NDA 21-977

NRP 104
(lisdexamfetamine dimesylate)

New River Pharmaceuticals, Inc.

DIVISION OF PSYCHIATRY DRUG PRODUCTS

Lyudmila N. Soldatova, Ph.D.
DPA I/ONDQA

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 21-977

2. REVIEW #: 4

3. REVIEW DATE: February 14, 2007

4. REVIEWER: Lyudmila N. Soldatova, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	20-SEP-2006
Review #2	22-SEP-2006
Review #3	08-DEC-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	26-DEC-2006
Amendment	07-FEB-2007
Amendment	08-FEB-2007
Amendment	09-FEB-2007
Amendment	12-FEB-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	New River Pharmaceuticals, Inc.
Address:	1861 Pratt Drive, Suite 1090, Blacksburg, VA 24060
Representative:	Suma Krishnan, Vice President Product Development

Telephone: (540) 953-0237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN and INN): Lisdexamfetamine Dimesylate
c) Code Name/# (ONDC only): NRP 104
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: For the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 30mg, 50mg and 70mg

13. ROUTE OF ADMINISTRATION: Oral

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:

USAN/INN: Lisdexamfetamine Dimesylate

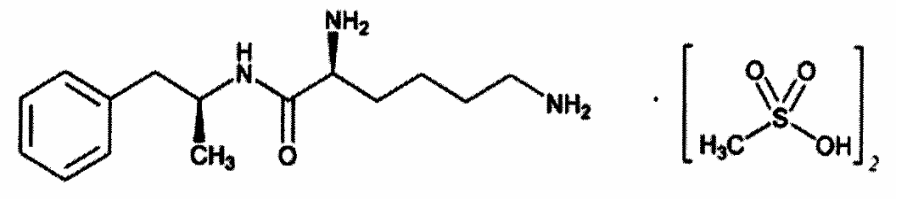
Chemistry Review Data Sheet

Chemical Name: (2S)-2,6-Diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate.

Chemical Formula: $C_{15}H_{25}N_3O\bullet(CH_4O_3S)_2$
Molecular Weight: 455.60

CAS registry #: 608137-32-3 (dimesylate salt)

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
--------	II	---- - ---- ---- -- -------- ------	--------- --- ------ --- ------- ----- ------	3	Adequate	17-NOV-2005 (Review #4 by Dr. A. Mueller; latest amend-ment dated 05-Jul-2005)	-- -- --- --- -- -
-------	II	----- - -------	--------- --- ------ --- ------- ----- ------	3	Adequate Inadequate	17-MAY-2005 (Review #9 by Dr. Skanchy; amendment dated 4/18/2005) 11-JUL-2006 (Review #10 by Dr. Zh. Sun; latest amend-ment dated 5/08/2006)	-- -- --- --- -- -
--------	II	----- - -------	---------- ------ --- ----	3	Adequate	18-JUN-2002 Review #3 by Dr. Furness; amendment dated 4/05/2002	-- ----- ------- ------ -- -- ------ ---- - ----- ------ - ----

[redacted]	III	[redacted]	[redacted]	3	Adequate	19-SEP-2000 (Review #21 by Dr. Donald Klein)	[redacted]
[redacted]	III	[redacted]	[redacted]	3	Adequate	25-APR-2002 (Review #1 by Dr. Jila Boal)	[redacted]

[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 relevant revisions 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	67,482	Commercial IND (ADHD)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Data supported the efficacy of NRP104	27-JUL-06	Yeh-Fong Chen, Ph.D.
Clinical	Application may be approved when agreement is reached on product labeling.	25-JAN-07	Michelle M. Chuen, M.D.
EES	Acceptable	15-MAY-06	
Pharm/Tox	Approvable; issue with the lowering of the specification for [redacted] is resolved by CMC reviewer (refer to	21-SEP-06	Ikram Elayan, Ph.D.

	Attachment 3, Review #4)		
Biopharm	Final dissolution method and specifications recommended by OCP, and were accepted by NRP on 2/1/07	30-JAN-07	Andre Jackson, Ph.D.
LNC	USAN available	NA	NA
Methods Validation	Acceptable Methods will not be sent to FDA Labs.	As per this review	Lyudmila N. Soldatova, Ph.D.
DMETS	Acceptable	30-NOV-06	Linda Wisniewski
EA	Acceptable, categorical exclusion granted as per information from New River Pharmaceuticals in this NDA	As per this review	Lyudmila N. Soldatova, Ph.D.
Microbiology	N/A		
CSS	--- ---------- - ---- ---------- ---------- ---------- -- -- -------- - - -------- ------ --- - ---- ---	12-SEP-06	Katherine Bonson, Ph.D.

The Chemistry Review for NDA 21-977

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-977 for NRP 104 (lisdexamfetamine dimesylate) Capsules is recommended APPROVAL from the CMC standpoint. The ---------- of retest period for drug substance batches manufactured at both manufacturing sites, ---------- ---- ----------, is granted. The 24-month expiration date for NRP104 capsules, 30 mg (manufactured using ----- -------), 50 mg and 70 mg packaged as 100 ct in 60 cc/------- bottles is granted.

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

None as per this review.

II. Summary of Chemistry Assessments

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

BACKGROUND

Lisdexamfetamine dimesylate (NRP104) is a small molecule (New Chemical Entity), a pro-drug that is being developed by New River Pharmaceuticals Inc. as a once-a-day treatment for attention deficit hyperactivity disorder (ADHD) in pediatric populations (ages 6-12). The sponsor claims lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive. When taken orally the amide linkage is metabolically hydrolyzed in the gastrointestinal tract, releasing active d-amphetamine. The applicant submitted the original IND 67,482 for NRP104 for treatment of ADHD and was allowed to proceed on April 23, 2004.

DRUG PRODUCT

NRP104 Capsules will be available in three immediate release dosage strengths: 30 mg, 50 mg, and 70 mg, with administration as once-a-day in the morning. A maximum daily dose of 70 mg is proposed. The applicant has not selected a preferred trade name at the time of the NDA resubmission and hence the code name NRP104 is used throughout the submission. **The trade name Vyvanse was considered acceptable by DMETS on November 30, 2006.** The NRP104 Capsules are comprised of common excipients: microcrystalline cellulose (NF), croscarmellose sodium (NF), magnesium stearate (NF), and gelatin capsule size 3. The excipients used in the capsules formulation are of compendial, NF quality. The color of the capsule is dependent on the dosage formulation: **white/orange color – for 30 mg strengths, white/blue – for 50 mg strengths, blue/orange– for 70 mg strength.** The capsule shells contain gelatin, titanium dioxide, and

one or more of the following: D&C Red #28, D&C Yellow #10, FC&C Blue #1 and FD&C Red #40, to discriminate the capsules by color. [redacted] manufactured NRP104 Capsules for clinical use [redacted] and will manufacture commercial product as well [redacted]. The applicant used [redacted] of drug substance in the [redacted] → 30 mg capsule, [redacted] → 50 mg and 70 mg capsule) for manufacture of the registration batches (for clinical supplies). The [redacted] has been added to support the 30 mg strength, so the 30 mg strength is the only strength that can be currently generated from [redacted]. **The applicant is not seeking approval of the drug product manufactured using [redacted].** The commercial drug product will be packaged in 60 cc/100 counts [redacted] bottles. Registration batches executed for clinical supplies have been manufactured with essentially the same process throughout development of the formulation. [redacted]

The release specifications for NRP104 capsules included [redacted]. The applicant was requested to include [redacted] in the release specifications, and acceptance criterion for [redacted] – in the stability specifications during the first review cycle, since this impurity is a potential degradation product. The applicant had complied to this request in their later amendment (24-OCT-06). Acceptable validated analytical methods are provided in the submission. **In the previous review cycle, the NRP was requested to update specification for dissolution of the NRP104 capsules in the commercial release and stability specifications for drug product based on the final dissolution method and specification recommended by the Agency (Q=[redacted]% dissolved in 15 minutes). NRP has accepted the recommended specification Q=[redacted]% in 15 minutes (February 1, 2007) and updated drug product release and stability specifications accordingly. Following the FDA's recommendation, the NRP has made changes to the drug product container labels for 30 mg, 50 mg and 70 mg Vyvanse capsules according to the DMETS request outlined in the AE Letter dated 12/21/2006.**

The [redacted] batches of 30 mg, 50 mg and 70 mg strengths of NRP104 capsules have been manufactured to date in batch sizes ranging from [redacted] capsules to [redacted] capsules. All batches were manufactured at the commercial site, [redacted] The applicant provided Certificates of Analysis (CoAs) for all these batches. The anticipated maximum commercial production scale will be approximately [redacted] capsules per batch.

Originally, the applicant provided [redacted]-month stability data at 25° C/60% RH and 30° C/65% RH, and [redacted]months stability data at 40° C/75% RH for 3 registration batches of each strength, 30 mg (generated from [redacted] drug substance [redacted]), 50 mg and 70 mg capsules produced with drug substance manufactured at [redacted] facility and packaged in 100 ct/60 cc [redacted] bottles. In the same review cycle NRP has provided the 24-month stability data on the registration batches of the NRP 104 capsules 30 mg, 50 mg and 70 mg to further support the 24-months expiration date for the drug product (electronic Amendment dated 19-SEP-06). This data suggested that there was essentially no difference between the assay and related substances (total and single largest) data at release and that reported at 24 months. Based on this real time stability data for the[redacted] registration batches manufactured using drug substance from [redacted] (refer to Review #2, pp. 34, 35), the 24 month expiration date for NRP104 capsules, 30 mg (manufactured using [redacted]), 50 mg and 70 mg packaged as 100 ct in 60 cc/ [redacted] bottles could have been granted when compliance with the final dissolution specifications ([redacted]% dissolution in 15 minutes) will be confirmed. The applicant was requested to provide the 15-minutes dissolution data for all stability batches of NRP104 capsules 30 mg, 50 mg and 70 mg to demonstrate compliance with the final dissolution method and specification recommended by OCP. **In this Amendment (26-DEC-2006), NRP has informed that dissolution profiles for primary stability batches were not generated. NRP has provided 15 and 20 minutes time points from the dissolution profiles of the 1 batch (non-commercial size batches) of each 30 mg strength capsules, 50 mg strength and 70 mg strengths capsules through the [redacted] months storage at 25ºC/60% RH, and through the [redacted]months storage at 40ºC/75% RH. The dissolution profiles for these supportive stability batches demonstrated compliance with specification [redacted]% dissolved in 15 minutes for 50 mg and 70 mg capsules, and the potential compliance with the same specification (when the S2 level will be tested) for the 30 mg capsule batches. Therefore, based on the preliminary evaluation of the 24-month stability data for primary stability batches, and additional information on the 15-minutes dissolution data for supportive batches, the 24-month expiration date for NRP104 capsules, 30 mg (manufactured using [redacted]), 50 mg and 70 mg packaged as 100 ct in 60 cc/[redacted] bottles could be granted. In the Amendment dated 24-OCT-06, applicant provided[redacted]months stability data at 25ºC/60% RH and[redacted]months data at 40ºC/75% for one 30 mg capsule batch manufactured from [redacted]. In response to Agency recommendation (AE Letter dated 12/21/2006) to obtain more manufacturing experience with 30 mg capsules produced from [redacted], and to provide the minimum [redacted]-months long-term stability data for at least three batches, NRP committed to generate additional batches using the [redacted], and place these batches on stability (Amendment dated 26-DEC-2006). The firm has proposed with the Agency agreement that the approval of the NRP104 capsules of any strength manufactured using [redacted] will be made through a post approval process.**

Manufacturing, testing, and packaging sites for drug substance and drug product were found acceptable by the Office of Compliance.

DRUG SUBSTANCE

The drug substance, lisdexamfetamine dimesylate has two chiral centers, [redacted]. Lisdexamfetamine dimesylate is a highly soluble (792 mg/ml in water) amorphous white to off-white powder. [redacted]

[redacted]

[redacted] In this Amendment (12/26/2006), the NRP has provided levels of [redacted] in the drug substance batches of commercial scale ([redacted] manufactured by both suppliers, [redacted] batches) and [redacted] batches), demonstrating the level of [redacted] in all these batches of [redacted] Based on this information, NRP's justification for not including a specification for [redacted] in the drug substance specifications is acceptable. The NRP intended to remove testing of the [redacted] from the NRP104 specifications upon meeting the current specifications for the first [redacted] validation /commercial batches of NRP104. In this Amendment (12/21/2006), NRP has provided [redacted] data for [redacted] commercial/ validation batches at release. These data demonstrate that the [redacted] met the proposed specifications of NMT [redacted] % (area %). NRP should continue testing drug substance for [redacted], and request for discontinuation of testing should be proposed as a post-approval supplement. Sponsor also informed that the [redacted] method is currently optimized at [redacted] and is capable of quantitating the [redacted] with the LOQ of [redacted] That is acceptable, and consistent with the current specifications of [redacted] % for [redacted] including [redacted] On request, NRP has provided validation data for the optimized [redacted] method at [redacted] including LOQ values. The validation data do not support capability of the [redacted] method to reliably quantify [redacted]) at the limit of NMT [redacted]%. NRP proposed to monitor the [redacted] by both the [redacted] methods. The [redacted] method will pick [redacted] and, hence, a specification of NMT [redacted]% will ensure that

level of the [redacted] is below [redacted]%. This approach was found acceptable; respective updates were included in the drug substance release and stability specifications. **NRP's commitment to continue specifying [redacted] as a quality attribute of the drug substance and drug product batches is accepted.**

Commercial drug substance will be manufactured and packaged by [redacted]

[redacted]

The [redacted] months of long term and [redacted] month of accelerated stability data for [redacted] batches manufactured at [redacted] was provided in the original submission. In the Amendment dated 24-OCT-06, the recommendation was made to NRP to provide available long-term stability data for the additional batches manufactured at [redacted] including data for identified and [redacted]. **In this Amendment (26-DEC-06), NRP has updated the stability data up to [redacted] months at 25ºC/60% RH for Batch #1002 manufactured at [redacted] facility, and accelerated stability data for [redacted] months. The [redacted]-month long term stability data generated for [redacted] batch 1002 suggests that NRP104 manufactured at [redacted] is stable at long-term conditions, similar to all batches made at the primary vendor [redacted]) to date. Despite the fact NRP has not provided data for identified impurities in the [redacted] batches at both, long-term and accelerated conditions, the analogous data for the [redacted] batches demonstrate that the identified impurities are most likely, the process impurities, and they do not increase with time.** In addition, the batch release data for [redacted] additional validation/commercial batches at full commercial scale [redacted] manufactured at [redacted] demonstrate that all tested parameters, including data for identified and [redacted], were within the specification limits. **Considering the stability data for one batch of the drug substance manufactured at [redacted] and the similarity of the release data for [redacted] additional validation batches from [redacted], the [redacted] months of retest period for drug substance batches manufactured at [redacted] could be granted, as proposed by the applicant. Based on the [redacted] months stability data provided in the original NDA submission (refer to the Review #1, section S.7.3), [redacted] months of retest period for drug substance batches manufactured at [redacted] could be granted. However, for the purpose of having the identical retest date for the drug substance irrelevant from the specific manufacturing site, the [redacted] months of retest period for drug substance batches manufactured at [redacted] and at [redacted] is granted.**

A "Protect from Light" statement was recommended to add to the labeling of storage packages of the drug substance, since the stress studies demonstrated the photosensitivity of NRP104.

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

NRP 104 (lisdexamfetamine dimesylate) capsules 30 mg, 50 mg and 70 mg will be marketed in 60 cc/100 counts [redacted] bottles. [redacted]l. The maximum recommended daily dose for children is 70 mg/day.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F). Dispense in tight, light-resistant container as defined in USP.

The applicant makes the post-approval stability commitments to place on stability the first three commercial batches for each strength, and, thereafter, at least one batch per year will be placed on stability under long-term conditions through up to [redacted] months.

This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(b).

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-977 for NRP104 capsules is recommended **Approval** status from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Felecia Curtis

C. CC Block

See DFS.

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

/s/

Lyudmila Soldatova
2/14/2007 02:32:16 PM
CHEMIST

Ramesh Sood
2/14/2007 02:42:43 PM
CHEMIST