlo L. Darko, Ph.D.

Telephone: 203.222.8801

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: NeoProfen™
   b) Non-Proprietary Name (USAN): Ibuprofen Lysine
   c) Code Name/#: Ibuprofen L-Lysinate
   d) Chem. Type/Submission Priority:
      - Chem. Type: 2
      - Submission Priority: Priority

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

10. PHARMACOL. CATEGORY: Early Treatment of Patent Ductus Arteriosus (PDA)

11. DOSAGE FORM: Injection

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14. Rx/OTC DISPENSED: X Rx ___OTC

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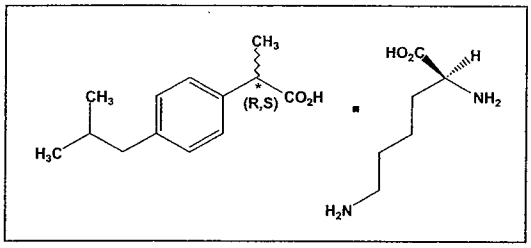

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[redacted]	III	[redacted]		4	N/A	---	---
[redacted]	III	[redacted]		3	Adequate	01-Jun-04 and 10-Jul-03	Reviewed by R. Madurawe and D. Lewis
[redacted]	V	[redacted]		1	Pending	---	Microbiology Review (by R. Mello)

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Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	*to be initiated post approval*	----	----
DMETS	Trade Name: NeoProfen™ is Acceptable	06-Jan-2006	C. Holquist (in Meeting Minutes)
EA	Categorical Exclusion Requested		Pending (see CMC Review #2)
Microbiology	Pending		R. Mello

The Chemistry Review for NDA 21-903

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (21-903) is recommended as **APPROVABLE** from the perspective of chemistry, manufacturing, and controls. Information requests/deficiency letters were sent to the applicant outlining the information that is needed to complete this application (see Information Request Letters at the end of this review and in CMC Review #2). The applicant's responses to the IR letters will be evaluated in CMC Review #2.

A consult to Microbiology is currently PENDING.

The overall evaluation from the Office of Compliance for cGMP compliance is ACCEPTABLE. The Establishment Evaluation Report is attached at the end of this review.

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

There are no Phase 4 commitments, agreements, or risk management steps.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug product, NeoProfen™ is a clear, colorless, sterile, aqueous solution for intravenous injection containing 17.1 mg/mL of (±)-ibuprofen-L-lysine (equivalent to 10 mg/mL of (±)-ibuprofen) in Water for Injection, USP. The solution is neutral, non-buffered, [redacted] There are no additional excipients with the exception of [redacted] produced upon pH adjustment to neutrality. The formulation does not contain antimicrobial preservatives. The drug product is packaged in single-use, 2-mL glass vials with gray rubber stopper closures and aluminum seals with flip-off caps. The applicant has proposed supplying NeoProfen™ in a carton containing 3 vials, which is a supply consistent with the recommended first course of treatment. The application provided for a single strength (10 mg/mL ibuprofen) of the drug product. Each vial contains 2 mL of solution with a total of 34.18 mg of ibuprofen lysine salt (20.0 mg ibuprofen). Farmacon-IL proposed storage of the drug product at room temperature. A stability update to support the storage condition and proposed expiration date was submitted mid-review and will be evaluated in CMC Review #2. The applicant indicated that NeoProfen™ has not been marketed previously, although a similar ibuprofen formulation, Imbun®, is commercially available in Europe. The Imbun® product is also an ibuprofen lysine salt but is distinguished by containing racemic lysine as the amine component in place of L-lysine. The European formulation also contains a weight equivalent of mannitol as an excipient. Ibuprofen as the free acid is marketed widely worldwide and in the US as tablets, oral suspensions, and drops. Ibuprofen potassium is also marketed in the US in liqui-gel capsules.

The drug substance, (±)-ibuprofen-L-lysine (1:1), is a white solid salt which contains [redacted] and has been shown to undergo slight discoloration, from white to pale yellow, upon storage. The nature and stoichiometry of the [redacted] was not well-characterized in the original CMC submissions. The identity of the drug substance has been confirmed by physical and spectroscopic methods although the characterization is not comprehensive. Notably, crystallinity and polymorph data for the drug substance were not included in the original CMC submissions. The drug substance is prepared by a simple [redacted]. The resulting material is isolated as a 1:1 mixture of salt diastereomers. The effect of precipitation rate and time on the diastereomeric ratio has not been studied. The drug substance is chiral and has a measurable optical rotation. A 1:1 mixture of ibuprofen enantiomers in the drug substance has been confirmed by chiral HPLC and is controlled in the drug substance by specification. Notably, the two enantiomers are known to interconvert *in vivo* via their respective CoA thio-esters with the S-isomer being the pharmacologically active form. The drug substance is stored in [redacted]. Notably, the drug substance, in addition, to undergoing slight discoloration from white to pale yellow upon storage, also tends to absorb moisture and undergo changes by differential scanning calorimetry (DSC). These changes were not well-characterized and their significance was not established in the original CMC submissions. A significant increase in impurities has not been detected upon storage. A stability update to support the proposed retest date and bulk storage at room temperature was submitted mid-review and will be evaluated in CMC Review #2.

B. Description of Intended Use of Drug Product

NeoProfen™ is indicated for [redacted]. The recommended first course treatment regime is defined as three intravenous doses. NeoProfen should be prepared for infusion and infused continuously over a period of 15 minutes. NeoProfen may be diluted with either Normal Saline (NS) or Dextrose (D5W). The doses are patient weight-based with an initial dose of 10 mg/kg and two follow-up doses of 5 mg/kg, each dose separated by a 24 hr period. If the ductus arteriosis significantly closes, a second course of treatment is recommended. The drug product is packaged as single-use, 2-mL glass vials with gray rubber stopper closures and aluminum seals with flip-off caps. The applicant originally proposed a [redacted] expiration date for the drug product. However, data are not available to support this proposal. Additional stability data were submitted in amendments during the review cycle. These data will be evaluated and a final expiration date will be recommended in CMC Review #2.

C. Basis for Approvability or Not-Approval Recommendation

The "approvable" recommendation is based on noted concerns and deficiencies in the chemistry, manufacturing, and controls section of this NDA. Information requests were sent to the applicant outlining the concerns and deficiencies that should be addressed to ensure the safety and quality of the drug product. This application is recommended as "approvable" rather than "not approvable" because the applicant should be able to resolve the deficiencies readily. Farmacon-IL's responses to the IR letters will be evaluated in CMC Review #2.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name:	Raj N. Misra, Ph.D. (with minor revisions by Monica D. Cooper, Ph.D.)
Chemistry Team Leader Name:	Kasturi Srinivasachar, Ph.D.
Project Manager Name:	Daryl Allis

C. CC Block

Orig. NDA 21-903
HFD-110/Division File

36 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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/s/

Monica Cooper
2/3/2006 08:56:00 PM
CHEMIST
On Behalf of Raj Misra

Kasturi Srinivasachar
2/8/2006 05:47:57 PM
CHEMIST