CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-513

Chemistry Review(s)

NDA 21-513

ENABLEX®
(darifenacin)
Extended-release tablets

Novartis Pharmaceuticals Corp.

Sarah C. Pope, Ph.D.
Division of Reproductive and Urologic Drug Products
(DRUDP, HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-513

2. REVIEW #3

3. REVIEW DATE: 21-DEC-2004

4. REVIEWER: Sarah C. Pope, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Chemistry Review #1	24-SEP-2003
Chemistry Review #2	30-SEP-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Revised blister labels.	21-DEC-2004
PI/PPI	20-DEC-2004
Container/Carton labels	16-DEC-2004
Amendment	22-OCT-2004
Amendment	27-AUG-2004
Amendment	21-JUN-2004
Amendment	16-JUN-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corp. Global Regulatory CMC
Address:	One Health Plaza East Hanover, NJ 07936

Chemistry Review Data Sheet

Representative: Kenneth Kopec

Telephone: 862-778-7757

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: ENABLEX® Extended-release tablet
   b) Non-Proprietary Name (USAN): Darifenacin
   c) Code Name/# (ONDC only): NA
   d) Chem. Type/Submission Priority (ONDC only): 1/S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: A selective muscarinic M3 receptor antagonist (M3-SRA), for use in the treatment of overactive bladder.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 7.5 and 15 mg

13. ROUTE OF ADMINISTRATION: Oral

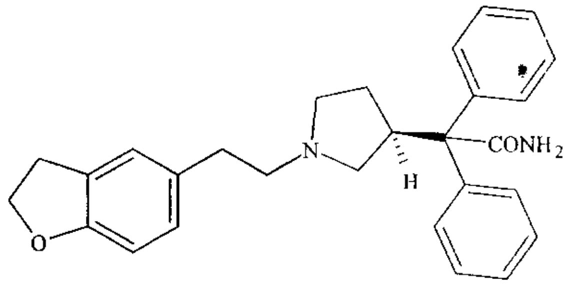
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

    __X__Not a SPOTS product

Chemistry Review Data Sheet

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



Darifenacin ($C_{28}H_{30}N_2O_2$)
(*S*)-2-{1-[2[(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide
MW = 426.55 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau

[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")

Chemistry Review Data Sheet

[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	DOCUMENT DATE
IND 45,457	03-JUN-1994
IND [	]
Patent #5,096,890	Expires 13-MAR-2010
Patent #6,106,864	Expires 21-AUG-2016

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	---	---
EES	Acceptable	22-JUN-2004	Ms. J. D'Ambrogio
Pharm/Tox	Acceptable	01-OCT-2003	Dr. S. Thornton
Biopharm	Acceptable	20-DEC-2004	Dr. S. Apparaju
LNC	NA	---	---
Methods Validation	To be submitted post-approval	30-NOV-2004	Dr. S. Pope
DMETS/DDMAC	Trade name unacceptable; resolved by Division.	21-SEP-2004	Dr. L. Kim-Jung
EA	Acceptable	15-SEP-2003	Dr. A. Fensalau

APPEARS THIS WAY
ON ORIGINAL

Executive Summary Section

The Chemistry Review for NDA 21-513

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls standpoint, this NDA can be approved. Final labeling issues (container/carton, physician's package insert and patient information) remaining from Chemistry Review #2 (dated 30-SEP-2004) have been resolved. There are no outstanding CMC deficiencies for this application.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Drug Substance

Darifenacin is a new molecular entity manufactured by Pfizer Ireland Pharmaceuticals (Ringaskiddy, Ireland). The drug substance is [ ] in six [ ] steps, [ ] The chiral center found in darifenacin originates in [ ]

[ ] Acceptable controls have been proposed for both starting materials. In-process specifications for critical steps and intermediates further assure the stereochemical and chemical purity of the drug substance.

Darifenacin is a white to almost white crystalline powder. The overall structure and stereochemistry of the desired (S) enantiomer has been confirmed using mass spectrometry, infrared spectroscopy, nuclear magnetic spectroscopy, and Xray [ ] No polymorphs, solvates, or hydrates have been identified for darifenacin, and no control of polymorphic forms is required for the drug substance.

The regulatory specification for darifenacin includes physical [ ] testing, along with determination of assay. [ ] The proposed methods have been properly and adequately validated. The proposed acceptance criteria have been reviewed and are acceptable to ensure drug substance quality.

The retest period for the drug substance is [ ]

All of the preceding Chemistry, Manufacturing, and Controls/drug substance information has been previously reviewed in the first Chemistry Review of NDA 21-513 (by Dr. A. Fensalau).

Executive Summary Section

The following review covers the complete response to the Agency's approvable action on 02-OCT-2003. The complete response includes no revisions to any drug substance information. Accordingly, the drug substance information remains acceptable

Drug Product

Darifenacin tablets have been proposed in two tablet strengths, 7.5 mg and 15 mg. A third strength (30 mg) was used extensively in chemical development, but was not proposed for commercialization. Darifenacin tablets are administered once daily, for the treatment of overactive bladder.

The tablets are composed of the drug substance, dibasic calcium phosphate, hypromellose, and magnesium stearate. [ ] are used to manufacture each dosage strength; the [ ] is subsequently [ ] tablets. The resulting tablets are color- and clear-coated, to yield the final drug product.

Manufacturing details, container/closure configurations, and regulatory specifications have all been reviewed and were determined to be acceptable (see Chemistry Review #1).

The complete response contained updated stability data, in support of the Sponsor's request for an increased (36-month) expiration dating period. Additionally, the Sponsor has submitted updated container/carton labels. All remaining drug product information is identical to that originally submitted during the first review, and no other changes have been proposed.

The provided stability data support the Sponsor's request for an increased (36-month) expiration dating period. This is an extension from the originally-requested expiry of — months. When stored at controlled room temperature 15 to 30°C (59-86°F) and protected from light, darifenacin tablets are stable throughout the proposed 36-month expiry.

The current review covers final labeling issues, including the final review of container/carton and Package Insert/Patient Information labeling. All other review issues have been previously reviewed (see Chemistry Review dated 30-SEP-2004, by Dr. S. Pope).

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

Darifenacin tablets (7.5 or 15 mg) are administered once daily, for the treatment of overactive bladder.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been submitted to assure the drug product's identity, strength, quality, purity, potency and stability. Final draft labeling including Container/Carton labels, the Package Insert, and Patient Information, have been submitted and are acceptable. Therefore, from a CMC standpoint, this New Drug Application may be Approved.

Executive Summary Section

III. Administrative

A. **Reviewer's Signature** - Electronic signature
B. **Endorsement Block** - Electronic signature
C. **CC Block** - Electronically submitted

APPEARS THIS WAY
ON ORIGINAL

Redacted 5

page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

Sarah Pope
12/21/04 01:44:05 PM
CHEMIST

Swapan De
12/21/04 01:56:18 PM
CHEMIST
signed for MooJhong Rhee

NDA 21-513

ENABLEX (darifenacin) Extended Release Tablets, 7.5, 15 mg

CHEMISTRY DIVISION DIRECTOR REVIEW 2

Applicant: Novartis Pharmaceutical Corp.
Address: One Health Plaza
East Hanover, NJ
Representative Kenneth Kopec
(862)778-7757

Indication: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency

Presentations: 7.5 mg tablets: white, round, convex, coated tablets
bottles of 90; unit dose blister packages of 100 (10/strip)
15 mg tablets: peach, round, convex, blister
bottles of 90; unit dose blister packages of 100 (10/strip)

EER Status: Acceptable 24-AUG-2004

Consults: DMETS – ENABLEX is acceptable 3-NOV-2004
DDMAC – ENABLEX acceptable -24-SEP-2004
DRUDP had determined that it is acceptable (per DShames 10/1/2003)
Statistics – none
EA – no consult - waiver requested - granted

ENABLEX NDA 21-513 was submitted 03-DEC-2002

The **drug substance** is manufactured by:

Pfizer, Ringaskiddy, IRE

Structural characterization of the drug substance, and chirality determination was satisfactory. The [ ] which is a [ ] may be sourced from:

[ ]

[redacted]

[redacted]

The manufacturing process and controls were found acceptable. Satisfactory work was performed to characterize the impurity profile and the impurity tests and acceptance criteria were found to be acceptable. Other specifications were also found acceptable. A re-test period of [redacted] is supported by submitted stability data. Storage is at room temperature. The stability commitment and protocol are acceptable.

Conclusion
Drug substance information is acceptable.

The **drug product** is a film coated extended release tablet in strengths of 7.5 and 15 mg. Manufacturer:

Pfizer, Brooklyn

or

[redacted]

The manufacturing method is [redacted] process. Adequate in-process controls are in place. Each strength is a slightly different formulation. The proposed regulatory specifications are acceptable. The dissolution method and acceptance criteria have been found acceptable by Biopharm. Submitted stability data support the proposed 36 month expiry for all strengths and packaging presentations. The stability commitment and protocol are acceptable. Labeling was updated and is acceptable. Note that the established now is now darifenacin which is USAN.

All associated DMFs are acceptable.

Overall Conclusion
From a CMC perspective the application an approval action is recommended.

Eric P Duffy, PhD
Director, DNDC II/ONDC

Addendum 2-SEP-2003

It should be noted that the [redacted] manufacturing site was withdrawn in April 2003.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Eric Duffy
12/13/04 05:36:40 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-513

ENABLEX®
(darifenacin)
Extended-Release Tablets

Novartis Pharmaceuticals Corp.

Sarah C. Pope, Ph.D.
Division of Reproductive and Urologic Drug Products
(DRUDP, HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-513

2. REVIEW #2

3. REVIEW DATE: 30-SEP-2004

4. REVIEWER: Sarah C. Pope, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Chemistry Review #1	24-SEP-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	22-OCT-2004
Amendment	27-AUG-2004
Amendment	21-JUN-2004
Amendment	16-JUN-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corp. Global Regulatory CMC
Address:	One Health Plaza East Hanover, NJ 07936
Representative:	Kenneth Kopec
Telephone:	862-778-7757

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: ENABLEX® Extended Release Tablet
   b) Non-Proprietary Name (USAN): Darifenacin
   c) Code Name/# (ONDC only): NA
   d) Chem. Type/Submission Priority (ONDC only): 1/S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: A selective muscarinic M3 receptor antagonist (M3-SRA), for use in the treatment of overactive bladder.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 7.5 and 15 mg

13. ROUTE OF ADMINISTRATION: Oral

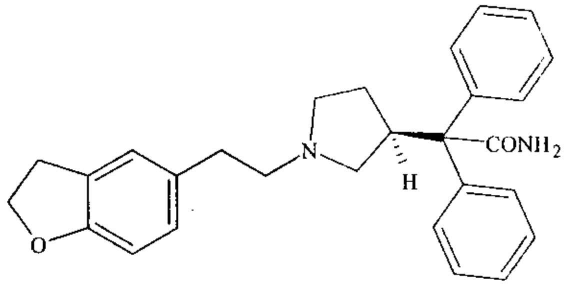
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

    ___X__Not a SPOTS product

Chemistry Review Data Sheet

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



Darifenacin ($C_{28}H_{30}N_2O_2$)
(*S*)-2-{1-[2[(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide
MW = 426.55 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau
	III			3	Adequate	03-SEP-2003	See CMC Rev #1 by Dr. A. Fensalau

[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")

Chemistry Review Data Sheet

[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	DOCUMENT DATE
IND 45,457	03-JUN-1994
IND [redacted]	[redacted]
Patent #5,096,890	Expires 13-MAR-2010
Patent #6,106,864	Expires 21-AUG-2016

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	---	---
EES	Acceptable	22-JUN-2004	Ms. J. D'Ambrogio
Pharm/Tox	NA		
Biopharm	Pending	Pending	Dr. S. Apparaju/Dr. M. Kim
LNC	NA	---	---
Methods Validation	To be submitted.	---	---
DMETS/DDMAC	Trade name unacceptable; resolved by Division.	21-SEP-2004	Dr. L. Kim-Jung
EA	Acceptable	15-SEP-2003	Dr. A. Fensalau

APPEARS THIS WAY
ON ORIGINAL

Executive Summary Section

The Chemistry Review for NDA 21-513

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls standpoint, this NDA can be approved pending satisfactory resolution of final labeling issues (Physicians' Package Insert and Patient Information).

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

Not Applicable

II. Summary of Chemistry Assessments

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

Drug Substance

Darifenacin is a new molecular entity manufactured by Pfizer Ireland Pharmaceuticals (Ringaskiddy, Ireland). The drug substance is [ ] in six [ ] steps, [ ] The chiral center found in darifenacin originates in [ ]

[ ] Acceptable controls have been proposed for both starting materials. In-process specifications for critical steps and intermediates further assure the stereochemical and chemical purity of the drug substance.

Darifenacin is a white to almost white crystalline powder. The overall structure and stereochemistry of the desired (S) enantiomer has been confirmed using mass spectrometry, infrared spectroscopy, nuclear magnetic spectroscopy, and Xray. [ ] No polymorphs, solvates, or hydrates have been identified for darifenacin, and no control of polymorphic forms is required for the drug substance.

The regulatory specification for darifenacin includes physical [ ] testing, along with determination of assay. [ ] The proposed methods have been properly and adequately validated. The proposed acceptance criteria have been reviewed and are acceptable to ensure drug substance quality.

The retest period for the drug substance is —

All of the preceding Chemistry, Manufacturing, and Controls/drug substance information has been previously reviewed in the first Chemistry Review of NDA 21-513 (by Dr. A. Fensalau). The following review covers the complete response to the Agency's approvable action on 02-

OCT-2003. The complete response includes no revisions to any drug substance information. Accordingly, the drug substance information remains acceptable.

Drug Product

Darifenacin tablets have been proposed in two tablet strengths, 7.5 mg and 15 mg. A third strength (30 mg) was used extensively in chemical development, but was not proposed for commercialization. Darifenacin tablets are administered once daily, for the treatment of overactive bladder.

The tablets are composed of the drug substance, dibasic calcium phosphate, hypromellose, and magnesium stearate. [ ] are used to manufacture each dosage strength; the [ ] is subsequently [ ] into tablets. The resulting tablets are color- and clear-coated, to yield the final drug product.

Manufacturing details, container/closure configurations, and regulatory specifications have all been reviewed and were determined to be acceptable (see Chemistry Review #1).

The complete response contained updated stability data, in support of the Sponsor's request for an increased (36-month) expiration dating period. Additionally, the Sponsor has submitted updated container/carton labels. All remaining drug product information is identical to that originally submitted during the first review, and no other changes have been proposed.

The provided stability data support the Sponsor's request for an increased (36-month) expiration dating period. This is an extension from the originally-requested expiry of [ ] months. When stored at controlled room temperature 15 to 30°C (59-86°F) and protected from light, darifenacin tablets are stable throughout the proposed 36-month expiry.

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

Darifenacin tablets (7.5 or 15 mg) are administered once daily, for the treatment of overactive bladder.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been submitted to assure the drug product's identity, strength, quality, purity, potency and stability. Therefore, from a CMC standpoint, this New Drug Application may be Approved, pending satisfactory resolution of Patient Information and Physicians' Package Insert labeling.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: S. Pope/28-OCT-2004
ChemistryTeamLeaderName/Date: M. Rhee/28-OCT-2004
ProjectManagerName/Date: J. Makie/28-OCT-2004

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 15

page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

Sarah Pope
11/3/04 11:19:18 AM
CHEMIST

Moo-Jhong Rhee
11/3/04 02:30:41 PM
CHEMIST
I concur

OFFICIAL MEMORANDUM

TO: NDA 21-513

FROM: SARAH C. POPE, PH.D.

SUBJECT: FILING OF COMPLETE RESPONSE TO 02-OCT-2003 ACTION

DATE: 8/26/2004

THROUGH: MOO-JHONG RHEE, PH.D.

Reference is made to the Sponsor's proposed Complete Response dated 16-JUN-2004. No additional Chemistry, Manufacturing and Controls information has been submitted, with the exception of updated stability data. The Sponsor has also revised the requested expiration dating period for the drug product, originally proposed at [ ] The currently-proposed expiration dating period is 36 months, in conjunction with the updated stability data.

The CMC review of the complete response will include resubmission of all sites to the Office of Compliance for assessment of cGMP conformance. Additionally, all listed Drug Master Files will be reviewed and/or assessed for adequacy. The Sponsor has submitted updated Container/Carton labeling, which will be consulted to the Division of Medication Errors and Technical Services (DMETS) for review.

According to a 03-AUG-2004 internal meeting, the Complete Response to the approvable action (02-OCT-2003) for NDA 21-513 has been filed.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Sarah Pope
8/26/04 11:43:42 AM
CHEMIST

Moo-Jhong Rhee
8/26/04 01:55:16 PM
CHEMIST
I concur

NDA 21-513

ENABLEX (darifenacin HBr) Extended Release Tablets, 7.5, 125 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Novartis Pharmaceutical Corp.
Address: One Health Plaza
East Hanover, NJ
Representative Kenneth Kopec
(862)778-7757

Indication: Treatment of overactive bladder

Presentations: 7.5 mg tablets: white, round. convex, coated tablets
bottles of 30 and 10; unit dose blister packages of 100
100 mg tablets: peach, round, convex, blister
bottles of 30 and 100; unit dose packages of 100

EER Status: Acceptable 22-SEP-2003

Consults: DMETS – ENABLEX is acceptable 27-FEB-2002
DDMAC – ENABLEX not acceptable
DRUDP has determined that it is acceptable (per DShames 10/1/2003)
Statistics – none
EA – no consult - waiver requested - granted

ENABLEX was submitted 03-DEC-2002. Six information requests were made, and in response 10 amendments were submitted. The review was completed 25-SEP-2003.

The **drug substance** is manufactured by:

Pfizer, Ringaskiddy, IRE

Structural characterization of the drug substance, and chirality determination was satisfactory. The [ ] which is [ ] may be sourced from:

The manufacturing process and controls were found acceptable. Satisfactory work was performed to characterize the impurity profile and the impurity tests and acceptance criteria were found to be acceptable. Other specifications were found acceptable. A re-test period of —— is supported by submitted stability data. Storage is at room temperature. The stability commitment and protocol are acceptable.

Conclusion
Drug substance information is acceptable.

The **drug product** is a film coated extended release tablet in strengths of 7.5 and 15 mg. Manufacturer:

Pfizer, Brooklyn

or

[ ]

The manufacturing method is [ ] process. Adequate in-process controls are in place. Each strength is a slightly different formulation. The proposed regulatory specifications are acceptable. The dissolution has now (29-SEP-2003) been finalized by Biopharm. Submitted stability data support the proposed —— expiry for all strengths and packaging presentations. The stability commitment and protocol are acceptable Labeling review will be deferred to the new review cycle..

All associated DMFs are acceptable.

Overall Conclusion
From a CMC perspective the application an approval action is recommended.

Eric P Duffy, PhD
Director, DNDC II/ONDC

Addendum 2-SEP-2003

It should be noted that the [ ] manufacturing site was withdrawn in April 2003.

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

/s/

Eric Duffy
10/2/03 10:15:58 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-513

ENABLEX™
(darifenacin hydrobromide)
Extended Release Tablets

Novartis Pharmaceuticals Corp.

Allan Fenselau, Ph.D.
Division of Reproductive and Urologic Drug Products
(HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. **NDA 21-513**

2. **REVIEW: # 1**

3. **REVIEW DATE: 24-SEP-2003**

4. **REVIEWER: Allan Fenselau**

5. **PREVIOUS DOCUMENTS: None**

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

Submission(s) Reviewed	Document Date
Original	03-DEC-2002
Amendment (BC)	20-JAN-2003
Amendment (BC)	18-FEB-2003
Amendment (BC)	18-MAR-2003
Amendment (C)	14-APR-2003
Amendment (XS)	23-APR-2003
Amendment (BC)	12-MAY-2003
Amendment (BC)	21-JUL-2003
Amendment (BL)	11-AUG-2003
Amendment (BC)	10-SEP-2003
Amendment (BC)	23-SEP-2003

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

Name:	Novartis Pharmaceuticals Corp.
	Global Regulatory CMC
Address:	One Health Plaza
	East Hanover, NJ 07936
Representative:	Kenneth Kopec
Telephone:	862-778-7757

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   - **a) Proprietary Name:** **ENABLEX™ Extended Release Tablet**
   - **b) Non-Proprietary Name (USAN):** **Darifenacin hydrobromide**
   - **c) Code Name/# (ONDC only):** **NA**
   - **d) Chem. Type/Submission Priority:** **1/S**

9. **LEGAL BASIS FOR SUBMISSION: Not Applicable**

10. PHARMACOLOGICAL CATEGORY: A selective muscarinic M3 receptor antagonist (M3-SRA) for use in the treatment of overactive bladder.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 7.5mg and 15mg

13. ROUTE OF ADMINISTRATION: Oral

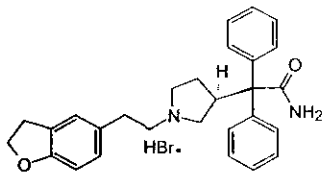
14. R_X/OTC DISPENSED: _X_ R_X ___OTC

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

_____SPOTS product – Form Completed
_X_ Not a SPOTS product

NOTE: The magnesium stearate used in the core formulation of darifenacin hydrobromide ER tablets is of bovine origin. A Certificate of Suitability has been provided.

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



$C_{28}H_{30}N_2O_2$·HBr CAS-133099-07-7
M.W.: 507.5 [Free base: 426.55]

***(S)*-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide**

DARIFENACIN HYDROBROMIDE

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	III			4	NA	03-SEP-2003	Adequate info. provided in NDA
	III			4	NA	03-SEP-2003	Adequate info. provided in NDA
	III			4	NA	03-SEP-2003	Adequate info. provided in NDA
	III			4	NA	03-SEP-2003	Adequate info. provided in NDA
	III			4	NA	03-SEP-2003	Adequate info. provided in NDA
	III			4	NA	03-SEP-2003	Adequate info. provided in NDA

[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 –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 NA (I.E., there is enough data in the application, therefore the DMF did not need to be reviewed)**

B. Other Documents:

Documents	Document Date
INDs: 45,457	Filed 03-JUN-1994
Patents: 5,096,890	expires 13-MAR-2010
6,106,864	expires 21-AUG-2016

18. STATUS: ONDC

CONSULTS/ CMC RELATED REVIEWS	RECOMMEND-ATION	DATE	REVIEWER
Biometrics	NA	-----	-----
EES	Acceptable	22-SEP-2003	J.D'Ambrogio
Pharm/Tox	NA	----	----
Biopharm	Pending	24-SEP-2003	M.-J.Kim
LNC	NA	-----	-----
Methods Validation	To be submitted to FDA labs.	-----	-----
OPDRA	Acceptable	29-AUG-2003	D.Toyer
EA	Acceptable	15-SEP-2003	A.Fenselau
Microbiology	NA	----	-----

EXECUTIVE SUMMARY
Chemistry Review for NDA 21-513

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval of NDA 21-513 can be recommended after satisfactory resolution of the following chemistry, manufacturing and controls [CMC]-related labeling issues that pertain to the drug product ENABLEX (darifenacin hydrobromide) Extended Release Tablets, 7.5mg and 15mg.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Drug Substance

Darifenacin HBr drug substance is a new molecular entity [NME] manufactured by Pfizer Ireland Pharmaceuticals (in Ringaskiddy, Ireland). The drug substance [ ] in six steps]

The starting materials are well-characterized and have rigorous specifications that are similar to those expected for a drug substance. One proposed [ ] found in the final product. [ ] The synthesis has [ ] producing further reassurance on the stereochemical purity of the final product. In-process specifications for critical steps, along with control of critical process parameters and specifications established for [ ] materials, also assure the quality of darifenacin HBr. The drug substance manufacturing process involves no [ ] sterilization processes.

Darifenacin HBr drug substance is a white to almost white crystalline powder. The solubility of darifenacin HBr in [ ] with a resulting [ ] The solubility across the physiological pH range is greater than — mg/mL. The elemental composition of darifenacin HBr reference standard, batch — as determined by [ ] is consistent with the proposed molecular formula $C_{28}H_{31}BrN_2O_2$. The structure was confirmed by a combination of mass spectrometry, infrared spectroscopy, nuclear magnetic resonance spectroscopy, and [ ] X-ray [ ] The overall structure and absolute stereochemistry of the (*S*)-form of darifenacin HBr [ ]

] Finally, after extensive evaluation, no polymorphs, solvates, or hydrates were found for darifenacin HBr; consequently, no control of polymorphs will be required.

The regulatory specification for darifenacin HBr includes Physical Tests [ ]]

The key methods employ different types of high performance liquid chromatography [HPLC]. All methods in the specification have been properly and adequately validated.

The acceptance criteria for the drug substance specification have been justified based on batch analysis results for release and stability. Primary data were derived from studies with — batches manufactured by the proposed commercial synthesis. The drug substance used in the stability studies was stored for up to 24 months at 25°C/60% relative humidity [RH] and 30°C/60% RH and up to 6 months at 40°C/75% RH. The range of results from these stability studies has been applied in establishing acceptance criteria for the drug substance specification that ensure production of darifenacin HBr with a consistent quality appropriate for its intended use in the manufacture of extended release [ER] tablets.

Stability studies included stress testing as well as the standard stability program described above. The stress testing studies used a variety of conditions to establish the nature and extent of potential drug substance degradation pathways. The studies were conducted both [ ]. Based on an evaluation of these data, — degradation products are possible, each of which is readily detectable by the methodology employed in the registration stability program. The registration stability program evaluated three batches of darifenacin HBr manufactured using the proposed commercial process. These studies demonstrated that darifenacin HBr drug substance is stable over a wide range of storage conditions when stored as indicated. The data in this report support the proposed —— re-test period for darifenacin HBr.

Drug Product

An extended release [ER] presentation of the drug product was the focus of an extensive formulation development program to provide patients with a once-daily dosing regime. Two dose strengths (7.5mg and 15mg) were identified for commercialization. In addition to these proposed commercial strengths, a 30mg extended release [ER] tablet was developed in parallel, but is not to be marketed. Data (from registration stability, process development studies, and bioequivalence studies) accumulated with this formulation, where relevant, have been used in the submission to support or bracket data for the lower strength formulations.

The tablets are composed of darifenacin HBr, dibasic calcium phosphate ([ ] hydroxypropyl methylcellulose [hypromellose] ([ ] and magnesium stearate [ ] These excipients are tested to ensure compliance with pharmacopoeial monographs as appropriate. The formulations are based on [— and are used to produce tablets of strengths 7.5mg and 15mg (as darifenacin). Following] to produce 8 mm round shallow convex shaped tablets, the tablets are film-coated with a colored coat (to aid product differentiation) and clear over-coat [ ] Stability studies did not identify any problems from using the proposed excipients with darifenacin HBr.

The effects of various factors on the *in vitro* dissolution, homogeneity, and processing properties of the ER tablet formulation were carefully examined. Particle size was found to have no significant effect on the above properties; nevertheless, a particle size distribution specification requirement within the distribution range studied during formulation development was established to ensure batch-to-batch consistency. Hypromellose, included in the tablet core for modifying the release of darifenacin HBr from the tablet matrix, is the critical excipient in the

formulations. The hypromellose concentration, however, has been varied by ± 10% of the total formula weight with no adverse influence on the *in vitro* performance of the tablet.

Development studies were conducted to investigate the influence of manufacturing process parameters on tablet attributes and performance. Dry granulation via roller compaction was [ ] in the manufacturing process. The results of the development studies determined the — roller compaction pressure, which is maintained by monitoring throughout the proposed commercial manufacturing process. [ ]

Manufacture of the drug product will be carried out at the Pfizer facility in Brooklyn, NY. The commercial process for manufacturing darifenacin HBr ER tablets follows a typical tabletting process. The tablets are packaged into the appropriate primary pack (unit dose blisters or bottles). The proposed manufacturing process has no critical steps that require in-process controls for either the tablet blends or tablet cores. Two process parameters [ ] are monitored and maintained. All critical parameters of the drug product are tested at the final product stage. Manufacturing experience has demonstrated that the process is insensitive to the scale of manufacture and is robust to the proposed range of manufacturing equipment.

The container/closure systems for commercial use include high-density polyethylene [HDPE] bottles, — Aclar® Rx160 blisters with aluminum foil backing, and — Aclar® UltRx 2000 blisters with aluminum foil backing. Photostability studies revealed that the light peach color of the 15mg tablet tended to fade when packaged in [ ] No other adverse effects were observed. No fading was observed when the tablets were stored in bottles or in blister packs protected from light by storing in their secondary container. Stability studies carried out with the packaged 7.5mg tablets indicated that the proposed container/closure systems were compatible with drug product and provided adequate protection.

The regulatory specification for darifenacin HBr drug product includes [ ] The HPLC methods are appropriate modifications of the methods used in drug substance testing. The methods are well-described, particularly the critical Dissolution test. All methods in the specification have been properly and adequately validated.

The drug product acceptance criteria are based upon data obtained from tablets manufactured by the proposed commercial process. — batches of the 7.5mg ER tablets and — batches of the 15mg ER tablets were included in these studies. These batches were manufactured at scales between [ ] kg; the batch sizes from the proposed manufacturing site in Brooklyn, NY were [ ] of the proposed commercial batch size of [ ] kg. The data used to justify the product specification include release data for key tablet batches used in Phase 2/3 clinical trials and registration stability data up to and including 24 months. The acceptance criteria will remain in effect throughout the shelf life of the product. The specification will ensure the quality of each product with respect to appearance, identity of active component, assay (mg active/tablet), uniformity of dosage unit, impurities, and dissolution.

The stability of darifenacin HBr ER tablets was studied extensively during development. [ ]

[ ]

The stability program was designed to cover 7.5mg, 15mg, and 30mg tablets in a variety of packs including HDPE bottles and — Aclar® blisters with Al lidding foil. Although the 30mg tablets will not be commercialized, data from this strength were used in conjunction with the other strengths to define the product shelf life. Nineteen batches of darifenacin HBr ER tablets were manufactured at between [ ] of the proposed commercial scale at site, using the appropriate dosage form composition and the proposed commercial process. A bracketing strategy based on [ ] for the HDPE bottles was developed to limit the sample numbers needed for analysis. Consequently, only — lots of the 30 count HDPE bottles were included in the stability program, whereas —or more lots of bottles containing 100, or tablets were tested during the [ ] stability program. Studies with the — [ ] blister film had established their functional equivalence, permitting a reduction in the number of lots enrolled in the stability studies.

The stability study data documented the suitable stability of darifenacin HBr ER tablets after 24 months of storage at 25°C/60% RH and 30°C/60% RH or after six months storage at 40°C/75% RH. The Assay values at release for 7.5mg and 15mg tablets decreased slightly over the 24 months under long-term storage. The content of total impurities rose negligibly. Similar findings were obtained with dissolution testing: dissolution profiles remained well within the acceptance criteria at the 3 time points.

[ ] tests were also included in these studies: [ ] Levels of the enantiomer of darifenacin remained constant and low [ ] but these changes did not affect any of the attributes that have been included in the proposed specification. No issues with microbiological quality in the stability program were encountered. Because of these results, testing for the [ ] [ ] has not been included in the proposed specification.

The observations generated by the stability studies to date support the claim for [ ] expiration dating period for both tablet sizes (7.5mg and 15mg) in all packaging configurations (HDPE bottles and Aclar blisters) when stored at controlled room temperature—15 to 30°C (59° to 86°F)—and protected from light.

All manufacturing and testing sites have been recommended for Approval by the Office of Compliance [OC].

B. Intended Use of the Drug Product

ENABLEX Extended Release Tablets are proposed for the treatment of the symptoms of overactive bladder (OAB). The recommended starting dose of ENABLEX Extended Release Tablets is 7.5mg once daily. For those patients starting on 7.5mg daily and requiring greater symptom relief, the dose may be increased to 15mg daily, as early as two weeks after starting therapy, based on individual response. ENABLEX Extended Release Tablets should be taken once daily with liquid. They may be taken with or without food, and should be swallowed whole and not chewed, divided, or crushed. When stored at controlled room temperature—15 to 30°C

(59 to 86°F)—and protected from light, both tablet sizes (7.5mg and 15mg) in all packaging configurations (HDPE bottles and Aclar blisters) have a —— expiration dating period.

C. Basis for Approvability or Not-Approval Recommendation

All product quality issues that relate to the safety and efficacy of this drug product have been adequately addressed to support a recommendation to approve this NDA submission. The drug substance has been satisfactorily characterized by a variety of physicochemical methods. The manufacturing process is adequately controlled to assure consistent production of quality material. The drug substance specification includes attributes with acceptable tests and acceptance criteria to assure the quality of this material.

The two dose strengths—7.5mg and 15mg dosages—employ the same components that are considered safe for use. In all cases, tablet formulation is based on producing a drug product with equivalent properties, which has been demonstrated—particularly with regard to *in vitro* dissolution. Manufacturing operations are well-described with sufficient control to assure consistent production of quality material.

The attributes included in drug product specification—along with their test methods and acceptance criteria—are adequate for assuring drug product quality. Acceptable stability of the product was displayed under stress conditions and normal and accelerated storage conditions, permitting a recommendation of ɕ ɔ shelf life for the product.

Several items in the Label and Package Insert have been identified as having potential for contributing to user error. These comments have been conveyed by the Division to the sponsor. Until responses are received the recommendation for the Label and Package Insert is Approvable.

All of the manufacturing, packaging, and testing sites have undergone inspection and been found to be in compliance with cGMPs.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.FENSELAU/24-SEP-2003: Same date as draft review
D.T.Lin/Date:
J.KING/Date:

C. CC Block

HFD-820
E.DUFFY/Date:
D.-G.WU/Date:

Redacted 105

page(s) of trade secret and/or confidential commercial information

(b4)

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

/s/

Allan Fenselau
9/25/03 04:45:35 PM
CHEMIST

David T. Lin
9/25/03 05:08:01 PM
CHEMIST
I concur.

NDA FILEABILITY CHECKLIST

NDA Number: 21-513 **Applicant: Pfizer, Inc.** **Stamp Date: 03-DEC-2002**
Drug Name: ENABLEX™ (darifenacin HBr), Extended Release Tablets **Letter Date: 03-DEC-2002**

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES
The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes/ No	Comment
1	On its face, is the section organized adequately?	Y	
2	Is the section indexed and paginated adequately?	Y	CMC Pagination is non-sequential. Location is given as pg.no. in subsection, e.g., "General Information." Referencing in review the location of data in the submission is difficult/awkward.
3	On its face, is the section legible?	Y	
4	Are all of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	Y	See attached list (from amendment dated 20-JAN-2003).
5	Is a statement provided that all facilities are ready for GMP inspection?	Y	
6	Has an environmental assessment report or categorical exclusion been provided?	Y	Module 1: "Environmental Assessment"
7	Does the section contain controls for the drug substance [DS]?	Y	Module 3.2.S.4.
8	Does the section contain controls for the drug product [DP]?	Y	Modules 3.2.P.4 and 3.2.P.5.
9	Has stability data and analysis been provided to support the requested expiration date?	Y	DS: Module 3.2.S.7. DP: Module 3.2.P.8.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Y	
11	Have draft container labels been provided?	Y	Module 1: "Labeling"
12	Has the draft package insert been provided?	Y	Module 1: "Labeling"
13	Has an Investigational Formulations section been provided?	Y	Module 3.2.P.2.
14	Is there a Methods Validation package?	Y	Module 3.2.R.2.
15	Is a separate microbiological section included?	Y	Not applicable

If the NDA is not fileable from a manufacturing and controls perspective, state on a separate page why it is not.

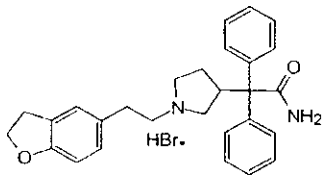
Reviewing Chemist: Date:
Allan Fenselau

Team Leader Date:
David Lin

cc:
Original NDA 21-513 HFD-580/Chem/A.Fenselau HFD-580/PM/J.King
HFD-580/Division File HFD-830/DivDir/E.Duffy

NDA Number: 21-513 Applicant: Pfizer Inc.
Drug Name: ENABLEX (darifenacin hydrobromide)

DARIFENACIN HBr
$C_{28}H_{30}N_2O_2 \bullet HBr$
M.W.: 507.5
(*S*)-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide



LISTING of MANUFACTURING and TESTING SITES USED in the MANUFACTURE of the DRUG PRODUCT, ENABLEX ER Tablets

DMF NO./ TYPE	CFN	HOLDER	DESCRIPTION	LOA	Insp. Ready (on 2/15/03)	ADDRESS
DARIFENACIN HYDROBROMIDE						
-----	9611016	Pfizer Ireland Pharmaceuticals	DS manuf. /testing (release & stability)	-----	Yes	Ringaskiddy, Ireland
ENABLEX Extended Release Tablets						
-----	2410924 2627208	Pfizer, Inc.	DP manuf./pckging./testing (release & stability)	-----	Yes Yes	Brooklyn, NY
-----				-----	Yes	
-----	Not relevant			-----	Not relevant	

Abbreviations used: DS, Drug Substance; DP, Drug Product.

Have all DMF References been identified? YES

SUPPORTING DOCUMENTS:

DMF No.	LOA	Manufacturer	Location	Manufactured Item(s)
DMF	Yes			
DMF	Yes			
DMF	Yes			
DMF	Yes			
DMF	Yes			
DMF	Yes			
DMF	Yes			

Redacted 1

page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

Allan Fenselau
1/27/03 07:16:20 AM
CHEMIST

David T. Lin
1/27/03 07:51:56 AM
CHEMIST
I concur.

NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Drug Master File (DMF)

Sufficient information available in application. See page 7 of Chemistry Review.

/S/

9/3/07

NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Environmental Assessment

Environmental assessment is acceptable. See page 7 of Chemistry Review addressing Environmental Assessment.

/S/

9/3/03

NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Microbiology Sterility Review

Not applicable to this application (microbiology review is not required for oral tablets).

/S/

9/3/03

NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Facilities Inspection (EES)

Refer to pages ---- of Chemistry Review addressing Establishment Inspections.

NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Methods Validation

Methods validation to be conducted at FDA lab. See page 7 of Chemistry Review.

/S/
9/3/03