CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-518

CHEMISTRY REVIEW(S)

Addendum to CMC Review # 2 of NDA 21-518

From: **Donna F. Christner, Ph.D.**
To: **NDA 21-518**
Date: **19-Nov-2004**
Subject: **Removal of — from packaging**

The sponsor has submitted a fax to be followed by an archival Amendment to NDA 21-518 on 19-Nov-2004 committing to remove the graphic logo from all VESIcare packaging. Mock artwork will be submitted as soon as possible. This was in response to a teleconference held on 19-Nov-2004 where the sponsor was informed that DDMAC re-evaluated the — on the external cartons and believes it violates 21 CFR 1.21(a)(1). (See DFS for teleconference minutes). A copy of the sponsor's fax is reproduced below.

NDA 21-518
VESIcare (solifenacin succinate)
5 mg and 10 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Yamanouchi Pharma America, Inc.
Paramus, NJ

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

Presentations: 23mL — , bottle/30 or 90 count; —

—

EER Status: Acceptable 10/16/2003

Consults: DMETS – See comments below in drug product section - labeling
EA – none - categorical exclusion
Micro - acceptable

Original Submission: 12-DEC-2002

Drug Substance Solifenacin succinate is a white crystalline powder, freely soluble in water. — ; have been observed. It contains two chiral centers and levels of the enantiomers and diastereomers are controlled by —

— analysis is used to measure Chiral Purity, while other potential impurities are measured using either GC or HPLC. The manufacturing process and controls are considered adequate. Specifications are considered acceptable. It is manufactured by Yamanouchi Pharmaceutical Co., Ltd. at its Takahagi Plant in Akahama, Takahagi-shi, Japan. The drug substance is relatively stable and based on the data submitted, a retest period of — , is granted.
Conclusion Drug substance is acceptable.

Drug Product VESIcare® Tablets are available in 5 mg (coated light yellow) and 10 mg (coated light pink) strengths consisting of — solifenacin succinate, Lactose monohydrate, NF, Corn Starch, NF, Hypromellose 2910, USP, and Magnesium Stearate, NF, and film coated — Hypromellose 2910, USP, Talc, USP, Polyethylene Glycol 8000, NF, Titanium Dioxide, USP and either Yellow Ferric

Oxide (5 mg tablets) or Red Ferric Oxide (10 mg tablets). The drug product is manufactured at the Yamanouchi Norman OK facility, and packaged at —

Stability data included in the application supports an expiry of 24 months for the drug product whereas the firm had requested — . – the AP letter should indicate that the granted expiry is 24 months.

Following completion of the cycle 1 CMC, and AE action letter, was issued requesting additional data to support the dissolution specification of — /30 min., additional data were submitted supporting the proposed specification. All specifications are acceptable

All associated DMFs are acceptable.

Use of the trade name "Vesicare" was discussed with the firm 18-NOV-2004 (JBeitz), and an agreement was reached to revise to "VESIcare". PI and immediate and carton labels were revised and submitted – acceptable. All labeling is acceptable.
Conclusion Drug Product is acceptable

Overall Conclusion:
From a chemistry perspective, the application is recommended for approval.

Eric P. Duffy, PhD

Director, DNDC II/ONDC

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
11/19/04 09:15:47 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-518

Vesicare
(Solifenacin succinate Tablets)

Yamanouchi Pharma, Inc.

Donna F. Christner, Ph.D.
Division of Reproductive and Urologic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-518

2. REVIEW #: 2

3. REVIEW DATE: 18-Nov-2004

4. REVIEWER: Donna F. Christner

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	19-DEC-2002
Amendment	25-APR-2003
Amendment	08-MAY-2003
Amendment	13-JUN-2003
Amendment	25-JUN-2003
Amendment	18-JUL-2003
Amendment	24-JUL-2003
Amendment	19-SEP-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	24-Mar-2004
Amendment	18-May-2004
Amendment	18-Jun-2004
Amendment	24-Sep-2004
Amendment	09-Nov-2004

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Yamanouchi Pharma America, Inc
Address:	Mack Centre IV, 4th Floor S. 61 Paramus Road Paramus, NJ 07652
Representative:	Rudolph W. Lucek Vice President, Drug Regulatory Affairs
Telephone:	201-909-3041

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Vesicare®
b) Non-Proprietary Name (USAN): solifenacin succinate
c) Code Name/# (ONDC only): YM905
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Muscarinic receptor antagonist

11. DOSAGE FORM: Immediate release tablet

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: oral

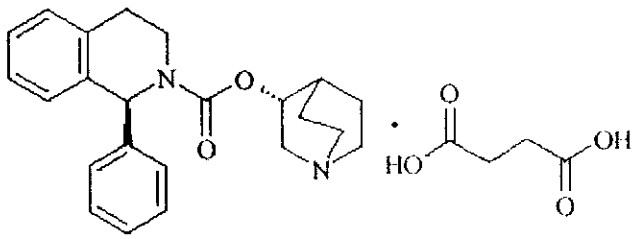
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

_____SPOTS product – Form Completed

____x__Not a SPOTS *

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



USAN Name:	Solifenacin succinate*
INN Name:	Solifenacin
CAS Number:	242478-38-2
Molecular Formula:	$C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$
Molecular Weight:	480.56

Chemical Name: **butanedioic acid**, compd. with (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (1:1)

(3R)-1-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate monosuccinate

(+)-(1S, 3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate monosuccinate

*The drug product has been formulated and dosed using the succinate salt of solifenacin.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	III	/	/	3	Adequate	15-SEP-2000	Reviewed by R. Seevers for DMF Bundle/Strike Force
/	III	/	/	3	Adequate	22-APR-2002	Reviewed by R. Frankewich for NDA 21-156/SCP-002
/	III	/	/	3	Adequate	25-SEP-2001	Reviewed by J. Salemme for NDA 21-319
/	III	/	/	1	Adequate	27-MAY-2003	
/	III	/	/	3	Adequate	07-SEP-2001	Reviewed by D. Klein for NDA 21-278
/	III			1	Adequate	19-MAY-2003	
/	III	/	/	1	Adequate	23-MAY-2003	
/	III	/	/	3	Adequate	18-APR-2000	Reviewed by X. Ysern for NDA 21-202
/	IV		/	1	Adequate	19-MAY-2003	
				1	Adequate	19-MAY-2003	

[1] Action codes for DMF Table:

Chemistry Review Data Sheet

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 58,135	
17-JAN-2002 pre-NDA, CMC meeting	IND 58,135	Minutes of pre-NDA, CMC meeting
27-FEB-2002 Memorandum	IND 58,135	Special Protocol Assessment: Stability Protocol
CMC Review #1	NDA 21-518	First cycle CMC review

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	**Acceptable**	17-OCT-2003	
Pharm/Tox	N/A		
Biopharm	Acceptable	16-OCT-2003	D.J. Chatterjee
LNC	N/A		
Methods Validation	Samples will be submitted to FDA Labs		
DMETS	Not Acceptable	20-Oct-2004	Jinhee Jahng
	Accepted by Division	17-Nov-2004	
EA	Acceptable	17-JAN-2002	Rajiv Agarwal (preNDA meeting)
Microbiology	Acceptable	01-MAY-2003	Stephen Langille

The Chemistry Review for NDA 21-518

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can be APPROVED from a CMC standpoint.

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

This section is not applicable.

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE

Solifenacin succinate is a new molecular entity (NME). It is a white crystalline powder that is freely soluble in water. — have been observed. Structural elucidation has been established via — various standard spectroscopic methods (— and — .

Solifenacin succinate contains two chiral centers and formation/final levels of the enantiomer and diastereomers are controlled by —
— analysis is used to measure Chiral Purity, while other potential impurities are measured using either GC or HPLC —). Other tests include Description, Identification (—

A retest period of — was proposed. Based on the data submitted to date, **a retest period of — can be granted.** This has been accepted by the sponsor.

During the IND stage, both —
— were accepted by the Division as starting materials.

DRUG PRODUCT

Vesicare® is a film-coated, immediate-release tablet for once-daily oral administration indicated for the —
— . The tablets are formulated and dosed as the succcinate salt of solifenacin. The tablets are available in 5 mg (coated light yellow) and 10 mg (coated light pink) strengths

consisting of — solifenacin succinate, Lactose monohydrate, NF, Corn Starch, NF, Hypromellose 2910, USP, and Magnesium Stearate, NF, and film coated — Hypromellose 2910, USP, Talc, USP, Polyethylene Glycol 8000, NF, Titanium Dioxide, USP and either Yellow Ferric Oxide (5 mg tablets) or Red Ferric Oxide (10 mg tablets). — package configurations are available: 30 or 90 tablets in a 23cc — bottle.

For the commercial-size tablet manufacturing, — are prepared. —

Phase 1 studies utilized a solifenacin succinate — The formulation for Phase 2 studies was almost identical to the Phase 3 and the to-be-marketed formulation, except for a lower level of hypromellose — and the film-coat color (— vs. yellow or pink). Comparative dissolution studies showed the Phase 2 and Phase 3 tablets to be equivalent. — — Phase 3 clinical supplies were manufactured in the Palo Alto, CA facility. Commercial supplies will be manufactured in the Norman, OK facility, where — commercial-scale, site-specific batches have been manufactured and placed on stability. Comparative dissolution studies show the Phase 3 clinical supplies and the site-specific batches to be comparable. The APPROVABLE letter requested additional dissolution data be submitted to justify the sponsor's acceptance criteria.

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

Vesicare® oral tablets are formulated for once daily administration. Both the 5 mg and 10 mg tablets are available in - presentations. Two tablet counts (30 and 90 tablets) are available in 23 cc bottles with child-resistant caps. —

The sponsor has requested a — expiry based on long-term stability data of 24 months for the Palo Alto/Phase 3 supplies, and — for the Norman, OK/site-specific tablets. Based on this submitted data, **an expiry of 24 months is granted**. The sponsor has accepted the expiry.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor submitted the additional dissolution data requested at the end of the first review cycle and outlined in the APPROVABLE letter. Analysis of the data led to the conclusion that the original dissolution criteria (Q= – at 30 minutes) are adequate to monitor the quality of the tablets.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Donna F. Christner, Ph.D./Date: 18-Nov-2004
Moo-Jhong Rhee, Ph.D./Date
Jean Makie/Date

C. CC Block

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/s/

Donna Christner
11/19/04 07:31:11 AM
CHEMIST

Final review, editorial change made

Moo-Jhong Rhee
11/19/04 09:23:04 AM
CHEMIST
I concur

NDA 21-518
Vesicare(solifenacin succinate)
5 mg and 10 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Yamanouchi Pharma America, Inc.

Indication: Muscarinic receptor antagonist for treatment of overactive bladder

Presentations: film-coated, immediate-release tablet , 30 or 90 tablets in a 23cc — bottle.

EER Status: Acceptable 10/16/2003

Consults: OPDRA , acceptable; EA, not applicable (categorical exclusion)

Vesicare Tablet is a product of solifenacin succinate, a muscarinic receptor antagonist for treatment of overactive bladder. Solifenacin succinate is a white crystalline powder, freely soluble in water. — have been observed. It contains two chiral centers and formation/final levels of the enantiomer and diastereomers are controlled by

analysis is used to measure Chiral Purity, while other potential impurities are measured using either GC or HPLC. It is manufactured by Yamanouchi Pharmaceutical Co., Ltd. At its Takahagi Plant in Akahama, Takahagi-shi, Japan. The drug substance is relatively stable and based on the data submitted to date, a retest period of — was granted.

Vesicare® Tablet is available in 5 mg (coated light yellow) and 10 mg (coated light pink) strengths consisting of — solifenacin succinate, Lactose monohydrate, NF, Corn Starch, NF, Hypromellose 2910, USP, and Magnesium Stearate, NF, and film coated — Hypromellose 2910, USP, Talc, USP, Polyethylene Glycol 8000, NF, Titanium Dioxide, USP and either Yellow Ferric Oxide (5 mg tablets) or Red Ferric Oxide (10 mg tablets). — package configurations are available: 30 or 90 tablets in a 23cc — bottle, —

— . The drug product is manufactured at Yamanouchi's facility at Palo Alto, CA , packed at —

Each tablet of 150 mg contains — lactose — The applicant requested an exclusion of a test for — from the release specifications for the fact that the drug substance is — The data was

forwarded to Microbiology Staffs for consult and based on their recommendation, the request was accepted. Stability data included in the application supports an expiry of 24 months for the drug product.

The CMC review was previously completed and an information request letter dated 13-JUN-2003 was forwarded to the applicant. All deficiencies contained in the letter have now been addressed. Regarding Environmental Assessment, the sponsor has made a request for a categorical exclusion under 21CFR25.31(b). The have calculated the increase in the amount of solifenacin free base to be – , well below the limit of <1ppb. The categorical exclusion was granted in the 17-JAN-2002. DDMC and DMETS have also found that the use trade name "Vesicare" is acceptable.

Overall Conclusion:
From a chemistry perspective, the application is recommended for approval, pending an acceptable cGMP inspection.

Duu-Gong Wu, PhD
Deputy Director, DNDC II/ONDC

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/s/

Eric Duffy
10/17/03 12:09:08 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-518

Vesicare
(Solifenacin succinate Tablets)

Yamanouchi Pharma America, Inc.

Donna F. Christner, Ph.D.
Division of Reproductive and Urologic Drug Products

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III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment 11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 11

S DRUG SUBSTANCE [Solifenacin succinate, Yamanouchi Pharmaceutical] 11

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Chemistry Review Data Sheet

1. NDA 21-518

2. REVIEW #: 1

3. REVIEW DATE: 17-OCT-2003

4. REVIEWER: Donna F. Christner

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	19-DEC-2002
Amendment	25-APR-2003
Amendment	08-MAY-2003
Amendment	13-JUN-2003
Amendment	25-JUN-2003
Amendment	18-JUL-2003
Amendment	24-JUL-2003
Amendment	19-SEP-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Yamanouchi Pharma America, Inc
Address:	Mack Centre IV, 4th Floor S. 61 Paramus Road Paramus, NJ 07652
Representative:	Rudolph W. Lucek Vice President, Drug Regulatory Affairs
Telephone:	201-909-3041

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Vesicare®
b) Non-Proprietary Name (USAN): solifenacin succinate
c) Code Name/# (ONDC only): YM905
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Muscarinic receptor antagonist

11. DOSAGE FORM: Immediate release Tablet

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: oral

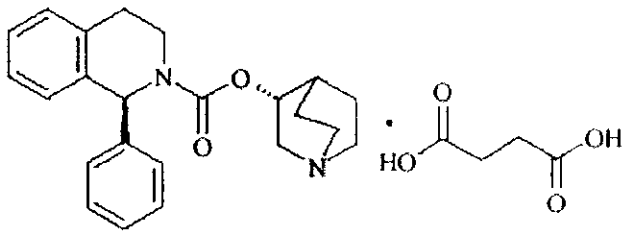
14. Rx/OTC DISPENSED: __x_Rx ___OTC

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

___x___Not a SPOTS product*

/

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



USAN Name:	Solifenacin succinate*
INN Name:	Solifenacin
CAS Number:	242478-38-2
Molecular Formula:	$C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$
Molecular Weight:	480.56

Chemical Name: butanedioic acid, compd. With (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (1:1)

(3R)-1-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate monosuccinate

(+)-(1S, 3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate monosuccinate

*The drug product has been formulated and dosed using the succinate salt of solifenacin.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	15-SEP-2000	Reviewed by R. Seevers for DMF Bundle/Strike Force
	III			3	Adequate	22-APR-2002	Reviewed by R. Frankewich for NDA 21-156/SCP-002
	III			3	Adequate	25-SEP-2001	Reviewed by J. Salemme for NDA 21-319
	III			1	Adequate	27-MAY-2003	
	III			3	Adequate	07-SEP-2001	Reviewed by D. Klein for NDA 21-278
	III			1	Adequate	19-MAY-2003	
	III			1	Adequate	23-MAY-2003	
	III			3	Adequate	18-APR-2000	Reviewed by X. Ysern for NDA 21-202
	IV			1	Adequate	19-MAY-2003	
				1	Adequate	19-MAY-2003	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,135	
17-JAN-2002 pre-NDA, CMC meeting	IND 58,135	Minutes of pre-NDA, CMC meeting
27-FEB-2002 Memorandum	IND 58,135	Special Protocol Assessment: Stability Protocol

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	17-OCT-2003	
Pharm/Tox	N/A		
Biopharm	Acceptable	16-OCT-2003	D.J. Chatterjee
LNC	N/A		
Methods Validation	Samples will be submitted to FDA Labs		
DMETS	Acceptable	24-SEP-2003	Denise Toyer
EA	Acceptable	17-JAN-2002	Rajiv Agarwal (preNDA meeting)
Microbiology	Acceptable	01-MAY-2003	Stephen Langille

The Chemistry Review for NDA 21-518

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is APPROVABLE from a CMC standpoint upon resolution of Dissolution Specification and approved labeling.

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

None required.

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE

Solifenacin succinate is a new molecular entity (NME). It is a white crystalline powder that is freely soluble in water. — , have been observed. Structural elucidation has been established via — , various standard spectroscopic methods — , and —

Solifenacin succinate contains two chiral centers and formation/final levels of the enantiomer and diastereomers are controlled by — C analysis is used to measure Chiral Purity, while other potential impurities are measured using either GC or HPLC — —). Other tests include Description, Identification — — A retest period of was proposed. Based on the data submitted to date, **a retest period of can be granted.** This has been accepted by the sponsor.

During the IND stage, — — were accepted by the Division as starting materials.

DRUG PRODUCT

Vesicare® is a film-coated, immediate-release tablet for once-daily oral administration indicated for the

The tablets are formulated and dosed as the succcinate salt of solifenacin. The tablets are available in 5 mg (coated light yellow) and 10 mg (coated light pink) strengths consisting of solifenacin succinate, Lactose monohydrate, NF, Corn Starch, NF, Hypromellose 2910, USP, and Magnesium Stearate, NF, and film coated Hypromellose 2910, USP, Talc, USP, Polyethylene Glycol 8000, NF, Titanium Dioxide, USP and either Yellow Ferric Oxide (5 mg tablets) or Red Ferric Oxide (10 mg tablets). package configurations are available: 30 or 90 tablets in a 23cc bottle,

For the commercial-size tablet manufacturing, are prepared.

Phase 1 studies utilized a solifenacin succinate The formulation for Phase 2 studies was almost identical to the Phase 3 and the to-be-marketed formulation, except for a lower level of hypromellose (and the film-coat color (vs. yellow or pink). Comparative dissolution studies showed the Phase 2 and Phase 3 tablets to be equivalent. Phase 3 clinical supplies were manufactured in the Palo Alto, CA facility. Commercial supplies will be manufactured in the Norman, OK facility, where commercial-scale, site-specific batches have been manufactured and placed on stability. Comparative dissolution studies show the Phase 3 clinical supplies and the site-specific batches to be comparable. The acceptance criterion for the dissolution test remained to be determined in the next review cycle.

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

Vesicare® oral tablets are formulated for once daily administration. Both the 5 mg and 10 mg tablets are available in presentations. Two tablet counts (30 and 90 tablets) are available in 23 cc bottles with child-resistant caps.

The sponsor has requested a — expiry based on long-term stability data of 24 months for the Palo Alto/Phase 3 supplies, and — for the Norman, OK/site-specific tablets. Based on this submitted data, **an expiry of 24 months can be granted**. The sponsor has accepted the expiry.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is an NME that is well characterized and controlled. The manufacturing process is robust.

The drug product is adequately controlled by the release specifications, except for Dissolution. The sponsor will submit additional data to support their proposed acceptance criterion. The manufacturing process is robust.

The sponsor responded adequately to the 13-JUN-2003 deficiency letter.

This NDA is APPROVABLE from a CMC standpoint pending resolution of the request to modify the Dissolution specification and approved labeling.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Donna F. Christner/Date: 16-OCT-2003
Moo-Jhong Rhee/Date
Jean King/Date

C. CC Block

97 Page(s) Withheld

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

/s/

Donna Christner
10/17/03 11:35:44 AM
CHEMIST

I incorporated the changes in the body of the review and attached the EES report as an appendix

Moo-Jhong Rhee
10/17/03 12:11:43 PM
CHEMIST
I concur

14 Page(s) Withheld