CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-276

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To:	NDA 22-276
From:	Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date:	23-Jul-2008
Drug:	Nicardipine Hydrochloride Injection
Route of administration:	Intravenous Injection
Strength:	25 mg/10 ml vial
Subject:	**"Approval"** recommendation for NDA 22-276

Introduction: This NDA, submitted by Teva Parenteral Medicines, Inc., is a 505 (b)(2) submission for a new formulation of PDL BioPharma's approved product, Cardene I.V., a calcium channel blocker. Teva's Nicardipine Hydrochloride Injection has the same active ingredient, dosage form, strength, route of administration, and conditions of use as PDL BioPharma's Cardene® I.V. Teva's proposed drug differs from the reference listed drug with respect to the inactive ingredients; [redacted] in Cardene I.V., citric acid monohydrate, has been replaced with benzoic acid, and [redacted] in Cardene I.V, sorbitol, has been replaced with sodium chloride. b(4)

Drug Substance: The drug substance CMC information has been referenced to [redacted] (LoA dated 19-OCT-2006). Nicardipine Hydrochloride is a calcium ion flux inhibitor (calcium channel blocker). Nicardipine hydrochloride is a pale yellow, crystalline powder [redacted] The drug substance is slightly soluble in water but soluble in methanol. DMF [redacted] was reviewed on July 31, 2007 (Review #3 by Dr. S. Saha) and found to be adequate. The Amendment to DMF dated February, 12, 2008 was reviewed by Dr. Lyudmila Soldatova (Review #4 dated May 6, 2008) and found to be adequate. The OC recommendation for the manufacturer of the drug substance, [redacted] is Acceptable based on District recommendation (OC recommendation 29-NOV-2007). The applicant drug substance specification is similar to that in the DMF [redacted] except that Teva [redacted], and included the microbial testing of the drug substance, since it is intended for the parenteral drug product. The applicant assigned a [redacted] re-test date for the drug substance from the month the batch was initially tested, and will dispose all raw materials at the manufacturer expiration date. b(4)

Drug product: Nicardipine Hydrochloride Injection will be available as a 25 mg/10 ml/vial sterile solution for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. Each ml contains 2.5 mg nicardipine hydrochloride, 0.305 mg benzoic acid, and 7.5 mg sodium chloride in Water for Injection. Additional sodium hydroxide may have been added to adjust the pH to 3.5 (target pH). All excipients are compendial grade and have been used previously in approved products at higher levels in terms of the concentration actually administered to patients. Nicardipine hydrochloride injection is to be used only after dilution with compatible diluents. An admixture study has been performed to support the labeling claims, and labeling was adequately revised to reflect the container recommendation for commercial product. The drug product is manufactured using [redacted] b(4)

conditions that minimize degradation. Teva initially provided very limited stability data for one batch of the drug product. Upon further request by the reviewer, Teva provided updated 12-month stability data for one batch of the drug product and 9-month stability data for two other batches at long-term storage condition, and additional 6-month stability data for two batches at the accelerated conditions. The accelerated stability data showed significant changes happening during the [redacted] storage. The company did not have any intermediate storage stability data. An expiration date of nine months is granted for the Nicardipine Hydrochloride drug product based on the provided stability data. b(4)

An "Approval" recommendation from the standpoint of product quality microbiology was obtained for [redacted] process (Bryan Riley, Ph.D., Microbiology Review #1 dated March 31, 2008). b(4)

An overall "Acceptable" recommendation for the facilities was provided by the Office of Compliance on 20-Mar-08.

Recommended action: The application is recommended as **"Approval"** from CMC perspective.

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/s/

Ramesh Sood
7/23/2008 01:29:03 PM
CHEMIST

NDA 22-276

Nicardipine Hydrochloride Injections

Teva Parenteral Medicines, Inc.

Division of Cardiovascular and Renal Products

Lyudmila N. Soldatova, Ph.D.
DPAI/ONDQA

Review of Chemistry, Manufacturing, and Controls

Chemistry Review Data Sheet

1. NDA 22-276

2. REVIEW #2

3. REVIEW DATE: June 4, 2008

4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-SEP-2007
Amendment	30-OCT-2007
Amendment	15-NOV-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	02-MAY-2008
Amendment	02-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Parenteral Medicines, Inc.
Address:	19 Hughes Irvine, CA 92618-1902
Representative:	Susan O'Brien Director, Regulatory Affairs

Telephone: (949) 455-4724

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Nicardipine Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

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

The reference listed drug productis Cardene® I.V. Injections, holder PDL BioPharma, Inc.

10. PHARMACOL. CATEGORY: Short term treatment of hypertension

11. DOSAGE FORM: Sterile solution

12. STRENGTH/POTENCY: 2.5 mg/ml

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: __x__ Rx ___ OTC

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

___x___Not a SPOTS product

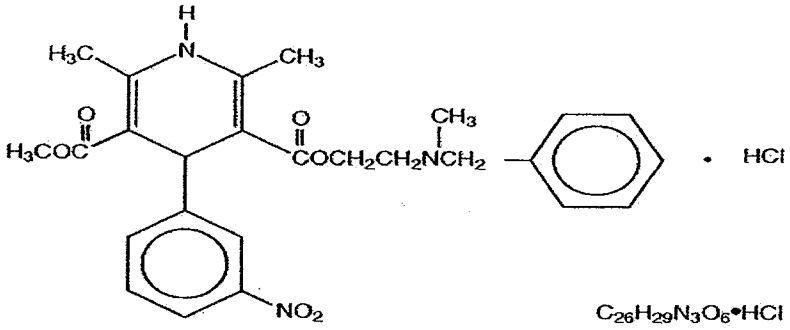
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m* -nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride

Chemistry Review Data Sheet

Molecular Formula: $C_{26}H_{29}N_3O_6$. HCl

Molecular Weight: 515.99



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	06-MAY-2008 Dr. L.Soldatova	
	III			3	Adequate	22-DEC-2005	
	III			3	Adequate	6-APR-2006	
				3	Adequate	12-AUG-2005	

b(4)

[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 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
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Clinical	N/A		Thomas Marciniak, M.D.
Microbiology	Acceptable	31-MAR-2008	Bryan Riley, Ph.D.
EES	Acceptable	20-MAR-2008	Office of Compliance
Pharm/Tox	Approvable	31-MAR-2008	Charles Resnick, Ph. D.
OCPB	N/A		Elena Mishina, Ph.D.
LNC	USAN name is granted for drug substance in the innovator's NDA for Cardene I.V.		Lyudmila N. Soldatova, Ph.D.
Methods Validation	Acceptable	As per this Review	Lyudmila N. Soldatova , Ph.D.
DMETS	Pending		
EA	Categorical Exclusion is granted	13-MAR-2008	Lyudmila N. Soldatova, Ph.D.

The Chemistry Review for NDA 22-276

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-276 for Nicardipine Hydrochloride Injections is recommended **APPROVAL** from the CMC standpoint. The drug substance and drug product manufacturing facilities were found Acceptable according to the overall OC recommendation on March 20, 2008. **Based on the provided stability data, 9-month expiry is granted for the Nicardipine Hydrochloride Injections drug product.**

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

This NDA is a 505 (b)(2) submission for a new formulation of PDL BioPharma's approved product, Cardene I.V., a calcium channel blocker. Teva's Nicardipine Hydrochloride Injection has the same active ingredient, dosage form, strength, route of administration, and conditions of use as PDL BioPharma's Cardene® I.V. Teva's proposed drug differs from the reference listed drug with respect to the inactive ingredients; [redacted] in Cardene I.V., citric acid monohydrate, has been replaced with benzoic acid, [redacted] in Cardene I.V, sorbitol, has been replaced with sodium chloride. b(4)

DRUG PRODUCT

No proprietary name was proposed for the drug product, so the generic drug name will be used, Nicardipine Hydrochloride Injection. Nicardipine Hydrochloride Injection will be available as a 25 mg/10 ml/vial sterile solution for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. Each ml contains 2.5 mg nicardipine hydrochloride, 0.305 mg benzoic acid, and 7.5 mg sodium chloride in Water for Injection. Additional sodium hydroxide may have been added to adjust the pH to 3.5 (target pH). All excipients are compendial grade and have been used previously in approved products at higher levels in terms of the concentration actually administered to patients. Nicardipine hydrochloride injection is to be used only after dilution with compatible diluents. An admixture study has been performed to support the labeling claims, and labeling was adequately revised to reflect the container recommendation

for commercial product (clarification is provided in the Amendment dated May 2, 2008). The drug product is manufactured using [redacted] under conditions that minimize degradation. The Approval recommendation from the standpoint of product quality microbiology was obtained for [redacted] (Bryan Riley, Ph.D., Microbiology Review #1 dated March 31, 2008). The drug product manufacturer, Teva Parenteral Medicines, Inc., has received the Acceptable OC recommendation on March 20, 2008, [redacted] (testing for benzoic acid) was recommended as Acceptable (OC recommendation from 06-NOV-2007). **Teva has provided response to the IR letter dated April 25, 2008.** Teva has tightened limits for the [redacted] derivative impurity (significant metabolite) and the total impurities in the drug product to NMT [redacted] and NMT [redacted] respectively, based on the levels observed in the stability studies. Teva has not provided upon request stability data at the intermediate conditions, instead, the firm proposed to [redacted] the specification for impurity [redacted], since stability data demonstrates that [redacted] does not meet the acceptance criterion of NMT [redacted] at the accelerated conditions. On request (IR dated May 28, 2008), applicant revised the specification limit [redacted] since the [redacted] limit is not supported by the appropriate qualification data. The release and stability specification for final drug product is updated to include revised limit for [redacted] derivative impurity and for the total impurities. Teva provided additional 12-month stability data for one batch of the drug product and 9-month stability data for two other batches at long-term storage condition, and additional 6-month stability data for two batches at the accelerated conditions. **Based on the provided stability data, and keeping in mind that level of [redacted] specification limit for this impurity at the accelerated storage conditions, that stability data at the intermediate condition was not provided, that level of [redacted] was reached at [redacted] at the long-term storage conditions, and that only 9-month long-term stability data was provided for two pilot batches, only 9-month expiry could be granted for the Nicardipine Hydrochloride drug product.** On request (IR dated May 28, 2008), Teva has revised the Stability Commitment for Nicardipine Hydrochloride Injection marketed product to include the 6-months stability studies under the accelerated conditions in addition to the long-term stability studies for the first three commercial lots.

b(4)

DRUG SUBSTANCE

The sponsor is referencing DMF [redacted] for information on the drug substance Nicardipine Hydrochloride (LoA dated 19-OCT-2006). Nicardipine Hydrochloride is a calcium ion flux inhibitor (calcium channel blocker). Nicardipine hydrochloride is a pale yellow, crystalline powder [redacted]. The drug substance is slightly soluble in water but soluble in methanol. DMF [redacted] has been reviewed on July 31, 2007 (Review #3 by Dr. S. Saha) and found to be adequate. The Amendment to DMF dated February, 12, 2008 has been reviewed by Dr. Lyudmila Soldatova (Review #4 dated May 6, 2008) and found to be adequate. The OC recommendation for the manufacturer of the drug substance, [redacted], is Acceptable based on District recommendation (OC recommendation 29-NOV-2007). The applicant drug substance specification is similar to that in the DMF [redacted] except for Teva has [redacted], and included the microbial testing of the drug substance, since it is intended for the parenteral drug product. Testing of the [redacted]

b(4)

and Teva's specification. The applicant assigned a [redacted] re-test date for the drug substance from the month the batch was initially tested, and will dispose all raw materials at the manufacturer expiration date. b(4)

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

Nicardipine Hydrochloride Injection will be packaged in a single use 10 mL amber glass vial with a [redacted] The product should be stored at 20° to 25°C (68° to 77°F). It is protected from light by an amber vial and shelf carton. Nicardipine Hydrochloride Injection is formulated to be further diluted to concentration of 0.1 mg/ml with either Dextrose (5%) Injection, USP, Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP, Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP, Dextrose (5%) and 40 mEq Potassium, USP, Sodium Chloride (0.45%) Injection, USP, and Sodium Chloride (0.9%) Injection, USP. [redacted] b(4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-276 for Nicardipine Hydrochloride Injections is recommended APPROVAL from the 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: Alisea Crowley

C. CC Block

See DFS.

14 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Lyudmila Soldatova
6/4/2008 12:12:38 PM
CHEMIST

Ramesh Sood
6/4/2008 03:44:54 PM
CHEMIST

NDA 22-276

Nicardipine Hydrochloride Injections

Teva Parenteral Medicines, Inc.

Division of Cardiovascular and Renal Products

Lyudmila N. Soldatova, Ph.D.
DPAI/ONDQA

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-276

2. REVIEW #1

3. REVIEW DATE: May 06, 2008

4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-SEP-2007
Amendment	30-OCT-2007
Amendment	15-NOV-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Parenteral Medicines, Inc.
Address:	19 Hughes Irvine, CA 92618-1902
Representative:	Susan O'Brien Director, Regulatory Affairs
Telephone:	(949) 455-4724

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Nicardipine Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

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

The reference listed drug productis Cardene® I.V. Injections, holder PDL BioPharma, Inc.

10. PHARMACOL. CATEGORY: Short term treatment of hypertension

11. DOSAGE FORM: Sterile solution

12. STRENGTH/POTENCY: 2.5 mg/ml

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: __x__ Rx ____ OTC

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

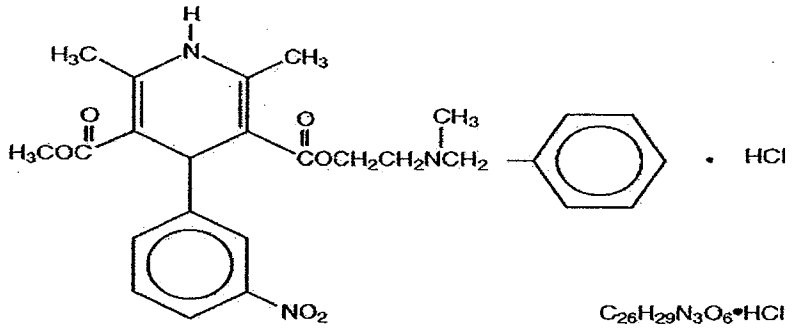
__x__Not a SPOTS product

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

Chemical Name: (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m* -nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride

Molecular Formula: $C_{26}H_{29}N_3O_6$. HCl

Molecular Weight: 515.99



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b(4)

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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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Pending		Thomas Marciniak, M.D.
Microbiology	Acceptable	31-MAR-2008	Bryan Riley, Ph.D.
EES	Acceptable	20-MAR-2008	Office of Compliance
Pharm/Tox	Approvable	31-MAR-2008	Charles Resnick, Ph. D.
OCPB	Pending		Elena Mishina, Ph.D.
LNC	USAN name is granted for drug substance in the innovator's NDA for Cardene I.V.		Lyudmila N. Soldatova, Ph.D.
Methods Validation	Acceptable	As per this Review	Lyudmila N. Soldatova , Ph.D.
DMETS	Teva will not use a brand name for its product but will use the generic name, nicardipine hydrochloride injection		Lyudmila N. Soldatova , Ph.D. (statement provided in the original submission)
EA	Categorical Exclusion is granted	13-MAR-2008	Lyudmila N. Soldatova, Ph.D.

The Chemistry Review for NDA 22-276

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-276 for Nicardipine Hydrochloride Injections is recommended APPROVABLE from the CMC standpoint. The drug substance and drug product manufacturing facilities were found Acceptable according to the overall OC recommendation on March 20, 2008. The approval is contingent upon satisfactory resolution of the drug product deficiencies.

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

This NDA is a 505 (b)(2) submission for a new formulation of PDL BioPharma's approved product, Cardene I.V., a calcium channel blocker. Teva's Nicardipine Hydrochloride Injection has the same active ingredient, dosage form, strength, route of administration, and conditions of use as PDL BioPharma's Cardene® I.V. Teva's proposed drug differs from the reference listed drug with respect to the inactive ingredients; [redacted] in Cardene I.V., citric acid monohydrate, has been replaced with benzoic acid, and [redacted] in Cardene I.V, sorbitol, has been replaced with sodium chloride. b(4)

DRUG PRODUCT

No proprietary name was proposed for the drug product, so the generic drug name will be used, Nicardipine Hydrochloride Injection. Nicardipine Hydrochloride Injection will be available as a 25 mg/10 ml/vial sterile solution for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. Each ml contains 2.5 mg nicardipine hydrochloride, 0.305 mg benzoic acid, and 7.5 mg sodium chloride in Water for Injection. Additional sodium hydroxide may have been added to adjust the pH to 3.5 (target pH). All excipients are compendial grade and have been used previously in approved products at higher levels in terms of the concentration actually administered to patients. The reference listed drug Cardene I.V. contains citric acid and sorbitol [redacted] and Teva has calculated that the [redacted] of their product matches that of Cardene I.V. Nicardipine b(4)

hydrochloride injection is to be used only after dilution with compatible diluents. An admixture study has been performed to support the labeling claims. The drug product is manufactured using [redacted] under conditions that minimize degradation. The formal microbiology consult was requested, and review was performed by Bryan Riley, Ph.D. (Microbiology Review #1 dated March 31, 2008); the recommendation is Approval from the standpoint of product quality microbiology. The drug product manufacturer, Teva Parenteral Medicines, Inc., has received the Acceptable OC recommendation on March 20, 2008; DO approval of this facility is based on last inspection (5/8-22/07). [redacted] (testing for benzoic acid) was recommended as Acceptable (OC recommendation from 06-NOV-2007), based on profile. The release specification for final drug product is acceptable except for the limit for [redacted] derivative that is set very high, at NMT [redacted] The batch results from three pilot scale batches show levels of [redacted], and stability data at 25°C/60% RH shows [redacted]. However, it is known that this degradation product is a metabolite. Teva should justify limit of NMT [redacted] for impurity [redacted] derivative. Analytical methods for release and stability testing of the drug product are described and adequately validated. Batch analysis for three pilot scale exhibit stability lots demonstrate that all test parameters comply with the proposed specifications. Teva has submitted the 3-months stability data at 25°C/60% RH and 40°C/75% RH, and a [redacted] shelf-life is claimed. The limited stability data demonstrates that [redacted] does not meet the acceptance criterion of NMT [redacted] at the accelerated conditions of 40°C/75% RH. Due to this, Teva should have performed stability studies at the intermediate storage condition but they have not done that. Additionally, Teva has to provide additional stability data to support the requested expiry.

b(4)

DRUG SUBSTANCE

The sponsor is referencing DMF [redacted] information on the drug substance Nicardipine Hydrochloride (LoA dated 19-OCT-2006). Nicardipine Hydrochloride is a calcium ion flux inhibitor (calcium channel blocker). Nicardipine hydrochloride is a pale yellow, crystalline powder [redacted] The drug substance is slightly soluble in water but soluble in methanol. DMF [redacted] has been reviewed on July 31, 2007 (Review #3 by Dr. S. Saha) and found to be adequate. The Amendment to DMF dated February, 12, 2008 has been reviewed by Dr. Lyudmila Soldatova (Review #4 dated May 6, 2008) and found to be adequate. The OC recommendation for the manufacturer of the drug substance, [redacted] is Acceptable based on District recommendation (OC recommendation 29-NOV-2007). The applicant drug substance specification is similar to that in the DMF [redacted] except for Teva [redacted] and included the microbial testing of the drug substance, since it is intended for the parenteral drug product. [redacted] and Teva's specification. The applicant assigned a [redacted] re-test date for the drug substance from the month the batch was initially tested, and will dispose all raw materials at the manufacturer expiration date.

b(4)

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

Nicardipine Hydrochloride Injection will be packaged in a single use 10 mL amber glass vial with a [redacted] The product should be stored at 20° to 25°C (68° to 77°F). It is protected from light by an amber vial and shelf carton. Nicardipine Hydrochloride Injection is formulated to be further diluted to concentration of 0.1 mg/ml with either Dextrose (5%) Injection, USP, Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP, Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP, Dextrose (5%) and 40 mEq Potassium, USP, Sodium Chloride (0.45%) Injection, USP, and Sodium Chloride (0.9%) Injection, USP. [redacted] b(4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-276 for Nicardipine Hydrochloride Injections is recommended APPROVABLE from the 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: Alisea Crowley

C. CC Block

See DFS.

62 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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
5/6/2008 02:40:14 PM
CHEMIST

Ramesh Sood
5/6/2008 02:54:28 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-276
Applicant:	Teva Parenteral Medicines, Inc.
Letter Date:	28 Sep 2007
Stamp Date:	01 Oct 2007
PDUFA Date:	01 Aug 2008
Tradename:	Nicardipine Hydrochloride Injection
Established Name:	Nicardipine Hydrochloride
Dosage Form:	Sterile solution, 2.5 mg/mL
Route of Administration:	Intravenous injection
Indication:	Short term treatment of hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary
This NDA is a 505 (b)(2) eCTD submission for a new formulation of PDL BioPharma's approved product, Cardene I.V., a calcium channel blocker. Currently there is no IND application associated with this NDA, however, a pre-NDA meeting (t-con) was held on Sep. 06, 2007 with the Applicant under pre-IND 77,270. This product cannot be submitted as an ANDA because it contains excipients which are different from Cardene I.V. and do not qualify under the "excipient exception" rule. The Agency agreed that no bioequivalence studies need be conducted for this sterile dosage form which will be administered as a solution. The only CMC issue discussed related to the specifications for the drug product, in particular, the qualification of impurities above the ICH threshold. The applicant was requested to conform to ICH Q3B regarding the reporting, identification and qualification of degradation products.

Drug Substance
Nicardipine hydrochloride is a pale yellow, crystalline powder which [redacted] The drug substance is slightly soluble in water but soluble in methanol. CMC information for the drug substance is in DMF [redacted], which has been reviewed as recently as July 27, 2007 and found to be adequate. Teva has established specifications for nicardipine hydrochloride which are similar to [redacted]. A retest date of [redacted] is proposed. b(4)

Drug Product
Nicardipine hydrochloride injection is a sterile solution packaged in a single use 10 mL amber glass vial with a [redacted]. The excipients are benzoic acid, [redacted] sodium chloride [redacted] and sodium hydroxide for pH adjustment. All are compendial grade and have been used previously in approved products at higher levels in terms of the concentration actually administered to patients. The reference listed drug Cardene I.V. contains citric acid and sorbitol [redacted] b(4)

agents and the Applicant has calculated that the [redacted] of their product matches that of Cardene I.V. The target pH is 3.5.

The drug product is manufactured [redacted] under conditions that minimize degradation. b(4)

The product can be stored at room temperature and 3 months' stability data at 25°C/60% RH and 40°C/75% RH have been submitted and a [redacted] shelf-life is claimed. Nicardipine hydrochloride injection is to be used only after dilution with compatible diluents and an admixture study has been performed to support the labeling claims.

Critical Issues for Review

Drug Substance

- [redacted] specifications currently include a limit for the [redacted] however, a footnote states that this test will no longer be performed since [redacted] is not of significance for a solution drug product. Is this justified? b(4)
- Are the proposed bacterial endotoxin limits acceptable?

Drug Product

- Since this is a parenteral dosage form, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- In the stress degradation studies, the [redacted] derivative has been identified as a degradant under all conditions e.g. heat, light, acid, base and oxidation. It seems unusual that the [redacted] under at least some of these conditions.
- The limited stability data provided show that [redacted] does not meet the acceptance criterion at accelerated temperatures. In accordance with ICH, this should trigger studies at intermediate storage conditions. Apparently, this was not done even though their stability plan provides for this. In addition, the postapproval commitment for the first 3 commercial batches is only for room temperature studies. b(4)
- Has the compatibility of the drug product with all the diluents listed in the package insert been satisfactorily established? The diluted solution is stated to be stable for 24 hours. Is his statement supported with stability data?

Labeling

No proprietary name has been proposed for this product which should be called Nicardipine Hydrochloride Injection instead of [redacted] b(4)

Comments and Recommendations

The application is fileable. Facilities will be entered into EES and the reviewer should verify the accuracy and completeness of the entries. A consult request will be sent to OPS/ Microbiology staff. A single CMC reviewer is recommended for this NDA since the microbiologist will be reviewing a substantial portion of the drug product section.

Kasturi Srinivasachar	Oct.23, 2007
Pharmaceutical Assessment Lead	Date
Ramesh Sood, Ph.D.	Oct 23, 2007
Branch Chief	Date

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

/s/

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