CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-518

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

PATENT INFORMATION

1. Active Ingredient(s):	solifenacin succinate
2. Strength(s):	5 mg and 10 mg
3. Trade Name:	VESICARE®
4. Dosage Form/Route of Administration:	Tablet, Oral
5. Application Firm Name:	Yamanouchi Pharma America
6. NDA Number:	21-518
7. First Approval Date:	None
8. Exclusivity:	Subject to patent rights, first NDA can be submitted five years from date of pending NDA approval.
9. Patent Information:	
Patent Number/Expiration Date:	USP 6,017,927/ Dec. 27, 2015*
Type of Patent:	Utility patent claiming product
Patent Owner:	Yamanouchi Pharmaceutical Co., Ltd.

* Subject to patent term extension provisions of 35 USC §156 et seq.

NDA 21-518 VESIcare
Solifenacin succinate 5 and 10 mg

EXCLUSIVITY SUMMARY for NDA # NDA 21-518
Trade Name Requested VESIcare
Generic Name Solifenacin succinate
Applicant Name Yamanouchi Pharma-America HFD- 580
Approval Date November 19, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /__/

   b) Is it an effectiveness supplement? YES /__ / NO /_X__/

   If yes, what type (SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_X__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_ _/ NO /_ X __/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9**:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #_3_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor

of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # __ YES /_ _/ ! NO /___/ Explain:

Investigation #2

IND # ____ YES /___/ ! NO /___/ Explain:

Investigation #3

IND # _____ YES /_ __/ ! NO /___/ Explain:

Investigation #4

IND # _____ YES /_ __/ ! NO /___/ Explain:

Investigation #5

IND # _____ YES /__/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__/

If yes, explain: _____

_____

_____

{See appended electronic signature page}

Jean Makie, M.S., R.D.
Signature of Preparer Date

Title: Project Manager

NDA 21-518 VESIcare
Solifenacin succinate 5 and 10 mg

{See appended electronic signature page} Date

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Donna Griebel
11/19/04 02:58:57 PM

DEBARMENT CERTIFICATION

Yamanouchi Pharma America, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-518 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: May 20, 2004 **Action Date:** November 19, 2004

HFD 580 **Trade and generic names/dosage form:** VESIcare (solifenacin succinate), 5 and 10 mg tablets

Applicant: Yamanouchi Pharma-America. **Therapeutic Class:** 1

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: overactive bladder (OAB)

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ X **No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg** ____	**mo.** ____	**yr.** birth	**Tanner Stage** ____
Max ____	**kg** ____	**mo.** ____	**yr.** 4	**Tanner Stage** ____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **X Disease/condition does not exist in children**

The basis for this partial waiver is that the diagnosis of OAB is difficult to clinically define in healthy pediatric patients aged birth through 4 years old.

- ☐ **Too few children with disease to study**

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.** 5	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 17	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

In their October 22, 2004 submission, the Sponsor stated their intention to initiate pediatric evaluation of solifenacin succinate via an open label, single dose PK study — in children (age 5-11 years old) and adolescents (age 12-17 years old) with OAB. The Division grants deferral of pediatric studies under PREA for treatment of OAB in pediatric patients for ages five to 11 years old and adolescents for ages 12 to 17 years old.

Date studies are due (mm/dd/yy): May 18, 2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

(See appended electronic signature page)

_____

Regulatory Project Manager

cc:

HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

APPEARS THIS WAY
ON ORIGINAL

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg**____	**mo.**_____	**yr.**____	**Tanner Stage**_____
Max____	**kg**____	**mo.**_____	**yr.**____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ɛction D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-518**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Donna Griebel
11/19/04 02:19:47 PM

Waiver Request

Request for a Waiver from Conducting Clinical Studies in Pediatric Patients

NDA 21-518 is being submitted in support of the approval of Vesicare® (solifenacin succinate) for use in the relief of symptoms of urinary frequency, urinary incontinence or urinary urgency associated with overactive bladder. Pursuant to consultation with pediatric experts we are requesting a waiver from the requirement to conduct clinical studies of Vesicare® in pediatric patients for use in the treatment of overactive bladder. This request is based on our understanding that overactive bladder, the indication being sought, is not a condition that occurs in children.

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 23, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: NDA 21-518 VESIcare® (solifenacin succinate) Tablets

Reference is made to the letter submitted to NDA 21-518 on November 19, 2004, in which Yamanouchi Pharma America, Inc., committed to remove the — from all VESIcare packaging. Since the has already been deleted from the bottle labels and blister backings, the artwork for these components is not included in this submission. Artwork for all cartons, revised to delete the —, is being included in this submission.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W. Lucek
Vice President, Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

Attachment
YM No. 2004-0268

8 Draft Labeling Page(s) Withheld

Regulatory Review Memorandum

From: Jean Makie, M.S., R.D., Sr. Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (DRUDP)

To: **NDA 21-518**

Regarding: Correction of Approval Letter for NDA 21-518 (VESIcare), dated November 19, 2004

Date of memorandum: November 22, 2004

Sponsor: Yamanouchi Pharma America, Inc.
Mack Centre IV, S 61 Paramus Rd.
Paramus, New Jersey

Drug: solifenacin succinate

Pharmacologic class: M_3 muscarinic receptor antagonist

Tradename: VESIcare

Dosage strength: 5 and 10 mg

Route of administration: oral

Proposed indication: "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency"

Executive Summary and Recommendation: An Approval (AP) letter for VESIcare was issued by the Office of Drug Evaluation (ODE) III on November 19, 2004. This letter contains language regarding pending revisions to the Sponsor's external cartons. Further internal review of this letter now warrants this language to be corrected. Therefore, the attached November 19, 2004 AP letter (which was faxed on November 19, 2004, but not mailed to the Sponsor) has been superceded and corrected by the revised approval letter dated November 19, 2004.

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 19, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: NDA 21-518 VESIcare® (solifenacin succinate) Tablets

Yamanouchi Pharma America, Inc., commits to remove the — from all VESIcare packaging. Mock artwork of all revised cartons will be submitted to the Agency as soon as possible.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Robert E. Desjardins

for Rudolph W. Lucek
Vice President, Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

YM No. 2004-0262

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 23, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Approval letter

Total no. of pages including cover: 22

Comments: see comment below.

Document to be mailed: **YES** NO

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Dear Rudy,

A copy of the revised Approval letter for VESIcare (solifenacin succinate) is attached for your immediate receipt. An official copy of this letter will be sent to you via postal mail.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

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

/s/

Julie Beitz
11/19/04 03:25:06 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 19, 2004

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-518 VESIcare Tablets (solifenacin succinate);
Yamanouchi Pharma America, Inc.

Solifenacin succinate is a selective muscarinic M_3 receptor antagonist. This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's approval action for solifenacin 5 mg and 10 mg immediate release oral tablets given once daily for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. This submission represents a complete response to the Agency's October 17, 2003, approvable letter and adequately addresses our concerns regarding solifenacin effects on QT, dissolution acceptance criteria, and labeling.

QT Prolongation

Solifenacin is a substrate of CYP3A4. Co-administration of solifenacin with ketoconazole 400 mg, a potent inhibitor of CYP3A4, resulted in a 3-fold higher AUC compared to solifenacin alone. In addition, solifenacin exposure was shown to increase 2-fold in patients with severe renal impairment. The administration of potent 3A4 inhibitors to patients with severe renal impairment can be expected to further increase solifenacin exposure in these patients.

In the original NDA, the effect of solifenacin on rate-corrected mean QT change from baseline (using Fredericia's correction) was evaluated in phase 3 placebo-controlled trials. The placebo-subtracted mean change from baseline in QTcF on solifenacin 5 and 10 mg was approximately 5 msec. To address this finding further, the sponsor conducted Study R905-CL-022, a prospectively designed study in which 60 patients received multiple ascending doses of solifenacin (ranging from 10-50 mg) after a placebo run-in period. The mean change from baseline in QTcF was noted as follows: 0.89 msec on placebo, 0.26 msec on 10 mg solifenacin, 3.46 msec on 20 mg solifenacin, and 0.77 msec on 30 mg solifenacin. At doses of 40 and 50 mg, mean QTcF changes were negative (-3.82 and -8.46 msec respectively) for reasons that are not readily explained. Of note, all patients administered 50 mg dropped out prematurely due to anticholinergic side effects. The strengths of this study were the inclusion of placebo measurements, evaluation of solifenacin doses that were 5- to10-fold higher than to-be-marketed doses, and a relatively large sample size. The major limitation of the study was the lack of concurrent controls (positive and placebo) so that it was not possible to conclude with assurance that a mean QTcF change of 5 or 10 msec had been excluded. Other limitations included high intra-subject variability, no more than one replicate measure per time point, and the practice of rounding off QT readings to the nearest 10 msec.

In the 2003 approvable letter, the Agency requested that the sponsor conduct and submit for review a prospective, randomized, double-blind QT study that evaluated solifenacin doses that achieve exposures comparable to those achieved in the 022 study, and that included positive and placebo controls. The sponsor agreed to conduct Study 905-CL-043 and received Agency input on its design. Study subjects were female volunteers aged 19 to 79 years. They were randomized to one of two treatment groups after receiving a placebo dose and a moxifloxacin dose sequentially. One group (n=51) completed a sequence of daily solifenacin doses beginning with 10 mg, escalating to 20 mg and finally to 30 mg. The remaining patients (n=25) completed a parallel sequence of placebo and moxifloxacin doses. The results of this study were reviewed by the Division of Reproductive and Urologic Drug Products (DRUDP), as well as by Dr. Norman Stockbridge from the Division of Cardiorenal Drug Products, and by staff from the Office of Clinical Pharmacology and Biopharmaceutics, and the Office of Biostatistics. The placebo-subtracted

mean change from baseline in QTcF was noted as follows: 2 msec (90% CI = -3, 6) on 10 mg solifenacin, and 8 msec (90% CI = 4, 13) on 30 mg solifenacin. The mean change from baseline in QTcF on moxifloxacin for each of three sessions was 11 (90% CI = 7, 14), 12 (90% CI = 8, 17), and 16 msec (90% CI =12, 21), respectively. Thus, the effect of solifenacin 30 mg was somewhat lower than that observed for the moxifloxacin positive control.

These findings have been included in product labeling under **CLINICAL PHARMACOLOGY**, Cardiac Electrophysiology, and under **PRECAUTIONS**, Patients with Congenital or Acquired QT Prolongation. Of note, the sponsor has proposed a starting dose of 5 mg daily which may be increased to 10 mg daily. Doses greater than 5 mg are not recommended for patients with severe renal impairment, patients with moderate hepatic impairment, and patients administered therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. Use in patients with severe hepatic impairment is not recommended.

Dissolution Acceptance Criteria
The sponsor's complete response adequately addresses this issue.

Labeling
In the approvable letter, the sponsor was asked to address prevention and management of serious sequelae of constipation with use of solifenacin. Since the incidence of constipation on the 5 mg dose is lower than that on the 10 mg dose (5.4% vs. 13.4%), the current recommendation to begin dosing at 5 mg daily should minimize this concern. The patient package insert also addresses constipation and serious adverse events expected to occur with the use of anticholinergic agents such as solifenacin.

Phase 4 Studies
The safety and effectiveness of solifenacin in pediatric patients have not been established. We are waiving the pediatric study requirement for patients aged birth to four years, and are deferring pediatric studies for ages 5 to 17 years for this application. The sponsor commits to conducting pediatric studies under the Pediatric Research Equity Act for the treatment of overactive bladder in pediatric patients aged 5 to 11 years old and adolescents aged 12 to 17 years old. The final report should be submitted to the Agency no later than May 18, 2009.

Tradename Review
Although the Division of Medication Errors and Technical Support (DMETS) had previously found the proposed tradename "Vesicare" to be acceptable, they recently raised the possibility of confusion due to the similarity of "Vesicare" and "Benicar" when these names are handwritten. Benicar was not marketed when DMETS last considered the "Vesicare" tradename. Both products are available as a 5 mg yellow tablet and are taken once daily. However, the recommended dosing for Benicar, an anti-hypertensive, is 20 mg/day or 40 mg/day. The 5 mg dosage strength comprises [redacted] of prescriptions for Benicar (IMS Health) suggesting relatively low use. In addition, "Vesicare" and Benicar would not normally be shelved near each other in the pharmacy. To minimize potential confusion and/or shelving errors, the sponsor has agreed to prominently present the first half of the tradename, "VESI", in capital letters in all product labeling and packaging materials.

/S/

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
11/19/04 12:51:38 PM
DIRECTOR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 19, 2004

FROM: Juan (Joanne) Zhang, Mathematical Statistician (HFD-705)

TO: George Benson, M.D. (HFD-580)

SUBJECT: NDA 21518, Evaluation of QT data from Study 905-CL-043

I. INTRODUCTION

This is a statistical consult of the QT study (905-CL-043) of the NDA 21518 for VESICARE (Solifenacin succinate). Solifenacin succinate is an antimuscarinic compound being developed for the management of OAB (Overactive Bladder). Some similar compounds have shown electrocardiographic QT prolongation. The purpose of this clinical study was to evaluate the effect of escalating repeat doses of solifenacin on QTc interval in healthy women aged 19 to 79 years. Moxifloxacin, a drug with known mild QTc prolongation, was included as an active control to validate the assay sensitivity of the study.

I was asked to address whether the sponsor's analysis was reasonable.

II. SPONSOR'S STUDY DESIGN

The sponsor performed a five-session study (the sponsor erroneously claimed it was a sequential crossover study). In Session 1, a day before dosing, all subjects had one baseline measurement which was then followed by a single dose of 400 mg moxifloxacin. After at least a three-day washout, starting in Session 2, all subjects had their second time baseline measurements which was then followed by the placebo on the second day. Then all the subjects were randomized to one of the two treatment groups (Group A and Group B). In Session 3, all subjects in each group had their third time baseline measurements. Then the 51 subjects in Group A received oral solifenacin 10 mg for 14 days and the 25 subjects in Group B received matching placebo for 13 days and 400 mg moxifloxacin at Day 14. In Session 4, all subjects in Group A received solifenacin 20 mg for 5 days and the subjects in Group B received matching placebo for 5 days. In the last Session 5, subjects in Group A received solifenacin 30 mg for 14 days and subjects in Group B received placebo for 13 days and moxifloxacin at Day 14. The study design is summarized in the table below.

	Treatment Group A	Treatment Group B
Session 1	1-day baseline (no drug) On Day 0	
	Moxifloxacin (400 mg) on Day 1	
Session 2	1-day baseline (no drug) on Day 0	
	Placebo on Day 1	
Session 3	1-day baseline (no drug) on Day0	1-day baseline (no drug) on Day 0
	Solifenacin 10 mg x 14 days	placebo x13 days; moxi on Day 14
Session 4	Sollifenacin 20 mg x 5 days	placebo x 5 days
Session 5	Solifenacin 30 mg x 14 days	placebo x 13 days; moxi on Day 14

The QT intervals were measured at times 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours on Day 0 and Day 1 at Sessions 1 and 2; Day 0, Day 13 and Day 14 at Session 3 and Day 13 and Day 14 at Session 5. The original plan in the protocol was to analyze the data based on Group A only. According to the sponsor, "the purpose of Group B in this study is purely to characterize any gross session or time-related trends in the study". After observing the data, the sponsor did find that a strong period effect exists in the study; hence they decided to perform their analyses based on Group A and Group B data for Sessions 3 and 5 to evaluate the effect of solifenacin succinate on the QT interval at the time of peak plasma concentration of the drug. The sponsor used the nonparametric Hodges-Lehmann-Moses method to look at the MEDIAN of the baseline adjusted drug placebo differences; however, they used parametric method to look at the MEAN of the baseline adjusted differences between moxifloxacin and placebo. We do not think the H-L-M is the only method to analyze the data and also the interpretation by using different criteria (median for the drug and mean for the active control) is problematic. We analyzed the data from difference angles by examining the mean of both the drug-placebo difference and moxifloxacin-placebo differences.

III. RESULTS AND CONCLUSIONS

We evaluated the data using mainly three different methods to compare the baseline adjusted drug and placebo differences at Tmax. The data were also examined based on the data from Group A alone as proposed originally in the protocol. The effect of moxifloxacin was examined at three different sessions.

<u>Method 1: Mean comparison at individual Tmax.</u>

For each subject k in Group A, we corrected her QTcF (Fridericia correction) by her baseline at her Tmax, Tmax(k), here, k=1,2, …, n. n is the sample size in Group A. For simplicity, we use QTcF_A(k) to represent the baseline adjusted values for Group A. In Group B, at each time Tmax(k) from Group A, we calculated the mean of baseline adjusted QTcF over m subjects at Tmax(k), here m is the sample size in Group B; and denoted this average corrected QTcF in Group B as MeanQTcF_B(k).

Note that each MeanQTcF_B(k) is a random variable. We create another column corresponding to each MeanQTcF_B(k) as follows:

QTcF_B(k)=MeanQTcF_B(k)+z*sd.

Here, z is a random number from N(0,1) and s.d is the standard error of MeanQTcF_B(k).

Group A		Group B	Group B (data used)
Tmax(1)	QTcF_A(1)	MeanQTcF_B(1)	QTcF_B(1)
Tmax(2)	QTcF_A(2)	MeanQTcF_B(2)	QTcF_B(2)
...		...	...
Tmax(n)	QTcF_A(n)	MeanQTcF_B(n)	QTcF_B(n)

Based on the data constructed above, we could either perform a matched-pair t-test or a parallel two group t-test or perform a bootstrapping procedure using column 1 and column 3. The point estimators of the difference, and 2.5^{th}, 5th, 95th and 97.5^{th} percentiles are provided in Table 1 under Method 1 (matched, parallel and Bootstrapping 1). The reason for bootstrapping is that we believe the values of QTcF_B(k) from Group B are not mutually independent. Because of this, we also looked at other ways of bootstrapping our data.

In Bootstrapping 2, for each subject in Group A at her Tmax, we randomly pick up a subject from Group B, get the QTcF value at that Tmax and then perform a bootstrap procedure. The results are listed in Table 1.

In Bootstrapping 3, corresponding to each subject's Tmax from Group A, we have m observations from Group B (m is the sample size of Group B). Suppose n is the sample size for Group A, then we have mn observations. A bootstrap procedure was performed based on those mn observations, with random selection of subjects from each group, with QTcF values from Group B time-matched with those from Group A. The results are also listed in Table 1. The bootstrapping results were based on 10,000 bootstrap samples.

Method 2: mean comparison at population Tmax from Group B

First find the average Tmax from Group A and suppose it is T0. In our example, T0 is around 5.30 hours. Then we get the baseline adjusted QTcF for each subject from Group B at T0. Then we performed a two group t-test based on n observations from Group A and m observations from Group B. Since we only have observations at distinct time points, we provided the results at 6 hours since that is the closest time point to the population Tmax. The results for this method are also listed in Table 1.

Method 3: mean comparison at population Tmax for both Group A and Group B

The only difference between Method 3 and Method 2 is which Group A values were used. After obtaining the population Tmax, T0, all the QTcF values for each subject from both groups were calculated at T0, here we use 6 hours. The results are provided in Table 1.

Table 1 Point Estimates of the Differences between the Two Groups and the Corresponding Percentiles *

Method 1		**Point estimate**	**2.5th percentile**	**5th percentile**	**95th percentile**	**97.5th percentile**
Bootstrapping 1	S10-P3	-0.491	-5.090	-4.336	3.136	3.813
	S30-P5	6.424	2.543	3.143	9.687	10.351
Bootstrapping 2	S10-P3	0.498	-2.501	-2.033	2.929	3.422
	S30-P5	6.795	4.000	4.434	9.379	9.933
Bootstrapping 3	S10-P3	0.460	-3.633	-3.003	3.923	4.577
	S30-P5	6.823	2.493	3.228	10.516	11.236
matched	S10-P3	-0.531	-4.321	3.259	-5.046	3.985
	S30-P5	6.437	3.129	9.745	2.496	10.378
parallel	S10-P3	-0.531	-4.438	3.377	-5.186	4.125
	S30-P5	6.437	2.164	10.710	1.346	11.528
Method 2						
Hour=6	S10-P3	1.841	-2.775	6.458	-3.659	7.342
	S30-p5	8.379	3.663	13.095	2.760	13.998
Method 3						
Hour=6	S10-P3	-2.319	-6.828	-6.103	1.465	2.189
	S30-p5	8.130	3.384	4.147	12.112	12.875

* 2.5th (5th) and 97.5th (95th) percentiles corresponding to a two sided 95% (90%) Confidence Interval

We also performed the analysis at Tmax based on Group A alone. This is the original plan written in the protocol. We looked at the baseline adjusted time-matched QTcF differences at Tmax between the drug and placebo (Sessions 3 & 5 drug versus Session 2 placebo). The effect of moxifloxacin at three different sessions was also evaluated. The point estimators of the differences and the 2.5th, 5th, 95th and 97.5th percentiles are provided in Table 2.

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Table 2 Results Based Group A Analysis and the Effect of Moxifloxacin at Three Different Sessions

		Point estimator	2.5th percentile	5th percentile	95th percentile	97.5th percentile
Group A alone at Tmax						
	S10-P *	15.350	11.742	18.958	11.051	19.649
	S30-P *	16.522	12.525	20.520	11.760	21.285
Time-matched Moxi effect at Tmax						
	M – P *	10.668	6.856	14.480	6.126	15.210
	M3-P3 *	11.836	7.596	16.077	6.784	16.889
	M5-P5 *	15.676	11.558	19.793	10.769	20.582

* S10, S30: Solifenacin 10 mg and 30 mg, respectively.
M, P: Moxifloxacin and placebo at Session 2.
M3, P3: Moxifloxacin and placebo at Session 3.
M5, P5: Moxifloxacin and placebo at Session 5.

Even though we proposed three different methods to compare the means between Group A and Group B, we prefer using Method2. The other two methods need more assumptions. Therefore, using Fridericia's correction, our finding is that the mean difference between Solifenacin 10mg and placebo is 1.841 msec with 90% CI, (-2.775, 6.458) and the mean difference between Solifenacin 30mg and placebo is 8.379 msec with 90% CI, (3.663, 13.095). The sponsor's numbers for the above two are 0, (-5, 5) for the low dose and 7, (2,12) for the high dose, respectively.

The results for moxifloxacin are compatible with those provided by the sponsor.

In conclusion, if comparing Group A with Group B, our numbers are not that far from the numbers provided by the sponsor showing some QTc prolongation (upper confidence limit >10 msec) at the 30mg dose for the drug, but not at the 10mg dose. However, if we performed the analysis based on Group A alone, as shown in Table 2, the results suggest greater QTc prolongation for both doses of solifenacin.

Juan (Joanne) Zhang, Ph.D.

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/s/

Juan Zhang
11/19/04 02:02:42 PM
BIOMETRICS

Mike Welch
11/19/04 02:06:27 PM
BIOMETRICS

Stella Machado
11/19/04 02:12:35 PM
BIOMETRICS

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2566 Fax: (201) 291-7929

November 19, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: **NDA 21-518 VESIcare® (solifenacin succinate) Tablets**

Yamanouchi Pharma America, Inc., commits to remove the — from all VESIcare packaging. Mock artwork of all revised cartons will be submitted to the Agency as soon as possible.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Robert E. Desjardins

for Rudolph W. Lucek
Vice President, Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

YM No. 2004-0262

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: November 17, 2004 Teleconference Minutes are attached for your reference

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

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Teleconference Minutes

NDA: 21-518 **Sponsor**: Yamanouchi Pharma-America, Inc.

Drug: Solifenacin succinate **Date**: November 19, 2004 **Time**: 11:00-11:15 AM

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
George Benson, M.D., Urology Team Leader, DRUDP
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER)
Jean Makie, M.S., R.D., Project Manager, DRUDP
Barbara Chong, Division of Drug Marketing, Advertising, and Communications (DDMAC)

Yamanouchi Attendees
Robert Desjardins, M.D., Chief Development Officer

Discussion Issues: This teleconference was held by the Division to inform the sponsor that DDMAC re-evaluated the — displayed on the external cartons and believes that this — violates 21 CFR 1.21(a)(1), which pertains to a failure to reveal material facts.

Sponsor response: The Sponsor agreed to take these recommendations into consideration and, after further internal deliberation, committed to contacting the Division immediately with their decision.

Addendum: The Sponsor telephoned the Division at 11:45 AM on November 19, 2004 and committed to remove the — from all external cartons and to provide final draft carton labels as soon as feasible. This commitment will be faxed to the Division today.

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/s/

George Benson
11/19/04 12:20:06 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Approval letter

Total no. of pages including cover: 22

Comments: see comment below.

Document to be mailed: **YES** NO

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Dear Rudy,

A copy of the Approval letter for VESIcare (solifenacin succinate) is attached for your immediate receipt. An official copy of this letter will be sent to you via postal mail.

Sincerely,

Jean Makie, M.S., R.D. /S/
Sr. Regulatory Project Manager

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

/s/

Julie Beitz
11/19/04 03:24:06 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-518	Efficacy Supplement Type SE-	Supplement Number	
Drug: solifenacin succinate (VESIcare), 5 and 10 mg		Applicant: Yamanouchi Pharma-America	
RPM: Jean Makie		HFD- 580	Phone # 301-827-7270

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority Class 2 resubmission
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	November 19, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	N/A 21 CFR 314.50(i)(1)(*i*)(A) () Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	(505(b)(2) application) **No**
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (9/15/03, 10/17/04)

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE (October 17, 2003)
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DDMAC and ODS reviews completed;10/21/04; 9/16/04; 10/3/03; 10/14/03; 9/26/03; 9/25/03; 9/16/03; 8/9/02)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X (standard PREA language only)
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X (9/19/00)
• Pre-NDA meeting (indicate date)	X (7/1/02)
• Pre-Approval Safety Conference (indicate date; approvals only)	X (10/4/04)
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X, (10/17/03, 10/19/04)
[redacted]	
❖ Clinical review(s) *(indicate date for each review)*	X (Review #1, 10/17/03; Review # 2, 11/18/04)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (see clinical review 10/17/03)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A (not currently required)
❖ Statistical review(s) *(indicate date for each review)*	X (Review # 1, 10/16/03; Review # 2, 11/19/04)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (review # 1, 10/17/03; Review # 2, 11/19/04)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	[redacted]
• Clinical studies	X
• Bioequivalence studies	N/A
[redacted]	
❖ CMC review(s) *(indicate date for each review)*	X (CMC Review #1, 10/17/03; CMC Review # 2, 11/19/04)
❖ Environmental Assessment	[redacted]
• Categorical Exclusion *(indicate review date)*	X (EA acceptable; See Chemistry Review #1)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (5/1/03)
❖ Facilities inspection (provide EER report)	See Chemistry Review #1: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
[redacted]	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (Review #1, 10/16/03; Review # 2, 10/13/04, 10/17/04))
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X 10/13/04
❖ CAC/ECAC report	X (5/27/03)

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

'f you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/

Jean Makie
11/19/04 12:55:37 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: November 17, 2004 Teleconference Minutes are attached for your reference

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

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Teleconference Minutes

NDA: 21-518 **Sponsor**: Yamanouchi Pharma-America, Inc.

Drug: Solifenacin succinate **Date**: November 17, 2004 **Time**: 3:00 – 4:15 PM

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
George Benson, M.D., Urology Team Leader, DRUDP
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER)
Goudong Fang, Medical Reviewer, DRUPD
Jean Makie, M.S., R.D., Project Manager, DRUDP
Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., OCPB, Clinical Pharmacology Team Leader, DRUDP
Juan Zhang, Ph.D., Biostatistics Reviewer, Quantitative Methods Research Staff (QMR)
Edward Nevius, Ph.D., Division Director, Division of Biometrics II
Mike Welch, Ph.D., Biostatistics Team Leader, Division of Biometrics II
Steve Wilson, Ph.D., Biostatistics Team Leader, Deputy Division of Biometrics II

Yamanouchi Attendees
Rudy Lucek, Vice President, Regulatory Affairs
Neila Smith, M.D., Director, Drug Safety
Maskazu Andoh, Associate Director, Clinical Statistics
Robert Desjardins, M.D., Chief Development Officer
Susan Ridge, Director, Project Management
Christine Mulhauser, Director, Regulatory Affairs, CMC

Kenji Yasukawa, Senior Manager, Project Coordination Department, Yamanouchi Pharmaceutical Co., Japan

GlaxoSmithKline Attendees
Thomas Kline, Director, U.S. Regulatory Affairs
Sergio Forero-Schwanhaeuser, M.D., Director Medical Affairs
Venkat Sethuraman, Principal Statistician, Biomedical Data Sciences

Discussion Issues: This teleconference was scheduled at the request of the Division to discuss remaining labeling issues pertaining to the package insert (PI), patient package insert (PPI), carton and container labeling, and tradename. Prior to the call, the sponsor provided a revised PPI and PI with supporting comments to the Division; archival copies are to follow.

Issue 1: PPI: The Division proposed two changes to the PPI; the Sponsor accepted and agreed to submit a final draft PPI to the Division on November 18, 2004.

Issue 2: PI: The Division proposed multiple changes to the PI. Additional discussions occurred regarding the proposed Tables 1 – 5, proposed language in the "Cardiac Electrophysiology" section, and proposed language in the "Information for Patients" section. All outstanding PI issues were resolved and the Sponsor committed to submitting a final draft PI to the Division on November 18, 2004.

Issue 3: Tradename: The Division reiterated its concern for patient safety due to the potential for look-alike confusion between Benicar and Vesicare (the two names share orthographic characteristics that increase the likelihood for a dispensing error to occur). Discussion was held regarding further tradename characteristic changes and that could lessen the possibility of medication errors. The tradename issue was not resolved, however, the Division committed to immediately investigate the color presentation of Benicar labeling so that this discussion with the Sponsor could be continued.

Action Items:

1. The Division will send revised language for Table 1 and text under the "Cardiac Electrophysiology" section.
2. The Sponsor will submit electronic copies of the PPI and PI on November 18, 2004.
3. The Division will continue to discuss tradename issues with the Sponsor

Addendum:

Immediately following the teleconference, the Division telephoned the Sponsor to alert them to the similarity with Benicar's multicolored presentation of labeling (the Benicar website was provided). The Division reiterated its previous recommendation that the Sponsor develop packaging and labeling that emphasizes the VESI part of the name using capital letters, bolding, a special font, a different color, etc. to distinguish Vesicare as much as possible from the already marketed Benicar. The Division also suggested that .. The Sponsor concurred with these recommendations and committed to submit revised final draft color mock-ups of the carton and container labels to the Division on November 18, 2004.

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/s/

George Benson
11/18/04 02:59:36 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: additional PI comments

Total no. of pages including cover: 1

Comments: see comment below.

Document to be mailed: **YES** **NO**

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Dear Rudy,

Attached are minor changes for the PI. When you make these, submit the all labeling electronically as final draft labeling.

1. Line 29. Clin-pharm wants this changed. Take out the word — The sentence should now read "There is no significant effect of food on the pharmacokinetics of solifenacin."
2. Line 111 — should be QTcF
3. Line 202 – should be 76.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Phase IV postmarketing commitment: PREA studies

Total no. of pages including cover: 2

Comments: see comment below.

Document to be mailed: **YES** **NO**

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Dear Rudy,

As you know, PREA requires a sponsor to commit to conducting pediatric phase IV study(ies) if the Division does not completely waive such a requirement. The Division's postmarketing commitment for solifenacin is:

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Pediatric studies under PREA for the treatment of overactive bladder in pediatric patients for ages five to 11 years old and adolescents for ages 12 to 17 years old.

   Final Report Submission: May 18, 2009

Submit clinical protocols to your IND for this product. Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

If Yamanouchi agrees to this phase IV commitment, you will need to fax a letter clearly stating your commitment and then follow-up with an overnight submission.

Please call me if you have questions. Jean

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

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/s/

Jean Makie
11/18/04 03:25:38 PM

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 18, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Rockville, MD 20705

Ladies and Gentlemen:

Re: NDA 21-518 VESIcare® (solifenacin succinate) Tablets
Final Draft Labeling

We are herewith submitting copies of the final draft labeling for VESIcare. Submitted herewith are the final draft package insert, patient package insert, and packaging components (cartons and labels) incorporating all changes agreed to with the Agency.

This amendment is provided herewith in hardcopy and electronically on 1 CD-ROM. The size of this submission is approximately 3 MB and has been checked for computer viruses using VirusScan Enterprise version 7.0.0 and has been found to be virus free.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W. Lucek
Vice President, Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

Attachment
YM No. 2004-0256

Desk Copy: Ms. Jean Makie, Regulatory Project Manager (Hard Copy Only)
Division of Reproductive and Urologic Drug Products, HFD-580

19 Draft Labeling Page(s) Withheld

Makie, Jean

om: Christine Rice Mulhauser [Christine.RiceMulhauser@yamanouchi-america.com]
nt: Thursday, November 18, 2004 7:00 PM
o: Jean Makie (E-mail)
Subject: Submission final labeling Part 2 of 2

VESIcare 10mg)0 Count Carton | VESIcare 10mg 0 Count Bottle | VESIcare 10mg .) Count Carton | VESIcare 10mg .0 Count Bottle | VESIcare 10mg .) Count Carton | VESIcare 10mg lister Backing... | VESIcare 5mg 0 Count Carton | VESIcare 5mg) Count Bottle L | VESIcare 5mg) Count Bottle S

VESIcare 5mg Count Carton.p | VESIcare 5mg Count Sample | VESIcare 5mg Tablet Sample B | VESIcare 5mg Count Bottle L | VESIcare 5mg Count Carton. | VESIcare 5mg lister Backing.p | VESIcare 5mg ample Blister Ba | mmsinfo.txt (494 B)

Dear Jean:

Attached below are the final draft labeling (trade and sample, cartons and labels) for Vesicare tablets. All changes agreed to with the Agency are incorporated into these final drafts.

An offical hard copy and an electronic copy are being submitted to the Document Control Room.

Regards,

Christine Mulhauser
Director, Regulatory Affairs, CMC
Yamanouchi Pharma America, Inc.

17 Draft Labeling Page(s) Withheld

ADMINISTRATIVE REVIEW OF NDA ACTION PACKAGE
OFFICE OF DRUG EVALUATION III

NDA: 21-518
Drug: Vesicare (solifenacin succinate) Tablets
Classification: 1 S
Sponsor: Yamanouchi
Project Manager/CSO: Jean Makie

Reviewer: Bronwyn Collier, ADRA ODE III
Review Date: November 17, 2004

Review Cycle 1

Date Submitted: December 19, 2002
Date Received: December 19, 2002
Goal Date: October 19, 2003
Extended Goal Date: N/A
Action: Approvable October 17, 2003

Review Cycle 2

Date Submitted: May 18, 2004
Date Received: May 20, 2004
Goal Date: November 20, 2004
Extended Goal Date: N/A
Proposed Action: approval

	STATUS	COMMENTS
ACTION LETTER	draft	
EXCLUSIVITY CHECKLIST	draft	
DEBARMENT STATEMENT	verified	
PEDIATRIC PAGE	draft	
TRADE NAME REVIEW	completed	Issues on trade name still being negotiated with the sponsor.
DSI AUDITS	completed 1st cycle	
FACILITY INSPECTIONS	acceptable	October 17, 2003

REVIEWS	STATUS	COMMENTS
DIV. SUMMARY REVIEW	draft	
CLINICAL	completed	
SAFETY UPDATE	completed	included in clinical review
FINANCIAL DISCLOSURE	completed	

STATISTICAL	completed	
BIOPHARM	completed	
CMC	draft	
EA	included in 1st CMC review	
MICRO (validation of sterilization)	N/A	
STABILITY (stats)	included in CMC review	
PHARM/TOX	completed 1st review cycle	
CAC (stats)	completed 1st review cycle	
CAC/ECAC REPORT	completed 1st review cycle	

Labeling: draft
Postmarketing Commitments: PREA requirements
Advisory Committee Meeting: N/A

Comments: Documents in draft must be finalized prior to taking an action. Trade name issues must be resolved prior to taking an action. Applicable regulations and policies have otherwise been addressed.

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

/s/

Bronwyn Collier
11/17/04 10:13:21 AM
CSO

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 17, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: NDA 21-518 Vesicare® (solifenacin succinate) Tablets
Patient Package Insert and Package Insert

Reference is made to your November 16, 2004 fax in which you provided suggested revisions to the Vesicare Patient Package Insert and the Vesicare Package Insert.

We have revised the draft Patient Package Insert to incorporate all of the Agency's revisions as requested and a copy of the Patient Package Insert with all incorporated revisions is enclosed. All references to line numbers refer to the enclosed Package Insert version, dated November 17, 2004.

We have revised the draft Vesicare Package Insert to incorporate all of the Agency's changes as requested except as indicated in the highlighted text of the enclosed revised package insert.

Specifically, with respect to the Package Insert:

1. Lines 210 – 211 Information for Patients

   We have clarified the caution statement to read:

   "...exercise caution — potentially dangerous activities..."

2. In response to your statistical comment concerning the analysis of the incontinence episodes in Table 5, Line 159, you are correct in that the p-value is derived from a secondary analysis using baseline as a covariate. Study 018 was conducted in Europe under the auspices of Yamanouchi, The Netherlands and the inclusion of baseline as a covariate in the analysis was prespecified as a secondary analysis in the statistical analysis plan. This analysis was conducted to address points raised in the CPMP directive "Points to Consider on Adjustment for Baseline Covariate" which recommended the use of such an adjustment for baseline.

3. Lines 88 –119 Cardiac Electrophysiology

In this section the Agency cites figures for numbers of subjects, point estimates and confidence intervals for QTc results that do not agree with those reported in the final study report for Study 043. We have not been able to verify the source of the Agency's figures. A listing of the figures as they appeared in our original draft package insert dated November 16, 2004, your suggested revision and the line number in the enclosed package insert on which the figure appears is provided below for your convenience. We have also highlighted the figures in the package insert and our suggested revision. Specifically, we believe the point estimates and confidence intervals to be used in Table 1 for QTc using the Fridericia method should be derived from Table 16 of the Study 043 study report, copy of which is submitted herewith. Similarly, we believe the point estimates and confidence intervals appearing on Lines 112 and 113 should be derived from Table 35 for session 1 and Table 18 for session 3 and 5 as they were reported in the final study report for Study 043, copies of these tables are submitted herewith.

We would request that since the figure changes requested are minor and are not clinically significant that we use the figures as originally reported in the final study report for Study 043. If the Agency feels that these numbers should remain as presented in the Agency's draft of the Cardiac Electrophysiology section submitted in your fax of November 16, 2004, we would request that the Agency provide us with the sources documenting these figures, as we have not been able to verify them.

Package Insert Line Number	Agency's Draft of November 16, 2004	Figures Reported in 043 Study Report
94		
107 – Table		
112 - 113		

Yamanouchi

Point for Discussion

We wish to discuss the following issue with the Division at our teleconference scheduled for 3:00 pm, November 17, 2004:

In the Cardiac electrophysiology section there is an extensive description of the design of Study 043. We believe that this extensive study description could be distracting and confusing to practitioners and potentially reduces the communication of the important information concerning the effect of Vesicare on the QTc interval. We therefore, recommend shortening the study design description by deleting:

Lines 91 to 94

Lines 103 to 105

Line 107 - Table 1
Header

Lines 111 to 113

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W. Lucek
Vice President, Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

Attachment
YM No. 2004-0255

9.3. Analysis of Central Tendency (Adjusted for Session Effects)

In order to adjust for the observed session-related effects for solifenacin relative to placebo, Groups A and B were compared in a parallel group fashion using the nonparametric Hodges-Lehmann-Moses method. Estimated median differences in change from baseline at t_{max} of solifenacin for Group A (solifenacin, sessions 3 and 5) compared to Group B (placebo, sessions 3 and 5) are provided in Table 16 and Table 17, and graphically presented in Figure 4. For Session 3, a total of 54 subjects in Group A and 24 subjects in Group B contributed to the comparison of interest. For Session 5, a total of 51 subjects in Group A and 23 subjects in Group B contributed to the comparison of interest.

Following repeat dosing of 10 mg of solifenacin compared to placebo, the upper bounds of the 90% CI for the median differences were completely contained within 10 msec, regardless of QTc correction method or choice of baseline.

Following repeat dosing of 30 mg of solifenacin compared to placebo, the upper bounds of the 90% CI for the median differences were greater than 10 msec, with a maximum upper bound of 13msec.

Table 16 Table of Main Results for comparisons of interest using the Hodges Lehmann-Moses Estimator (Time-matched baseline (n=3))

Parameter	Session	Comparison (Group A-B)	Point Estimate[1]	90% CI
QTcF	Session 3	Solifenacin 10mg - Placebo (P3)	0	(-5, 5)
	Session 5	Solifenacin 30mg- Placebo (P5)	7	(2, 12)
QTci	Session 3	Solifenacin 10mg - Placebo (P3)	0	(-5, 5)
	Session 5	Solifenacin 30mg- Placebo (P5)	6	(1, 11)
QTciL	Session 3	Solifenacin 10mg - Placebo (P3)	0	(-5, 5)
	Session 5	Solifenacin 30mg- Placebo (P5)	6	(1, 12)
QTcB	Session 3	Solifenacin 10mg - Placebo (P3)	-1	(-7, 3)
	Session 5	Solifenacin 30mg- Placebo (P5)	7	(1, 11)
QT	Session 3	Solifenacin 10mg - Placebo (P3)	3	(-4, 11)
	Session 5	Solifenacin 30mg- Placebo (P5)	7	(0, 13)
HR	Session 3	Solifenacin 10mg - Placebo (P3)	-2	(-4, 1)
	Session 5	Solifenacin 30mg- Placebo (P5)	0	(-3, 2)

Source: Attachment 5, Table 26
1. represents difference of adjusted medians
Note: above results are rounded to the nearest integer (accounts for asymmetry of CI).

Table 35 Change From Baseline QTcF (Time-matched baseline (n=3))

Group	Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
A					
Session 1	Moxi 400mg (M)	15 (1.6)	Moxi 400mg - Placebo @T_{max} of M	11	(7, 14)
Session 3	Solifenacin 10 mg (S10)	13 (1.6)	solifenacin 10mg-Placebo @ T_{max} of S10	15	(11, 19)
Session 5	Solifenacin 30 mg (S30)	14 (1.9)	solifenacin 30 mg–Placebo @ T_{max} of S30	16	(12, 20)
Session 2	Placebo @ T_{max} of M	4 (1.6)			
Session 2	Placebo @ T_{max} of S10	-3 (1.6)			
Session 2	Placebo @ T_{max} of S30	-2 (1.6)			
B					
Session 1	Moxi 400mg (M)	15 (2.2)	Moxi 400mg - Placebo @ T_{max} of M	12	(8, 17)
Session 2	Placebo (P) @ T_{max} of M	3 (1.8)			
Session 3	Moxi 400mg (M3)	29 (3.0)	Moxi 400mg (M3) – Placebo (P) @ T_{max} of M3	27	(23, 32)
	Placebo (P3) @ T_{max} of M3	16 (2.3)	Placebo (P3) - Placebo (P) @ T_{max} of M3	15	(10, 19)
	Placebo (P) @ T_{max} of M3	2 (2.0)			
Session 5	Moxi 400mg (M5)	28 (3.0)	Moxi 400mg (M5) – Placebo (P) @ T_{max} of M5	28	(24, 33)
	Placebo (P5) @ T_{max} of M5	12 (2.0)	Placebo (P5) - Placebo (P) @ T_{max} of M3	12	(7, 17)
	Placebo (P) @ T_{max} of M5	0 (1.8)			

Source: Attachment 3, Table 1, Attachment 5, Table 9 and Table 10

1. represents arithmetic mean
2. represents difference between adjusted arithmetic means

Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI).

Table 18 Table of Main Results for comparison of interest using paired t-test (Group B)

Parameter	Session	Comparison	Point Estimate[1]	90% CI
QTcF	Session 3	Moxi 40mg (M3) - Placebo (P3)	12	(8, 17)
	Session 5	Moxi 40mg (M5) - Placebo (P5)	16	(12, 21)
QTci	Session 3	Moxi 40mg (M3) - Placebo (P3)	12	(7, 17)
	Session 5	Moxi 40mg (M5) - Placebo (P5)	16	(12, 21)
QTciL	Session 3	Moxi 40mg (M3) - Placebo (P3)	12	(7, 16)
	Session 5	Moxi 40mg (M5) - Placebo (P5)	16	(12, 21)
QTcB	Session 3	Moxi 40mg (M3) - Placebo (P3)	18	(13, 24)
	Session 5	Moxi 40mg (M5) - Placebo (P5)	18	(12, 24)
QT	Session 3	Moxi 40mg (M3) - Placebo (P3)	1	(-5, 8)
	Session 5	Moxi 40mg (M5) - Placebo (P5)	12	(6, 19)
HR	Session 3	Moxi 40mg (M3) - Placebo (P3)	5	(3, 8)
	Session 5	Moxi 40mg (M5) - Placebo (P5)	1	(-1, 4)

Source: Attachment 5, Table 27 - Table 32

1. represents difference of adjusted means

Note: above results are rounded to the nearest integer (accounts for asymmetry of CI).

Point estimate and 90% CI from above Table 16-Table 18 are presented graphically in Figure 4.

APPEARS THIS WAY ON ORIGINAL

NDA 21518

Supervisory Medical Officer's Memorandum

From: George S. Benson, MD, Medical Team Leader
Division of Reproductive and Urologic Drug Products

To: Donna Griebel, MD, Deputy Division Director
Division of Reproductive and Urologic Drug Products

Regarding: Recommendation for regulatory action

Date NDA submitted: May 20, 2004
Date of memorandum: November 16, 2004

Sponsor: Yamanouchi Pharma America, Inc.
Mack Centre IV, S 61 Paramus Rd.
Paramus, New Jersey

Drug: solifenacin succinate
Pharmacologic class: M_3 muscarinic receptor antagonist
Tradename: Vesicare
Dosage strength: 5 and 10 mg
Route of administration: oral

Proposed indication: "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency"

Related IND/NDA's: IND 58,135

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1. Materials Used in Conducting the Review:

A. Primary Medical Officer review of NDA 21-518 (complete response to approvable action) including safety update
B. "Thorough QT" study (Trial 905-CL-043)
B. Clinical Pharmacology review of Trial 905-CL-043
C. Cardio-Renal consultation concerning the QT issue
D. Statistical review of Trial 905-CL-043
E. Chemistry review of complete response to approvable action
F. Consultations from DMETS, DDMAC, and DSRCS

2. Executive Summary and Recommendation:

In my opinion, solifenacin succinate in doses of 5 and 10 mg once daily should be approved for the indication "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency." The three deficiencies listed in the "approvable" letter of October 17, 2003, have been adequately addressed. The risks associated with the use of this drug are acceptable and can be adequately managed with labeling.

3. Background:

NDA 21-518 received an "approvable" action on October 17, 2003. The original NDA submission contained substantial evidence that solifenacin is effective for the treatment of overactive bladder. The original NDA also met the required ICH guidance criteria for safety exposure and, in general, the safety concerns with solifenacin were found to be similar to those of other approved antimuscarinic drugs.

Primarily because insufficient data were submitted to exclude a clinically relevant effect of solifenacin on QT interval prolongation, NDA 21-518 initially received an "approvable" action and 3 deficiencies were listed in the "approvable" letter:

A. The application "lacks sufficient information to conclude that solifenacin is not associated with clinically relevant QT interval prolongation."

B. "The current dissolution acceptance criterion (~) at ~ minutes) is unacceptable."
C. "Labeling remains unresolved. Overall comments on labeling are deferred until data are available from the QT study. In addition, solifenacin appears to be associated with the occurrence of constipation, and rarely, serious sequelae of this adverse event. Please address the prevention and management of such serious sequelae in the revised labeling."

A "Complete Response to Approvable Action" was submitted on May 20, 2004.

A review of the additional submitted QT data ("thorough" QT study) is included in **Part 4** of this memorandum. The dissolution acceptance criterion is discussed in **Part 8d (Chemistry)** and the constipation issue is addressed in **Part 5** of this memorandum.

4. Review of QT Data:

The specific deficiency relating to QT prolongation described in the "approvable" letter is as follows:

"This application lacks sufficient information to conclude that solifenacin is not associated with clinically relevant QT interval prolongation. Such information is necessary prior to marketing approval in order to determine if the drug is safe for the full targeted populations. Evidence from preclinical studies indicates that solifenacin inhibits the potassium current in Chinese hamster ovary (CHO) cell HERG channels at an IC_{50} of 0.27 micromolar. Electrocardiograms obtained in four randomized, controlled trials conducted to establish the efficacy and safety of the 5 and 10 mg doses of solifenacin suggest that solifenacin at these doses is associated with a placebo-subtracted mean change in corrected QT (QTc) from baseline of approximately 5 msec. The lack of a positive control group and a concurrent placebo group in the study designed specifically to evaluate the effect of solifenacin on QTc at clinically relevant ranges of plasma concentrations, Study 905-CL-022, precludes conclusive determination of the degree of QT prolongation associated with solifenacin. The data from this study revealed a variable impact on QTc across the solifenacin doses studied (10-50 mg), with the mean change from baseline being negative at the two highest doses studied."

The following information was requested to address this deficiency:

"Submit the results from a randomized, placebo-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at the plasma concentrations achieved at steady state when solifenacin is co-administered with a potent CYP3A4 inhibitor. This study should include a positive control, such as moxifloxacin, in order to assure assay sensitivity and to provide a benchmark for comparison with the QT effect of solifenacin. The primary endpoint, corrected QT interval, should be measured by multiple 12-lead ECG's taken at baseline and at

steady state. The study population should be predominantly female, preferably patients with overactive bladder, whose mean age is consistent with the age distribution of overactive bladder patients in the community. The number of subjects should be sufficient to rule out a clinically important mean prolongation of the corrected QT interval by solifenacin. We recommended that you submit a protocol for our review prior to initiating this study."

To address this deficiency, the sponsor submitted the results of "thorough" **QT study 905-CL-043.** The basic design of the protocol was agreed to by the Division prior to study initiation.

The design of this "thorough" QT study was difficult primarily because of the inherent characteristics of solifenacin. It was necessary to dose subjects for at least 10 days to reach steady state concentrations due to the long half-life of solifenacin (>50 hours) and to escalate the dose from therapeutic to supratherapeutic doses slowly to protect against anticholinergic side effects. Because of the substantial time separation of 15 and 33 days between baseline ECG assessments (Session 3 Day –1) and the on-treatment ECG assessments (Session 3, Day 14 and Session 5, Day 14), a separate placebo control group was included to monitor for any time-dependent session effects (Group B). The sponsor and the Division considered the Group B results to be "exploratory."

The trial was a five-period, sequential, crossover study. Subjects were randomized to one of two treatment groups (Group A or Group B) (Table 1).

Table 1. Basic "Thorough" QT Study Design

	Treatment Group A	Treatment Group B
Session 1	1 day baseline (no drug) ; moxifloxacin (400 mg) on Day 1	
Session 2	1 day baseline (no drug) ; placebo on Day 1	
Session 3	1 day baseline (no drug) solifenacin 10 mg x 14 days	1 day baseline (no drug) placebo x 13 days ; moxifloxacin (400 mg) on Day 14
Session 4	Solifenacin 20 mg x 5 days	Placebo x 5 days
Session 5	Solifenacin 30 mg x 14 days	placebo x 13 days ; moxifloxacin (400 mg) on Day 14

Dosing was single-blind in Sessions 1 and 2. All subjects (Groups A and B) received a single oral dose of 400 moxifloxacin in Session 1 and a single oral dose of placebo in Session 2. There was at least a 3 day washout between Sessions 1 and 2. There was no washout between Session 2 and the start of dosing in Session 3.

Dosing was double-blind in Sessions 3 to 5. Subjects randomized to Treatment Group A received increasing doses of solifenacin. Subjects randomized to Treatment Group B received placebo on each corresponding study day, except for Session 3, Day 14 and Session 5, Day 14 when they received a 400 mg dose of moxifloxacin. There was no washout between Sessions 3 through 5.

In Sessions 1, 2, and 3, there was a one day baseline (no drug) prior to the start of dosing.

Dose rationale: The 5 and 10 mg doses were demonstrated to be safe and effective in four large studies submitted for NDA approval. The maximum dose of 30 mg was chosen based on the results of a ketoconazole drug interaction study (Study 036), which showed that 400 mg ketoconazole daily for 20 days increased the AUC and C_{max} of a single 10 mg dose of solifenacin by 2.8-fold and 1.5-fold, respectively. Based on a simulation of the steady state exposure for 10 mg solifenacin in combination with ketoconazole, the administration of 30 mg solifenacin daily in the present study was expected to result in plasma concentrations that exceeded the plasma concentrations resulting from 10 mg solifenacin daily dosed in combination with a potent CYP 3A4 inhibitor.

ECG assessments: All ECG's were obtained after the subject had rested in the supine position for at least 15 minutes. Three 12-lead ECG's taken approximately 1 minute apart were obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours on Day –1 of Sessions 1, 2, and 3. For each session, baseline was the average of all individual ECG's obtained on Day –1.

Three 12-lead ECG's taken approximately 1 minute apart were obtained prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose on the following days:

- Session 1, Day 1
- Session 2, Day 1
- Session 3, Days 13 and 14
- Session 5, Days 13 and 14.

Conduction intervals from the 12-lead ECG's were manually read and confirmed by , using lead II of the 12-lead ECG and a validated high resolution digitizing pad system. All ECG's were read blinded.

Baseline values: Baseline QTc (all correction methods) for each individual and for each regimen (or session) was obtained by two methods:

- Session-averaged baseline (n=33): Baseline for each session (1, 2, and 3) was defined as the average of pre-dose values collected on Day –1 (11 pre-dose time points, with 3 replicate ECG measurements (11 times 3 = 33 ECG measurements).

- Time-matched baseline (n=3): Baseline for each session (1, 2, and 3) was defined as the average of pre-dose (Day –1) values at a time point (3 replicate ECG measurements) corresponding to the same post-dose time point.

For both methods, baseline values for sessions 3 and 5 were determined from Session 3 (Day –1).

QT correction methods: Four methods were used to correct measured QT intervals for heart rate:

Population approaches:
- Fridericia's correction
- Bazett's correction

Individual approaches:
- Individual (linear) correction QTci
- Individual (non-linear) correction QTciL

Patient population: All subjects were healthy adult female volunteers. The mean age was 51 years. Thirty-five women (41%) were under 55 years of age and 51 women (59%) were 55 years of age or older. Half of the women were white and one-third were Hispanic. Seventy-six subjects completed the trial (Table 2).

Table 2. Subject Disposition

	Treatment Group A: Solifenacin	Treatment Group B: Placebo/Moxi	Total
Total dosed	58	28	86
Total withdrawn after dosing	7	3	10
Total completed	51	25	76

Results:

A. Analysis of Central Tendency (unadjusted for sessions effects)

The sponsor believes that the data analyses unadjusted for session were inappropriate. The results for QTcF (session averaged baseline) are shown in Table 3. For Group A, mean changes in QTcF from baseline along with associated 90% CI at the time of T_{max} for moxifloxacin 400 mg, solifenacin 10 mg and solifenacin 30 mg are compared to placebo (Session 2). The Group B results for mean change in QTcF from baseline at T_{max} for placebo (Sessions 3 and 5) and moxifloxacin (Sessions 3 and 5) compared to placebo (Session 2) are also provided for session-averaged baseline.

Table 3. Change from baseline QTcF at T_{max} (Session averaged baseline (n=33)

Group	Regimen	Mean	Comparison	Point estimate	90% CI
Group A					
Session 1	**Moxi 400mg**	14	Moxi 400 mg – placebo @ T_{max} of M	**12**	(9,15)
Session 3	**Solifenacin 10 mg (S10)**	14	Soli 10 mg – placebo @ T_{max} of (S10)	**15**	(12,18)
Session 5	**Solifenacin 30 mg (S30)**	15	Soli 30 mg – placebo @ T_{max} of S30	**17**	(14,20)
Session 2	Placebo @ T_{max} of M	3			
Session 2	Placebo @ T_{max} of S10	-1			
Session 2	Placebo @ T_{max} of S30	-2			
Group B					
Session 1	Moxi 400 mg	15	Moxi 400 – placebo @ T_{max} of M	13	(10,17)
Session 2	Placebo @ T_{max} of Moxi	2			
Session 3	Moxi 400 (M3)	29	Moxi (M3) – placebo @ T_{max} of M3	27	(23,30)
Session 3	Placebo @ T_{max} of M3	17	Placebo (P3) – placebo (P) @ T_{max} of M3	14	(11,18)
Session 5	Moxi 400 mg	29	Moxi 400 (M5) – placebo (P2) @ T_{max} of M5	27	(23,31)
Session 5	Placebo (P5) @ T_{max} of M5	12	Placebo (P5) – P2 @ T_{max} of M3	11	(7,14)
Session 3			Moxi (M3) – placebo M3	12	(8,17)
Session 5			Moxi (M5)- placebo M5	16	(12,21)

The mean changes from baseline in QTcF at T_{max} for placebo Session (P3) and placebo Session 5 (P5) were significantly larger than placebo Session 2 (P), which the sponsor believes indicates session-related effects in QTc. In addition, the mean change from baseline QTcF for moxifloxacin in sessions 3 and 5 (M3 and M5) were significantly higher than moxifloxacin in Session 1. For these reasons, the sponsor believes that the unadjusted analyses of central tendency, based on Group A within-subject comparisons (all regimens compared to placebo in Session 2) which show QTcF point estimate increases of 15 and 17 msec for 10 and 30 mg solifenacin are inappropriate.

B. Analysis of central tendency (adjusted for session effects):

To adjust for the observed session-related effects for solifenacin relative to placebo, the sponsor compared Groups A and B in a parallel group fashion using the nonparametric Hodges-Lehmann-Moses method. The sponsor believes that this methodology utilizing medians is the most appropriate method for comparing Groups A and B. Estimated median differences in change from baseline at T_{max} of solifenacin for Group A (solifenacin , sessions 3 and 5) were compared to Group B (placebo, sessions 3 and 5) (Tables 4 and 5). For session 3, a total of 54 subjects in Group A and 24 subjects in Group B had sufficient data for analysis. For session 5, a total of 51 subjects in Group A and 23 subjects in Group B had sufficient data for analysis.

Table 4. Comparisons using the Hodges-Lehmann-Moses estimator (Time matched baseline, n=3).

Parameter	Session	Comparison (Group A-B)	Point estimate	90% CI
QTcF	Session 3	Solifenacin 10 mg – placebo (P3)	0	(-5,5)
QTcF	Session 5	Solifenacin 30 mg – placebo (P5)	7	(2,12)
QTci	Session 3	Solifenacin 10 mg – placebo (P3)	0	(-5,5)
QTci	Session 5	Solifenacin 30 mg – placebo (P5)	6	(1,11)

Table 5. Comparisons using the Hodges-Lehmann-Moses estimator (Session averaged baseline, n=33).

Parameter	Session	Comparison (Group A-B)	Point estimate	90% CI
QTcF	Session 3	Solifenacin 10 mg – placebo (P3)	2	(-2,6)
QTcF	Session 5	Solifenacin 30 mg – placebo (P5)	9	(4,13)
QTci	Session 3	Solifenacin 10 mg – placebo (P3)	1	(-3,5)
QTci	Session 5	Solifenacin 30 mg – placebo (P5)	7	(3,12)

To adjust for the observed session-related effects for moxifloxacin relative to placebo for both sessions 3 and 5, Group B was analyzed using a paired t-test approach (Table 6).

Table 6. Comparison using paired t-test approach for moxifloxacin.

Parameter	Session	Comparison	Point estimate	90% CI
QTcF	Session 3	Moxi (M3) – placebo (P3)	12	(8,17)
QTcF	Session 5	Moxi (M5)- placebo (P5)	16	(12,21)
QTci	Session 3	Moxi (M3) – placebo (P3)	12	(7,17)
QTci	Session 5	Moxi (M5)- placebo (P5)	16	(12,21)

Outlier analysis:

The outlier analyses are not adjusted for session effects.

Four subjects experienced increases in mean QTcF that were greater than 60 msec from the time-matched baseline. Three of these subjects were receiving 30 mg solifenacin in Session 5 at the time that the increase in QTcF was observed and the fourth was receiving 400 mg moxifloxacin in Session 3.

There were no subjects with a mean QTcF > 500 msec or a mean QTcF that was greater than 60 msec from the session-matched baseline. There were no QTcF, QTci, or QTciL values >500 msec in any group or regimen.

Subjects who had QTcF changes between 30 and 60 msec and greater than 60 msec are shown in Table 7.

Table 7. Summary of subjects by category of max QTcF change from baseline (session-averaged n=33) in mean data by group and session

	QTcF (msec) Change From Baseline (n=33)			
Session/ regimen	Increase <30	30<increase>60	Increase >60	Total
Treatment Group A				
1/ Moxi 400	50 (86%)	8 (14%)	0	58
2/ Placebo	57 (100%)	0	0	57
3/ Soli 10 mg	30 (56%)	24 (44%)	0	54
5/ Soli 30 mg	20 (39%)	31 (61%)	0	51
Treatment Group B				
1/ Moxi 400	22 (79%)	6 (21%)	0	28
2/ Placebo	27 (96%)	1 (4%)	0	28
3/ Placebo	18 (69%)	8 (31%)	0	26
Moxi 400	10 (39%)	16 (26%)	0	26
5/ Placebo	21 (84%)	4 (16%)	0	25
Moxi 400	10 (40%)	15 (60%)	0	25

Pharmacokinetic analysis:

Blood samples for PK analysis of moxifloxacin were obtained at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose on Session 1, Day 1. To maintain the single-blind across sessions 1 and 2, blood samples were also obtained at the same time points post-dose on Session 2, Day 1. Blood samples for PK analysis of both moxifloxacin and solifenacin were obtained at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose on Session 3, Day 14 and Session 5, Day 14. The frequency of T_{max} by regimen and sampling time is shown in Table 8.

Table 8. Frequency of T_{max} by Dosing Regimen and Sampling Time

Tmax (h)	Session 1 Moxi	Session 3 Moxi	Session 5 Moxi	Session 3 Soli 10 mg	Session 5 Soli 30 mg	Total
0.5	13	5	2	0	0	20
1	17	3	4	0	0	24
1.5	13	5	5	0	0	23
2	15	4	4	3	3	29
3	15	4	5	11	12	47
4	8	1	1	13	4	27
6	0	0	0	21	21	42
8	0	0	0	4	11	15
12	0	0	0	1	0	1
24	0	0	0	1	0	1
Total	81	22	21	54	51	229

The sponsor believes that, because of the significant session effects, Group A should be compared with Group B and the statistical method of choice is the Hodges-Lehmann-Moses analysis of median QTci. The sponsor believes that the median QTci changes relative to placebo are 0 msec for the 10 mg dose and 6 msec for the 30 mg dose of solifenacin.

The following outlines the Division's approach to the review of the QT data.

A. The Cardiorenal consultant initially questioned whether the study demonstrated an effect of the positive control moxifloxacin. "The implausible effect of moxifloxacin suggests that the correct answer is to make no inference regarding solifenacin. However, if one were to say that the effect of moxifloxacin was, in three assessments, on the order of 15 msec, for whatever reason, then the effects of solifenacin are not reassuring." Furthermore, "the effects of placebo in Period 2, moxifloxacin in Periods 1, 3, and 5, and solifenacin 30 mg in Period 5 all look disturbingly similar. I question, therefore whether this study successfully distinguished the moxifloxacin effect and I cannot hazard a guess about the magnitude of effect of solifenacin excluded."

   These issues were discussed at a face-to-face meeting with the sponsor on October 26, 2004. The Division requested that the sponsor submit QTcF/plasma concentration datasets for moxifloxacin in Sessions 1, 3, and 5 and for solifenacin in Sessions 3 and 5. These datasets demonstrated that the slopes of the 3 moxifloxacin regression lines were nearly equivalent and differed only in baseline at time 0 (y-intercept of the linear regression line). Based on these data, the Division believes that an effect of moxifloxacin was demonstrated.

B. The annotated waveforms were reviewed by the cardiology consultant. "Overall, the quality of these data is adequate for the purpose for which they were intended. Although there were some differences in the intervals assessed by rhythm data and derived data, the measurements within each domain seemed to be consistent. The study had few outlying values of QTcF. In one case the value was probably a spurious result of atypical preceding beats' RR intervals. In two other cases, there are no obvious recording issues, and the QT interval has probably been somewhat underestimated. Nevertheless, these outliers in single time points are unlikely to herald drug-related risk."

C. When evaluating only those patients in Group A, the QTcF of solifenacin 10 mg and solifenacin 30 mg are approximately 15 and 17 msec respectively. (These numbers are obtained by subtracting the placebo values during Session 1.) However, the Division agrees that the placebo data obtained in Sessions 1, 3, and 5 demonstrate marked session effects, which impacts on how the QTcF data obtained from only Group A can be interpreted.

D. The placebo values in Session 3 and Session 5 are much higher than in Session 1. There are also session effects (differences) in baseline values. I agree with the sponsor that, because of these marked session effects, the data are more appropriately

analyzed by comparing the QTcF values for 10 mg (Session 3) and 30 mg (Session 5) (Group A) with the corresponding time matched placebo values during Session 3 and Session 5 (Group B).

E. The sponsor elected to compare the 10 mg and 30 mg solifenacin data in Group A with the placebo data in Sessions 3 and 5 (Group B) using the Hodges-Lehmann-Moses non-parametric method using medians. The median difference of change from baseline in QTci (individual QT correction) for 10 and 30 mg of solifenacin succinate compared to placebo was 0 msec (90% CI = -5,5) and 6 msec (90% CI=1,11), respectively. The sponsor further believes that moxifloxacin exhibited a mean change from baseline in QTci (individual QT correction), relative to placebo, of 10 msec (90% CI=6, 13). (The moxifloxacin point estimate and CI are derived from the moxifloxacin data in Session 1.)

F. The Division preferred to perform an analysis evaluating mean data and the Division's statistical consultant compared the 10 mg and 30 mg solifenacin data in Group A with the placebo data in Sessions 3 and 5 (Group B) using different methodology. This analysis used data at T_{max} and the means of Groups A and B were compared using a paired t-test. The statistical consultant believes that Group B is adequately powered to make such a comparison. The results (Table 9) show similar QTcF values to the sponsor's analysis using QTci, medians, and the Hodges-Lehmann-Moses approach.

Table 9. Analysis of Group A Sessions 3 and 5 Solifenacin Data Utilizing Sessions 3 and 5 Placebo Values (Group B). Paired t-test Analysis Using Means

	Delta QTcF (90% CI)
Solifenacin 10 mg (Group A – Session 3) at T_{max} minus placebo Group B – Session 3	2 msec (-3,6)
Solifenacin 30 mg (Group A- Session 5) at T_{max} minus placebo Group B – Session 5	8 msec (4,13)

The statistical consultant also analyzed the moxifloxacin QTcF data during Sessions 1, 3, and 5 (Table 10).

Table 10. Moxifloxacin – placebo QTcF values

	Delta QTcF (90% CI)
Moxifloxacin – placebo (Session 1)	11 (7, 15)
Moxifloxacin – placebo (Session 3)	12 (8, 16)
Moxifloxacin – placebo (Session 5)	16 (12, 20)

G. The clinical pharmacologist also analyzed the QTcF data using methodology making no Group A to Group B comparisons. Only the baseline, placebo, and drug readings from the 51 patients in Group A were used. The mean QTcF at each time point was determined and the maximum selected. The mean and 95% CI for this time was determined. A time matched correction for placebo effect for all subjects in Group A was performed. Then the y-intercept from the linear regression line through the QTcF

vs. plasma concentration plot was subtracted from the result. By using this method, the changes in baseline in the different sessions were corrected and the corresponding delta QTcF estimates (95% CI) were: moxifloxacin 11 msec (8-14), solifenacin 10 mg 5 msec (3-8), and solifenacin 30 mg 9 msec (6,13). The clinical pharmacology reviewer believes that multiple methods of correction lead to a similar mean delta QTcF: 10-12 msec for moxifloxacin, 3-5 msec for solifenacin 10 mg, and 8-10 msec for solifenacin 30 mg.

H. The CardioRenal consultant agreed that the changes seen with solifenacin were "about 5 msec with 10 mg and about 9 msec with 30 mg."

Conclusion: I believe that the QTc changes seen with solifenacin are <5 msec for the 10 mg dose and < 10 msec for the 30 mg dose. There does appear to be a dose relationship. The 30 mg dose covers the expected plasma concentration of the 10 mg dose in the presence of a potent CYP 3A4 inhibitor. A dose of solifenacin greater than 5 mg is not recommended in patients taking concomitant potent CYP 3A4 inhibitors, in patients with severe renal impairment, and in patients with moderate hepatic impairment. Use of solifenacin in patients with severe hepatic impairment is not recommended.

I do not think that there is a significant arrhythmogenic risk with the use of solifenacin. I believe that the issue of QT prolongation can be adequately managed with labeling. The effect of solifenacin on the QT interval is included in the CLINICAL PHARMACOLOGY, Cardiac Electrophysiology section and in the PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation section of the label.

5. **Review of Constipation Risk Management:**

In the "approvable" letter of October 17, 2003, the issue of constipation risk management was listed as a deficiency:

"Labeling remains unresolved. Overall comments on labeling are deferred until data are available from the QT study. In addition, solifenacin appears to be associated with the occurrence of constipation, and rarely, serious sequelae of this adverse event. Please address the prevention and management of such serious sequelae in the revised labeling."

In the placebo controlled phase 3 studies, constipation was an adverse event in 2.9% of placebo subjects, 5.4% of subjects taking 5 mg solifenacin, and 13.4% of patients taking 10 mg solifenacin. The number of patients who interrupted or discontinued therapy was 3/1307 placebo, 2/667 5 mg solifenacin, and 37/1117 10 mg solifenacin. The incidence of constipation for a recently approved antimuscarinic drug [Sanctura (trospium)] for overactive bladder is 10% and for a widely used antimuscarinic drug [Detrol LA (tolterodine)] for overactive bladder is 6%.

The recommended starting dose of 5mg of solifenacin proposed by the sponsor is important in mitigating this adverse event. The "information for patients" section of the label and the PPI both contain information which includes "patients should be advised to

contact their physician is they experience severe abdominal pain or become constipated for 3 or more days." The ADVERSE EVENTS section of the label is now clear that the three SAE's'related to constipation seen in the controlled trials (fecal impaction, colonic obstruction, and intestinal obstruction) all occurred at the 10 mg dose.

Physician's are aware that constipation is an adverse event seen with anticholinergic drugs. The starting dose of 5 mg and information in the PI and PPI are, in my opinion, adequate to address the risk-management issues of constipation with solifenacin.

6. **Overview of Safety and Review of Safety Update:**

The numbers of patients with overactive bladder treated with solifenacin at doses ranging from 2.5 mg to 20 mg which were submitted in the original NDA submission are shown in Table 11.

Table 11. Number of patients exposed to different doses of solifenacin in clinical trials submitted with the original NDA.

Study	Treatment Groups						
	Solifenacin					**Place bo**	Tolterodine 2 mg bid
	2.5 mg	**5 mg**	**10 mg**	**20 mg**	**Any dose**		
Phase 3 stuides							
905-CL-013 (US)			340		340	332	
905-CL-014 (US)			318		318	316	
Subtotal US			**658**		**658**	**648**	
905-CL-015 (EU)		279	268		547	267	**263**
905-CL-018 (EU)		299	307		606	301	
Subtotal EU		**578**	**575**		**1153**	**568**	263
SUBTOTAL (Phase 3)		**578**	**1233**		**1811**	**1216**	263
Phase 2 studies							
905-CL-005 (EU)	41	37	35	37	150	38	**37**
905-CL-006 (US)	54	52	51	54	211	53	
Sutotal	95	89	86	91	361	91	37
SUBTOTAL (Phase 3+Phase 2)	**95**	**667**	**1319**	**91**	**2172**	**1307**	300
Open-label, extension study							
905-CL-016 (US)			892 (443[1])		892 (443[1])		
TOTAL OAB Patients (All patient safety data)	95	667	1768	91	2621	1307	300

[1] Patients who previously received 10 mg YM905 in Studies 013 and 014.

Gender, age, and race: Overall, 2621 patients (555 men and 2066 women) with overactive bladder were exposed to solifenacin in the trials submitted with the original

NDA. Of these 2621 patients, 667 (146 men and 521 women) were exposed to 5 mg, 1768 (353 men and 1415 women) were exposed to 10 mg, and the remainder were exposed to either 2.5 mg or 20 mg. A total of 937 patients were 65 years of age or older and 290 were 75 years of age or older. Seven-hundred eighteen (718) patients had at least 6 months of exposure and 308 patients had at least 1 year of exposure to solifenacin 10 mg daily. In the phase 2 and phase 3 studies, approximately 97% of patients who received 5 mg and 91% of those who received 10 mg solifenacin were Caucasian.

The four-month safety update for the original NDA submission was submitted on April 25, 2003. The update included additional safety data from Trials 016 and 019, the open label extensions of the United States and European 4 phase 3 trials. These additional data brought the total number of patients exposed to solifenacin for one year to 476 (337 on 10 mg).

At the time of the current NDA "complete response" submission, 3942 patients with OAB had been treated in phase 2 and phase 3 trials including the 2621 patients from the original NDA submission and 1321 from the amendment. Six hundred thirty-nine patients have been treated for 40 to 52 weeks and 645 for more than 52 weeks. The most recent safety update covering the period April 15, 2004, to September 15, 2004, was submitted on September 30, 2004.

Deaths:

There were eleven deaths reported in the original NDA submission in patients in the combined Phase 2 and 3 trials including the extension studies. In seven of the eight patients (hemiparesis followed by pulmonary embolus, post-operative complications following coronary artery bypass graft, subdural hematoma, ruptured aortic aneurysm, bleeding following hip surgery, brain tumor, and "cardiac insufficiency") I agree with the investigators that the cause of death was "not" or "probably not" related to study drug. In the eighth patient, relationship to study drug can not be determined. This patient [#015-11533 (10 mg solifenacin succinate)] was a 75-year-old Caucasian woman. The investigator was informed by phone that she died 28 days after starting taking study drug. The presumptive cause of death was indicated as "acute heart failure." No autopsy was performed. The last contact with the patient was on Visit 3. No further information could be obtained.

In the "complete response" submission, 4 additional deaths were reported.

Two of these 4 deaths occurred in a Japanese study (905-CL-037) which was placebo-controlled, and one each occurred in European (905 CL-019) and US (905 UC-007) open label studies. One patient (Patient #152-2, Japanese study 037) was found dead in the bathroom (medical examiner stated that the death occurred 4 days prior to the discovery). The investigator considered the event unassessable due to lack of information. The second patient (Patient #253-2, Japanese study 037) developed acute bronchitis and pneumonia complicated by respiratory distress followed by cardiac "distress," resulting in death. The investigator considered this death unrelated to study drug. The third death

(Patient #10551, European study 019) occurred after discontinuation of the study. This 76-year-old female with well-controlled diabetes who was randomized to solifenacin 10 mg in the double-blind study and received 5 mg at the start of the extension study. Thirty-five days later the dose was increased to 10 mg. Study drug was discontinued another 10 days later after 133 days of solifenacin treatment. Two days later she collapsed at home due to postural hypotension and was hospitalized. The investigator considered the collapse to probably be treatment-related. The patient recovered after a one-week hospitalization. Two months after withdrawal from the trial the patient died of a pulmonary embolus as a result of right leg venous thrombosis. The cause of death was considered unrelated by the sponsor. The fourth patient (Patient #01503, Study UC-007), who was an 84-year-old female with a medical history of hypertension and transient ischemic attacks, died suddenly 18 days after she was randomized to solifenacin 5 mg. The investigator considered the death secondary to the patient's arteriosclerotic cardiovascular disease and unrelated to solifenacin.

I believe that none of the deaths can be reasonably attributed to study drug.

Serious adverse events:

In the original NDA submission, ten SAE's in the four major phase 3 trials were judged by the investigator to be probably or possibly related to study drug. Three were considered to be secondary to expected antimuscarinic side effects and included two patients with fecal impaction and one patient with intestinal obstruction.

Narrative summaries of these 10 patients are included in the appendices of the medical officer's review. Two patients experienced syncope. Patient 11024 (5 mg solifenacin) experienced syncope; he had a history of encephalitis, vertigo and had experienced syncopal episodes prior to entering the study. Patient 21454 was hospitalized for atrial fibrillation and syncope 7 days after starting 10 mg solifenacin. The occurrence of the syncopal episode was temporally related to initiation of atenolol. Patient 11579 (5 mg solifenacin) experienced "tachyarrhythmia" diagnosed as "tachyarrhythmia absoluta" and underwent cardioversion. She had a prior history of arrhythmia and cardioversion. Patient 10886 (10 mg solifenacin) was diagnosed with a "possible" myocardial infarction on the EKG performed at the completion of the study; he was asymptomatic. The other SAE's are unlikely to be related to study drug.

In the open label studies 016 (United States) and 019 (Europe), 12 patients experienced SAE's which were thought to be possibly or probably related to study drug. One of the patients (#20256 – 5 mg solifenacin) experienced fecal impaction which required hospitalization. Patient #1325015 (10 mg solifenacin) experienced increasing symptoms of diverticulitis and rectal bleeding. Patient #10551 (10 mg solifenacin) was a 77-year-old-woman who "collapsed" at home during the extension phase of Trial 019. She was diagnosed with "postural hypotension" and recovered without sequelae. The other SAE's are unlikely to be related to study drug.

One patient in QT study 022 experienced the SAE of acute urinary retention. Patient #022-015 was a 72-year-old Black man with a medical history of benign prostate hyperplasia and urinary retention, which had required urethral catheterization 5 to 6 years previously. The patient had been treated with solifenacin 14 days at 10 mg/day and 14 days at 20 mg/day. On Day 8 of treatment at the 30 mg solifenacin dose level, the patient presented with urinary retention and was hospitalized for catheterization. The event resolved a week later and the patient was discontinued from the study.

The overall incidence of serious adverse events and the nature of the individual serious adverse events in the updated safety pools do not suggest a specific risk pattern and no new safety concerns were identified. The only exception is a patient who developed angioneurotic edema temporally related to taking solifenacin 5 mg. This case will be added to the ADVERSE EVENTS portion of the label.

Overall adverse events:

In the combined 4 major placebo-controlled phase 3 studies, the overall frequency of treatment-emergent adverse events was 52.1% in the placebo groups and 45.8% and 62.7% in the solifenacin 5 and 10 mg groups, respectively. The number (%) of patients discontinuing the trials because of an adverse event were 66 (5.4%), 21 (3.6%), and 85 (6.9%) in the placebo, 5 mg solifenacin, and 10 mg solifenacin groups, respectively.

The number and % of patients with treatment emergent adverse events is shown in Table 12.

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Table 12. Number and % of subjects with TEAEs by system organ class: combined United States and European phase 3 studies

System Organ Class MedDRA preferred term	Combined Studies (013/014, 015/018): n (%)			
	Placebo	YM 905 5 mg	YM 905 10 mg	Tolter 4 mg
Number of patients	1216	578	1233	263
Number of patients with any AE	634 (52.1)	265 (45.8)	773 (62.7)	127 (48.3)
Gastrointestinal disorders	198 (16.3)	117 (20.2)	495 (40.1)	69 (26.2)
Dry mouth	51 (4.2)	63 (10.9)	340 (27.6)	51 (19.4)
Constipation	35 (2.9)	31 (5.4)	165 (13.4)	8 (3.0)
Nausea	24 (2.0)	10 (1.7)	40 (3.3)	3 (1.1)
Dyspepsia	12 (1.0)	8 (1.4)	48 (3.9)	4 (1.5)
Abdominal pain upper	12 (1.0)	11 (1.9)	15 (1.2)	4 (1.5)
Vomiting	11 (0.9)	1 (0.2)	14 (1.1)	0
Infections and infestations	189 (15.5)	67 (11.6)	182 (14.8)	23 (8.7)
UTI	34 (2.8)	16 (2.8)	59 (4.8)	2 (0.8)
Nervous system disorders	113 (9.3)	29 (5.0)	114 (9.2)	16 (6.1)
Headache	55 (4.5)	11 (1.9)	52 (4.2)	12 (4.6)
Musculoskeletal & connective tissue	94 (7.7)	22 (3.8)	92 (7.5)	14 (5.3)
Eye disorders	52 (4.3)	32 (5.5)	99 (8.0)	8 (3.0)
Vision blurred	22 (1.8)	22 (3.8)	59 (4.8)	4 (1.5)
Dry eye	7 (0.6)	2 (0.3)	20 (1.6)	0
General disorders	62 (5.1)	16 (2.8)	83 (6.7)	13 (4.9)
Renal and urinary disorders	41 (3.4)	17 (2.9)	60 (4.9)	13 (4.9)
Urinary retention	7 (0.6)	0	17 (1.4)	0
Dysuria	5 (0.4)	2 (0.3)	9 (0.70	3 (1.1)
Psychiatric disorders	41 (3.4)	10(1.7)	41 (3.3)	6 (2.3)
Respiratory disorders	30 (2.5)	3 (0.5)	55 (4.5)	5 (1.9)
Cough	3 (0.2)	1 (0.2)	13 (1.1)	1 (0.4)
Vascular disorders	27 (2.2)	16 (2.8)	22 (1.8)	5 (1.9)
Hypertension NOS	7 (0.6)	8 (1.4)	6 (0.5)	3 (1.1)

In general, the largest percentage of patients with adverse events experienced gastrointestinal disorders: dry mouth, constipation and nausea. The incidence of blurred vision was <5% , but was consistently higher in solifenacin groups than in the placebo group. All of these events are expected anticholinergic side effects. No clinically important differences in the adverse event profile of solifenacin were found when considering gender and age. A meaningful comparison of races was precluded by the fact that the overwhelming majority of patients were Caucasian.

No adequately designed studies have compared the adverse events seen with solifenacin with approved anticholinergic drugs for the treatment of overactive bladder. The rate for constipation seen with the 10 mg solifenacin dose (13.4%) does appear to be higher than the rates reported in the labels of the other products.

Laboratory abnormalities:

Liver function abnormalities:

The number and percentage of patients with hepatic function abnormalities of 1X, 3X, and 10X upper limit of normal are shown in Table 13.

Table 13. Number and % of patients with one or more abnormalities of hepatic function tests 1x, 3x, or 10x ULN

Hepatic function Analyte (Limit multiple)	Placebo n (%)	YM905 5 mg n (%)	YM905 10 mg n (%)	Tolterodine 4 mg n (%)
ALT				
Abnormal	89 (7.3)	41 (7.1)	68 (5.5)	16 (6.1)
3xULN	6 (0.5)	6 (1.0)	6 (0.5)	2 (0.8)
10xULN	1 (0.1)	0	0	0
AST				
Abnormal	70 (5.8)	19 (3.3)	48 (3.9)	4 (1.5)
3xULN	2 (0.2)	3 (0.5)	3 (0.2)	0
10xULN	1 (0.1)	0	0	0
Bilirubin				
Abnormal	68 (5.6)	11 (1.9)	69 (5.6)	1 (0.4)
3xULN	0	0	0	0
10xULN	0	0	0	0
ALKP				
Abnormal	38 (3.1)	32 (5.5)	46 (3.7)	10 (3.8)
3x ULN	1 (0.1)	0	0	0
10x ULN	0	0	0	0
γ-GGT				
Abnormal	61 (5.0)	51 (8.8)	74 (6.0)	21 (8.0)
3xULN	29 (2.4)	16 (2.8)	22 (1.8)	5 (1.9)
10xULN	2 (0.2)	2 (0.3)	0	0
All 5 analytes				
Abnormal	0	0	0	0
3xULN	0	0	0	0
10xULN	0	0	0	0

TEAV: treatment emergent abnormal value

The data show that the active treatment groups are not different from the placebo group. For patients with normal liver function tests at baseline and 3xULN during treatment, or with abnormal values up to 3xULN at baseline and further higher abnormal values, there

were 19 in the placebo group and 26 in the solifenacin 5 mg and 10 mg groups for the combined Phase 3 US and European studies.
There was a case report from Study 905-CL-038 conducted in Japan of a patient who experienced elevated liver function tests and was clinically diagnosed with interstitial pneumonitis. Patient #2001 was a 69-year-old woman with a history of hyperthyroidism. She was enrolled in Phase 2 Study 905-CL-038 (5mg solifenacin once daily). Six months after the start of solifenacin treatment, she began taking the herbal medicine saibokutou for a sore throat. Ten days later her liver function tests showed abnormalities. At the 28th study week (193 days on solifenacin), solifenacin was discontinued. Six days later she was urgently admitted to the hospital because of loss of consciousness. She was diagnosed with interstitial pneumonia and hypoxemia. Her status improved 4 days after hospitalization (she was treated with steroids), but her liver function tests showed further deterioration (Table 14).

Table 14. Summary liver function tests

Test (normal Range IU/L)	Baseline 11/13/02	3 weeks 12/19/02	8 weeks 01/16/03	13 weeks 03/13/03	27 weeks 05/30/03	Interrupt 06/05/03	Follow-up	
							06/09/03	07/10/03
AST (10-40)	25	20	17	21	155	89	64	18
ALT (5-45)	20	16	15	18	164	152	84	32
γ-GGT (16-73)	30	25	21	21	465	632	1233	93
ALKP (104-338)	489	364	415	334	1150	1733	443	N/A

Her discharge diagnosis was motor speech disorder due to cerebral infarction. The investigator judged the event to not be related to study medication (solifenacin) but rather to be secondary to the herbal medication saibokutou based on the results of a drug lymphocyte stimulation test (DLST). Abdominal ultrasound showed no abnormalities. A CT scan of the chest revealed a "granular-reticular shadow" and a pleural effusion. No information concerning hepatitis serology was submitted. No biopsies were performed.

In my opinion, the relationship of study drug to this patient's "interstitial pneumonitis" and elevated liver function tests can not be determined. The patients use of herbal medication is confounding.

Thrombocytopenia:

Patient #15-10687 in study 905-CL-015 had a normal platelet count of 184,000 at screening which decreased to 28,000 at the end of study (Day 92). She was randomized to the 5 mg solifenacin group. She continued into the extension study (905-CL-019) at the 5 mg dose. During the course of Trial 905-CL-019, platelet counts returned to normal (188,000, 183,000, and 190,000) at 3 different visits while on study drug. She was taking no other medications and the event was judged by the investigator as possibly related to

study drug. I believe that this event was unlikely to be related to study drug. No other cases of thrombocytopenia were reported.

In summary, the majority of adverse events related to solifenacin are secondary to its known anticholinergic properties. No other significant safety concerns were identified in the safety data base.

7. **Overview of Efficacy:**

In support of the efficacy of solifenacin for the indication treatment of overactive bladder, the sponsor submitted the results of 4 major phase 3 clinical trials. Trials 013 and 014 were conducted in the United States and evaluated the 10 mg dose of solifenacin. Trials 015 and 016 were conducted in Europe, Africa, Australia, and New Zealand and evaluated the 5 mg and 10 mg doses of solifenacin.

Financial disclosure: Financial disclosure information was submitted and is adequate. One investigator involved in Trials 006, 013, and 016 filed a financial disclosure form. This form was mistakenly filed. The monies received were from (an independent company, not a subsidiary of Yamanouchi). I believe that adequate documentation for this incorrect filing is included in the NDA application. None of the other investigators or sub-investigators had financial interest requiring disclosure.

In addition, the sponsor submitted the results of phase 2 dose-finding studies 005 (performed in Europe, Africa, Australia, and New Zealand) and 006 (performed in the United States).

All four major trials were double-blind, placebo-controlled, and of 12 weeks duration.

Key inclusion/exclusion criteria were as follows:

Inclusion criteria in 013 and 014 included: Symptoms of overactive bladder (urinary frequency with urgency and/or incontinence), age >18 years, an average of >8 micturitions/24 hours, and either an average of >1 urinary incontinence episode/24 hours or an average of >1 urinary urgency episode/24 hours, documented in a 3-day diary in the screening phase.

Exclusion criteria in 013 and 014 included: Stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Trial 014 also included the exclusion criteria of urinary retention as demonstrated by post-void residual urine volume of >150 cc as evidenced by a bladder scan.

Inclusion criteria in 015 and 018 included: Symptoms of overactive bladder (urinary frequency with urgency and/or incontinence) for >3 months, age >18 years, an average of >8 micturitions/24 hours, and either an average of >3 urinary incontinence episodes or an average of >3 urinary urgency episodes documented in a 3 day diary in the screening phase.

Exclusion criteria in 015 and 018 included: stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Both of these trials also excluded patients with urinary retention defined as a post-void residual urine volume of >200 cc as evidenced by a bladder scan.

Endpoints:

The primary efficacy endpoint in all four trials was the mean change from baseline to endpoint in the number of micturitions/24 hours.

Secondary efficacy endpoints in all four trials included mean change from baseline to endpoint in 1) number of incontinence episodes/24 hours 2) number of urgency episodes/24 hours 3) mean volume voided/micturition and 4) number of nocturia episodes/24 hours.

The results of the primary efficacy analysis (number of micturitions/24 hours) are shown in Table 15.

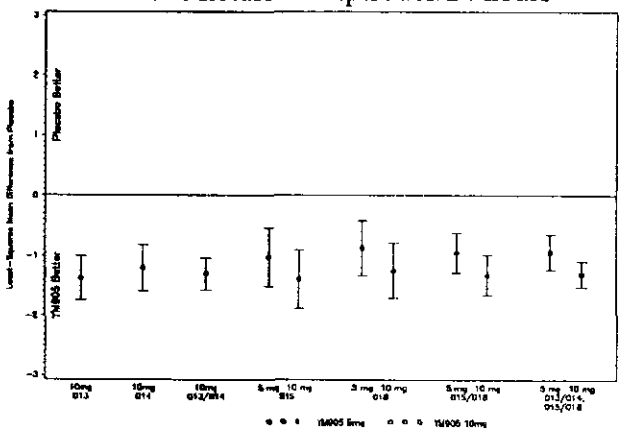
Table 15. Mean change from baseline to endpoint in mean number of micturitions/24 h: pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)	p-value	Bonferroni-Holm adjusted p value
013	Placebo	309	11.5±0.18	−1.5±0.15			N/A
	YM905 10 mg	306	11.7±0.18	−3.0±0.15	−1.37 (−1.74, −1.01)	<0.001	
014	Placebo	295	11.8±0.18	−1.3±0.16			N/A
	YM905 10 mg	298	11.5±0.18	−2.4±0.15	−1.20 (−1.59, −0.81)	<0.001	
013/014	Placebo	604	11.7±0.13	−1.4±0.11			N/A
	YM905 10 mg	604	11.6±0.12	−2.7±0.11	−1.30 (−1.56, −1.03)	<0.001	
015	Placebo	253	12.2±0.26	−1.2±0.21			
	YM905 5 mg	266	12.1±0.24	−2.2±0.18	−1.02 (−1.50, −0.53)	<0.001	<0.001
	YM905 10 mg	264	12.3±0.24	−2.6±0.20	−1.39 (−1.87, −0.91)	<0.001	<0.001
	Tolter 4 mg	250	12.1±0.22	−1.9±0.19	−0.73 (−1.22, −0.24)	0.004	N/A
018	Placebo	281	12.3±0.23	−1.7±0.19			
	YM905 5 mg	286	12.1±0.23	−2.4±0.17	−0.87 (−1.33, −0.42)	<0.001	<0.001
	YM905 10 mg	290	12.1±0.21	−2.9±0.18	−1.25 (−1.70, −0.79)	<0.001	<0.001
015/018	Placebo	534	12.3±0.17	−1.4±0.14			
	YM905 5 mg	552	12.1±0.16	−2.3±0.12	−0.94 (−1.28, −0.61)	<0.001	<0.001
	YM905 10 mg	554	12.2±0.16	−2.8±0.13	−1.32 (−1.65, −0.99)	<0.001	<0.001
US & EU combined (13/14,15/18)	Placebo	1138	11.9±0.11	−1.4±0.09			
	YM905 5 mg	552	12.1±0.16	−2.3±0.12	−0.94 (−1.23, −0.65)	<0.001	<0.001
	YM905 10 mg	1158	11.9±0.10	−2.7±0.09	−1.31 (−1.52, −1.09)	<0.001	<0.001

In each of the four major trials, the number of micturitions in the solifenacin groups was decreased approximately 1-1.5 episodes/24 hours compared to placebo. These changes were statistically significant at the $p < 0.001$ level in all four studies. The statistical reviewer agrees that the change from baseline to endpoint versus placebo in all 4 major efficacy trials is statistically significant.

95% confidence intervals for micturition/24h change from baseline means for individual studies, combined US, combined EU and combined US/EU studies are shown in Figure 1.

Figure 1. 95% Confidence Intervals for Mean Change from Baseline for Micturition Episodes/24 hours



The mean change from baseline in incontinence episodes/24 hours (a secondary endpoint) is shown in Table 16.

Table 16. Mean change from baseline to endpoint in mean number of incontinence episodes/24 h: pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)	p-value	Bonferroni-Holm adjusted p value
013	Placebo	237	3.0±0.20	−1.1±0.16			
	YM905 10 mg	225	3.1±0.22	−2.0±0.19	−0.80 (−1.19, −0.42)	<0.001	N/A
014	Placebo	238	2.9±0.18	−1.2±0.15			
	YM905 10 mg	230	2.9±0.17	−2.0±0.15	−0.74 (−1.07, −0.41)	<0.001	N/A
013/014	Placebo	475	2.9±0.13	−1.2±0.11			
	YM905 10 mg	455	3.0±0.14	−2.0±0.12	−0.77 (−1.03, −0.52)	<0.001	N/A
015	Placebo	153	2.7±0.23	−0.8±0.18			
	YM905 5 mg	141	2.6±0.22	−1.4±0.15	−0.68 (−1.13, −0.23)	0.003	0.003
	YM905 10 mg	158	2.6±0.23	−1.5±0.18	−0.75 (−1.19, −0.31)	<0.001	0.002
	Tolter 4 mg	157	2.3±0.15	−1.1±0.17	−0.59 (−1.03, −0.15)	0.009	N/A
018	Placebo	153	3.2±0.24	−1.3±0.19			
	YM905 5 mg	173	2.6±0.18	−1.6±0.16	−0.66 (−1.07, −0.24)	0.002	0.004
	YM905 10 mg	165	2.8±0.20	−1.6±0.18	−1.48 (−0.90, −0.06)	0.026	0.026
015/018	Placebo	306	3.0±0.17	−1.0±0.13			
	YM905 5 mg	314	2.6±0.14	−1.5±0.11	−0.66 (−0.96, −0.35)	<0.001	<0.001
	YM905 10 mg	323	2.7±0.15	−1.5±0.13	−0.60 (−0.91, −0.30)	<0.001	<0.001
US & EU combined (13/14,15/18)	Placebo	781	2.9±0.10	−1.1±0.09			
	YM905 5 mg	314	2.6±0.14	−1.5±0.11	−0.73 (−1.01, −0.45)	<0.001	<0.001
	YM905 10 mg	778	2.9±0.10	−1.8±0.09	−0.72 (−0.91, −1.52)	<0.001	<0.001

The statistical reviewer believes that 3 of the 4 major trials demonstrate a statistically significant change in the secondary endpoint incontinence episodes. The fourth study

(018) shows a mean change from baseline of –1.6 episodes with solifenacin (-1.3 episodes with placebo) (p-value = 0.22). The above table is from a secondary analysis with baseline included as covariate. The sponsor believes that this analysis is more appropriate because of the baseline differences between placebo and the two active treatment groups. The sponsor's primary analysis shows that the difference from placebo is not statistically significant for the solifenacin 10 mg treatment group (0.22). In the primary analysis, the 5 mg dose could not be compared to placebo because of the hierarchical testing approach. This issue, as it relates to labeling, was discussed with the sponsor during a teleconference on November 17, 2004. The inclusion of baseline as a covariate in the statistical analysis plan was prespecified as a secondary analysis. The statistical reviewer believes that the inclusion of the p-value (<0.02) in the label for the secondary endpoint mean number of incontinence episodes/24 hours is acceptable.

Mean voided volume also increased by a statistically significant amount (approximately 20 to 50 cc) in all four trials. The mean change from baseline to endpoint in number of urgency episodes/24 hours was approximately a decrease of 1 to 2.

No adequately designed trials directly comparing solifenacin to approved antimuscarinic drugs for overactive bladder have been performed. The magnitude of the changes in number of micturitions and incontinence episodes seen with solifenacin and approved drugs, however, appear similar.

In summary, four adequately controlled trials enrolling an appropriate patient population have demonstrated that solifenacin decreases urinary frequency and incontinence episodes and is effective for the treatment of overactive bladder.

8. **Clinically Relevant Issues from Other Discipline's Reviews:**

   a. **Statistics:**

   The statistician reviewed the 4 randomized, double-blind, placebo-controlled, parallel-arm, multicenter clinical studies of primary interest for assessing the efficacy of solifenacin 5 or 10 mg tablets. "All four studies include the 10 mg dose and 2 studies include the 5 mg dose. For the primary endpoint, the mean change in number of micturitions per 24 hours, both Vesicare doses are statistically significantly better than placebo in all comparisons. The same is true for one of the two secondary variables the Medical Officer requested: the mean change in volume voided per micturition. On the other secondary variable of interest to the Medical Officer, the mean change in number of incontinence episodes, the Vesicare doses are statistically

significantly better than placebo in three of the four studies. The statistician believes that these results support the efficacy of Vesicare 5 or 10 mg tablets for the relief of symptoms of urinary incontinence or urgency associated with overactive bladder." Statistics was again consulted to review the statistical analysis of the "thorough QT study." These statistical comments are included in section 4 of this memorandum.

b. Pharmacology/Toxicology:

Following review of the initial NDA submission, the pharmacology/toxicology reviewer recommended "approval." "Final analysis of mouse and rat carcinogenicity studies should be electronically submitted for review and statistical analysis." The pharmacology/toxicology reviewer believed that this issue could be adequately managed with labeling.

The final analysis of the mouse and rat carcinogenicity studies was submitted and the CAC concurred with the Division that both the mouse and rat studies are negative for carcinogenicity. The pharmacology/toxicology reviewer believes that the NDA should be approved from a pharmacology/toxicology viewpoint.

c. Clinical pharmacology:

The clinical pharmacology reviewer found the NDA application to be "acceptable."

Dose selection: In two relatively large phase 2 dose finding studies (005 and 006), the 5 mg dose was established as the lowest effective dose in one study and 10 mg as the lowest effective dose in the other study. In one of the studies, efficacy was maximized at the 10 mg dose while in the other study maximal efficacy was not established even at the 20 mg dose. In the phase 3 studies, the 10 mg dose was numerically somewhat superior to the 5 mg dose with respect to the primary endpoint of mean number of micturitions/24 hours, although this difference was statistically significant only at Day 28. Based on efficacy and tolerability, the 5 and 10 mg doses are acceptable to the clinical pharmacology reviewer as the to-be-marketed doses. I agree with this dose selection.

Following the administration of solifenacin, Cmax is achieved in 3 to 6 hours. The half-life ($t_{1/2}$) is 48 to 60 hours. Solifenacin has one major metabolite (M2) which has negligible activity and 3 minor metabolites (M3, M4, and M5). M3 has the most muscarinic receptor activity among the metabolites (3-fold lower than the parent), but demonstrates significantly lower plasma levels than solifenacin. Solifenacin is excreted primarily in the urine (approximately 70%) and feces (approximately 23%). The drug shows linear pharmacokinetics between 5 and 100 mg oral doses.

There is a 20-25% increase in the C_{max} and AUC in the elderly as compared to younger subjects.

In moderately hepatically impaired patients there is a 2-fold increase in $t_{1/2}$ and a 35% increase in AUC of solifenacin. The clinical pharmacology reviewer recommends not to exceed a 5 mg daily dose of solifenacin in this group of patients and I agree with this recommendation. Patients with severe hepatic impairment have not been studied and the use of solifenacin in this group of patients is not recommended.

In patients with severe renal impairment a 2-fold increase in AUC was observed. The clinical pharmacology reviewer recommends not to exceed a 5 mg daily solifenacin dose in this group of patients and I agree with this recommendation.

Solifenacin is metabolized primarily by CYP 3A4 with a minor contribution from CYP 2C19. In a drug-drug interaction study with 400 mg ketoconazole daily, the C_{max} and AUC were increased by approximately 1.5 and 3-fold, respectively. Based on this finding, the clinical pharmacology reviewer recommends not to exceed a 5 mg dose of solifenacin when used in combination with ketoconazole and other potent CYP 3A4 inhibitors and I agree with this recommendation.

The CLINICAL PHARMACOLOGY and DOSAGE and ADMINISTRATION sections of the label include all of the clinical pharmacology recommendations.

d. Chemistry

The "approvable" letter of October 17, 2003, contained the following chemistry deficiency:

"The current dissolution acceptance criterion (, at 30 minutes) is unacceptable."

The chemistry review of the compete response to "approvable" action states: "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." The reviewer concludes that "this application can be approved from a CMC standpoint pending acceptable labeling."

e. Microbiology:

Following review of the initial NDA submission, the microbiology consultant recommended approval from the standpoint of microbial product quality.

9. **Review of Consultations:**

a. Division of Scientific Investigations:

Three study sites in Europe (Drs. Al-Shukri, Halaska, and Kuzmin) and three sites in the United States (Drs. Harris, Fincher, and Kaufman) were inspected prior to issuing

the original "approvable letter. The data submitted in support of this NDA by all 6 sites "appear acceptable."

b. DDMAC

In the initial consultation concerning the tradename (August 9, 2002), DDMAC "did not have concerns about the name Vesicare with regard to promotional claims." DDMAC now believes (consult dated October 22, 2004), however, that

' I believe that the tradename "Vesicare" is acceptable. DDMAC also believed that

The Division/Office, however, found the tradename acceptable.

In addition, DDMAC provided extensive comments on the PI which were taken into consideration at the time of labeling.

c. DMETS:

DMETS initial consult (August 9, 2002) concerning the proprietary name "Vesicare" concluded that "DMETS has no objections to the use of the proprietary name, Vesicare. In conducting this review, DMETS searched several standard published drug product reference texts as well as several FDA databases for existing drug names which sound alike or look alike to Vesicare to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted. The Saegis Pharma-In-Use database was also searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners with the FDA.

DMETS was again consulted in July, 2003, to re-review the proprietary name "Vesicare." The consultation concluded that "since the initial Vesicare proprietary name review, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Vesicare."

DMETS was again consulted following the complete response to "approvable" action on May 18, 2004, and the consult was completed October 22, 2004. The consult stated:

"DMETS has completed the review of your proposed trade name, Vesicare, and has identified several new concerns which may preclude the ability for Vesicare to coexist safely with another already U.S. marketed product. As a result, DMETS has reversed

their initial decision and the use of the proprietary name, Vesicare, is no longer recommended."

"In reviewing the proprietary name "Vesicare", the primary concern for name confusion was Benicar, which already exists in the U.S. marketplace. The following issues and recommendations have been identified:

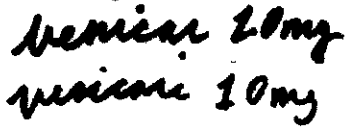
DMETS has identified the potential for look-alike confusion between Benicar and Vesicare. The initial DMETS safety review (ODS consult 02-0117) for Vesicare was completed in August 2002 and the name was found acceptable. While Benicar was introduced into the U.S. marketplace (approved on April 25, 2002) a couple of months prior to the proprietary name review of Vesicare, the potential safety of the name pair of Vesicare and Benicar may have been omitted because the launch of Benicar was in close proximity to the submission of Vesicare's application. Additionally, the DMETS' Phonetic Orthographic Computer Analysis (POCA) database, which is where the name Benicar was identified, had not been developed at the time of this initial review.

Benicar is an angiotensin II receptor blocking agent approved for once-daily treatment of mild-to-moderate hypertension alone or in combination with other antihypertensives. Both names share a similar looking prefix ("Beni-" vs. "Vesi-") and similar suffixes ("-car" vs. "-care"). The "B" in Benicar, if scripted with a lowercase "b" resembles the letter, "V". Similarly, the "n" in Benicar looks like an "s" if not precisely scripted and handwritten in cursive. Although Vesicare has one more letter than Benicar (eight vs. seven), the two names share orthographic characteristics that increase the likelihood for a dispensing error to occur. Inadvertent administration of either medication places the patient at risk for suboptimal treatment for their respective disease state. It also subjects each patient to the risks and adverse effects associated with each drug. These similarities, compounded by the fact that they also share numerous product characteristics, further increases the likelihood for confusion.

Considerations for Confusion between Benicar and Vesicare include the following:

- Benicar and Vesicare are both tablets sharing a dosage strength of 5 mg. Although the usual Benicar dosage range is 20 mg to 40 mg, the fact that a 5 mg strength exists, introduces the possibility that this 5 mg tablet may be used for certain patients. In addition, Vesicare is available in a 10 mg strength. A 20 mg dose may be achieved with two 10 mg tablets. If a prescription for "Benicar 20 mg po qd" were misinterpreted for "Vesicare 20 mg po qd", the dispensing pharmacist may potentially substitute the non-existing 20 mg strength with two 10 mg tablets.

- Post-marketing data have shown that the number "10" can be mistaken for "20" and vice versa. A prescription written for "Benicar 20 mg" could be mistaken for "Vesicare 10 mg" and vice versa. See writing sample below.



Benicar 20 mg Vesicare 10 mg

- Benicar and Vesicare have an overlapping dosage schedule (once daily) and route of administration (oral). A prescription written for "Benicar 5 mg po qd" may be misinterpreted as "Vesicare 5 mg po qd" and vice versa. Similarly, prescriptions written for "Benicar 20 mg po qd" and "Vesicare 10 mg po qd" may be mistaken for each other (see writing sample above).

- Benicar and Vesicare have different indications for use. Unfortunately, this may not be enough to prevent confusion and errors because this information is not always available to the pharmacist or practitioner interpreting the drug order. Also, the two medications could be prescribed by the same practitioner population (family practice, internal medicine, geriatrics), further increasing the likelihood for confusion.

DMETS has identified significant potential for confusion with Vesicare, particularly in the case of handwritten orders."

The primary reason why DMETS objects to the tradename Vesicare is the possibility of confusion with Benicar in handwritten orders. When reviewing the sample handwritten orders provided in the consult dated October 22, 2004, it appears that this confusion would most probably occur when a lower case "B" was written for Benicar or a lower case "V" for Vesicare. In the previously conducted prescription analysis studies including two written prescription studies (inpatient and outpatient) involving health care practitioners within the FDA (see consult from August 9, 2002), the "V" in Vesicare is prominent and I do not think it would be confused with the "B" in Benicar. Likewise, I do not believe that writing a lower case "b" for Benicar would be confused with the Vesicare "V" as written in the actual written prescription studies which involved health care practitioners within the FDA.

Although a 5 mg strength is available for both products, IMS data for Benicar indicate that the — are most commonly dispensed. The 5 mg tablet accounts for only — of prescriptions. The 5 mg dose usage in 2003 and year-to-date figures through August, 2004, is stable at — of all Benicar prescriptions. The recommended starting dose for Benicar is 20 mg and this dose can be increased to 40 mg. No mention is included in the labeling for the use of the 5 mg Benicar tablet in the DOSAGE and ADMINISTRATION section of the Benicar labeling.

Both Benicar and Vesicare are supplied in 5 mg dose strengths. If 5 mg Benicar were substituted for 5 mg Vesicare, or vice versa, significant adverse effects would not be expected to occur. The 5 mg dose of the anti-hypertensive drug Benicar is one-fourth of the recommended starting dose and the 5 mg dose of solifenacin poses no significant safety concerns.

In verbal studies conducted at the time of the first DMETS consult, "Vesicare" was correctly identified as beginning with the letter "V" by all respondents.

The tradename safety issue was discussed with the sponsor. The sponsor was asked to develop packaging and labeling to emphasize the the "Vesi" part of the tradename to better distinguish it from Benicar. The sponsor proposed the tradename VESIcare for use in packaging, labeling, and advertising. I believe that this tradename adequately differentiates the drug from the already marketed Benicar and is acceptable.

d. DSRCS:

The comments and editorial changes recommended by DSRCS for the PPI were incorporated except for some minor changes in wording.

10. **Risk-Benefit Considerations and Overall Regulatory Recommendation:**

Solifenacin has been demonstrated to be effective for the treatment of overactive bladder in four well-controlled phase 3 studies in an appropriate patient population. Although no adequately designed trials have directly compared the efficacy of solifenacin with other anticholinergic drugs approved for this indication, the magnitude of the improvement seen with solifenacin appears comparable to the approved drugs. No significant safety concerns in addition to the recognized anticholinergic side effects were identified. Based on the results of the "thorough QT study," I do not think that there is an arrhythmogenic risk with the use of solifenacin. Because of the QTc dose response seen in the 10 and 30 mg solifenacin groups, however, I do think that this information should be included in the label, including the PRECAUTIONS section of the label. The incidence of constipation may be somewhat higher than in the other approved anticholinergic drugs, but I do not think that sufficient data are available to conclude this with certainty. The incidence of "severe" cases of constipation is low, and this adverse event is well characterized in both the label and patient information leaflet.

Pediatric Development Plan: In an October 22, 2004, submission, the sponsor indicated their intention to initiate pediatric evaluation of solifenacin succinate via an study , in children (ages 5-11 years) and adolescents (ages 12-17 years) with overactive bladder. A partial, deferred pediatric waiver was granted and the study completion date is May 18, 2009.

11. **Labeling issues:**

Final labeling negotiations with the sponsor have been concluded. On November 19, 2004, the sponsor agreed to remove the from the carton labeling. DDMAC believes that the There are no unresolved issues pertaining to NDA 21518 and I think the drug should be approved.

APPEARS THIS WAY
ON ORIGINAL

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/s/

George Benson
11/19/04 03:04:21 PM
MEDICAL OFFICER

Donna Griebel
11/19/04 03:06:32 PM
MEDICAL OFFICER
I concur with Dr. Benson's review findings and conclusions.
I concur with his recommendation for approval of
this NDA.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 16, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Revised Draft PI and PPI changes are attached

Total no. of pages including cover: 21

Comments: see comment below.

Document to be mailed: YES NO

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Dear Rudy,

Please find attached a revised PI and PPI from the Division.

Sincerely,

LSI

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

20 Draft Labeling Page(s) Withheld

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 10, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Draft Labeling changes are attached

Total no. of pages including cover: 15

Comments: see comment below.

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Dear Rudy,

In follow-up to my telephone call today, please find attached revised labeling from the Division. We are continuing to work on the Cardiac Electrophysiology section and hope to get comments to you on Monday, November 15, 2004.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

14 Draft Labeling Page(s) Withheld

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 10, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: November 8, 2004 Teleconference Minutes are attached for your reference

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **NO**

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Teleconference Minutes

NDA: 21-518 **Sponsor**: Yamanouchi Pharma-America, Inc.

Drug: Solifenacin succinate **Date**: November 8, 2004 **Time**: 1:00 – 1:30PM

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
George Benson, M.D., Urology Team Leader, DRUDP
Goudong Fang, Medical Reviewer, DRUPD
Jean Makie, M.S., R.D., Project Manager, DRUDP

Yamanouchi Attendees:
Rudy Lucek, Vice President, Regulatory Affairs
Neila Smith, M.D., Director, Drug Safety
Maskazu Andoh, Associate Director, Clinical Statistics
Robert Desjardins, M.D., Chief Development Officer
Susan Ridge, Director, Project Management
Christine Mulhauser, Director, Regulatory Affairs, CMC

Kenji Yasukawa, Senior Manager, Project Coordination Department, Yamanouchi Pharmaceutical Co., Japan

GlaxoSmithKline Attendees:
Thomas Kline, Director, U.S. Regulatory Affairs
Jeff Wilkins, M.D., Group Director, Clinical Development

Background: The Division faxed initial labeling changes and recommendations to the Sponsor on November 4, 2004. Today's teleconference was held to convey concerns raised by the Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) regarding the Sponsor's proposed trade name, Vesicare.

Discussion Issues: Tradename acceptance.

DRUDP informed the Sponsor that, in reviewing the proprietary name "Vesicare", DMETS identified (using their Phonetic Orthographic Computer Analysis database) the potential for look-alike confusion between Benicar and Vesicare. Benicar is an angiotensin II receptor blocking agent approved for once-daily treatment of mild-to-moderate hypertension alone or in combination with other antihypertensives. Both names share a similar looking prefix ("Beni-" vs. "Vesi-") and similar suffixes ("-car" vs. "-care"). The "B" in Benicar, if scripted with a lowercase "b" resembles the letter, "V". Similarly, the "n" in Benicar looks like an "s" if not precisely scripted and handwritten in cursive. Although Vesicare has one more letter than Benicar (eight vs. seven), the two names share orthographic characteristics that increase the likelihood for a dispensing error to occur. Inadvertent administration of either medication places the patient at risk for

suboptimal treatment for their respective disease state. It also subjects each patient to the risks and adverse effects associated with each drug. DMETS believes that these similarities, compounded by the fact that they also share numerous product characteristics, further increase the likelihood for confusion. See below for a side-by-side written comparison of Benicar and Vesicare.

benicar 20mg	vesicare 10mg
Benicar 20 mg	Vesicare 10 mg

Additionally, DMETS found Benicar and Vesicare to have an overlapping dosage schedule (once daily) and route of administration (oral). A prescription written for "Benicar 5 mg po qd" may be misinterpreted as "Vesicare 5 mg po qd" and vice versa. Similarly, prescriptions written for "Benicar 20 mg po qd" and "Vesicare 10 mg po qd" may be mistaken for each other.

DRUDP also informed the Sponsor that the Division of Drug Marketing, Advertising, and Communications (DDMAC) also objects to the tradename "Vesicare" because —

DRUDP informed the Sponsor that, although it had accepted the tradename "Vesicare" from an — , it remained concerned with potential risks related to the look-alike confusion between Benicar and Vesicare. DRUDP asked the Sponsor to consider revising the characterization of the Vesicare to encourage visual differentiation, which may mitigate potential prescription transcription errors. As an example, the Division suggested that the Sponsor develop packaging and labeling that emphasizes the VESI part of the name - using capital letters, bolding, a special font, a different color, etc. to distinguish Vesicare as much as possible from the already marketed Benicar.

Sponsor Response: The Sponsor stated that it was not opposed to modifying the characterization of the tradename, Vesicare, and committed to send the Division revised proposal(s) on November 9, 2004.

The Sponsor then notified the Division that it had some questions regarding the Division's changes to the package insert (PI), specifically regarding the values used to characterize PK parameters and gender differences in Cmax and AUC. These concerns will be sent today to the Division along with the Sponsor's revised PI.

Division Comments: DRUDP agreed to review these concerns and committed to continue label negotiations with the Sponsor. The Division also informed the Sponsor that there were three Chemistry, Manufacturing, and Control (CMC) comments regarding their proposed carton and container labels; these will be faxed to the Sponsor later today.

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/s/

George Benson
11/18/04 07:58:59 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 10, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: October 26, 2004 Meeting Minutes are attached for your reference

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

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Meeting Minutes

NDA: 21-518 **Sponsor**: Yamanouchi Pharma-America, Inc.

Drug: Solifenacin succinate **Date**: October 26, 2004 **Time**: 2:00 – 3:30PM

Location: Parklawn, Chesapeake Conference Room

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
George Benson, M.D., Urology Team Leader, DRUDP
Julie Bietz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER)
Goudong Fang, Medical Reviewer, DRUPD
Lynnda Reid, Pharmacology/Toxicology Team Leader/Reviewer, DRUPD
Jean Makie, M.S., R.D., Project Manager, DRUDP
Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Leslie Kenna, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., OCPB, Clinical Pharmacology Team Leader, DRUDP
He Sun, Ph.D., Clinical Pharmacology Reviewer, OCPB
Juan Zhang, Ph.D., Biostatistics Reviewer, Quantitative Methods Research Staff (QMR),
Edward Nevius, Ph.D., Division Director, Division of Biometrics II
Mike Welch, Ph.D., Biostatistics Team Leader, Division of Biometrics II
Charles Anello, Sc.D., Office of Biostatistics, CDER
Norman Stockbridge, M.D., Acting Director, Division of CardioRenal Drug Products

Sponsor Attendees:

Yamanouchi Attendees
Rudolph Lucek, Vice President, Regulatory Affairs
Neila Smith, M.D., Director, Drug Safety
Masakazu Andoh, Associate Director, Clinical Statistics
Robert Desjardins, M.D., Chief Development Officer

GlaxoSmithKline Attendees
Thomas Kline, Director, U.S. Regulatory Affairs
Alison Graham, Manager, Clinical Pharmacology Statistics and Programming
Venkat Sethuraman, Principal Statistician, Biomedical Data Sciences
Alan S. Hollister, M.D. Ph. D, Clinical Pharmacology Unit Director
John K. Finkle, M.D., FACP, FACC, Cardiovascular Therapeutic Area Director, Global Clinical Safety and Pharmacovigilance

Michael J. Fossler, Pharm. D. Ph.D., F.C.P. Principal Clinical Pharmacokineticist; Clinical Pharmacokinetics Modeling and Simulation
Lisa Cass, Ph.D.; Clinical Research Progam Manager; Clinical Pharmacology and Discovery Medicine

Outside Consultants

By Telephone:

Background: A brief teleconference was held with the Sponsor on October 14, 2004. Division attendees were Dr. Griebel, Dr. Benson, Dr. Ortiz, and Ms. Makie. During the teleconference, the Division told the Sponsor that it was continuing its review of the results from the Sponsor's QT study (905-CL-043), submitted as part of a Complete Response on May 20, 2004. Additionally, the Division noted Dr. Stockbridge's reservations regarding the interpretability of these data. As a result, the Division encouraged a meeting, preferably face-to-face, with those members of the Sponsor's team who were involved in the analysis of this study, including QT consultative experts. On October 15, 2004, the Division faxed to the Sponsor referenced QT information from Dr. Stockbridge's consultative review of study 905-CL-043 as background material for today's (October 26, 2004) meeting. The following four additional discussion points were sent by the Division on October 25, 2004 for the Sponsor to address during today's meeting:

1. Variation in moxifloxacin QTc in periods 1, 3, and 5
2. Variation in placebo QTc in periods 2, 3, and 5
3. Variation in baselines in periods 1, 2, and 3 (Groups A and B)
4. Choice of nonparametric Hodges-Lehmann-Moses method to compare session related effects in Groups A and B

Discussion Issues: The Sponsor provided a detailed slide presentation on the design, conduct, and results of study 905-CL-043. The presentation addressed the four issues listed above. The Division asked multiple clarification questions in response to data displayed. No final agreements or decisions regarding Study 905-CL-043 were reached at the conclusion of the meeting. The Division stated it would continue to review the QTc results previously submitted and would request any additional follow-up information concerning the Hodges-Lehmann-Moses method and/or the QTc datasets in writing.

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/s/

George Benson
11/18/04 07:54:44 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DUPLICATE

DATE: November 10, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: November 9, 2004 Stats teleconference minutes attached

Total no. of pages including cover:

Comments: see comment below.

Document to be mailed: **YES** **NO**

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Teleconference Minutes

NDA: 21-518 **Sponsor**: Yamanouchi Pharma-America, Inc.

Drug: Solifenacin succinate **Date**: November 9, 2004 **Time**: 5:00 – 5:05 PM

FDA/CDER/DRUDP Attendees:
Juan Zhang, Ph.D., Biostatistics Reviewer, Quantitative Methods Research Staff (QMR),
Edward Nevius, Ph.D., Division Director, Division of Biometrics II
Mike Welch, Ph.D., Biostatistics Team Leader, Division of Biometrics II
Jean Makie, M.S., R.D., Project Manager, of Reproductive and Urologic Drug Products (DRUDP)

Yamanouchi Attendees:
Christine Mulhauser, Director, Regulatory Affairs, CMC

Discussion Issues: The Agency telephoned the sponsor to request that they modify the "ecgmean.xpt" file submitted on May 20, 2004 by adding a column, labeled as Tmax (hr), for each patient in Group A, for sessions 3 and 5. The Sponsor committed to submit this updated dated set on November 10, 2004.

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/s/

Mike Welch
11/10/04 01:01:50 PM

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 9, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: NDA 21-518 Vesicare® (solifenacin succinate) Tablets
Response to FDA Comments from FAX dated 11/8/04

Reference is made to the FAX dated November 8, 2004, in which Chemistry, Manufacturing and Controls comments on the cartons and labels were provided. Each of your comments is listed in the attached document followed by our response.

Reference is also made to the teleconference held on November 8, 2004 between representatives from Yamanouchi, GlaxoSmithKline and your Division. During that meeting, a comment was discussed regarding the Vesicare trade name. Our response to this comment is also provided in the attached document.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

for Rudolph W. Lucek
Vice President, Drug Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

Attachment
YM No. 2004-0249

Response to FDA FAX dated November 8, 2004

FDA Comment
The carton and labels contain the

Response

We have revised the carton and label by removing the

FDA Comment

The is more prominent (color and size) than the strength and the established name. This detracts from the readability of the most important information on the main display panel. Please revise accordingly.

Response

We need some clarification before we can respond to this comment. Please clarify what you mean by Yamanouchi was also concerned that the strength be very clear on the front of the carton. Therefore, the strength is located

FDA Comment

Decrease the prominence and relocate the manufacturer name to the label so as not to interfere with the readability of the proprietary name.

Response

We have revised the r label by relocating the proprietary name to the , as requested. Please see **Attachment 3** for an example using the 10 mg 100-count

FDA Comment from November 8, 2004 teleconference

DMETS has a concern with a look alike issue with the proposed trade name of Vesicare and a newly approved product, Benicar. When the trade names are written in lower case letters, the trade names look similar. Therefore, the Division proposes that the sponsor increase the visual difference in the trade names by changing the presentation of the Vesicare trade name.

Response

We have reviewed your proposal and are providing two options for changing the presentation of the Vesicare trade name. As mentioned in response to the first comment, draft cartons and labels using the 5 mg 30-count carton as an example are provided in **Attachments 1 and 2**. The example included in **Attachment 1** contains the Vesicare name on the cartons and labels — This is our preferred option. In the example included in **Attachment 2**, —
Please let us know which option the Agency prefers.

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1

7 Draft Labeling Page(s) Withheld

Yamanouchi

DUPLICATE

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

September 24, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

BL

ORIG AMENDMENT

RECEIVED
SEP 27 2004
FDR/CDER

Ladies and Gentlemen:

Re: NDA 21-518 Vesicare® (solifenacin succinate) Tablets
Response to Request for Information

Reference is made to our June 18, 2004 submission and your telephone request to submit mockups showing the placement of the sample sticker on the cartons and labels of the bottles of 30 to be used as samples.

We wish to inform you that to assure that important information on the carton and label is not obscured by the placement of — on these packaging components, we have decided to —

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W. Lucek

Rudolph W. Lucek
Vice President, Drug Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

Attachment
YM No. 2004-0209

14 Draft Labeling Page(s) Withheld

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 8, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Draft Labeling changes are attached

Total no. of pages including cover: 1

Comments: see comment below.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Dear Rudy,

In follow-up to our teleconference today, please find below Chemistry, Manufacturing, and Control (CMC) comments and recommendations pertaining to your cartons and containers for solifenacin succinate. We request a prompt written response to these in order to continue with our review of your NDA.

- The carton and labels contain the words — This should be deleted because it can be taken as advertising. If you prefer to retain — on the cartons, it should be moved to —

- The — .s more prominent (color and size) than the strength and the established name. This detracts from the readability of the most important information on the main display panel. Please revise accordingly.

- Decrease the prominence and relocate the manufacturer name to the lower portion of the label so as not to interfere with the readability of the proprietary name.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

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

/s/

Jean Makie
11/8/04 01:46:33 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Follow-up questions/comments to the October 26, 2004 Guidance Meeting

Total no. of pages including cover:

Comments: see comment below.

Document to be mailed: **YES** NO

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Dear Rudy,

Please find below additional statistical comments that the Division requests your team to address as follow-up to Tuesday's solifenacin QT meeting:

1. Please submit the programs implementing the Hodges-Lehmann procedure as requested during the meeting held on October 26, 2004. We also request that you submit the derived data sets that were used in this program in the required SAS transport electronic format.

2. Our statistical team would like to verify their understanding of exactly how the procedure was performed; their understanding is described below. Please verify that the procedure has been portrayed correctly. If not, provide a detailed description of the procedure with an example.

3. Please address more fully the issue whether the procedure utilized has similar power to the standard procedures proposed in the protocol utilizing within-patient responses.

4. We would like to arrange a teleconference to discuss technical issues regarding whether the Hodges-Lehmann procedure employed is actually the only standard procedure that could be utilized for the proposed parallel-group analysis.

Additionally, we acknowledge receipt of the QTcF plots pertaining to both solefenacin and moxifloxacin that were faxed to the Division yesterday, October 27, 2004.

- Please submit the datasets for plasma concentrations and corresponding QTc for moxifloxacin (all sessions) and for solifenacin, 10 mg and 30 mg.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Our current understanding of the procedure utilized in the submission:

To better understand your implementation of Hodges-Lehmann-Moses method, we want to understand how you constructed your data based on Tmax for the Hodges-Lehmann non-parametric analysis. For simplicity, let's assume there are 10 subjects in the drug group (Group A) and 5 subjects in the placebo group (Group B). For each subject in Group A, you have a Tmax, then you subtract the QTcF at this Tmax from time-matched baseline in Group A. You then adjust QTcF from baseline in Group B at this Tmax for all the subjects in Group B.

For example, suppose Tmax of Subject 1 in Group A is 2 hr, the QTcF at 2 hr for Subject 1 is 420 msec and the baseline for this subject at 2 hr is 400 msec, then the baseline adjusted QTcF at the Tmax for Subject 1 is 20 msec. On the other hand, suppose five QTcF from Group B at 2 hr are 410, 390, 400, 415, 395 and five baselines from Group B at 2 hr are 410, 390, 395, 400 and 400. Then the baseline adjusted QTcF from Group B are 0, 0, 5, 15 and -5. After this is done for all the 10 subjects in Group A, you will have the following table, 10 values in Group A and 5 x 10=50 values in Group B. Then you form 10 x 50=500 differences, order them and find the median of the 500 differences (your point estimator).

Group A	Group B
(Baseline adjusted QTcF at Tmax)	(Baseline adjusted QTcF at the Group A Tmax)
20 msec	0 msec
	0
	5
	15
	-5
Tmax2	t21
	t22
	t23
	t24
	t25
Etc.	Etc.
Tmax10	t01
	t02
	t03
	t04
	t05

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

/s/

George Benson
10/28/04 04:31:01 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Draft Labeling changes are attached

Total no. of pages including cover: 19

Comments: see comment below.

Document to be mailed: **YES** **NO**

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Dear Rudy,

In follow-up to my telephone call today, please find attached revised labeling from the Division. We are continuing to work on the Cardiac Electrophysiology section and hope to get comments to you either tomorrow or Monday (November 8, 2004). There may also be some additional changes beyond this specified section. At present, the Division prefers to send our initial recommendations to you so that you can begin discussions with your drug development team.

Sincerely

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

14 Draft Labeling Page(s) Withheld

DUPLICATE

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 12, 2004

N 000 BL
ORIG AMENDMENT

RECEIVED
NOV 15 2004
FDR/CDER

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: NDA 21-518 Vesicare® (solifenacin succinate) Tablets
Response to FDA Comments

Reference is made to your November 9 and November 10, 2004 faxes in which you provided suggested revisions to the Vesicare Patient Package Insert (PPI) and the Vesicare Package Insert (PI).

We have revised the draft labeling (PPI and PI) to incorporate all of the Agency's changes as requested except as indicated in the highlighted text of the enclosed documents. We have also highlighted any new information that was incorporated into these documents in response to an Agency request.

Specifically, with respect to the Package Insert:

1. As agreed with the Agency, we have changed all the pharmacokinetic parameters and exposure estimates for the pre-clinical studies to those as originally reported in our draft Package Insert dated September 21, 2004.

2. Lines 55 – 57 Gender
   We do not agree with the statement that — We believe that this statement is fundamentally misleading in that it is derived from Study 905-CL-004. Study 905-CL-004 was a small study having only 6 subjects/gender/dose and the conclusion that there is a gender difference in Vesicare exposure is being driven by the unusually high exposure seen in one female subject following a single dose of Vesicare. This gender difference in exposure seen following a single dose of Vesicare was not maintained at steady state. We believe that from the weight of evidence, it can be concluded that there is not significant gender difference in Vesicare exposure. We believe that Study 905-CL-029, a significantly larger study having 12 subjects/gender/age/dose, and which demonstrated that there is no effect of gender on Vesicare exposure, is the definitive study on which to base labeling.

3. Lines 159 - 160 Clinical Studies

We do not agree with the aforementioned statement or that a statistical comparison of dose strengths is valid. The clinical studies were not designed or powered to statistically compare Vesicare dose strengths and therefore no statistical comparisons or inferences should be made.

Lines 161 – 162 Clinical Studies

We do not believe that the Clinical Studies section is the appropriate place for this statement. This statement belongs in the Dosage and Administration section and is already covered by the current dosing statement in that section.

4. Lines 202 - 203 Information for Patients

To be consistent with the labeling for all other drugs in this therapeutic class and to broaden the cautionary statement, we have modified the cautionary statement concerning blurred vision to:

"Because Vesicare may cause blurred vision, patients should be advised to exercise caution."

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W. Lucek
Vice President, Drug Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

Attachment
YM No. 2004-0252

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Yamanouchi Pharma America, Inc.	DATE OF SUBMISSION November 12, 2004
TELEPHONE NO. *(Include Area Code)* (201) 909-3041	FACSIMILE *(FAX)* Number *(Include Area Code)* (201) 909-5244
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Mack Centre IV, 4th Floor S. 61 Paramus Road Paramus, NJ 07652	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Rudolph W. Lucek, Vice President, Drug Regulatory Affairs Mack Centre IV, 4th Floor S. 61 Paramus Road Paramus, NJ 07652 Phone: (201) 909-3041 Fax: (201) 909-5244

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-518

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* solifenacin succinate	PROPRIETARY NAME *(trade name)* IF ANY VESICARE®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM: Tablet	STRENGTHS: 5 mg and 10 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

—

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314 94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Comments

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached Information

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 58,135 YM905 (solifenacin succinate)

See Attached Information for DMF Listing

RECEIVED
NOV 15 2004
FDR/CDER

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* **Response to FDA Comments**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Rudolph W. Lucek	Rudolph W. Lucek, Vice President, Drug Regulatory Affairs	11/12/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Mack Centre IV, 4th Floor, S. 61 Paramus Road, Paramus, NJ 07652	(201) 909-3041

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h: Establishment Information

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product. Include name, address, contact, telephone number, registration number (CFN), DMF number and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Substance:

Solifenacin succinate is manufactured by:

Yamanouchi Pharmaceutical Co., Ltd.
Takahagi Plant
160-2, Akahama,
Takahagi-shi, Ibaraki-ken, 318-0001, Japan

All manufacturing operations, including stability studies on validation and commercial batches, sample storage and testing of materials are conducted at the aforementioned drug substance manufacturing site. The site will be ready for inspection after submission of original NDA application.

Registration Number:	3002808523
Contact in Japan:	Takeo Ogawa General Manager of Takahagi Plant +81-(0)293-4111
Contact in US:	Christine Mulhauser Director, Regulatory Affairs, CMC (201) 909-3043

Drug Product:

The drug product is manufactured, packaged, tested and released by:

Yamanouchi Pharma Technologies Inc.*
Norman Manufacturing Center
3300 Marshall Avenue
Norman, OK 73072

The site will be ready for inspection after submission of Original NDA application.

* Yamanouchi Pharma Technologies, Inc., the manufacturer of the drug product, is part of the Shaklee Corporation manufacturing site in Norman, which is registered under Establishment Registration Number 1627673. Yamanouchi Pharma Technologies resides on the same campus as Shaklee Corporation and is operated as a separate facility dedicated to the production of pharmaceuticals.

Registration Number: 1627673

Contact: Timothy A. DiLiberti
Vice President QA/RA
Telephone: (405) 217-6414

Provided below is a list of DMF reference letters included in Module 3, specifically Section 3.2.P.7 and Section 3.2.P.4, of the NDA application:

Section 3.2.P.7			
Company Name	**DMF #**	**Material**	**Use**

Section 3.2.P.4			
Company Name	**DMF #**	**Material**	**Use**

A copy of each of the DMF reference letters listed above is included in the appropriate section in Module 3.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 9, 2004

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Draft PPI changes are attached

Total no. of pages including cover: 5

Comments: see comment below.

Document to be mailed: **YES** **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Dear Rudy,

Please find attached a revised PPI from the Division. As discussed during yesterday's (November 8, 2004) teleconference, the tradename remains an issue. Additionally, a decision has not yet been reached as to whether or not any information concerning QT will be included in the PPI.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

4 Draft Labeling Page(s) Withheld

Makie, Jean

From: Christine Rice Mulhauser [Christine.RiceMulhauser@yamanouchi-america.com]

Sent: Thursday, November 18, 2004 6:59 PM

To: Jean Makie (E-mail)

Subject: Submission final labeling Part 1 of 2

Dear Jean:

Attached below are the cover letter and final draft labeling (Patient Package Insert and Package Insert) for Vesicare tablets. All changes agreed to with the Agency are incorporated into these final drafts. Final draft mock-ups of the cartons and labels are being sent in a second e-mail.

An official hard copy and an electronic copy are being submitted to the Document Control Room.

Regards,

Christine Mulhauser
Director, Regulatory Affairs, CMC
Yamanouchi Pharma America, Inc.

APPEARS THIS WAY
ON ORIGINAL

Yamanouchi

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

November 8, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Ladies and Gentlemen:

Re: NDA 21-518 Vesicare® (solifenacin succinate) Tablets

Reference is made to your fax dated November 4, 2004. We have revised our draft package insert **(Attachment 1)** to incorporate all of the Agency's changes as requested in your fax. Any revised/additional text has been highlighted (Table 2 with the — has been included and highlighted). As a follow-up to our teleconference of November 8, 2004, we are providing a listing of the pharmacokinetic parameters that you requested we revise. A listing of the parameter as it appeared in our original draft package insert dated September 21, 2004, your suggested revision and the line in the enclosed package insert on which the parameter appears is provided in the table below for your convenience.

Package Insert* Line Number	September 21, 2004 Draft	FDA November 4, 2004 Request
27		
28		
29		
49		
80		
190		
216		
217		
221		
222		

*Package Insert dated November 8, 2004

We would request that since the parameter changes requested are very minor, are not clinically significant, and would make our package insert inconsistent with the approved labeling in Europe that we use the parameters as originally submitted in our draft package insert dated September 21, 2004. If the Agency feels that these numbers should be revised as requested in your fax of November 4, 2004, we would request that the Agency provide us with the sources documenting these revisions, as we have not been able to verify them.

Additionally, in the package insert section "Gender", line 57 the Agency inserted the following statement:

/

We do not agree with the above revision. It appears that the Agency's request to include a statement that , was derived from Study 905-CL-004. This study had only 6 subjects/gender/dose and after the first dose of Vesicare 10 mg one female subject has a Cmax and AUC, which was significantly higher than the other five subjects. However, following the 20 mg Vesicare dose exposure in males was higher than in females and at steady state there was a much smaller difference in Cmax and AUC between males and females then seen after the first dose. Please refer to in-text Figure 11-7 in the study report 905-CL-004, a copy is provided herewith in **(Attachment 2)** for your convenience.

Study 905-CL-029 was the definitive study in NDA 21-518 that compared the pharmacokinetics having 12 subjects/gender/age/dose and it was concluded that there was no significant change in solifenacin pharmacokinetics between men and women.

	Cmax		**AUC**	
	Men	Women	Men	Women
5 mg	32.3	32.3	646	628
10 mg	62.6	63.2	1248	1223

We are also including a copy of Section 2.7.2.3.5 Comparison of PK Parameters Between Men and Women, from the original NDA CTD Module 2, Summary of Clinical Pharmacology **(Attachment 3)**.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Chris Smith

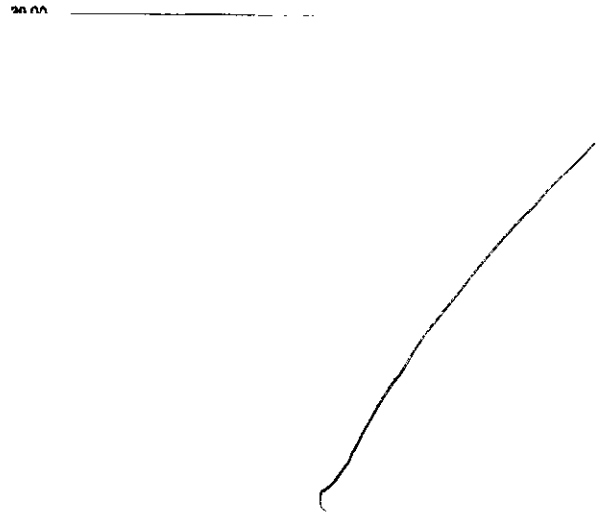
for

Rudolph W. Lucek
Vice President, Regulatory Affairs
Phone: (201) 909 – 3041
FAX: (201) 909 – 5244

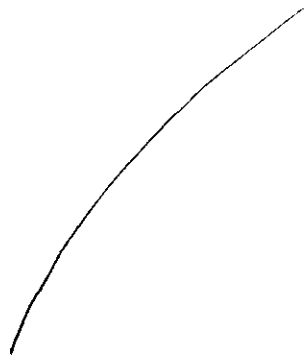
Desk Copy: Ms. Jean Makie, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

Attachment
YM No. 2004-0244

ATTACHMENT 2



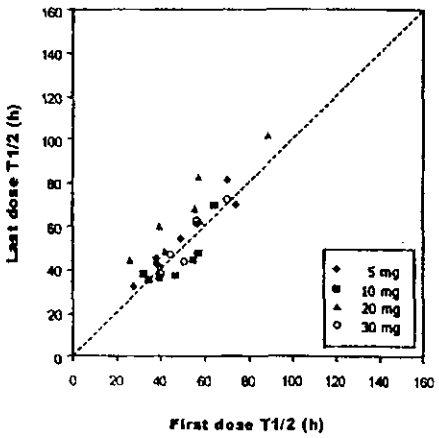
Text Figure 11-7. Individual plasma YM905 concentration curves of male and female subjects after the first dosing of 10 mg YM905.



Text Figure 11-8. Individual plasma YM905 concentration curves of male and female subjects after the first dosing of 20 mg YM905.

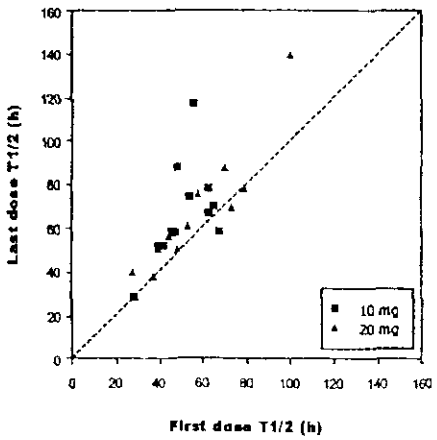
ATTACHMENT 3

Figure 2.7.2-26: Relation between last dose $t_{1/2}$ and first dose $t_{1/2}$ in study 905-CL-002.



The dashed line represents the line of identity.

Figure 2.7.2-27: Relation between last dose $t_{1/2}$ and first dose $t_{1/2}$ in study 905-CL-004.



The dashed line represents the line of identity.

2.7.2.3.5 Comparison of PK parameters between men and women

In 6 clinical pharmacology studies (905-CL-004, -010, -021, -022, -025 and -029) and in the phase 3 patient studies 905-CL-013, -014 and –018 data on solifenacin pharmacokinetics were obtained in men and women. However, in the healthy subject group of the clinical pharmacology study 905-CL-021 only 3 men and 3 women participated. Hence, due to the small number of subjects, results from this study will not be used in the present comparison. In study 905-CL-022 no distinction was made between men and women in calculating the summary statistics of the pharmacokinetic parameters. In study 905-CL–025, solifenacin succinate was administered together with digoxin, which could potentially have affected the pharmacokinetics of solifenacin. Therefore, the results of these studies were also not included in the present comparison. Of the clinical pharmacology studies values of t_{max}, C_{max}, AUC and $t_{1/2}$ were compared. In the population pharmacokinetic analysis of studies 905-CL-013 and –014 the pharmacokinetics of solifenacin were described in terms of the parameters Ka, CL/F and V/F (1-compartment model with first order absorption) after which the effect of sex on CL/F was evaluated. In study 905-CL-018 the effect of sex on trough levels was explored.

Time to maximum concentration (t_{max})

No consistent differences in mean values of t_{max} were observed between men and women (Table 2.7.2-46) independent of dose and duration of treatment. This indicates that the rate of absorption is similar in men and women.

Table 2.7.2-46: Summary of t_{max} values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			5.83 (2.04) N = 6	6.17 (2.56) N = 6	5.17 (2.23) N = 6	5.84 (2.04) N = 6
905-CL-010 (-keto)			6.22 (1.10) N = 9	5.38 (0.74) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			8.00 (2.53) N = 6	9.01 (1.11) N = 6	6.20 (3.49) N = 6	7.34 (1.03) N = 5
905-CL-029	5.32 (4.49) N = 22	4.64 (1.87) N = 22	4.39 (2.11) N = 23	4.86 (1.36) N = 22		

Data are expressed as mean (SD); t_{max} values are in hours; -Keto = in the absence of ketoconazole

Maximum concentration (C_{max})

There was no consistent difference in C_{max} between men and women (Table 2.7.2-47). In study 905-CL-004, a higher mean C_{max} value was found in women with a dose of 10 mg solifenacin succinate. However, with the 20 mg dose, a higher mean C_{max} value was found in men. In study 905-CL-010 mean C_{max} was higher in women. In study 905-CL-029 differences were minimal. In this study young and elderly men and women participated, but also in these sub groups no substantial differences were found. Consequently, there are no indications that C_{max} values are different in men and women.

Table 2.7.2-47: Summary of C_{max} values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			9.72 (2.06) N = 6	15.6 (5.3) N = 6	24.8 (5.7) N = 6	20.1 (4.1) N = 6
905-CL-010 (-keto)			12.5 (2.8) N = 9	16.7 (3.0) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			41.4 (10.9) N = 6	56.0 (15.1) N = 6	88.2 (34.6) N = 6	72.1 (24.7) N = 6
905-CL-029	32.3 (13.2) N = 22	32.3 (9.0) N = 22	62.6 (25.8) N = 23	63.2 (20.6) N = 22		

Data are expressed as mean (SD); C_{max} values are in ng/ml; -Keto = in the absence of ketoconazole

Area under the plasma concentration-time curve (AUC)

As was the case for C_{max}, no consistent differences in AUC were found between men and women (Table 2.7.2-48). In studies 905-CL-004 (single and multiple dosing) and 905-CL-010 (in the absence of ketoconazole) higher AUC values were found in women with a 10 mg dose although there was a considerable overlap of the ranges of individual values. However, with a 20 mg dose in study 905-CL-004, lower AUC values were found in women. In study 905-CL-029 values obtained in men and women were virtually identical at doses of 5 and 10 mg. These data indicate that there are no consistent differences in AUC in men and women.

APPEARS THIS WAY
ON ORIGINAL

Table 2.7.2-48: Summary of AUC values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			673 (180) N = 6	986 (429) N = 6	1878 (424) N = 6	1169 (457) N = 6
905-CL-010 (-keto)			679 (219) N = 9	863 (306) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			879 (232) N = 6	1157 (351) N = 6	1801 (748) N = 6	1428 (530) N = 6
905-CL-029	646 (273) N = 22	628 (205) N = 22	1248 (525) N = 23	1223 (391) N = 22		

Data are expressed as mean (SD); AUC values are in ng.h/ml, after a single dose AUC = AUC_{0-inf}, after multiple dosing AUC = AUC_{0-24h}; -Keto = in the absence of ketoconazole

Terminal elimination half-life ($t_{1/2}$)

Data obtained in 3 studies indicated that small differences in $t_{1/2}$ between men and women might exist (Table 2.7.2-49). In studies 905-CL-004 and –010 somewhat longer $t_{1/2}$ values in women were observed with a dose 10 mg solifenacin succinate. However, with a dose of 20 mg in study 905-CL-004 $t_{1/2}$ was shorter in women. This was again observed in study 905-CL-029 in young and elderly women at doses of 5 and 10 mg.

Table 2.7.2-49: Summary of $t_{1/2}$ values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			51.2 (10.7) N = 6	52.9 (13.8) N = 6	65.3 (20.5) N = 6	48.1 (18.1) N = 6
905-CL-010 (-keto)			46.6 (8.6) N = 9	52.2 (13.8) N = 8		
	5 mg, multiple dose		**10 mg, multiple dose**		**20 mg, multiple dose**	
905-CL-004			65.3 (13.6) N = 6	69.5 (29.2) N = 6	82.3 (35.4) N = 6	56.9 (17.1) N = 6
905-CL-029	68.0 (18.0) N = 22	60.8 (18.9) N = 22	63.9 (17.7) N = 23	57.7 (16.2) N = 22		

Data are expressed as mean (SD); $t_{1/2}$ values are in hours; -Keto = in the absence of ketoconazole

Plasma protein binding

Plasma protein binding was determined in study 905-CL-029. There were no consistent signs of an effect of sex on the free fraction. In young men f_u was slightly lower compared with young women. The reverse was true in the elderly. With 5 mg solifenacin succinate once daily, mean (SD) f_u amounted to 0.0177 (0.0046) in young men and 0.0204 (0.0041) in young women. Slightly higher values were observed with 10 mg dosing. Mean f_u amounted to 0.0211 (0.0043) in elderly men. In elderly women a value of 0.0172 (0.0043) was observed. Similar values were again found with 10 mg solifenacin succinate.

Conclusion

Overall the clinical pharmacology studies did not indicate major differences in the pharmacokinetic behavior of solifenacin in men and women. This was consistent with the analysis of the data of the patient studies 905-CL-013, -014 and –018 in which no effect of sex on CL/F or trough values was found.

2.7.2.3.6 Comparison of PK parameters between young and elderly

For the comparison between young and elderly, PK parameters were taken from studies 905-CL-002 (young subjects), 905-CL-004 (elderly subjects) in which doses of 10 and 20 mg solifenacin succinate, formulated as a capsule, were administered. The most relevant data were obtained in study 905-CL-029 in which a direct comparison was made between

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 25, 2004

To: Christine Mulhouser for Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Discussion points for October 26, 2004 meeting

Total no. of pages including cover:

Comments: see comment below.

Document to be mailed: YES NO

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Christine,

Please find below four additional discussion points the Division requests your team to address during tomorrow's solifenacin QT meeting:

1. Variation in moxifloxacin QTc in periods 1, 3, and 5
2. Variation in placebo QTc in periods 2, 3, and 5
3. Variation in baselines in periods 1, 2, and 3 (Groups A and B)
4. Choice of nonparametric Hodges-Lehmann-Moses method to compare session related effects in Groups A and B

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager

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

/s/

George Benson
10/28/04 04:26:29 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 15, 2004

To: Christine Mulhouser for Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Preliminary information regarding your QT study

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Christine,

This fax is a follow-up to the brief teleconference held with you yesterday afternoon (October 14, 2004) at 4:30 pm. Division attendees were Dr. Donna Griebel, Dr. George Benson, Dr. Stephan Ortiz, and me.

During that discussion, it was explained that the Division has been reviewing the results of your QT study, which was submitted as part of your Complete Response. Additionally, we noted Dr. Norman Stockbridge's reservations regarding the interpretability of these data. As a result, we encouraged a meeting, preferably face-to-face, with those members of your team who were involved in the analysis of this study, including QT consultative experts.

Please find attached the referenced QT information that we committed to sending you. We believe this background material will be important to you in your preparation for this meeting. I will call you to discuss and confirm scheduling details.

Sincerely,

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager
FDA/CDER/Division of Reproductive and Urologic Drug Products

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/s/

George Benson
10/28/04 04:23:16 PM

Yamanouchi

DUPLICATE

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

September 21, 2004

N 000 BL
ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Rockville, MD 20705

Ladies and Gentlemen:

Re: NDA 21-518
Vesicare® (solifenacin succinate) Tablets
CORRECTION to September 17, 2004 Response to Request - Electronic Copy of the Professional Package Insert and the Patient Package Insert (Word Version)

Reference is made to our response submission dated September 17, 2004, which provided an electronic copy of the Professional Package Insert and the Patient Package Insert in Word format.

Upon review of the Professional Package Insert, we discovered that a paragraph was inadvertently deleted (lines 151 through 154). Therefore, we are providing herewith a new CD that contains the Professional Package Insert, amended to include the deleted paragraph, along with the Patient Package Insert, as originally submitted on September 17, 2004. Please replace the previous version of the Professional Package Insert with the attached corrected version. We regret any inconvenience this error may have caused you.

We consider the information contained in this submission to be **CONFIDENTIAL** and not to be disclosed to any person outside the Food and Drug Administration without prior notification and written consent of Yamanouchi Pharma America, Inc.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W Lucek

Rudolph W. Lucek
Vice President, Drug Regulatory Affairs
Phone: (201) 909-3041
FAX: (201) 909-5244

Desk Copy: Ms. Jean Makie, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

Attachment
YM No. 2004-0207

13 Draft Labeling Page(s) Withheld

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 15, 2004

TO: Dan Shames, M.D. Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Albert Perrine, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D.,M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review #2 of Patient Labeling for Vesicare (solifenacin succinate), NDA 21-518

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Vesicare (solifenacin succinate), NDA 21-518. . It has been reviewed by our office and DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on May 18, 2004. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

We also have the following comment:
The PI, PRECAUTIONS section, Information for Patients subsection, states "Patients should read the patient leaflet entitled: — ' before starting therapy with Vesicare." It is not clear how patients would be expected to receive a patient leaflet (PPI) with their prescription; distribution of a PPI for Vesicare would be voluntary. Unless the sponsor has a plan, such as packaging the medication and PPI in unit of use packaging, this statement should be deleted from the PI.

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

____3___ Draft Labeling Page(s) Withheld

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/s/

Jeanine Best
9/15/04 03:05:42 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/16/04 02:11:27 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 07/19/04	DESIRED COMPLETION DATE: 11/20/04	ODS CONSULT #: 02-0117-3

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Albert Perrine
Project Manager
HFD-580

PRODUCT NAME:
Vesicare (Solifenacin Succinate) Tablets
5 mg and 10 mg

NDA #: 21-518

NDA SPONSOR: Yamanouchi Pharma America, Inc.

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

RECOMMENDATIONS:

1. Upon further review, DMETS reverses the initial decision and does not recommend the use of the proprietary name, Vesicare. DMETS has identified several new concerns which may preclude the ability for Vesicare to coexist safely with another already U.S. marketed product.

. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. Upon further review, DDMAC reverses its initial decision and does not recommend the use of the proprietary name from a promotional perspective for the following reason. DDMAC objects to the tradename "Vesicare" because

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

FINAL PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 13, 2004

NDA#: 21-518

NAME OF DRUG: Vesicare (Solifenacin Succinate) Tablets
5 mg and 10 mg

NDA HOLDER: Yamanouchi Pharma America, Inc.

****** Information provided by IMS Health is not to be shared outside of FDA or with non-FDA staff without prior clearance by IMS Health. Clearance must be requested from IMS Health through Office of Drug Safety*******

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), for assessment of the proprietary name, "Vesicare", regarding potential name confusion with other proprietary or established drug names. The labels and labeling were reviewed in a previous consult (ODS consult 02-0117-1). Revised container labels, carton and insert labeling were provided for review and comment.

Vesicare was found acceptable by DMETS and DDMAC in consult 02-0117, dated AUG-09-2002.

PRODUCT INFORMATION

Vesicare is a competitive muscarinic receptor antagonist that is indicated for

Vesicare is recommended for use in both adult male and female patients. The current recommended dose is 5 mg once daily and if this dose is well tolerated, the dose may be increased to 10 mg once daily. In clinical trials, the most commonly seen adverse events were: dry mouth and constipation, although expected side effects also include blurred vision, urinary retention, and dry eyes. The proposed packaging configuration will include unit-of-use bottles of 30 and 90, bottles

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Vesicare to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Prescription analysis studies were conducted during the initial review and were not repeated during this review.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Vesicare. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC does not recommend the use of the proprietary name from a promotional perspective for the following reason. DDMAC objects to the tradename "Vesicare" because

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

2. Since our last review (ODS consult 02-0117-1), the Expert Panel identified one additional proprietary name that was thought to have the potential for confusion with Vesicare. This product is listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

[illegible]	[illegible]	[illegible]	[illegible]
Versiclear	1 % Lotion 25% Sodium Thiosulfate, 1% Salicylic Acid, 10% Isopropyl Alcohol, Menthol, Propylene Glycol, EDTA, and Colloidal Alumina	Apply twice daily.	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA identified Benicar which was considered to have significant orthographic similarities to Vesicare. This product is listed in Table 2 (see below), along with the dosage forms available and usual dosage.

Table 2: Potential Sound-Alike/Look-Alike Names Identified by POCA

[illegible]	[illegible]	[illegible]	[illegible]
Benicar	Olmesartan Tablets 5 mg, 20 mg, and 40 mg	5 mg to 40 mg once daily.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Vesicare, the primary concerns related to look-alike and sound-alike confusion with Benicar and Versiclear.

1. Benicar

a. Look-alike and Sound-alike Concerns

DMETS has identified the potential for look-alike confusion between Benicar and Vesicare. The initial DMETS safety review (ODS consult 02-0117) for Vesicare was completed in August 2002 and the name was found acceptable. While Benicar was introduced into the U.S. marketplace (approved on April 25, 2002) a couple of months prior to the proprietary name review of Vesicare, the potential

safety of the name pair of Vesicare and Benicar may have been omitted because the launch of Benicar was in close proximity to the submission of Vesicare's application. Additionally, the DMETS' Phonetic Orthographic Computer Analysis (POCA) database, which is where the name Benicar was identified, had not been developed at the time of this initial review.

Benicar is an angiotensin II receptor blocking agent approved for once-daily treatment of mild-to-moderate hypertension alone or in combination with other antihypertensives. Both names share a similar looking prefix ("Beni-" vs. "Vesi-") and similar suffixes ("-car" vs. "-care"). The "B" in Benicar, if scripted with a lowercase "b" resembles the letter, "V". Similarly, the "n" in Benicar looks like an "s" if not precisely scripted and handwritten in cursive. Although Vesicare has one more letter than Benicar (eight vs. seven), the two names share orthographic characteristics that increase the likelihood for a dispensing error to occur. Inadvertent administration of either medication places the patient at risk for suboptimal treatment for their respective disease state. It also subjects each patient to the risks and adverse effects associated with each drug. These similarities, compounded by the fact that they also share numerous product characteristics, further increases the likelihood for confusion. See Table 3 on page 6 for a side-by-side comparison of Benicar and Vesicare.

Considerations for Confusion between Benicar and Vesicare

- Benicar and Vesicare are both tablets sharing a dosage strength of 5 mg. Although the usual Benicar dosage range is 20 mg to 40 mg, the fact that a 5 mg strength exists, introduces the possibility that this 5 mg tablet may be used for certain patients. In addition, Vesicare is available in a 10 mg strength. A 20 mg dose may be achieved with two 10 mg tablets. If a prescription for "Benicar 20 mg po qd" was misinterpreted for "Vesicare 20 mg po qd", the dispensing pharmacist may potentially substitute the non-existing 20 mg strength with two 10 mg tablets.

- Post-marketing data has shown that the number "10" can be mistaken for "20" and vice versa. A prescription written for "benicar 20 mg" could be mistaken for "Vesicare 10 mg" and vice versa. See writing sample below.

Benicar 20 mg Vesicare 10 mg

- Benicar and Vesicare have an overlapping dosage schedule (once daily) and route of administration (oral). A prescription written for "Benicar 5 mg po qd" may be misinterpreted as "Vesicare 5 mg po qd" and vice versa. Similarly, prescriptions written for "Benicar 20 mg po qd" and "Vesicare 10 mg po qd" may be mistaken for each other (see writing sample above).

- Benicar and Vesicare have different indications for use. Unfortunately, this may not be enough to prevent confusion and errors because this information is not always available to the pharmacist or practitioner interpreting the drug order. Also, the two medications could be prescribed by the same

practitioner population (family practice, internal medicine, geriatrics), further increasing the likelihood for confusion.

DMETS has identified significant potential for confusion with Vesicare, particularly in the case of handwritten orders.

Table 3. Comparison of Benicar and Vesicare

Proprietary Name	Benicar	Vesicare
	[illegible]	[illegible]
Established Name	Olmesartan	Solifenacin Succinate
Sponsor	Sankyo	Yamanouchi Pharma Inc.
Indication	Hypertension	Urinary frequency, urgency or incontinence associated with overactive bladder
Dosage Strength	5 mg, 20 mg, and 40 mg	5 mg and 10 mg
How Supplied	Bottles of 30 and 90 Blister 10 cards x 10	Bottles of 30, 90 [illegible]
Usual Dose and Range	20 mg to 40 mg	5 mg to 10 mg
Frequency of Administration	Once daily	Once daily
Route of Administration	Oral	Oral
Dosage formulation	Tablets	Tablets
Storage conditions	Room temperature	Room temperature

b. IMS Health Data

**** Not to be shared outside of FDA or with non-FDA staff without prior clearance by IMS Health. Clearance must be requested from IMS Health through Office of Drug Safety*****

To help determine how often physicians are prescribing Benicar by the proprietary name and the usage of these products in the marketplace, DMETS requested drug usage data from IMS Health. The drug usage data from IMS Health for 2003 is included in Table 4 (refer to Table 4 on page 7). A review of the data provided by IMS Health indicates that for calendar year 2003, Benicar 20 mg [illegible] and Benicar 5 mg [illegible] Year-to-date 2004 IMS Health data indicates that the number of Benicar 5 mg prescriptions [illegible] (refer to Table 4 on page 7). This data suggests that [illegible] Benicar's insert labeling does not identify an indication for the 5 mg strength, but clearly, it is being prescribed by practitioners, and therefore the use of this strength can not be ignored. The frequency with which Benicar 20 mg is prescribed also supports DMETS concern regarding the potential for look-alike confusion between (Vesicare) 10 mg and the (Benicar) 20 mg strengths.

The number of dispensed prescriptions were [illegible]

Table 4. Drug Usage Data from IMS Health for 2003 and 2004

*** *Not to be shared outside of FDA or with non-FDA staff without prior clearance by IMS Health. Clearance must be requested from IMS Health through Office of Drug Safety*****

2. Versiclear Look-alike and Sound-alike Concerns

Versiclear and Vesicare have potential for look and sound-alike confusion. Versiclear is an antifungal agent which contains sodium thiosulfate and salicylic acid, and it is used topically in the treatment of tinea versicolor. Versiclear and Vesicare share common beginning letters "Ve-" and middle letter "-c-". The remaining letters overlap with one another, but are placed in different positions (see below). This similarity contributes to their sound and look-alike potential. Additionally, each name has three syllables, which further increases the likelihood for sound-alike confusion. However, Versiclear has an additional letter (nine vs. eight) and the "-l-", if scripted prominently, may help to distinguish the two names from each other. Despite phonetic and orthographic similarities, Versiclear and Vesicare differ in regards to product characteristics. They have different dosage formulations (lotion vs. tablet), route of administration (topical vs. oral), dosage frequency (twice daily vs. once daily), and dosage strengths (one strength available vs. multiple strengths). DMETS expects these products to safely coexist based on the degree of differing characteristics between Versiclear and Vesicare.

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III. COMMENTS TO THE SPONSOR:

In reviewing the proprietary name "Vesicare", the primary concern for name confusion was Benicar, which already exists in the U.S. marketplace.

A. DMETS has identified the potential for look-alike confusion between Benicar and Vesicare. The initial DMETS safety review (ODS consult 02-0117) for Vesicare was completed in August 2002 and the name was found acceptable. While Benicar was introduced into the U.S. marketplace (approved on April 25, 2002) a couple of months prior to the proprietary name review of Vesicare, the potential safety of the name pair of Vesicare and Benicar may have been omitted because the launch of Benicar was in close proximity to the submission of Vesicare's application. Additionally, the DMETS' Phonetic Orthographic Computer Analysis (POCA) database, which is where the name Benicar was identified, had not been developed at the time of this initial review.

Benicar is an angiotensin II receptor blocking agent approved for once-daily treatment of mild-to-moderate hypertension alone or in combination with other antihypertensives. Both names share a similar looking prefix ("Beni-" vs. "Vesi-") and similar suffixes ("-car" vs. "-care"). The "B" in Benicar, if scripted with a lowercase "b" resembles the letter, "V". Similarly, the "n" in Benicar looks like an "s" if not precisely scripted and handwritten in cursive. Although Vesicare has one more letter than Benicar (eight vs. seven), the two names share orthographic characteristics that increase the likelihood for a dispensing error to occur. Inadvertent administration of either medication places the patient at risk for suboptimal treatment for their respective disease state. It also subjects each patient to the risks and adverse effects associated with each drug. These similarities, compounded by the fact that they also share numerous product characteristics, further increases the likelihood for confusion. See Table 5 on page 9 for a side-by-side comparison of Benicar and Vesicare.

Considerations for Confusion between Benicar and Vesicare

- Benicar and Vesicare are both tablets sharing a dosage strength of 5 mg. Although the usual Benicar dosage range is 20 mg to 40 mg, the fact that a 5 mg strength exists, introduces the possibility that this 5 mg tablet may be used for certain patients. In addition, Vesicare is available in a 10 mg strength. A 20 mg dose may be achieved with two 10 mg tablets. If a prescription for "Benicar 20 mg po qd" was misinterpreted for "Vesicare 20 mg po qd", the dispensing pharmacist may potentially substitute the non-existing 20 mg strength with two 10 mg tablets.

- Post-marketing data has shown that the number "10" can be mistaken for "20" and vice versa. A prescription written for "benicar 20 mg" could be mistaken for "Vesicare 10 mg" and vice versa. See writing sample below.

Benicar 20 mg Vesicare 10 mg

- Benicar and Vesicare have an overlapping dosage schedule (once daily) and route of administration (oral). A prescription written for "Benicar 5 mg po qd" may be misinterpreted as "Vesicare 5 mg po qd" and vice versa. Similarly, prescriptions written

for "Benicar 20 mg po qd" and "Vesicare 10 mg po qd" may be mistaken for each other (see writing sample on page 8).

- Benicar and Vesicare have different indications for use. Unfortunately, this may not be enough to prevent confusion and errors because this information is not always available to the pharmacist or practitioner interpreting the drug order. Also, the two medications could be prescribed by the same practitioner population (family practice, internal medicine, geriatrics), further increasing the likelihood for confusion.

  DMETS has identified significant potential for confusion with Vesicare, particularly in the case of handwritten orders.

Table 5. Comparison of Benicar and Vesicare

Proprietary Name	Benicar	Vesicare
	[illegible]	[illegible]
Established Name	Olmesartan	Solifenacin Succinate
Sponsor	Sankyo	Yamanouchi Pharma Inc.
Indication	Hypertension	Urinary frequency, urgency or incontinence associated with overactive bladder
Dosage Strength	5 mg, 20 mg, and 40 mg	5 mg and 10 mg
How Supplied	Bottles of 30 and 90 Blister 10 cards x 10	Bottles of 30, 90, —
Usual Dose and Range	20 mg to 40 mg	5 mg to 10 mg
Frequency of Administration	Once daily	Once daily
Route of Administration	Oral	Oral
Dosage formulation	Tablets	Tablets
Storage conditions	Room temperature	Room temperature

B. The labels and labeling were reviewed in two previous consults (see ODS consult 02-0117-1 and 02-0117-2). In this review of the revised container labels, carton and insert labeling of Vesicare, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

   a. While the proprietary name sustains prominence on the label and labeling, the established name does not. Ensure that both the proprietary and established name are the most prominent information on the label and labeling.

   b. The — is more prominent (color and size) than the strength and the established name. This detracts from the readability of the most important information on the main display panel. Revise accordingly.

2. CONTAINER LABEL (30 Count, 90 Count → . Tablets)

   a. See GENERAL COMMENTS.

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3. BLISTER LABEL

4. CARTON LABELING

See GENERAL COMMENTS and 2b.

IV. RECOMMENDATIONS:

A. Upon further review, DMETS reverses the initial decision and does not recommend the use of the proprietary name, Vesicare. DMETS has identified several new concerns which may preclude the ability for Vesicare to coexist safely with another already U.S. marketed product.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

C. Upon further review, DDMAC reverses the initial decision and does not recommend the use of the proprietary name from a promotional perspective for the following reason. DDMAC objects to the tradename "Vesicare" because

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Jinhee L. Jahng, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Jinhee Jahng
10/20/04 09:34:45 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/21/04 10:46:09 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/21/04 01:41:04 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-518

Yamanouchi Pharma America, Inc.
Attention: Rudolph W. Lucek
Vice President, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Mr. Lucek:

We acknowledge receipt on May 20, 2004, of your May 18, 2004, resubmission to your new drug application (NDA) for Vesicare® (solifenacin succinate) 5 and 10 mg tablets for the treatment of overactive bladder.

We also acknowledge receipt of your chemistry amendment dated March 24, 2004, received on March 26, 2004.

We consider these two submissions to be a complete, class 2 response to our October 17, 2003, approvable letter. Therefore, the user fee goal date is November 19, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived of deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a waiver of pediatric studies for this application. We are denying this request and deferring submission of your pediatric studies until May 18, 2009. However, in the interim, please submit your pediatric development plans within 120 days from the date of this letter.

If you have any question, call Albert Perrine, Regulatory Project Manager, at (301) 827-7511.

Sincerely,

[See appended electronic signature page]

/S/

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
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Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-518

ADVICE LETTER

Yamanouchi Pharma America, Inc.
Attention: Rudolph W. Lucek, Vice President, Drug Regulatory Affairs
Mack Centre IV
S. 61 Paramus Road
Paramus, NJ 07652

Dear Mr. Lucek:

Please refer to your December 19, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesicare (solifenacin succinate) 10 mg.

We also refer to your submission dated December 5, 2003, and received on December 8, 2003. In this submission, you requested comments from the Division to the proposed outline of your anticipated Complete Response to the Action Letter, dated October 17, 2003. The Division's responses to your proposed questions are as follows:

Questions:

1. Do you concur with the proposed overall outline and plan for submission of the NDA amendment presented in Appendix 1.

   Division Response: Yes. The overall outline of the NDA amendment is acceptable.

2. Do you concur with the safety update proposal submitted in Appendix 2? Specifically:

   a. Do you agree with our proposal not to pool any new safety data from the studies outlined in Table 1 with the primary safety database submitted with the original NDA?

   Division Response: This proposal is acceptable.

   b. Do you concur with our proposed strategy as outlined in Table 1 for the reporting of safety data for the listed studies?

   Division Response: The proposed strategy is acceptable.

3. Please clarify your request in Deficiency #3 of the approvable letter to provide additional risk management strategies if needed, concerning constipation. YPA (Yamanouchi

Pharma America, Inc.) would greatly appreciate you sharing with us your views concerning the development and/or nature of such a risk management strategy.

a. Would wording in the labeling recommending initiating treatment with the 5 mg dose and titrating to 10 mg only if the drug is well tolerated and there exists a need for greater efficacy, fulfill your request?

   Division Response: An approach as outlined in Appendix 3 is acceptable. Depending upon the results of this analysis, initiating therapy with the 5 mg dose may be a significant portion of a risk management plan. An educational effort at the time of drug launch to reinforce the label recommendations may also be justified.

b. Do you concur with the proposal outlined in Appendix 3 to evaluate serious sequelae of constipation, and develop a risk management/revised labeling as appropriate, based on the outcome of this evaluation?

   Division Response: Yes. See above (3.a.)

We also refer to your submission dated February 17, 2004, and received on February 18, 2004. We have completed the Clinical Pharmacology and Biopharmaceutics review of your submission and have the following comment.

- Submit analyses using time-matched, baseline corrections (n=3) in addition to analyses using session-averaged baseline corrections (n=33).

Additional comments may be forwarded as we continue the reviews by other disciplines. If you have any questions, call Jean Makie, Sr. Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-518

INFORMATION REQUEST LETTER

Yamanouchi Pharma America, Inc.
Attention: Rudolph W. Lucek
Vice President
Drug Regulatory Affairs
Mack Centre IV
S. 61 Paramus Road
Paramus, NJ 07652

Dear Mr. Lucek:

Please refer to your December 19, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesicare (solifenacin succinate) 10 mg.

We also refer to your submission dated December 9, 2003 and received on December 10, 2003.

We have completed the review of your submission and have the following comments and information requests. Your response to these is requested.

1. The patient population, solifenacin doses, and study design with respect to Group A are acceptable. We agree with you that data from Group B are considered exploratory. Comparisons between Group A and Group B are considered hypothesis generating only.

2. The analysis of the primary endpoint QTcF should demonstrate that the upper bounds of the 90% confidence internal for the QTcF interval for solifenacin (minus placebo) is less than 10 msec.

3. Multiple baseline determinations of QT interval are obtained. How will these different baselines be used in calculating QT changes in the different sessions (particularly in Group A)? Specify in the protocol how these different baselines will be used to calculate the QT interval change in the five sessions.

4. Verify that: 1) EKG assessment will be digitized and 2) there is no "rounding" of QT data.

5. Annotated EKG recordings should be submitted with the study report.

6. An "outlier" analysis should be submitted.

If you have any questions, call Jean Makie, Sr. Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
1/28/04 08:57:36 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: December 19, 2003

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean Makie

Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Type A meeting minutes (11/7/03)

Total no. of pages including cover:

Comments: see comment below.

Document to be mailed: YES NO

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Type A Teleconference Minutes

NDA: 21-518 **Drug:** Solifenacin succinate

Sponsor: Yamanouchi Pharma America, Inc.

Date: November 7, 2003 **Time** 1:00 PM – 2:30 PM

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
Meeting Chair: George Benson, M.D., Urology Team Leader, DRUDP
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research
Goudong Fang, Medical Reviewer, DRUPD
Meeting Recorder: Jean King, MS, RD, Project Manager, DRUDP
Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP

Yamanouchi Pharma America, Inc. Attendees:
Robert Desjardins, M.D., President, R&D
Rudolph Lucek, Vice President, Regulatory Affairs
Lawrence Posner, M.D., Sr. Vice President, R&D
Susan Ridge, Director, Project Management
Neila Smith, M.D., Medical Director
Christine Mulhauser, Director, Regulatory Affairs, CMC
Masakazu Andoh, Ph.D., Statistics
Jim Ortega, Marketing
Cathy Ward, Vice President Marketing

GlaxoSmithKline Attendees:

Tom Kline, Regulatory Affairs
Roger Graham, Sr. Vice President, Marketing
Venkat Sethuraman, Ph.D., Statistics
Bernard Ilson, Clinical Affairs

Background: On October 17, 2003, the Division sent the sponsor an Approvable letter for solifenacin succinate (Vesicare). In response, the sponsor requested a Type A meeting on October 23, 2003, to discuss the design of the additional study that was requested by the Division to be conducted to investigate the effect of solifenacin succinate on the QT interval. This submission contained a synopsis of the study design, which was the primary issue discussed during this teleconference.

Issues Discussed: The sponsor proposed the following 3 objectives:

1. Obtain agreement on the design of the study to be conducted to investigate the effect of solifenacin succinate on the QT interval.
2. Obtain agreement on the proposed dosing regimen to be used in the QT study
3. Obtain agreement on the format for reporting the results and data obtained from the QT study.

The meeting Briefing Document also contained four questions (in italics), which are followed by the DRUDP responses.

a. *Does the Agency concur that the design of the proposed QT study is adequate to assess the effect of solifenacin succinate on the QT interval?*

   Division Response: The Division acknowledged the difficulty of designing a thorough QT study with a drug product that has a long half-life. Additionally, the dosing of solefenacin is such that multiple dose titration, rather than single dosing, is required to achieve the requisite Cmax plasma concentration to mimic 10 mg solifenacin plus 400 mg ketoconazole. The Division's primary concern with the proposed design is that it may be difficult to compare study drug to placebo given the variability and relatively few patients proposed in the parallel placebo control group.

   The Division and the Sponsor had a detailed discussion regarding potential alternative designs, including the feasibility of a crossover design or a modified parallel arm design.

   Division Response: The Division requested that the Sponsor submit a revised schema for the Division's review and comments prior to submitting a complete protocol, including a detailed statistical analysis plan (SAP), for review.

   Sponsor response: The sponsor agreed to submit a revised schema for the Division's review and feedback prior to their submission of a complete protocol and SAP.

b. *Does the Agency concur with the rationale for selecting the dosing regimen and that the plasma concentrations achieved at steady state at a dose of 30 mg is adequate to cover drug plasma concentrations resulting from 10 mg of Vesicare at steady state in the presence of 400 mg ketoconazole?*

   Division Response: Yes, the Division agrees with the proposed dosing regimen.

c. *Does the Agency concur with the target patient population, i.e. a minimum of approximately 50 subjects (40 active, 10 concurrent placebo controls) will be enrolled into the study. Eligible subjects will be healthy women who are 18 years of age or older. An attempt will be made to enroll subjects such that the overall age distribution is representative of the demographics of patients with overactive bladder as reflected by pivotal clinical studies with solifenacin?*

Division Response: Yes, the Division agrees that the proposed patient population is acceptable.

Sponsor response: The sponsor noted that approximately 20% of the patients in their Phase 3 studies were males, and asked the Division if enrollment of men in this QTc study was acceptable.

Division response: The Division responded that although there was no opposition to the enrollment of males, the Division preferred that a predominant percentage of patients were female. Additionally, premenopausal women should be included in this study.

d. *To expedite the submission of the QT study we propose to submit an abbreviated study report consisting of: 1) protocol design, 2) top line results presented as tabular listing of the effect of solifenacin succinate on QTc, 3) data listing for QT/QTc measurements with primary statistical analysis tables, 4) pharmacokinetic data sets and 5) complete safety data. Does the Agency agree?*

Division response: The Division asked the sponsor to clarify what would be included in their abbreviated report.

Sponsor Response: The sponsor stated that the abbreviated report would consist of all of the five items outlined in their question to the Division, plus QT data. The report would not be a finalized version. There would be no narratives for adverse events, just data and summary tables.

Division Response: The Division asked the sponsor if they had a timeline for when the final study report would be submitted.

Sponsor Response: The Sponsor stated that they believed a final report could be submitted approximately one month after their submission of the abbreviated study report.

Division Response: Based on this clarification, the Division agreed that it is acceptable for the sponsor to submit an abbreviated report. The Division recommended that the sponsor not round any of the QT data to the nearest 10 msec. Additionally, the Division requested that all QT data be submitted electronically. The Division of CardioRenal Drug Products has requested that annotated, digitized ECGs also be submitted for review.

Sponsor Response: The sponsor stated their intention to use digitized ECG analyses in this study and agreed that they would provide the QT data in the formats requested.

Action Items:

1. The Sponsor will submit a revised protocol schema for the Division's review.
2. The Division will provide meeting minutes to the sponsor within 30 days.

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/s/

George Benson
12/19/03 01:47:18 PM

NDA 21518 Serial 000

Medical Team Leader Memorandum

Date received: December 10, 2003
Review: December 17, 2003

Sponsor:
Yamanouchi Pharma America, Inc.
Mack Center IV
S. 61 Paramus Road
Paramus, NJ 07652

Drug: solifenacin succinate (Vesicare)
Indication: overactive bladder
Dose: 5 and 10 mg
Route of administration: oral

Protocol: "A Study to Evaluate the Effect of Repeat Oral Doses of Solifenacin on Cardiac Conduction as Assessed by 12-lead Electrocardiogram as Compared to Placebo and Single Oral Doses of Moxifloxacin" (protocol 905-CL-043)

Background:
An approvable letter was issued for solifenacin on October 17, 2003. Deficiency #1 was that "this application lacks sufficient information to conclude that solifenacin is not associated with clinically relevant QT interval prolongation." The information needed to address this deficiency was "submit the results from a randomized, placebo-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at the plasma concentrations achieved at steady state when solifenacin is co-administered with a potent CYP3A4 inhibitor." A teleconference was held with the sponsor on November 7, 2003, to discuss the design of the protocol synopsis and comments were sent to the sponsor in a letter dated November 20, 2003. The current submission (serial 000) is the QT study protocol 905-CL-043 submitted on December 9, 2003. The identical protocol was submitted to the solifenacin IND (58135 Serial 133).

Protocol Review:

Study design: This protocol is a five-period, sequential study. Subjects will be randomized to one of two treatment groups (A or B) according to the following scheme.

	Treatment Group A	Treatment Group B
Session 1	1 day baseline (no drug) moxifloxacin (400 mg) on Day 1	1 day baseline (no drug) moxifloxacin (400 mg) on Day 1
Session 2	1 day baseline (no drug) placebo on Day 1	1 day baseline (no drug) placebo on Day 1
Session 3	1 day baseline (no drug) solifenacin 10 mg x 14 days	1 day baseline (no drug) placebo x 13 days ; moxifloxacin (400 mg) on Day 14
Session 4	Solifenacin 20 mg x 5 days	Placebo x 5 days
Session 5	Solifenacin 30 mg x 14 days	placebo x 13 days ; moxifloxacin (400 mg) on Day 14

Dosing will be single-blind in Sessions 1 and 2. All subjects will receive a single oral dose of moxifloxacin in Session 1 and a single oral dose of placebo in Session 2. There will be at least a 3 day washout between Sessions 1 and 2. There will be no washout between Session 2 and the start of dosing in Session 3.

Dosing will be double-blind in Sessions 3 to 5. There will be no washout between any of these treatment sessions.

In Sessions 1, 2, and 3 there will be a one day baseline (no drug) prior to the start of dosing.

The total duration of each subject's participation in the study, from screening through follow-up, will be approximately 12 weeks.

Comment: The design of QT trials of a drug with a long half-life is difficult. A true randomized, cross-over design would be a prohibitively long study. I believe that the proposed design (Group A) is acceptable. It should be noted that Group B will be analyzed only in an exploratory fashion. The sponsor believes that "the purpose of Group B in this study is purely to characterize any gross session or time-related trends in the study, since the treatments in the primary analysis group (Group A) are being administered in a non-randomized or sequential fashion. If the analysis of Group B suggests any such gross trends, then data from Group B may be used as appropriate to interpret and/or make corrections to the QT interval results for Group A."

EKG assessment:

Conduction intervals from the 12-lead EKGs will be manually read and confirmed by an external cardiologist/vendor. All EKGs will be read blinded. The final conduction intervals entered into the database will be those generated by the reading cardiologist/vendor.

During Session 1 eleven 12-lead EKGs will be performed during the baseline Day -1 at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours and at the same time periods following

moxifloxacin dosing on Day 1. EKG's will be performed at the same times during baseline and following placebo during Session 2. EKG's will be performed at baseline Day –1 and on Days 13 and 14 during Session 3 and on Days 13 and 14 during Session 5. Three 12-lead EKGs taken approximately 1 minute apart will be obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours of Day –1 of Sessions 1, 2, and 3. For each session, baseline will be the average of all individual EKGs obtained on Day –1. Three 12-lead EKGs taken approximately 1 minute apart will be obtained prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post dose on the following days: Session 1, Day 1; Session 2, Day 1; Session 3, Days 13 and 14; and Session 5, Days 13 and 14.

Since Sessions 3 and 5 are double-blind, blood samples for PK analysis of both moxifloxacin and solifenacin will be obtained for all subjects (Group A and Group B).

Placebo tablets for solifenacin are available. On those days when moxifloxacin is administered, subjects will be blind-folded prior to taking the medication and the medication will be administered by an individual not involved with the evaluation of study subjects.

Comment: The timing and number of EKGs obtained for analysis are acceptable.

Study population:

Eligible subjects will be healthy adult women who are 18 years of age or older. To ensure that the overall age distribution is representative of the demographics of female patients with overactive bladder (as reflected by pivotal clinical studies with solifenacin), the sponsor proposes that subject enrollment will be stratified by age as follows:
Group 1: (approximately 40% of subjects) will be women 18-54 years of age
Group 2: (approximately 60% of subjects) will be women who are >55 years of age

Approximately 80 subjects will be enrolled to ensure that a total of approximately 60 subjects complete the study (Group A = 40 subjects and Group B = 20 subjects). Subjects will be enrolled at a minimum of 4 clinical sites. An attempt will be made to enroll a similar number of subjects in Group A and Group B at each site.

Comment: The patient population is acceptable.

Primary endpoints: QTcF and QTci, as calculated at T_{max} for each regimen using linear and/or nonlinear methods with both a population and an individual approach

Secondary endpoints: QTcB, QT interval and heart rate, other summary measures of the QTc interval data, and AUC, C_{max}, and T_{max} for plasma concentrations of solifenacin and moxifloxacin, and $t_{1/2}$ for each drug as data permit.

Inclusion/exclusion criteria: Important inclusion/exclusion criteria include subjects with a QTc interval > 440 msec and subjects who have any condition for which anticholinergic medication would be contraindicated.

Comment: The inclusion/exclusion criteria are acceptable.

Dose:

The maximum dose of 30 mg is proposed based on the results of a ketoconazole drug interaction study (Trial 036) which showed that 400 mg ketoconazole for 20 days increased the AUC and C_{max} of a single 10 mg dose of solifenacin by 2.8 fold and 1.5 fold, respectively. Given that solifenacin has a T1/2 of approximately 50 hours, subjects will be dosed for 14 days at each target dose level (10 and 30 mg) to achieve steady state concentration.

Comment: The maximum dose of 30 mg to be evaluated is acceptable.

Data analysis and statistical considerations:

No hypothesis will be tested. An estimation approach will be taken to characterize the effect on ECG parameters (QTc, QT, heart rate) for the comparisons of interest. Point estimates and 90% confidence intervals will be presented.

Primary comparisons of interest: For the subjects in Group A, and for the primary endpoints QTcF and QTci, the primary comparison of interest will be the change from baseline at time of the maximum concentration (T_{max}) for each active regimen relative to placebo at the same time point. The endpoint will be calculated as: [(QTc of active regimen at T_{max} – baseline) – (QTc of placebo at T_{max} of active regimen – baseline placebo)]. Baseline "will be defined as appropriate to the data, study design, and endpoint and full details will be provided the Reporting and Analysis Plan."

Comment: The baseline value used for each QT calculation should be clarified.

Data from Treatment Group B "will be analyzed in an exploratory fashion, as appropriate to the study design and the data, in order to characterize any period effects."

Sample size: The sponsor believes that, based on a SD of 6 msec, a sample size of 40 subjects in treatment Group A will provide at least a 90% power to detect statistically significant increases of at least 5 msec in QTcF.

Comment: A statistical consultation regarding sample size was requested. The statistician believes that "the power calculation presented for group A is sufficient to meet the stated criteria." The Division has requested other sponsors to designate a primary endpoint; "the upper bounds of the 90% confidence interval for the QTc (Fridericia) interval (minus placebo) should be less than 10 msec."

CardioRenal consultation: The CardioRenal consultant "has nothing to add to the comments made by Dr. Benson. In particular, the previously expressed concern about the moxifloxacin comparison appears to be adequately addressed in the proposed study."

Comments to be sent to sponsor:

1. The patient population, solifenacin doses, and study design with respect to Group A are acceptable. The Division agrees with the sponsor that data from Group B are considered exploratory. Comparisons between Group A and Group B are considered hypothesis generating only.
2. The analysis of the primary endpoint QTcF should demonstrate that the upper bounds of the 90% confidence internal for the QTcF interval for solifenacin (minus placebo) is less than 10 msec.
3. Multiple baseline determinations of QT interval are obtained. How will these different baselines be used in calculating QT changes in the different sessions (particularly in Group A)? Please specify in the protocol how these different baselines will be used to calculate the QT interval change in the five sessions.
4. Please verify that: 1) EKG assessment will be digitized and 2) there is no "rounding" of QT data
5. Annotated EKG recordings should be submitted with the study report.
6. An "outlier" analysis should be submitted.

George S. Benson, MD
Medical Officer
Division of Reproductive and Urologic Drug Products

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/

George Benson
1/9/04 05:44:27 PM
MEDICAL OFFICER

Donna Griebel
1/12/04 05:31:21 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-518

ADVICE LETTER

Yamanouchi Pharma America, Inc.
Attention: Rudolph Lucek
Vice-President, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Mr. Lucek:

Please refer to your November 11, 2003, correspondence to your new drug application (NDA) 21-518, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesicare (solifenacin succinate), 5 mg and 10 mg dose strengths. This submission contained a revised schema of the study design for your proposed solifenacin succinate QTc study.

We have reviewed this submission and have the following comments.

1. The basic trial design schematic on page 2 of the submission is acceptable.

2. Please respond to the following questions:

   a. Do the QT measurements align in arms A and B?
   b. Will the washout from solifenacin in arm A delay the last dosing with moxifloxacin in arm B?
   c. Is the 18-day period toward the end of arm B a placebo period?

3. Clarify whether the moxifloxacin doses will be blinded in this study.

4. Arm B (n = 20) may not be sufficiently powered to detect an effect.

If you have any questions, call Jean Makie, M.S., R.D., Regulatory Project Manager, at 301-827-4260.

Sincerely,

(See appended electronic signature page)

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
11/20/03 05:47:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Dr. Michael Halaska
Gynekologico-Porodnicka Kli
FN Na Bulovice
Praha
Czech Republic

Food and Drug Administration
Rockville MD 20857

NOV 18 2003

Dear Dr. Halaska:

Between August 11 and August 15, 2003, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 905-Cl-018 entitled: "A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multi-center Study of YM905 5mg and 10 mg in Patients with Overactive Bladder") of the investigational drug Vesicare® (solifenacin succinate) Tablets, performed for Yamanouchi Pharma America, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand you did not conduct this study under a U.S. Investigational New Drug Application (IND). For your future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical trials conducted under an IND. These comments are based on our review of the establishment inspection report, the documents submitted with that report, the Form FDA 483, Inspectional Observations issued to you at the conclusion of the inspection, and your written response dated September 18, 2003. The provisions of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND are provided below for future reference:

1. The study was not conducted in accordance with the protocol [21 CFR 312.60] in that:

   a. Subjects 20430 and 20814 were randomized to the study despite daily urine volume outputs of greater than 3000 mL at visit 2, an exclusion criterion.

   b. All subjects were asked to cough in a supine position rather than in a standing position as described in the Cough Provocation Test.

   c. Electrocardiograms (ECGs) for subjects 20421, 20426, 20428, 20429, 20816, 20818, 20827, 20828, 20830, and 21129 did not contain a minimum of four complexes.

   d. Subjects 21131 and 21132 were not randomized in sequence. Subject 21131 was assigned randomization number 8454 on October 31, 2001, and subject 21132 was assigned randomization number 8455 on October 30, 2001.

   e. ECGs for subjects 20829, 20831, and 20832 for Visit 5/End of Study Assessment were uninterpretable. ECGs were not repeated until approximately four months later.

2. You did not maintain adequate and accurate records [21 CFR 312.62(b)] in that ECGs were unsigned and/or undated by the interpreting physician.

We accept your written response of September 18, 2003. Your response and all related correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

CFN/FEI: 3004033262

Field Classification: VAI

Headquarters Classification:
____ 1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__x__failure to adhere to protocol (05)
__x__inadequate and inaccurate records (06)

Deficiency code: 05 and 06

cc:
HFA-224
HFD-580/Doc.Rm. NDA# 21-518
HFD-580/Review Div.Dir./Shames
HFD-580/MO/Fang
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File # 010985
HFD-/47 GCP Reviewer/Blay
HFR-SW150/DIB/Thornburg
HFR-SW150/BIMO Monitor/Martinez
HFR-SW150/Field Investigator/Martinez
HFC-134 Kadar (for foreign only)
GCF-1 Seth Ray

r/d: (Blay):
reviewed:
f/t:sg:11/10/03

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o:\blay\halaska.doc

Reviewer Note to Rev. Div. M.O.

29 subjects were randomized to the study. 21 of the files were reviewed in detail including source documents and CRFs and compared with the sponsor data listings. For six subjects, subject diary data was compared with sponsor data listings. The data generated by this site in support of the relevant application appears adequate.

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/s/

Joseph Salewski
11/24/03 11:17:26 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Salman Al-Shukri, M.D., D.Med.Sci., Ph.D.
Department of Urology
St. Petersburg Medical University n.a. Pavlov
17 Lva Tolstogo Str.
St. Petersburg
197089
Russia

NOV 18 2003

Dear Dr. Al-Shukri:

Between August 4 and 7, 2003, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 905-Cl-015 entitled: "A Randomized, Double-blind, Parallel Group, Placebo and Active Controlled, Multi-Centre Study of YM905 5 mg and 10 mg in Patients with Overactive Bladder") of the investigational drug Vesicare® (solifenacin succinate) Tablets, performed for Yamanouchi Pharma America. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand you did not conduct this study under a U.S. Investigational New Drug Application (IND). For your future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical trials conducted under an IND. These comments are based on our review of the establishment inspection report, the documents submitted with that report, the Form FDA 483, Inspectional Observations issued to you at the conclusion of the inspection, and your written response dated September 30, 2003. The provisions of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND are provided below for future reference:

You did not maintain adequate and accurate records [21 CFR 312.62(b)] in that:

a. Original electrocardiograms (ECGs) for 14 of 32 subjects for visit 1 were not available for review during the inspection.

b. Subject 10302's diary of June 22, 2001, indicated a total daily urine volume of 2980 mL after the subject's recording of a void volume of 150 mL at 8:40 PM. This volume was revised to 50 mL without explanation for the change by the sub-investigator. Based on a void volume of 150 mL, the total void volume would have been 3080 mL and would have excluded the subject from the study.

We accept your written response of September 18, 2003. Your response and all related correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

LSI

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

CFN/FEI: 3004054871

Field Classification: VAI

Headquarters Classification:
____1)NAI
__x_2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__x__inadequate and inaccurate records (06)

Deficiency code: 06

cc:
HFA-224
HFD-580/Doc.Rm. NDA# 21-518
HFD-580/Review Div.Dir./Shames
HFD-580/MO/Fang
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File # 010998
HFD-47/GCP Reviewer/Blay
HFR-SE340/DIB/Thornburg
HFR-SW150/BIMO Monitor/Martinez
HFR-SW150/Field Investigator/Martinez
HFC-134/Kadar (for foreign only)
GCF-1 Seth Ray

r/d: (Blay):
reviewed:
f/t: sg:11/10/03

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o:\blay\al-shukri.doc

Reviewer Note to Rev. Div. M.O.

The patient files of 21 of 32 randomized subjects were reviewed including laboratory reports, ECG tracings, patient diaries, and correspondence. The data appear adequate in support of the relevant submission.

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/s/

Joseph Salewski
11/24/03 11:16:28 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 2 2003

Dear Mr

Between July 30 and August 6, 2003, Ms. Byungja Marciante, representing the Food and Drug Administration (FDA), conducted an inspection of — , monitoring practices of a clinical study of the investigational drug Vesicare® (solifenacin succinate) Tablets. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

This inspection focused on Protocol #s 905-CL-013 and 905-Cl-014, both entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study to Assess the Efficacy and Safety of Daily Oral Administration of 10 mg YM905 Versus Placebo in Male and Female Subjects with Overactive Bladder". The majority of sponsor obligations including, but not limited to, selecting investigators, monitoring compliance, summarizing evidence of drug safety, retaining study records, and maintaining an effective IND, were contracted to — , and other firms by Yamanouchi Pharma America.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the monitoring of clinical studies of investigational new drugs and the protection of human subjects.

We appreciate the cooperation shown Investigator Marciante during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me, by letter at the address given below.

Sincerely yours,

/S/

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003073953

Field Classification: NAI

Headquarters Classification:
_x_1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580/Doc.Rm. NDA #21-518
HFD-580/Division Director/Shames
HFD-580/MO/Fang
HFD-580/PM/King
HFD-46/c/r/s/ GCP File #010522
HFD-46 Blay
HFR-CE350/DIB/Amador
HFR-CE3565/BIMO Monitor/Isbill
HFR-CE3565/Field Investigator/Marciante
GCF-1 Seth Ray

r/d:rab/9.11.03

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O:\blay — e21518nai02.doc

Reviewer's Note to Review Division's Medical Officer

Sponsor responsibilities for this study were contracted out to — by Yamanouchi. The inspection of — revealed that two sites were terminated for lack of compliance with protocol #905-Cl-014. FDA was informed of these site closures (for Drs — — in a letter dated August 29, 2003, addressed to Dr. Daniel Shames of the Division of Reproductive and Urologic Drug Products. This notification took place approximately two years after the sites were terminated. — is conducting an internal audit to determine why these site closures were not promptly reported to FDA.

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/s/

Joseph Salewski
11/10/03 11:19:39 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 2 2003

Igor Kuzmin, M.D., Ph.D.
Department of Urology
St. Petersburg Medical University n.a. Pavlov
17 Lva Tolstogo Str.
St. Petersburg
197089
Russia

Dear Dr. Kuzmin:

Between July 28 and 31, 2003, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 905-Cl-018 entitled: "A Randomized, Double-blind, Parallel Group, Placebo Controlled, Multi-Centre Study of YM905 5 mg and 10 mg in Patients with Overactive Bladder") of the investigational drug Vesicare® (solifenacin succinate) Tablets, performed for Yamanouchi Pharma America. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand you did not conduct this study under a U.S. Investigational Drug Application (IND). From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you conducted your study in compliance with the applicable regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

CFN/FEI: 3004054879

Field Classification: NAI

Headquarters Classification:
__x_ 1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580/Doc.Rm. NDA# 21-518
HFD-580/Review Div.Dir./Shames
HFD-580/MO/Fang
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File # 010997
HFD-47/GCP Reviewer/Blay
HFR-SE340/DIB/Thornburg
HFR-SW150/BIMO Monitor/Martinez
HFR-SW150/Field Investigator/Martinez
HFC-134/Kadar (for foreign only)
GCF-1 Seth Ray

r/d: (Blay):10/20/03
reviewed:JS: 10/16/03
f/t:sg:10/21/03

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o:\blay\kuzmin.doc

Reviewer Note to Rev. Div. M.O.
36 subjects were randomized to the study and the records of 21 subjects were reviewed. The primary efficacy variable (change in baseline in mean number of micturitions per 24 hours as derived from the micturition diary) was compared between that of the subject's diary and the submitted data for all subjects. Consent forms were present and signed for all subjects. The data appear adequate in support of the relevant submission.

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/s/

Joseph Salewski
11/10/03 11:18:39 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-518	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: Solifenacin succinate 5 and 10 mg		Applicant: Yarmanouchi Pharmceuticals
RPM: Jean King, M.S., R.D.	HFD-580	Phone # 301-827-4620
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 19, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A with AE action
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
[redacted]	
❖ Actions	
• Proposed action	() AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	() Materials requested in AP letter ( ) Reviewed for Subpart H (X) N/A with AE action
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release () Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A; labeling review will be noted as a deficiency in the AE letter
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DDMAC and ODS reviews completed; N/A; labeling noted as a deficiency in the AE letter
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A; labeling review noted as a deficiency in the AE letter
• Applicant proposed	X
• Reviews	X (DDMAC and ODS reviews completed; labeling noted as a deficiency in the AE letter
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X (9/19/2000)
• Pre-NDA meeting (indicate date)	X (7/1/2002)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A

• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
[illegible] Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X, 10/17/03
[illegible] Information	
❖ Clinical review(s) *(indicate date for each review)*	X 10/17/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (see clinical review 10/17/03)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A with AE action
❖ Statistical review(s) *(indicate date for each review)*	X 10/16/03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X 10/17/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
[illegible] Information	
❖ CMC review(s) *(indicate date for each review)*	X 10/17/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (EA acceptable; See Chemistry Review)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (5/1/03)
❖ Facilities inspection (provide EER report)	See Chemistry Review: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
[illegible] Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X 10/16/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	X (5/27/03)

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/s/

Jean R. King
10/20/03 09:42:19 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 17, 2003

To: Christine Mulhauser

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3043

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: 10/16/03 Teleconference minutes are attached

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

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Teleconference Meeting Minutes

Date: October 16, 2003 **Time:** 3:00-3:30pm **Location:** 17B-45

NDA: 21-518 **Indication:** Incontinence

Drug Name: Vesicare (solifenacin succinate) tablets

Sponsor: Yamanouch

Meeting Type: Guidance

Meeting Chair and Recorder: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader

Industry Participants: Christine Mulhauser, Director, Regulatory affairs, and others

Background:

Purpose of the Meeting: To resolve the acceptance criteria of the dissolution test.

Discussion/Decisions Made:

- FDA thinks that, based on the analysis of the dissolution data submitted in NDA, Q= — at — , is considered to be adequate for the quality control of the drug product.
- The sponsor states that, according to the dissolution test data of — additional batches, FDA proposed dissolution acceptance criterion is too tight, which might cause Stage-2 test more frequently than as being necessary.
- FDA suggests that the dissolution data of the — batches be submitted in the next review cycle.
- Sponsor agrees to submit those data including data at 20-minute time point when they resubmit this NDA.

Action Items:

- Fax meeting minutes to the sponsor within 30 days.
- The sponsor will submit the dissolution data of the additional — batches when sponsor resubmits this NDA.

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/s/

Moo-Jhong Rhee
10/17/03 10:29:44 AM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 17, 2003

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Approvable letter

Total no. of pages including cover:

Comments: The Agency's Approvable letter for NDA 21-518 (solifenacin succinate for the

is attached.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 9, 2003

To: Rudolph Lucek

Company: Yamanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Additional Information Regarding the Reanalysis of QT data

Total no. of pages including cover:

Comments: see comment below.

Document to be mailed: YES NO

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Dear Mr. Lucek,

We received your questions faxed to us on 10/8/03 regarding clarification of our reanalysis of the QT data using the Fridericia method. The Division's responses to your questions are attached.

Jean King, M.S., R.D.
Sr. Regulatory Project Manager
FDA/CDER/Division of Reproductive and Urologic Drug Products

Response to Questions Regarding the Fax dated 10/6/03
Questions faxed by Sponsor on 10/8/03

Question 1

1. Yes.
2. For each subject at each dose, there were **11 ECGs**. 9 ECGs performed on Day 1 of each dose and 1 ECG performed at 0 hour on days 12 and 13 of each dose. The rest of this assumption is correct.
3. No. Means were not calculated for each subject. The reported means were the mean of all points collected from each dose studied and not the mean of the subject means.
4. See 3 above.

Question 2

All corrections in this analysis were Fridericia corrections. For each point, a drug-related QT_C minus baseline QT_C calculation was made (D-B). Additionally, a time-matched placebo QT_C (time-matched to the preceding drug-related QT_C) minus baseline QT_C calculation was made (P-B). The baseline- and placebo-corrected QT_C was the difference of the two {(D-B) – (P-B)}. And as above, the mean of these calculations is the mean over all points in a treatment group, not the mean of the subject means.

Question 3

All corrections in this analysis were Fridericia corrections.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 17, 2003

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-518 Vesicare Tablets (solifenacin succinate); Yamanouchi Pharma America, Inc.

Solifenacin succinate is a selective muscarinic M_3 receptor antagonist. This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's approvable action for solifenacin 5 mg and 10 mg immediate release oral tablets given once daily for the Before this application may be approved it will be necessary for the sponsor to address the following deficiencies:

Approvability Issue: QT Prolongation

Solifenacin is a substrate of CYP3A4. Co-administration of solifenacin with ketoconazole 400 mg, a potent inhibitor of CYP3A4, resulted in a 3-fold higher AUC compared to solifenacin alone. In addition, solifenacin exposure was shown to increase 2-fold in patients with severe renal impairment. The administration of potent 3A4 inhibitors to patients with severe renal impairment can be expected to further increase solifenacin exposure in these patients.

The effect of solifenacin on rate-corrected mean QT change from baseline (using Fredericia's correction) was evaluated in phase 3 placebo-controlled trials. The placebo-subtracted mean change from baseline in QTcF on solifenacin 5 and 10 mg was approximately 5 msec. To address this finding further, the sponsor conducted Study R905-CL-022, a prospectively designed study in which 60 patients received multiple ascending doses of solifenacin (ranging from 10-50 mg) after a placebo run-in period. The mean change from baseline in QTcF was noted as follows: 0.89 msec on placebo, 0.26 msec on 10 mg solifenacin, 3.46 msec on 20 mg solifenacin, and 0.77 msec on 30 mg solifenacin. At doses of 40 and 50 mg, mean QTcF changes were negative (-3.82 and -8.46 msec respectively) for reasons that are not readily explained. Of note, all patients administered 50 mg dropped out prematurely due to anticholinergic side effects. The strengths of this study include placebo measurements, evaluation of solifenacin doses that were 5- to10-fold higher than to-be-marketed doses, and a relatively large sample size. The major limitation of the study is the lack of concurrent controls (positive and placebo) so that it is not possible to conclude with assurance that a mean QTcF change of 5 or 10 msec has been excluded. Other limitations include high intra-subject variability, no more than one replicate measure per time point, and the practice of rounding off QT readings to the nearest 10 msec.

Before the NDA can be approved, the sponsor will need to conduct and submit for review a prospective, randomized, double-blind QT study that evaluates solifenacin doses that achieve exposures comparable to those achieved in the 022 study (i.e., up to 30 or 40 mg solifenacin), and that includes positive and placebo controls. Given that solifenacin is likely to be prescribed to older female patients, many of whom may be co-prescribed 3A4 inhibitors or who may have varying degrees of renal impairment, we believe submission of the data from this QT study is required pre-approval so that product labeling can include dosing recommendations for solifenacin when co-administered with 3A4 inhibitors.

Approvability Issue: Dissolution Acceptance Criteria

In a teleconference with the sponsor on October 16, 2003, it was learned that an additional batches have been produced since submission of the original NDA. Additional dissolution data on these batches will need to be submitted in the sponsor's complete response in order to set dissolution acceptance criteria.

Labeling
Labeling comments are deferred at this time. The sponsor will be requested to submit draft labeling that incorporates the outcomes of the QT study requested in the approvable letter, and that addresses the prevention and management of serious sequelae of constipation with use of this drug. Additional risk management strategies may be needed.

Phase 4 Studies
No phase 4 studies are requested at this time.

Tradename Review
As of this writing, the proposed tradename "Vesicare" appears acceptable.

/S/

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
10/17/03 04:54:29 PM
DIRECTOR

Teleconference Minutes

NDA: 21,518 **Drug:** Solifenacin succinate

Sponsor: Yamanouchi Pharma America, Inc.

Date: October 16, 2003 **Time** 12:40 PM – 1:00 PM

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
Meeting Chair: George Benson, M.D., Urology Team Leader, DRUDP
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research
Goudong Fang, Medical Reviewer, DRUPD
Meeting Recorder: Jean King, MS, RD, Project Manager, DRUDP
Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP

Yamanouchi Pharma America, Inc. Attendees:
Robert Desjardins, M.D., President, R&D
Rudolph Lucek, Vice President, Regulatory Affairs
Lawrence Posner, M.D., Sr. Vice President, R&D
Susan Ridge, Director, Project Management
Neila Smith, M.D., Medical Director
Christine Mulhauser, Director, Regulatory Affairs, CMC

Background: On October 15, 2003, the sponsor faxed an additional analysis of their QTc data to reflect a change in their October 14, 2003, statement regarding an observed diurnal effect. The sponsor retracted their response from the October 14, 2003, meeting that they did not observe a diurnal effect and provided evidence which they believe demonstrates a diurnal peak at hour 16. In this fax, the sponsor requested a teleconference with the Clinical Biopharmaceutics Reviewers and the Division of CardioRenal Drug Products (DCRDP).

Issues Discussed:

1. The Division acknowledged receipt of the sponsor's fax and noted the sponsor's analysis found similar effects as observed by the Division.

2. The relevance and the significance of a second diurnal peak remain unclear to both DRUDP and DCRDP. The Division's review team had raised the issue of a possible diurnal effect as part of their exploratory review of the data submitted. Specifics of the study's conduct remain unclear that are relevant because they could impact interpretation of the circadian data (e.g., whether all patients were awakened prior to

the 1:00 AM ECG collection or, if awakened, how close in time prior to the performance of the ECG they were awakened, and/or whether the observed effect was related to the ingestion of a late meal).

3. Inclusion of a positive control in QT trial designs is critical to interpreting study results.

Sponsor response: The sponsor asked the Agency's opinion of the diurnal changes observed.

Division Response: The Division recently completed another exploratory analysis of the data from Trial 022, which examined each individual study participant for diurnal changes. There is no apparent consistent individual effect observed, which, therefore, raises further questions regarding the relevance of the overall observed mean diurnal change seen in our exploratory analysis.

The Division stated its recognition of best efforts to evaluate the QTc issue by both the sponsor and the reviewers. The Division will complete its review and take an action on October 17, 2003, because the PDUFA date (October 19, 2003) is a Sunday.

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/s/

George Benson
11/5/03 01:08:09 PM

NDA 21-518

Supervisory Medical Officer's Memorandum

From: George S. Benson, MD, Medical Team Leader
Division of Reproductive and Urologic Drug Products

To: Donna Griebel, MD, Deputy Division Director
Division of Reproductive and Urologic Drug Products

Julie Beitz, MD, Deputy Office Director, ODE III

Regarding: Recommendation for regulatory action

Date NDA submitted: December 19, 2002
Date of memorandum: October 16, 2003

Sponsor: Yamanouchi Pharma America, Inc.
Mack Centre IV, S 61 Paramus Rd.
Paramus, New Jersey

Drug: solifenacin succinate
Pharmacologic class: M_3 muscarinic receptor antagonist
Tradename: Vesicare
Dosage strength: 5 and 10 mg
Route of administration: oral

Proposed indication:

/

Related IND/NDA's: IND 58,135

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4.	Efficacy Summary	12
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1. Materials Used in Conducting the Review:

A. Primary Medical Officer review of NDA 21518 and safety update
B. Trial 905-CL-022 (QT study)
C. Consultation from the Cardiorenal Division concerning Trial 022
D. Fax from sponsor dated October 9, 2003, relating to the QT study
E. Fax from sponsor dated October 15, 2003, relating to the QT study
F. Selected portions of the ISS and ISE
G. Consultations from DMETS, DSI, DDMAC, DSRCS, and DDRE
H. Clinical pharmacology and statistical reviews

2. Executive Summary and Recommendations:

This NDA contains substantial evidence that solifenacin (YM905) is effective for the treatment of overactive bladder. The NDA also meets the required ICH guidance criteria for safety exposure and, in general, the safety concerns with solifenacin are similar to those of other antimuscarinic drugs. There are, however, in my opinion, insufficient data submitted to determine whether solifenacin has a clinically significant effect on prolongation of the QT interval, and is, therefore, safe in the intended patient population. I believe that solifenacin succinate (Vesicare) should receive an **approvable action** for the indication "

he reasons for this decision and the resolution item for this deficiency are discussed below.

<u>Review of QT data (pre-clinical studies, phase 3 clinical studies, and dedicated QT study (Trial 905-CL-022)</u>

A. Preclinical studies:

i) Solifenacin inhibited the potassium current in Chinese hamster ovary (CHO) cells stably expressing the HERG channel (using the whole-cell patch technique) at an IC_{50} value of 0.27 micromolar.

ii) Solifenacin at concentrations of 0.003, 0.03, and 0.3 micromolar had no effect on resting membrane potential, upstroke amplitude, or maximum rate of depolarization or action potential duration in an isolated dog Purkinje fiber preparation

iii) An inconsistent effect on the QT interval was observed in some dogs treated with 30 mg/kg/day of solifenacin for 4 weeks. QT interval values, however, remained within the normal range.

B. Phase 3 clinical studies:

The sponsor submitted 4 major placebo controlled efficacy and safety studies. EKGs were obtained in these studies at baseline and at study end. Changes in QTc (Bazett) interval values from baseline to endpoint are shown in Table 1.

Table 1. QTc (Bazett) changes from baseline to endpoint in 4 major trials

	Placebo	Solifenacin 5 mg	Solifenacin 10 mg
Trial 013 (N=672) Mean change (msec)	1.3	N/A	4.9
Trial 014 (N=634) Mean change (msec)	1.1	N/A	4.4
Trial 015 (N=1077) Mean change (msec)	-4.0	1.9	4.7
Trial 018 (N=907) Mean change (msec)	-0.5	1.6	1.4

In these four phase 3 trials, there appears to be a trend toward higher QTc changes in the drug versus placebo treated groups and a dose response in 1 of the 2 studies comparing the 5 and 10 mg doses.

Four patients in the phase 3 studies had a QTc value of >500 msec at any time during the study:

Trial 013: One patient (#14014) in the 10 mg solifenacin group had a baseline QTc (Bazett) of 450 msec and a QTc of 510 msec at week 12. She entered the open label portion of the study and her QTc at week 16 was 460 msec.

Trail 014: Two patients on solifenacin 10 mg had a QTc >500 msec at one point during double blind treatment. Patient #27003 had a QTc of 450 msec at screening. Her QTc at week 4 was 500 msec. She continued in the study without incident and at month 6 her QTc was 460 msec. Patient # 23010 had a baseline QTc of 470 msec and at Week 12 her QTc was 510. She subsequently entered the extension study and at month 3 her QTc was 480.

Trial 015: One patient (#10158) in the 10 mg solifenacin group had a QTc value that increased from 397 at screening to 507 msec at the end of the study. She experienced no adverse events.

Trial 018: One patient in the placebo group had a QTC at the end of the study of >500 msec.

A representative outlier analysis (from United States study 014) evaluating drug group, age, and sex is shown in Table 2.

Table 2. Outlier ΔQT_C and QT_C for Study 014[a]

Treatment Group	Gender	Age	ΔQT_C		QT_C	
			>30 <60 msec	> 60 msec	>450 <500 msec	>500 msec
Placebo	Female	22 - 60	10 (1.56)	0 (0)	16 (2.49)	0 (0)
Placebo	Female	60 – 89	12 (2.02)	0 (0)	23 (3.87)	0 (0)
Placebo	Male	22 - 60	2 (2.00)	0 (0)	4 (4.00)	0 (0)
Placebo	Male	60 – 89	5 (2.87)	0 (0)	4 (2.30)	0 (0)
Drug	Female	22 - 60	6 (0.98)	1 (0.16)	17 (2.76)	0 (0)
Drug	Female	60 – 89	20 (3.14)	2 (0.31)	44 (6.92)	2 (0.31)
Drug	Male	22 - 60	9 (6.92)	0 (0)	2 (1.53)	0 (0)
Drug	Male	59 – 89	2 (1.44)	0 (0)	9 (6.47)	0 (0)

[a]Data presented as number of outliers (percentage of total)

The 3 patients whose QTc was prolonged >60 msec and the 2 patients whose QTc was >500 msec were both in women on solifenacin.

Deaths: There were a total of 5 deaths in the combined Phase 2/3 studies. One patient died in Trial 013 and 2 patients died in each of Trials 015 and 018. Two of the deaths were in placebo treated patients, one in a tolterodine treated patient, and 2 were in patients randomized to 10 mg solifenacin. One of the deaths in a patient randomized to solifenacin occurred in a 68-year-old woman who experienced right-sided hemiparesis 81 days after starting study drug. Two weeks later she died and the cause of death was listed as a pulmonary embolism. The second death in a patient taking solifenacin occurred in a 75-year-old woman. The presumptive cause of death was "acute heart failure." An autopsy was not performed and "no further information could be obtained."

C. QT study (Trial 905-CL-022)

Study R905-CL-022 was a pharmacokinetic/pharmacodynamic (PK/PD) trial to determine the effect of escalating multiple doses of solifenacin on the QTc interval in men, pre- and postmenopausal women (n=20/group). The mean age of the men was 42.1 years, pre-menopausal women was 37.0 years, and the post-menopausal women was 60.6 years. The patient population was 60% Hispanic, 23% Caucasian, 13% Black, and 3% Asian. This study was an open-label, one-

sequence crossover, escalating multiple-dose trial. All subjects sequentially received placebo once daily for 2 days and then escalating doses (10 mg to 50 mg) for 14 days at each dose as described below:

Days 1-2: Placebo x 2 days (1 placebo tablet/day)
Days 3-16: 10mg YM905 x 14 days (1 x 10mg tablet/day)
Days 17-30: 20mg YM905 x 14 days (2 x 10mg tablet/day)
Days 31-44: 30mg YM905 x 14 days (3 x 10mg tablet/day)
Days 45-58: 40mg YM905 x 14 days (4 x 10mg tablet/day)
Days 59-72: 50mg YM905 x 14 days (5 x 10mg tablet/day)

The investigator stopped dosing during the 50 mg dose level phase of the study because of intolerable anticholinergic adverse events (constipation, dry mouth, blurred vision, tremor, and fixed dilated pupils). One patient at the 30 mg dose level experienced urinary retention. Actual patient disposition is shown in Table 3.

Table 3. Disposition of subjects

	Placebo (N=60)	10 mg (N=60)	20 mg (N=60)	30 mg (N=58)	40 mg (N=42)	50 mg (N=16)
Completed treatment	60	60	58	56	42	0
Prematurely discontinued	0 (0%)	0 (0%)	2 (3%)	2 (3%)	0 (0%)	16 (100%)

(None of the subjects completed the 50 mg dosing because this phase of the study was discontinued.)

Pharmacokinetics (PK) and Pharmacodynamics (PD)

Blood samples for PK analysis of solifenacin were collected as follows: 0 hour (prior to dose) and 1, 2, 4, 6, 8, 12, 16, and 24 hours after the solifenacin dose administered on Days 16, 30, 44, 58 and 64 or 68. In addition, blood samples for PK trough analysis of solifenacin were collected at 0 hour (prior to dose) on Days 2 (baseline), 14, 15, 28, 29, 42, 43, 56 and 57. A 12-lead ECG and vital signs were obtained at 0 hour (predose) and at approximately 1, 2, 4, 6, 8, 12, 16, and 24 hours after the solifenacin dose administered on Days 16, 30, 44, 58 and 64 or 68. In addition, a 12-lead ECG and vital signs were obtained at 0 hour (predose; steady-state) on Days 14, 15, 28, 29, 42, 43, 56, and 57.

The study did not include a concurrent placebo group or a positive control group. QT interval measurements, therefore, could only be compared to baseline values. The sponsor defined the baseline as the median of QT measurements performed at the 9 time points on Day 2 of the placebo run-in. The clinical pharmacology reviewer performed an analysis using these "baseline" measurements as well as an analysis using the average of 2

other "baseline" QT intervals (performed at screening and check-in). All reported QT values had been "rounded" to the nearest 10 msec.

The study protocol was reviewed by the CardioRenal Division in consultations dated August 7 and November 20, 2001. On August 7, 2001, the consultation concluded that "given the setting, the proposed study seems entirely adequate, except perhaps with respect to establishing a safety margin in dose." On November 20, 2001, the CardioRenal consultant stated that "the sponsor now says they will study higher doses if they appear to be tolerated, which is all one could reasonably ask." In addition, the consultant believed that "the ability to rule out an effect of a given size would be more compelling if the study had a positive control phase, so one could evaluate the study's power to detect a QT effect when one is really there."

The mean change in QTc (Fridericia) from "baseline" as calculated by the clinical pharmacology reviewer using the average of the screening and check-in QT intervals as baseline is shown in Table 4.

Table 4. Mean change in heart rate and QTc Fridericia from baseline

Treatment Group	Mean Change in HR (bpm)	Mean Change in ΔQT_C (msec)
Placebo	-0.34	0.89
10 mg	-1.09	0.26
20 mg	0.33	3.46
30 mg	1.70	0.77
40 mg	2.42	-3.82
50 mg	1.52	-8.46

Outlier QTc measurements of >450 msec are shown in Table 5.

Table 5. Outlier QT_C Measurements > 450msec

	QT_{CB}[a]	QT_{CF}[b]
N > 450msec	10 (0.33%)	1 (0.033%)
Max QT_C	468	462
Placebo	1	0
10mg	0	0
20mg	1	1
30mg	7	0
40mg	1	0
50mg	0	0

[a]Bazett-corrected QT interval
[b]Fridericia-corrected QT interval

Outlier values for baseline-corrected QT interval measurement changes are shown in Table 6.

Table 6. Outlier Values for Baseline-Corrected QT Interval Measurements Changes[a]

Category	ΔQT_{CT}[b]		ΔQT_{CS}[c]		Overall N
	>30msec	>60msec	>30msec	>60msec	
Placebo	54 (10.00)	1 (0.19)	2 (0.37)	0 (0)	540
10mg	54 (8.18)	0 (0)	4 (0.61)	0 (0)	660
20mg	81 (12.64)	1 (0.16)	14 (2.18)	0 (0)	641
30mg	57 (9.25)	4 (0.65)	28 (4.55)	0 (0)	616
40mg	32 (6.93)	0 (0)	8 (1.73)	0 (0)	462
50mg	3 (2.40)	0 (0)	0 (0)	0 (0)	125

[a]results presented as number of QT intervals (% of total)
[b]Fridericia-corrected QT interval minus Fridericia-corrected true baseline
[c]Fridericia-corrected QT interval minus Fridericia-corrected sponsor-defined baseline

The study report for Trial 905-CL-022 was reviewed by the CardioRenal Division (February 21, 2003). The consultant concluded that:

A. Heart rate does appear to be affected by solifenacin.
B. "There are important limitations to these data." Although the Division's review of November 21, 2001, recommended an assay-validating positive control, there is none in this study. The small diurnal variation in QTc, an effect that appears to be a few milliseconds difference between awake and asleep, might be exploited to show the study had the ability to resolve a small QT effect, but all of the data in this study are presumably from awake subjects, so this effect cannot be used to show assay sensitivity either. Consequently, one cannot be certain that a small QT effect would have been detected by this study. A Malik-style individualized QT correction is probably not feasible with these data, because there are not enough measurements off treatment. Acknowledging these limitations, the available data do not indicate an obvious problem.
C. The safety database has no events likely to represent arrhythmias.
D. The distribution in changes in QTcF appears to be fairly symmetric with respect to outliers high and low.
E. The study provided limited data beyond 40 mg, but this dose is a factor of four over the proposed maximum dose, providing some reassurance.
F. Solifenacin is predominantly metabolized by CYP 3A4, but ketoconazole only produced a 40% increase in plasma levels, so metabolic inhibition is not as large a factor as it might be.
G. Thus, for the most part, the setting – dose multiple, tolerance-limiting, pharmacokinetic insensitivity, lack of likely arrhythmia events – and the EKG data - lack of upward trend or high-end outliers – are reassuring. However, given the uncertainties in the discriminatory power, is that reassurance enough? The answer has to depend somewhat on the nature of the benefit achieved with treatment. For a small and unimportant symptomatic benefit, the degree of comfort is probably less than one might expect.

H. The Division Director "reinforced" the consultant's comments "on the limited adequacy of this trial to exclude an effect on QT interval without the use of an active control or other means of assessing assay sensitivity."

A teleconference was held with the sponsor on October 3, 2003. The Division's concerns regarding QT prolongation were expressed. In a subsequent fax, the sponsor was asked to make the case that study 022 is sufficiently robust to have detected a 5-10 msec change from baseline. The sponsor responded via fax on October 9, 2003, and a face-to-face meeting was held with the sponsor on October 14, 2003.

The sponsor believes that "the results of the Phase 3 (013, 014, 015, and 018) studies and long-term open label extension studies (016 and 019) in actual patients with overactive bladder and the results of the clinical pharmacology study (022) demonstrate that there is a small but significant effect of solifenacin on the QT interval (particularly in postmenopausal women) which is, however, not likely to be clinically significant even at maximally tolerated doses and levels of exposure to solifenacin. The consistency of the of the observed effects on QTc in the clinical pharmacology and Phase 3 studies provides a high level of confidence in the overall characterization of this effect in the population of interest. The data, furthermore, suggest that supramaximal exposure levels (at doses above 30 mg) are not associated with additional prolongation of the QT interval. These data provide an adequate basis for labeling and risk management in the administration of solifenacin to patients with overactive bladder, based on assessments in individuals at an appropriate age and gender. The description of the effect of solifenacin in labeling should reflect the observations in the population of interest as observed in the Phase 3 studies and the subset of postmenopausal women in the clinical pharmacology study." The sponsor further addressed the fact that "the observed change in baseline corrected QTc in the 40 and 50 mg dose groups was negative in the overall population. The reason for this is not clear." During the October 14, 2003, meeting, the sponsor presented modeling data which they believe shows that a 30 mg dose of solifenacin may prolong the QT interval by 10 msec.

Following the meeting on October 14, 2003, the sponsor sent a fax to the Division on October 15, 2003. The sponsor believes that re-analysis of the data from the dedicated QT study (022) shows diurnal variation which provides internal validation that the study was "sufficiently robust to have detected a 5-10 msec effect of the drug." The sponsor believes that there is "a statistically significant difference in the mean QTcF observed at 16 hours (1:00 AM) compared to all other time points on placebo. The p-value in the ANOVA for the effect of time is 0.0088, and the contrast of the 16 hour time point from the rest of the ECGs during 24 hours is responsible for this difference. The magnitude of the difference is 4.2 msec." The sponsor believes that "the ability to detect an apparent circadian or time-related difference of this magnitude (approximately 5 msec) within the

study that is statistically significant and not related to drug could provide additional internal validation for the study."

In summary, solifenacin inhibited the potassium current in Chinese hamster ovary (CHO) cells stably expressing the HERG channel (using the whole-cell patch technique) at an IC_{50} value of 0.27 micromolar. The phase 3 data appear to show an effect of solifenacin on the QTc interval (perhaps less than 5 msec). Four patients in the phase 3 studies taking solifenacin and one patient taking placebo had QTc values of >500 msec at some point during the trials. I do not believe that the results of the designated QT study 022 can be adequately interpreted. There is wide intrasubject variability and the lack of a positive control group and a true (concurrent) placebo group, in my opinion, preclude making conclusions concerning the presence and degree of QT prolongation. The demonstration of diurnal changes as a method of assaying study sensitivity of QT studies, has not, to my knowledge, been previously utilized in the regulatory drug approval process. The opinion of the CardioRenal consultant is that, without further specific information including whether the EKGs were performed while the patients were asleep or awake and the relationship of the EKGs to meals, an opinion concerning the observed diurnal effects can not be confidently given. Futhermore, the demonstration of diurnal variation by itself does not provide information to assess the actual amount of QT prolongation seen with solifenacin. Even with assuming that the drug prolongs the QT interval (as it appears to do in data from the phase 3 trials and which the sponsor characterizes as approximately 5 msec), I do not think that sufficient information is available to adequately label the product for safe use.

Resolution item for this deficiency:

The sponsor should submit the results from a randomized, placebo-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at plasma concentrations achieved at steady state with co-administration of solifenacin and maximum CYP 3A4 inhibition. This study should include a positive control, such as moxifloxacin, in order to assure assay sensitivity and to provide a benchmark for comparison with the QT effect of solifenacin. The primary endpoint, corrected QT interval, should be measured by multiple 12-lead EKGs taken at baseline and at steady state. The study population should be female, preferably patients with overactive bladder, whose mean age is consistent with the age distribution of overactive bladder patients in the community. The number of subjects should be sufficient to rule out a clinically important mean prolongation of the corrected QT interval by solifenacin.

3. Clinically Relevant Issues from other Disciplines' Reviews:

A. Statistics

The statistician reviewed the 4 randomized, double-blind, placebo-controlled, parallel-arm, multicenter clinical studies of primary interest for assessing the efficacy of solifenacin 5 or 10 mg tablets. "All four studies include the 10 mg dose and 2 studies include the 5 mg dose. For the primary endpoint, the mean change in number of micturitions per 24 hours, both Vesicare doses are statistically significantly better than placebo in all comparisons. The same is true for one of the two secondary variables the Medical Officer requested: the mean change in volume voided per micturition. On the other secondary variable of interest to the Medical Officer, the mean change in number of incontinence episodes, the Vesicare doses are statistically significantly better than placebo in three of the four studies. The statistician believes that these results support the efficacy of Vesicare 5 or 10 mg tablets for

B. Clinical Pharmacology

The clinical pharmacology reviewer found the NDA application to be "acceptable."

Dose selection: In two relatively large phase 2 dose finding studies (005 and 006), the 5 mg dose was established as the lowest effective dose in one study and 10 mg as the lowest effective dose in the other study. In one of the studies, efficacy was maximized at the 10 mg dose while in the other study maximal efficacy was not established even at the 20 mg dose. In the phase 3 studies, the 10 mg dose was numerically somewhat superior to the 5 mg dose with respect to the primary endpoint of mean number of micturitions/24 hours, although this difference was statistically significant only at Day 28. Based on efficacy and tolerability, the 5 and 10 mg doses are acceptable to the clinical pharmacology reviewer as the to-be-marketed doses. I agree with this dose selection.

Following the administration of solifenacin, Cmax is achieved in 3 to 6 hours. The half-life ($t_{1/2}$) is 48 to 60 hours. Solifenacin has one major metabolite (M2) which has negligible activity and 3 minor metabolites (M3, M4, and M5). M3 has the most muscarinic receptor activity among the metabolites (3-fold lower than the parent), but demonstrates significantly lower plasma levels than solifenacin. Solifenacin is excreted primarily in the urine (approximately 70%) and feces (approximately 23%). The drug shows linear pharmacokinetics between 5 and 100 mg oral doses.

There is a 20-25% increase in the C_{max} and AUC in the elderly as compared to younger subjects.

In moderately hepatically impaired patients there is a 2-fold increase in $t_{1/2}$ and a 35% increase in AUC of solifenacin. The clinical pharmacology reviewer

recommends not to exceed a 5 mg daily dose of solifenacin in this group of patients and I agree with this recommendation. Patients with severe hepatic impairment have not been studied.

In patients with severe renal impairment a 2-fold increase in AUC was observed. The clinical pharmacology reviewer recommends not to exceed a 5 mg daily solifenacin dose in this group of patients and I agree with this recommendation.

Solifenacin is metabolized primarily by CYP 3A4 with a minor contribution from CYP 2C19. In a drug-drug interaction study with 400 mg ketoconazole daily, the C_{max} and AUC were increased by approximately 1.5 and 3-fold, respectively. Based on this finding, the clinical pharmacology reviewer recommends not to exceed a 5 mg dose of solifenacin when used in combination with ketoconazole and other potent CYP 3A4 inhibitors and I agree with this recommendation.

C. Pharmacology/Toxicology

The pharmacology/toxicology reviewer recommended "approval." "Final analysis of mouse and rat carcinogenicity studies should be electronically submitted for review and statistical analysis." The pharmacology/toxicology reviewer believes that this issue can be adequately managed with labeling.

Solifenacin was not mutagenic or genotoxic in the standard battery of in vitro and in vivo assays. Preliminary results do not show any increase in tumor incidences following administration of solifenacin for 2 years in rats and mice and rats.

There were no effects on fertility or early reproductive parameters following administration of solifenacin to male and female mice or rats. There were no teratogennic effects observed in rats or rabbits. However, administration of solifenacin succinate to mice during the period of major organogenesis resulted in an increased incidence of cleft palate at doses that resulted in decreased maternal weight gain. Reduced fetal and pup weights, and delayed development were also observed in F1 generation mice. No reproductive or developmental effects were observed at doses approximately 2 fold that of the maximum recommended human dose (MRHD) in mice and rabbits and at the highest tolerated dose in rats (<1 the MRHD).

In utero and lactational exposures resulted in reduced fetal and pre-weaning pup weights, peripartum and postpartum mortalities, and delayed development.

Based on these findings, the pharmacology/toxicology reviewer has recommended that the label state that solifenacin is Pregnancy Category C and

that "There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Vesicare should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus" and that "It is not known whether solifenacin succinate in excreted in human milk. Because many drugs are excreted in human milk, Vesicare should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue Vesicare in nursing mother." I agree with these recommendations.

D. Chemistry

The chemistry reviewer believes that "this NDA can be approved from a CMC standpoint pending final acceptable recommendation from the Office of Compliance and approved labeling." This deficiency should be included in the "approvable" letter. On October 17, 2003, an "acceptable" recommendation was received from OC.

E. Microbiology

The reviewer recommended approval from the standpoint of microbial product quality.

4. Efficacy Summary

In support of the efficacy of solifenacin for the indication treatment of overactive bladder, the sponsor submitted the results of 4 major phase 3 clinical trials. Trials 013 and 014 were conducted in the United States and evaluated the 10 mg dose of solifenacin. Trials 015 and 016 were conducted in Europe, Africa, Australia, and New Zealand and evaluated the 5 mg and 10 mg doses of solifenacin.

Financial disclosure: Financial disclosure information was submitted and is adequate. One investigator involved in Trials 006, 013, and 016 filed a financial disclosure form. This form was mistakenly filed. The monies received were from — (an independent — . company, not a subsidiary of Yamanouchi). I believe that adequate documentation for this incorrect filing is included in the NDA application. None of the other investigators or subinvestigators had financial interest requiring disclosure.

In addition, the sponsor submitted the results of phase 2 dose-finding studies 005 (performed in Europe, Africa, Australia, and New Zealand) and 006 (performed in the United States).

All four major trials were double-blind, placebo-controlled, and of 12 weeks duration.

Key inclusion/exclusion criteria were as follows:

Inclusion criteria in 013 and 014 included: Symptoms of overactive bladder (urinary frequency with urgency and/or incontinence), age >18 years, an average of >8 micturitions/24 hours, and either an average of >1 urinary incontinence episode/24 hours or an average of >1 urinary urgency episode/24 hours, documented in a 3-day diary in the screening phase.

Exclusion criteria in 013 and 014: Stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Trial 014 also included the exclusion criteria of urinary retention as demonstrated by post-void residual urine volume of >150 cc as evidenced by a bladder scan.

Inclusion criteria in 015 and 018 included: Symptoms of overactive bladder (urinary frequency with urgency and/or incontinence) for >3 months, age >18 years, an average of >8 micturitions/24 hours, and either an average of >3 urinary incontinence episodes or an average of >3 urinary urgency episodes documented in a 3 day diary in the screening phase.

Exclusion criteria in 015 and 018 included: stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Both of these trials also excluded patients with urinary retention defined as a post-void residual urine volume of >200 cc as evidenced by a bladder scan.

Endpoints:

The primary efficacy endpoint in all four trials was the mean change from baseline to endpoint in the number of micturitions/24 hours.

Secondary efficacy endpoints in all four trials included mean change from baseline to endpoint in 1) number of incontinence episodes/24 hours 2) number of urgency episodes/24 hours 3) mean volume voided/micturition and 4) number of nocturia episodes/24 hours.

The results of the primary efficacy analysis (number of micturitions/24 hours) are shown in Table 7.

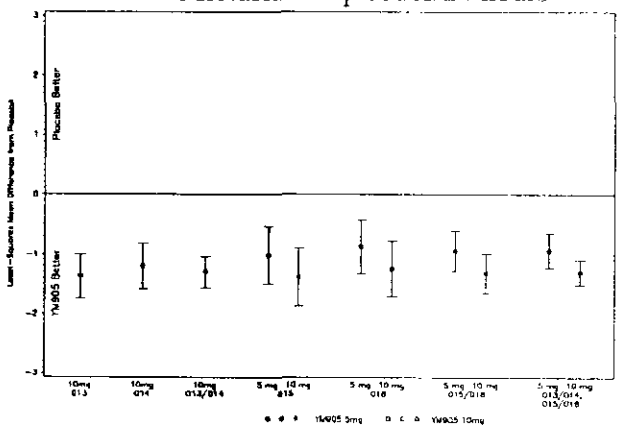
Table 7. Mean change from baseline to endpoint in mean number of micturitions/24 h: pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)	p-value	Bonferroni-Holm adjusted p value
013	Placebo	309	11.5±0.18	−1.5±0.15			N/A
	YM905 10 mg	306	11.7±0.18	−3.0±0.15	−1.37 (−1.74, −1.01)	<0.001	
014	Placebo	295	11.8±0.18	−1.3±0.16			N/A
	YM905 10 mg	298	11.5±0.18	−2.4±0.15	−1.20 (−1.59, −0.81)	<0.001	
013/014	Placebo	604	11.7±0.13	−1.4±0.11			N/A
	YM905 10 mg	604	11.6±0.12	−2.7±0.11	−1.30 (−1.56, −1.03)	<0.001	
015	Placebo	253	12.2±0.26	−1.2±0.21			
	YM905 5 mg	266	12.1±0.24	−2.2±0.18	−1.02 (−1.50, −0.53)	<0.001	<0.001
	YM905 10 mg	264	12.3±0.24	−2.6±0.20	−1.39 (−1.87, −0.91)	<0.001	<0.001
	Tolter 4 mg	250	12.1±0.22	−1.9±0.19	−0.73 (−1.22, −0.24)	0.004	N/A
018	Placebo	281	12.3±0.23	−1.7±0.19			
	YM905 5 mg	286	12.1±0.23	−2.4±0.17	−0.87 (−1.33, −0.42)	<0.001	<0.001
	YM905 10 mg	290	12.1±0.21	−2.9±0.18	−1.25 (−1.70, −0.79)	<0.001	<0.001
015/018	Placebo	534	12.3±0.17	−1.4±0.14			
	YM905 5 mg	552	12.1±0.16	−2.3±0.12	−0.94 (−1.28, −0.61)	<0.001	<0.001
	YM905 10 mg	554	12.2±0.16	−2.8±0.13	−1.32 (−1.65, −0.99)	<0.001	<0.001
US & EU combined (13/14,15/18)	Placebo	1138	11.9±0.11	−1.4±0.09			
	YM905 5 mg	552	12.1±0.16	−2.3±0.12	−0.94 (−1.23, −0.65)	<0.001	<0.001
	YM905 10 mg	1158	11.9±0.10	−2.7±0.09	−1.31 (−1.52, −1.09)	<0.001	<0.001

In each of the four major trials, the number of micturitions was decreased approximately 1-1.5 episodes/24 hours. These changes were statistically significant at the $p < 0.001$ level in all four studies. The statistical reviewer agrees that the change from baseline to endpoint versus placebo in all 4 major efficacy trials is statistically significant.

95% confidence intervals for micturition/24h change from baseline means for individual studies, combined US, combined EU and combined US/EU studies are shown in Figure 1.

Figure 1. 95% Confidence Intervals for Mean Change from Baseline for Micturition Episodes/24 hours



The mean change from baseline in incontinence episodes/24 hours (a secondary endpoint) is shown in Table 8.

Table 8. Mean change from baseline to endpoint in mean number of incontinence episodes/24 h: pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)	p-value	Bonferroni-Holm adjusted p value
013	Placebo	237	3.0±0.20	−1.1±0.16			
	YM905 10 mg	225	3.1±0.22	−2.0±0.19	−0.80 (−1.19, −0.42)	<0.001	N/A
014	Placebo	238	2.9±0.18	−1.2±0.15			
	YM905 10 mg	230	2.9±0.17	−2.0±0.15	−0.74 (−1.07, −0.41)	<0.001	N/A
013/014	Placebo	475	2.9±0.13	−1.2±0.11			
	YM905 10 mg	455	3.0±0.14	−2.0±0.12	−0.77 (−1.03, −0.52)	<0.001	N/A
015	Placebo	153	2.7±0.23	−0.8±0.18			
	YM905 5 mg	141	2.6±0.22	−1.4±0.15	−0.68 (−1.13, −0.23)	0.003	0.003
	YM905 10 mg	158	2.6±0.23	−1.5±0.18	−0.75 (−1.19, −0.31)	<0.001	0.002
	Tolter 4 mg	157	2.3±0.15	−1.1±0.17	−0.59 (−1.03, −0.15)	0.009	N/A
018	Placebo	153	3.2±0.24	−1.3±0.19			
	YM905 5 mg	173	2.6±0.18	−1.6±0.16	−0.66 (−1.07, −0.24)	0.002	0.004
	YM905 10 mg	165	2.8±0.20	−1.6±0.18	−1.48 (−0.90, −0.06)	0.026	0.026
015/018	Placebo	306	3.0±0.17	−1.0±0.13			
	YM905 5 mg	314	2.6±0.14	−1.5±0.11	−0.66 (−0.96, −0.35)	<0.001	<0.001
	YM905 10 mg	323	2.7±0.15	−1.5±0.13	−0.60 (−0.91, −0.30)	<0.001	<0.001
US & EU combined (13/14,15/18)	Placebo	781	2.9±0.10	−1.1±0.09			
	YM905 5 mg	314	2.6±0.14	−1.5±0.11	−0.73 (−1.01, −0.45)	<0.001	<0.001
	YM905 10 mg	778	2.9±0.10	−1.8±0.09	−0.72 (−0.91, −1.52)	<0.001	<0.001

The statistical reviewer believes that 3 of the 4 major trials demonstrate a statistically significant change in the secondary endpoint incontinence episodes. The fourth study (018) shows a mean change from baseline of −1.6 episodes (p-value = 0.22). The above table is from a secondary analysis with baseline included as covariate. The sponsor believes that this analysis is more appropriate because of the baseline differences between placebo and the two active treatment groups. The sponsor's primary analysis shows that the difference from placebo is not statistically significant for the solifenacin 10 mg treatment group (0.22).

Mean voided volume also increased by a statistically significant amount (approximately 20 to 50 cc) in all four trials. The mean change from baseline to endpoint in number of urgency episodes/24 hours was approximately a decrease of 1 to 2.

No adequately designed trials directly comparing solifenacin to approved antimuscarinic drugs for overactive bladder have been performed. The magnitude of the changes in number of micturitions and incontinence episodes seen with solifenacin and approved drugs, however, appear similar.

In summary, four adequately controlled trials enrolling an appropriate patient population have demonstrated that solifenacin decreases urinary frequency and incontinence episodes and is effective for the treatment of overactive bladder.

I believe that the indication for any future labeling should be for '

5. Safety Summary

The numbers of patients with overactive bladder treated with solifenacin at doses ranging from 2.5 mg to 20 mg are shown in Table 9.

Table 9. Patients with overactive bladder in clinical trials

Study	Treatment Groups						
	Solifenacin					Place bo	Tolterodine 2 mg bid
	2.5 mg	5 mg	10 mg	20 mg	Any dose		
Phase 3 stuides							
905-CL-013 (US)			340		340	332	
905-CL-014 (US)			318		318	316	
Subtotal US			**658**		**658**	**648**	
905-CL-015 (EU)		279	268		547	267	**263**
905-CL-018 (EU)		299	307		606	301	
Subtotal EU		**578**	**575**		**1153**	**568**	263
SUBTOTAL (Phase 3)		**578**	**1233**		**1811**	**1216**	263
Phase 2 studies							
905-CL-005 (EU)	41	37	35	37	150	38	**37**
905-CL-006 (US)	54	52	51	54	211	53	
Sutotal	95	89	86	91	361	91	37
SUBTOTAL (Phase 3+Phase 2)	**95**	**667**	**1319**	**91**	**2172**	**1307**	300
Open-label, extension study							
905-CL-016 (US)			892 (443[1])		892 (443[1])		
TOTAL OAB Patients (All patient safety data)	95	667	1768	91	2621	1307	300

[1] Patients who previously received 10 mg YM905 in Studies 013 and 014.

Gender, age, and race: Overall, 2621 patients (555 men and 2066 women) with overactive bladder were exposed to solifenacin in these trials. Of these 2621 patients, 667 (146 men and 521 women) were exposed to 5 mg, 1768 (353 men and 1415 women) were exposed to 10 mg, and the remainder were exposed to either 2.5 mg or 20 mg. A total of 937 patients were 65 years of age or older and 290 were 75 years of age or older. Seven hundred eighteen (718) patients had at least 6 months of exposure and 308 patients had at least 1 year of exposure to solifenacin 10 mg daily. In the phase 2 and phase 3 studies, approximately 97% of patients who received 5 mg and 91% of those who received 10 mg solifenacin were Caucasian.

The four-month safety update was submitted on April 25, 2003. The update included additional safety data from Trials 016 and 019, the open label extensions of the United States and European 4 phase 3 trials. This additional data bring the total number of patients exposed to solifenacin for one year to 476 (337 on 10 mg).

In addition to the above, the other sources of safety data include 15 completed clinical pharmacology trials, 3 ongoing clinical pharmacology trials, and one ongoing dose ranging study.

Deaths:

There were eleven deaths reported in patients in the combined Phase 2 and 3 trials including the extension studies. One patient died in Study 013, two patients died in each of Studies 015 and 018, two patients died in Study 016 and four patients died in Study 019. Two of the deaths were in placebo-treated patients, eight were in solifenacin 5 mg or 10 mg-treated patients, and one death was in a tolterodine-treated patient. All 8 deaths in solifenacin treated patients were considered "unrelated to study medication" by the investigator. In seven of the eight patients (hemiparesis followed by pulmonary embolus, post-operative complications following coronary artery bypass graft, subdural hematoma, ruptured aortic aneurysm, bleeding following hip surgery, brain tumor, and "cardiac insufficiency") I agree with the investigators that the cause of death was "not" or "probably not" related to study drug. In the eighth patient, relationship to study drug can not be determined. This patient [#015-11533 (10 mg solifenacin succinate)] was a 75-year old Caucasian woman. The investigator was informed by phone that she died 28 days after starting taking study drug. Presumptive cause of death was indicated as "acute heart failure." No autopsy was performed. The last contact with the patient was on Visit 3. No further information could be obtained.

Serious adverse events:

Ten SAE's in the four major phase 3 trials were judged by the investigator to be probably or possibly related to study drug. Three were considered to be secondary to expected antimuscarinic side effects and included two patients with fecal impaction and one patient with intestinal obstruction.

Narrative summaries of these 10 patients are included in the appendices of the medical officer's review. Two patients experienced syncope. Patient 11024 (5 mg solifenacin) experienced syncope; he had a history of encephalitis, vertigo and had experienced syncopal episodes prior to entering the study. Patient 21454 was hospitalized for atrial fibrillation and syncope 7 days after starting 10 mg solifenacin. The occurrence of the syncopal episode was temporally related to initiation of atenolol. Patient 11579 (5 mg solifenacin) experienced "tachyarrhythmia" diagnosed as "tachyarrhythmia absoluta" and underwent cardioversion. She had a prior history of arrhythmia and cardioversion. Patient 10886 (10 mg solifenacin) was diagnosed with a "possible" myocardial infarction on the EKG performed at the completion of the study; he was asymptomatic. The other SAE's are unlikely to be related to study drug.

In the open label studies 016 (United States) and 019 (Europe), 12 patients experienced SAE's which were thought to be possibly or probably related to study drug. One of the patients (#20256 – 5 mg solifenacin) experienced fecal impaction which required hospitalization. Patient #1325015 (10 mg solifenacin) experienced increasing symptoms of diverticulitis and rectal bleeding. Patient #10551 (10 mg solifenacin) was a 77-year-old-woman who "collapsed" at home during the extension phase of Trial 019. She was diagnosed with "postural hypotension" and recovered without without sequelae. The other SAE's are unlikely to be related to study drug.

One patient in QT study 022 experienced the SAE of acute urinary retention. Patient #022-015 was a 72-year-old Black man with a medical history of benign prostate hyperplasia and urinary retention, which had required urethral catheterization 5 to 6 years earlier. The patient had been treated with solifenacin 14 days at 10 mg/day and 14 days at 20 mg/day. On Day 8 of treatment at the 30 mg solifenacin dose level, the patient presented with urinary retention and was hospitalized for catheterization. The event resolved a week later and the patient was discontinued from the study.

Overall adverse events:

In the combined 4 major placebo-controlled phase 3 studies, the overall frequency of treatment-emergent adverse events was 52.1% in the placebo groups and 45.8% and 62.7% in the solifenacin 5 and 10 mg groups, respectively. The number (%) of patients discontinuing the trials because of an adverse event were 66 (5.4%), 21 (3.6%), and 85 (6.9%) in the placebo, 5 mg solifenacin, and 10 mg solifenacin groups, respectively.

The number and % of patients with treatment emergent adverse events is shown in Table 10.

Table 10. Number and % of subjects with TEAEs by system organ class: combined United States and European phase 3 studies

System Organ Class MedDRA preferred term	Combined Studies (013/014, 015/018): n (%)			
	Placebo	YM 905 5 mg	YM 905 10 mg	Tolter 4 mg
Number of patients	1216	578	1233	263
Number of patients with any AE	634 (52.1)	265 (45.8)	773 (62.7)	127 (48.3)
Gastrointestinal disorders	198 (16.3)	117 (20.2)	495 (40.1)	69 (26.2)
Dry mouth	51 (4.2)	63 (10.9)	340(27.6)	51 (19.4)
Constipation	35 (2.9)	31 (5.4)	165 (13.4)	8 (3.0)
Nausea	24 (2.0)	10(1.7)	40(3.3)	3 (1.1)
Dyspepsia	12 (1.0)	8 (1.4)	48 (3.9)	4 (1.5)
Abdominal pain upper	12 (1.0)	11 (1.9)	15 (1.2)	4 (1.5)
Vomiting	11 (0.9)	1 (0.2)	14 (1.1)	0
Infections and infestations	189 (15.5)	67 (11.6)	182 (14.8)	23 (8.7)
UTI	34 (2.8)	16 (2.8)	59 (4.8)	2 (0.8)
Nervous system disorders	113 (9.3)	29 (5.0)	114 (9.2)	16 (6.1)
Headache	55 (4.5)	11 (1.9)	52 (4.2)	12 (4.6)
Musculoskeletal & connective tissue	94 (7.7)	22 (3.8)	92 (7.50	14 (5.3)
Eye disorders	52 (4.3)	32 (5.5)	99 (8.0)	8 (3.0)
Vision blurred	22 (1.8)	22 (3.8)	59 (4.8)	4 (1.5)
Dry eye	7 (0.6)	2 (0.3)	20(1.6)	0
General disorders	62 (5.1)	16 (2.8)	83 (6.7)	13 (4.9)
Renal and urinary disorders	41 (3.4)	17 (2.9)	60 (4.9)	13 (4.9)
Urinary retention	7 (0.6)	0	17 (1.4)	0
Dysuria	5 (0.4)	2 (0.3)	9 (0.70	3 (1.1)
Psychiatric disorders	41 (3.4)	10(1.7)	41 (3.3)	6 (2.3)
Respiratory disorders	30 (2.5)	3 (0.5)	55 (4.5)	5 (1.9)
Cough	3 (0.2)	1 (0.2)	13 (1.1)	1 (0.4)
Vascular disorders	27 (2.2)	16 (2.8)	22 (1.8)	5 (1.9)
Hypertension NOS	7 (0.6)	8 (1.4)	6 (0.5)	3 (1.1)

In general, the largest percentage with adverse events experienced gastrointestinal disorders: dry mouth, constipation and nausea. The incidence of blurred vision was <5% , but was consistently higher in solifenacin groups than in the placebo group. All of these events are expected anticholinergic side effects. No clinically important differences in the adverse event profile of solifenacin were found when considering gender and age. A meaningful comparison of races was precluded by the fact that the overwhelming majority of patients were Caucasian.

No adequately designed studies have compared the adverse events seen with solifenacin with approved anticholinergic drugs for the treatment of overactive bladder. The rate for constipation seen with the 10 mg solifenacin dose (13.4%) does appear to be higher than the rates reported in the labels of the other products. I believe that the anticholinergic side effects of constipation and urinary retention can be adequately addressed with labeling.

Patients with constipation and urinary retention who discontinued therapy or required intervention are shown in Table 11.

Table 11. Patients with constipation or urinary retention leading to interruption or discontinuation of treatmentor requiring intervention: Combined Phase 2/3 Studies

	Combined Phase 2/3 Studies (005, 006, 013, 014, 015, 018, 016): n				
	Placebo	YM905 5 mg	YM905 10 mg	YM 905 20 mg	Tolter 4 mg
Number of patients	1307	667	1768	91	300
Number of patients with any AE	681	310	1117	67	150
Urinary retention:					
Number of patients who interrupted or discontinued treatment	1	0	9	1	0
Number of patients who required other therapy	0	0	4	1	0
Constipation					
Number of patients who interrupted or discontinued treatment	3	2	37	2	1
Number of patients who required other therapy	2	1	4	0	1

In long-term open-label studies, solifenacin treatment was discontinued in five patients (all at 10 mg) in Trial CL-016 and three patients (two at 10 mg and one at 5 mg) in Trial CL-019 because of urinary retention.

Laboratory abnormalities:

Liver function abnormalities:

The number and percentage of patients with hepatic function abnormalities of 1X, 3X, and 10X upper limit of normal are shown in Table 12.

Table 12. Number and % of patients with one or more abnormalities of hepatic function tests 1x, 3x, or 10x ULN

Hepatic function Analyte (Limit multiple)	Placebo n (%)	YM905 5 mg n (%)	YM905 10 mg n (%)	Tolterodin 4 mg n (%)
ALT				
Abnormal	89 (7.3)	41 (7.1)	68 (5.5)	16 (6.1)
3xULN	6 (0.5)	6 (1.0)	6 (0.5)	2 (0.8)
10xULN	1 (0.1)	0	0	0
AST				
Abnormal	70 (5.8)	19 (3.3)	48 (3.9)	4 (1.5)
3xULN	2 (0.2)	3 (0.5)	3 (0.2)	0
10xULN	1 (0.1)	0	0	0
Bilirubin				
Abnormal	68 (5.6)	11 (1.9)	69 (5.6)	1 (0.4)
3xULN	0	0	0	0
10xULN	0	0	0	0
ALKP				
Abnormal	38 (3.1)	32 (5.5)	46 (3.7)	10 (3.8)
3x ULN	1 (0.1)	0	0	0
10x ULN	0	0	0	0
γ-GGT				
Abnormal	61 (5.0)	51 (8.8)	74 (6.0)	21 (8.0)
3xULN	29 (2.4)	16 (2.8)	22 (1.8)	5 (1.9)
10xULN	2 (0.2)	2 (0.3)	0	0
All 5 analytes				
Abnormal	0	0	0	0
3xULN	0	0	0	0
10xULN	0	0	0	0

TEAV: treatment emergent abnormal value

The data show that the active treatment groups are not different from the placebo group. For patients with normal analytes at baseline and 3xULN during treatment, or with abnormal values up to 3xULN at baseline and further higher abnormal values, there were 19 in placebo group, and 26 in solifenacin 5 mg and 10 mg group for the combined Phase 3 US and European studies.

There was a case report from Study 905-CL-038 conducted in Japan of a patient who experienced elevated liver function tests and was clinically diagnosed with interstitial pneumonitis. Patient #2001 was a 69-year-old woman with a history of hyperthyroidism. She was enrolled in Phase 2 Study 905-CL-038 (5mg solifenacin once daily). Six months after the start of solifenacin treatment, she began taking the herbal medicine saibokutou for a sore throat. Ten days later her liver function tests showed abnormalities. At the 28th study week (193 days on solifenacin), solifenacin was discontinued. Six days later she was urgently admitted to the hospital because of loss of consciousness. She was diagnosed with

interstitial pneumonia and hypoxemia. Her status improved 4 days after hospitalization (she was treated with steroids), but her liver function tests showed further deterioration (Table 13).

Table 13. Summary liver function tests

Test (normal Range IU/L)	Baseline 02	3 weeks 02	8 weeks 03	13 weeks 03	27 weeks 03	Interrupt 3	Follow-up	
AST (10-40)	25	20	17	21	155	89	64	18
ALT (5-45)	20	16	15	18	164	152	84	32
γ-GGT (16-73)	30	25	21	21	465	632	1233	93
ALKP (104-338)	489	364	415	334	1150	1733	443	N/A

Her discharge diagnosis was motor speech disorder due to cerebral infarction, and the relationship between interstitial pneumonia and cerebral infarction could not be ruled out. The investigator judged the event to not be related to study medication (solifenacin) but rather to be secondary to the herbal medication saibokutou based on the results of a drug lymphocyte stimulation test (DLST). Abdominal ultrasound showed no abnormalities. A CT scan of the chest revealed a "granular-reticular shadow" and a pleural effusion. No information concerning hepatitis serology was submitted. No biopsies were performed.

In my opinion, the relationship of study drug to this patient's "interstitial pneumonitis" and elevated liver function tests is not clear. It is not possible to separate the possible causal effect of solifenacin from the herbal medication or other pathology.

Thrombocytopenia:

Patient #15-10687 in study 905-CL-015 had a normal platelet count of 184,000 at screening which decreased to 28,000 at the end of study (Day 92). She was randomized to the 5 mg solifenacin group. She continued into the extension study (905-CL-019) at the 5 mg dose. During the course of Trial 905-CL-019, platelet counts returned to normal (188,000, 183,000, and 190,000) at 3 different visits. She received no other therapy and the event was judged by the investigator as possibly related to study drug. I believe that this event was unlikely to be related to study drug. No other cases of thrombocytopenia were reported.

The safety concern of prolongation of the QT interval is discussed in Section 2 of this review and in the primary medical officer's review, the clinical pharmacology review and in the consultation from the CardioRenal Division.

In summary, the majority of adverse events related to solifenacin are secondary to its known anticholinergic properties. No other significant safety concerns were identified in the data base. As previously discussed in Section 2 of this review, the potential for solifenacin to prolong the QT interval and the magnitude of this effect can not be adequately assessed from the submitted data and this remains a significant safety concern.

Pediatric Plan: At the pre-NDA meeting, the sponsor requested to defer studies in pediatric patients until after filing of the NDA. The Division stated that "the sponsor will need to request a waiver or deferral (or some combination of the two) at the time of NDA submission. At this time, given preliminary concerns about QT prolongation, constipation, and urinary retention, a deferral of pediatric studies would appear appropriate." The sponsor submitted in the NDA application a request for a pediatric waiver because they believe that "overactive bladder" is a condition that does not occur in children

The recommended starting dose is 5 mg. I agree with this dosing recommendation.

6. Review of Consultations

Division of Scientific Investigations: Three study sites in Europe (Drs. Al-Shukri, Halaska, and Kuzmin) and three sites in the United States (Drs. Harris, Fincher, and Kaufman were inspected. The data submitted in support of this NDA by all 6 sites "appear acceptable."

DMETS: DMETS finds the tradename "Vesicare" acceptable from a safety perspective. Labeling issues are deferred because of the "approvable" action.

DSRCS: DSRCS provided comments on the PPI which will be considered at the time of labeling.

DDRE: The AERS database was searched for adverse events related to QT prolongation associated with oxybutynin and tolterodine. A total of 8 cases of QT prolongation (5) and torsade de pointes (3) were found for tolterodine and oxybutynin (4 cases each). "The cases involving tolterodine do not show a strong correlation for a QT effect as other factors are more likely involved (other medications, ischemia). In one patient, the event subsided with continuation of the drug. For oxybutynin, the cases are marginally better, but one involved an overdose and the others had minimal information." "The lack of quality cases over the time frame these drugs have been available (5 years

for tolterodine and 28 years for oxybutynin) would imply that they have a minimal risk of QT prolongation or torsade de pointes."
DDMAC: DDMAC believes that "[illegible] " I believe that the tradename "Vesicare" is acceptable. In addition, DDMAC provided extensive comments on the PI which will be considered at the time of labeling.

7. **Risk-Benefit Considerations:**

Solifenacin has been demonstrated to be effective for the treatment of overactive bladder in four well-controlled phase 3 studies in an appropriate patient population. Although no adequately designed trials have directly compared the efficacy of solifenacin with other approved anticholinergic drugs approved for this indication, the magnitude of the improvement seen with solifenacin appears comparable to the approved drugs. No significant safety concerns in addition to the recognized anticholinergic side effects were identified except for the QT issue discussed in Section 2 of this review. The risk of constipation may be somewhat higher than in the approved anticholinergic drugs, but I do not think that sufficient data are available to conclude this with certainty. The proportion of "severe" cases of constipation is low. The review team believes that this adverse event can be adequately managed with PI and PPI labeling and we will work with the sponsor to achieve this. I believe that the solifenacin effect size on the QT interval needs to be clarified with an adequate, "thorough" QT study before the drug can be approved from a safety standpoint.

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/s/

George Benson
10/17/03 03:49:16 PM
MEDICAL OFFICER

Donna Griebel
10/17/03 04:05:51 PM
MEDICAL OFFICER
I have read Dr. Benson's review and concur with his assessment that this NDA is approvable, and that a QT study that is both positive and placebo controlled is needed to adequately assess the impact of solifenacin on QT interval.

Meeting Minutes

NDA: 21,518 **Drug:** Solifenacin succinate

Sponsor: Yamanouchi Pharma America, Inc.

Date: October 14, 2003 **Time** 9:30 AM – 10:30 AM

FDA/CDER/DRUDP Attendees:
Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP)
Donna Griebel, M.D., Deputy Director, DRUDP
Meeting Chair: George Benson, M.D., Urology Team Leader, DRUDP
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research
Goudong Fang, Medical Reviewer, DRUPD
Meeting Recorder: Jean King, MS, RD, Project Manager, DRUDP
Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP
Lynnda Reid, Ph.D., Pharmacology/Toxicology Reviewer, DRUDP
Donna Christner, Ph.D., Chemistry Reviewer, DRUPD

Yamanouchi Pharma America, Inc. Attendees:
Masakazu Andoh, Associate Director, Statistics
Robert Desjardins, M.D., President, R&D
Rudolph Lucek, Vice President, Regulatory Affairs
Lawrence Posner, M.D., Sr. Vice President, R&D
Susan Ridge, Director, Project Management
Neila Smith, M.D., Medical Director
Roger Graham, Sr. Vice President, Sales and Marketing

Yamanouchi Pharmaceutical Co. Ltd.
Toshikazu Yoshinaga, Sr. Manager, International Regulatory Affairs
Kenii Yasukawa, Ph.D., Senior Manager, Project Coordination Group

GlaxoSmithKline
Thomas Kline, Director, US Regulatory Affairs
Bernard Ilson, M.D., Clinical Pharmacology, CVU Metabolic head

Consultant

Background: This Type C meeting was granted by the Division at the request of the sponsor. On October 9, 2003, the sponsor provided a position paper regarding their position on the robustness of the data from study 905-CL-022 to have detected a 5-10

millisecond (msec) change from baseline in QTc interval. This response was the focus of today's meeting.

Issues Discussed:

Sponsor Presentation: After introductions, the sponsor presented the key elements from their position paper to address their view that the data from Study 022 is sufficiently robust to detect a 5-10 msec change in QTc from baseline.

Additionally, the sponsor stated that they believe that the design of Study 022, which included post-menopausal women, showed a similar 5 msec change from baseline to that which was observed in all of their phase III studies. Also, based on modeling of the data, they stated that a 30 mg dose of solifenacin would be expected to cause a 10 msec QTc prolongation in post-menopausal females. The sponsor concluded that data submitted in NDA 21-518 fully characterize the effect of solifenacin on QTc, across both multiple dosages and age groups.

Division Response: The Division reiterated that a primary concern remains determining the magnitude of the QTc effect seen in Study 022. The Division asked the sponsor how many post-menopausal women were studied in the phase 3 long-term extension trials.

Sponsor Response: Post-menopausal status was not directly assessed by hormonal measures. Approximately 65% of the female patients were $\geq$ 55 years old.

Division Response: The Division asked whether normalization of the QT effect was observed when study drug was discontinued in the phase 3 trials.

Sponsor Response: An answer can not be provided because ECGs were not collected at the 2-week follow-up visit; only adverse event information was obtained.

Division Response: The Division asked whether data were available for post-menopausal women using the Fridericia correction method.

Sponsor Response: No, data were not analyzed specifically by post-menopausal status.

Division Response: The Division asked the sponsor to describe Cmax of solifenacin seen with maximal metabolic inhibition.

Sponsor Response: There was approximately a 1.4 fold increase in maximum concentration (Cmax) and 2.7 fold increase in area under the curve (AUC) when solifenacin was co-administered with 400 mg ketokonazole.

The sponsor also noted that the tolerance to the escalating dose, up through 50 mg, was achieved only through the use of titration.

Division Response: The Division recognized the difficulties facing sponsors with regard to evaluating QTc effect, particularly if 5 msec change from base line is the range of QTc achieved at maximum tolerated dose (MTD). However, in the absence of a positive control, it is difficult to determine if the results sufficiently reflect the magnitude of what one can expect to see when solifenacin is administered to the targeted population.

Sponsor Response: The sponsor recognizes that Study 022 does not have a positive control. However, the sponsor restated their position that they believe all studies conducted consistently demonstrated the same magnitude of effect around the 5 msec change from baseline.

Division Response: The Division and the Division of CardioRenal Drug Products asked the sponsor if they observed either a food or diurnal effect on the change in QTc.

Sponsor Response: No, the sponsor not find evidence of either food or diurnal effect.

Division Response: The Division of CardioRenal Drug Products stated that if a food effect were missed, that is not reassuring information. Similarly, if there were a "lot of noise" introduced into the measuring process, then one would expect to see a small magnitude of change.

Sponsor Response: The protocol did not specify collection of the ECG in relation to meals; the specific hour in day was specified around dose administration.

Division Response: In the Division's re-analysis of the sponsor's Study 022 data, two peaks were observed: one at hour 4 and another at hour 16 (post study drug administration). For placebo patients, this second peak at hour 16 was approximately 5 msec. The Division's evaluation of the QT data continues, as the significance of these observations remains unclear.

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George Benson
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 7, 2003

To: Rudolph Lucek

Company: Yarmanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Additional Information Regarding the Reanalysis of QT data

Total no. of pages including cover:

Comments: see comment below.

Document to be mailed: YES NO

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Dear Mr. Lucek,

We received your questions faxed to us this afternoon regarding clarification of our reanalysis of the QT data using the Fridericia method. The Division's responses to your questions are attached.

Jean King, M.S., R.D.
Sr. Regulatory Project Manager
FDA/CDER/Division of Reproductive and Urologic Drug Products

Response to Questions

1. In this analysis, distinction was made between the sponsor-defined baseline (median of 9 placebo QT intervals) and the "true" baseline (the mean of the pre-screening and check-in QT intervals). The term "true" is **strictly for purposes of distinction** between the baseline measures used by the sponsor and those used by this reviewer.
2. Baseline QT interval is the mean of the 2 pre-placebo QT intervals that were reported by the sponsor and not the median of the 9 placebo QT intervals.
3. Table 1 is the mean change~~s~~ in QT_C by treatment group. One column involves baseline-corrected QT_C changes and the other both baseline- and placebo-corrected QT_C changes.
4. Placebo-corrections involved correcting QT_C intervals for the time-matched placebo QT_C interval of the individual.
5. See response to question 2.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 6, 2003

To: Rudolph Lucek

Company: Yarmanouchi Pharma America

Fax number: 201-909-5244

Phone number: 201-909-3041

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-518: Reanalysis of QT data

Total no. of pages including cover:

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Dear Mr. Lucek,

(Fridericia corrections in Tables 1+2).

Enclosed is the reanalysis of the QT data we spoke with you about last Friday (October 3, 2003). As per our discussion, in the absence of a positive control, please make the case that Trial 022 is sufficiently robust to have detected a 5-10 msec change from baseline.

/S/

Jean King, M.S., R.D.
Sr. Regulatory Project Manager
FDA/CDER/Division of Reproductive and Urologic Drug Products

Figure 1. QT_C vs. RR for Fridericia- and Bazett-corrected QT Intervals using True Baseline Measures

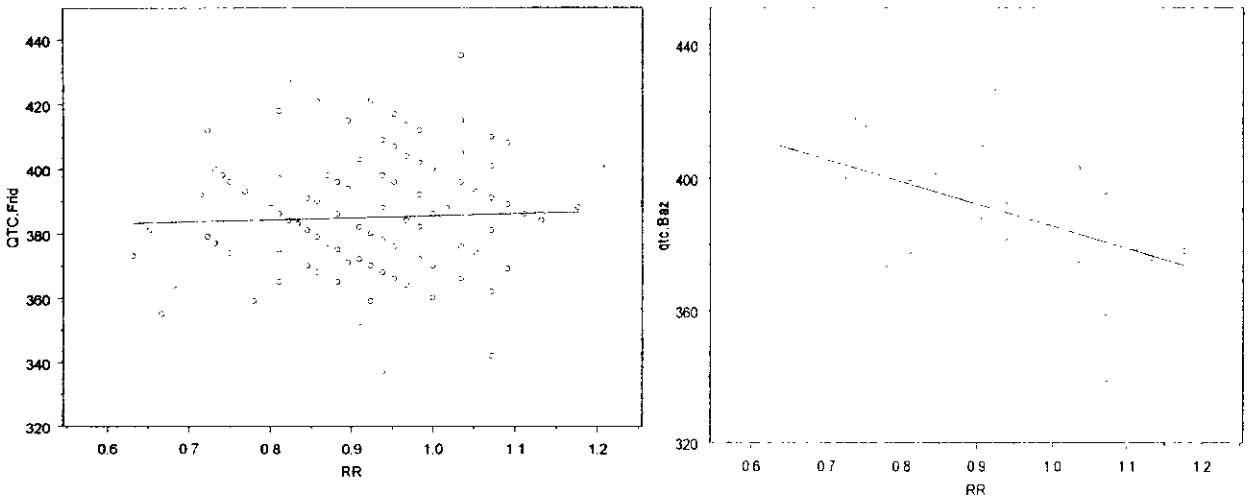

Table 1. Mean Changes in QT_C by Treatment Group

Treatment Group	Mean Change in HR (bpm)	Mean Change in Baseline-corrected QTC (msec)	Mean Change in Baseline- and Placebo-corrected QTC (msec)
Placebo	-0.34	0.89 (-0.95, 2.73)	-
10 mg	-1.09	0.26 (-1.36, 1.87)	-1.44 (-3.12, 0.25)
20 mg	0.33	3.46 (1.76, 5.15)	2.09 (0.35, 3.82)
30 mg	1.70	0.77 (-1.03, 2.57)	0.31 (-1.52, 2.14)
40 mg	2.42	-3.82 (-5.90, -1.74)	-5.39 (-7.65, -3.12)
50 mg	1.52	-8.46 (-12.71, -4.21)	-12.41 (-16.88, -7.94)

Table 2. Baseline-corrected QT_C Outliers by Treatment Group

Category	Baseline-corrected QTC		N
	> 30msec < 60msec	> 60msec	
Placebo	54 (8.18)	1 (0.15)	660
10mg	54 (8.18)	0 (0)	660
20mg	81 (12.64)	1 (0.16)	641
30mg	57 (9.25)	4 (0.65)	616
40mg	32 (6.93)	0 (0)	462
50mg	3 (2.40)	0 (0)	125

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Teleconference Minutes

NDA: 21,518 **Drug:** Solifenacin succinate

Sponsor: Yamanouchi Pharma America, Inc.

Date: October 3, 2003 **Time** 10:00 AM – 11:00 AM

FDA/CDER/DRUDP Attendees:
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
Meeting Chair: George Benson, M.D., Urology Team Leader, DRUDP
Julie Bietz, M.D., Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research
Goudong Fang, Medical Reviewer, DRUPD
Suzanne Thornton, Pharmacology/Toxicology Acting Team Leader, DRUPD
Moo Jhong Rhee, Ph.D. - Chemistry Team Leader, (HFD-580)
Meeting Recorder: Jean King, M.S., R.D., Project Manager, DRUDP

Yamanouchi Pharma America, Inc. Attendees:

Masakazu Andoh, Associate Director, Statistics
Robert Desjardins, M.D., President, R&D
Katsuhiko Ishida, DVM, Ph.D., Scientific Advisor, Nonclinical
Rudolph Lucek, Vice President, Regulatory Affairs
Christine Mulhauser, Director, Regulatory Affairs, CMC
Tuna Nyman, Associate Director, Regulatory Submissions
Lawrence Posner, M.D., Sr. Vice President, R&D
Susan Ridge, Director, Project Management
Neila Smith, M.D., Medical Director

Yamanouchi Pharmaceutical Co. Ltd.

Toshikazu Yoshinaga, Sr. Manager, International Regulatory Affairs

GlaxoSmithKline

Claire Khan, Vice President, CVUM, US Regulatory Affairs

Background: This teleconference was initiated by the Agency to provide the sponsor with an update on the status of the Division's ongoing review of their NDA 21-518 (solifenacin succinate), 5 and 10 mg tablets.

Issues Discussed:

1. Chemistry, Manufacturing and Controls (CMC), DMETS, and DDMAC Review Issues:

- The recently submitted color mockups of the Vesicare carton and container labels are under review. The Division is considering the comments received from DMETS and DDMAC pertaining to the prominence and placement of the —
- The Division is also considering the comments received from DMETS and DDMAC pertaining to the acceptability of the proposed trade name, Vesicare. DMETS found the trade name acceptable in terms of no current look-alike or sound-alike conflicts. DDMAC found the trade name, Vesicare, —

—

2. Clinical and Clinical Biopharmaceutics Review Issues:

- The studies, particularly Trial 022, involving the evaluation of QT prolongation remain under review.
- Two primary concerns regarding Trial 022 are no true concurrent placebo group and no positive control group. Additionally, the significance of the rounding methodology employed by the blinded centralized ECG reader remains under discussion.
- The Division will provide the sponsor with the reanalysis, including Fridericia corrections, of the QT data summarized during today's teleconference.

Sponsor Response: The sponsor agreed to submit a summary of the QT data available for this NDA. Their initial comments to the Division's concerns regarding the QT study 002 included their acknowledgement that there is a change in QT with solifenacin, however, the change was consistently in the 5 msec range in the Phase 1 (022) and Phase 3 studies. The sponsor also asked the Division whether labeling discussions could proceed based on their belief that this change is not large or clinically significant.

Division Response: The Division acknowledged the sponsor's position. However, the Phase 3 studies were not designed specifically to evaluate QT prolongation effect. Based on the results of Trial 022, the Division is unable to sufficiently determine the degree of QT prolongation of this drug, which is indicated for a non-life threatening condition. The issue of an acceptable degree of QT prolongation remains a consistent question posed to the Division. Additionally, the importance of positive and placebo controls in the conduct of thorough QT studies is continually evolving. We have had similar discussions regarding QT prolongation and the components of an adequate study design for QT evaluation with other sponsors. The Division has also had similar discussions with other sponsor's regarding the need for adequate QT data to support labeling. The Division invited the sponsor to submit summary documentation to support their belief that, in the absence of a positive control, Trial 022 is sufficiently robust to have detected a 5-10 msec change from baseline.

Action Items: The Division will provide the sponsor with a reanalysis, including Fridericia corrections, of the QT data summarized during today's teleconference.

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/s/

George Benson
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 30 2003

Rudolph Lucek
Yamanouchi Pharma America, Inc.
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, New Jersey 07652

Dear Mr. Lucek:

On June 5, 2003, Ms. Byungja Marciante, representing the Food and Drug Administration (FDA), conducted an inspection of Yamanouchi Pharmaceuticals' monitoring practices of a clinical study of the investigational drug Vesicare® (solifenacin succinate) Tablets. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

This inspection focused on Protocol #905-CL-013 entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study to Assess the Efficacy and Safety of Daily Oral Administration of 10 mg YM905 Versus Placebo in Male and Female Subjects with Overactive Bladder". The majority of sponsor obligations including, but not limited to, selecting investigators, monitoring compliance, summarizing evidence of drug safety, retaining study records, and maintaining an effective IND, were contracted to , and other firms.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the monitoring of clinical studies of investigational new drugs and the protection of human subjects.

We appreciate the cooperation shown Investigator Marciante during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me, by letter at the address given below.

Sincerely yours,

/S/

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003005576
Field Classification: NAI
Headquarters Classification:
_x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580/Doc.Rm. NDA #21-518
HFD-580/Division Director/Shames
HFD-580/MO/Fang
HFD-580/PM/King
HFD-46/c/r/s/ GCP File #010933
HFD-46 Blay
HFR-CE350/DIB/Amador
HFR-CE3565/BIMO Monitor/Isbill
HFR-CE3565/Field Investigator/Marciante
GCF-1 Seth Ray

r/d:rab/9.2.03
reviewed:JPS:9/11/03
f/t:ML:9/15/03

O:\blay\yamanouchi.doc

Reviewer's Note to Review Division's Medical Officer

Sponsor responsibilities for this study were contracted out tc — A separate inspection was requested for — Yamanouchi appears to have delegated its responsibilities appropriately.

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/s/

Joseph Salewski
10/7/03 03:52:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Richard Harris, M.D.
RMD Clinical Research Institute, LLC
1440 W. North Avenue, Suite 400
Melrose Park, Illinois 60160

SEP 30 2003

Dear Dr. Harris:

Between May 28 and June 6, 2003, Ms. Lisa Hayka, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #905-CL-013 entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study to Assess Efficacy and Safety of Daily Oral Administration of 10 mg YM905 Versus Placebo in Male and Female Subjects with Overactive Bladder") of the investigational drug Vesicare® (solifenacin succinate) Tablets, performed for Yamanouchi Pharma America. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection Ms. Hayka presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not adhere to the protocol [21 CFR 312.60].

   a. Subjects 031 and 032 did not have physical examinations or bladder scans performed at visit 1.

   b. Subject 031 had a positive urine culture and was referred to their primary physician for treatment. This adverse event was not followed up or reported in the Case Report Form.

2. You did not maintain adequate and accurate records [21 CFR 312.62(b)].

   a. The visit 5 bladder scan for subject 013 was not maintained.

   b. The visit 3 ECG report for subject 012 was not maintained.

   c. Screening bladder scans did not document the post-void residual volumes for subjects 001, 012, 013, 018, 020, 024, 031, 032, and 040.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

APPEARS THIS WAY
ON ORIGINAL

We appreciate the cooperation shown Investigator Hayka during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

/S/

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

FEI: 3003996693
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__x__failure to adhere to protocol (5)
__x__inadequate and inaccurate records (6)

Deficiency Codes: 5 and 6

cc:
HFA-224
HFD-580/Doc.Rm. NDA #21-518
HFD-580 Rev Div Dir
HFD-580/MO/ Fang
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File #010938
HFD-46 Blay
HFR-CE650/DIB/Baumgarten
HFR-CE6520/Bimo Monitor/Yuscius
HFR-CE650/Field Investigator/Hayka
GCF-1 Seth Ray

r/d: 8.18.03
reviewed: JPS:9/5/03
f/t:9/10/03 sg

c:/data/royblay/vai letters/harris.doc
o:\blay\harris.doc

Reviewer Note to Rev. Div. M.O.

45 subjects were randomized to the study with eleven subjects discontinuing from the study. Consent forms for all subjects were reviewed. Fifteen CRFs were reviewed in depth and compared with source data and the information reported to the FDA by the sponsor, including consent forms, inclusion/exclusion criteria, drug accountability, adverse event reporting, patient diaries, and the primary efficacy parameter. Data at this site appear acceptable in support of the relevant submission.

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/s/

Joseph Salewski
10/7/03 03:56:14 PM

3 Page(s) Withheld

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	ODS POSTMARKETING SAFETY REVIEW	
TO: Guodong Fang, M.D., HFD-580	**FROM:** Ronald Wassel, Pharm.D. DDRE (HFD-430)	**ODS PID # D030600** October 17, 2003

DATE REQUESTED:	**REQUESTOR/phone #:** Jean King, HFD-580 / 301-827-7270	
DATE RECEIVED: 10/8/2003		
DRUG: Solifenacin succinate	**NDA/IND:** # 21-518	**SPONSOR:** Yamanouchi Pharma America

THERAPEUTIC CLASSIFICATION: Anticholinergic (muscarinic antagonist; M_3 receptor blocker)

EVENT: QT prolongation and related events (ventricular arrhythmias, torsade de pointes)

Executive Summary: The AERS database was searched for adverse events related to QT prolongation associated with oxybutynin and tolterodine for information to assist in the review of the NDA for the investigational drug solifenacin. A total of 28 cases were retrieved (17 for tolterodine, 11 for oxybutynin) from which only 8 noted QT prolongation or torsade de pointes (4 for each drug). The cases involving tolterodine do not show a strong correlation for a QT effect and those for oxybutynin are only marginally better. Based on the small number of postmarketing cases over the time frame these drugs have been available (5 years for tolterodine, 28 years for oxybutynin), the limited information in the reports related to the event, and confounding factors (underlying conditions and other drugs), we cannot establish the association between QT prolongation or torsade de pointes and these drugs.

Reason for Request/Review: ORUDP requested a search of the AERS database for adverse events related to QT prolongation associated with oxybutynin and tolterodine, two approved antimuscarinic agents, to assist in the review of the NDA for solifenacin.

Search Date: 10/8/2003	**Search Type(s):** ☒ AERS SRS Literature Other _____

arch Criteria: Searches were conducted in AERS with oxybutynin and tolterodine using the following reaction terms:

Arrhythmia NOS (PT)
Cardiac arrest (PT)
Cardiac death (PT)
Electrocardiogram QT corrected interval prolonged (PT)
Electrocardiogram QT prolonged (PT)
Long QT syndrome (PT)
Sudden cardiac death (PT)
Sudden death (PT)
Torsade de pointes (PT)
Ventricular fibrillation (PT)
Ventricular tachycardia (PT).

Search Results:

Tolterodine:

. total of 17 unduplicated cases were retrieved. Four of the cases were domestic with the remaining from foreign sources and all were received by the Agency between 1998 and 2003 (a high of five cases in 2001 and a low of one case in 2003). Ten cases were in females and seven were in males (ages 37 to 83 years with a median of 72 years). Only four cases specifically noted QT prolongation (two) or torsade de pointes (two). The remaining 11 cases involved other events such as palpitations, atrial fibrillation, or sudden death (unwitnessed) that were unlikely related to tolterodine because of a poor temporal relationship, negative dechallenges, or the patients' pre-existing conditions. A brief summary of the cases involving QT prolongation or torsade de pointes follows. All four are from foreign sources.

QT prolongation—

- Case# 3800203; ISR# 3943502-4; Mfr.# A211627 (Switzerland, 2002)—A 37-year-old male with non-Hodgkin lymphoma, chronic kidney disease, hypertension, proteinuria, bladder hyperactivity, CMV infection, hypothyroidism, diabetes mellitus, hypomagnesemia, secondary neurovascular dystrophy, myeloproliferative syndrome, thromboembolia, and relapsing herpes genitalis was hospitalized secondary to graft-versus-host disease. After a prolonged hospital stay, the patient died in the ICU following cardiac and respiratory arrest of unknown origins. Autopsy did not reveal any cardiac signs or evidence of infarction. The report noted a prolonged QTc interval three months prior to admission (0.48 sec; normal range 0.25 to 0.45 sec) and a QTc interval of 0.53 sec on an unknown date. It is unknown when tolterodine was started and stopped. The reporter notes that QT prolongation is described for fluconazole, tacrolimus, and enteral nutrition with amino acids, which the patient was receiving.

- Case# 3460021; ISR# 3514459-5; Mfr.# 2000017777GB (Great Britain, 1999)—A 52-year-old female developed palpitations while on tolterodine. An ECG prior to minor ophthalmic surgery showed a borderline prolonged QT interval (automated QTc [Bazett]—453 ms, manual—433 ms; heart rate 64 bpm). Further ECG taken two months following discontinuation of tolterodine showed persistent prolongation of the QT interval, suggesting no implication from tolterodine.

Torsade de pointes—

- Case# 3984462; ISR# 4162678-X; Mfr.# 2003169187GB (Great Britain, 2003)—An 83-year-old female with atrial fibrillation and diabetes mellitus experienced a loss of consciousness and fell, leading to hospitalization. An ECG at the hospital revealed torsade de pointes and the patient was treated with amiodarone. The patient recovered while still receiving tolterodine, which wasn't discontinued until a week later.

- Case# 3242735; ISR# 3289281-8; Mfr.# 6779/20771 (Great Britain, 1999) —A 57-year-old male with a history of an untreated arrhythmia had been taking tolterodine for approximately six months then was admitted to the hospital for bladder surgery. He was treated with diclofenac, allopurinol, tolterodine, and codeine/paracetamol. In the OR, the patient was found to have paroxysmal atrial fibrillation with rapid ventricular response and the surgery was postponed. An exercise test was performed and the patient had episodes in the recovery phase of ventricular tachycardia and torsade de pointes with ST depression post v. tach. The cardiologist assessed the etiology as possibly due to ischemia. A coronary angiography confirmed three-vessel disease and the patient underwent successful bypass surgery. No pathological QT prolongations were found in the ECG recordings.

Search Results (cont.):

Oxybutynin:

total of 11 unduplicated cases were retrieved. Nine of the cases were domestic with the other two from foreign sources and all were received by the Agency between 1980 and 2003 with no more than two in any one year. Five cases were in females and four were in males (ages 44 to 85 years with a median of 65.5 years). Only four cases specifically noted QT prolongation (three) or torsade de pointes (one). The remaining seven cases involved other events such as palpitations, vertigo, multiple drug overdoses and cardiac arrest that were not related to QT prolongation or torsade de pointes. A brief summary of the cases involving QT prolongation or torsade de pointes follows.

QT prolongation—

- Case# 5499000; ISR# 1852900-4; Mfr.# 96007205 (USA, 1996)—A patient of unknown age and gender developed prolonged QT intervals following an overdose of oxybutynin (dose unknown).

- Case# 3924546; ISR# 4080448-8; Mfr.# ALZ-12126 (USA, 2001)—A 58-year-old female with no previous history of heart disease experienced prolonged QTc during the use of Ditropan XL (dose, frequency, therapy dates unknown). At the time, the patient was undergoing a series of ECGs at another physician's office as part of a study (not specified). An ECG performed within one month after starting Ditropan XL showed irregular sinus bradycardia with a ventricular rate of 42 bpm, prolonged QTc of 495 ms, prolonged QT interval of 528 ms, P duration of 118 ms, QRS duration of 86 ms, and PR interval of 170 ms. Prior to starting Ditropan XL an ECG was stated to be normal. Concomitant medications included Estrace, progesterone, and Celebrex. Ditropan XL was stopped at an unknown date. Two weeks after the previous ECG, a repeat ECG showed sinus bradycardia (ventricular rate unspecified), an otherwise normal ECG, QTc interval of 430 ms, QT interval of 446 ms, QRS duration of 98 ms, and PR duration of 152 ms. Pulse was 64 bpm. Cardiovascular exam was normal and auscultation revealed no murmurs, gallops, or abnormal sounds. Electrolytes including calcium, magnesium, and potassium were normal.

- Case# 3923348; ISR# 4078377-9; Mfr.# NSADSS2003010664 (Japan, 2001)—Phase III clinical trial of controlled release preparation of tolterodine tartrate vs. placebo vs. oxybutynin in patients with hyperactive bladder. A 70-year-old male received oxybutynin 9 mg daily from 4/11/01 to 7/03/01. Medical history included hypertension and concomitant medication included nifedipine. A pre-study ECG — , showed first-degree AV block and a QT interval of 412 m/sec. On — an ECG showed a QT interval of 472 m/sec, which was noted to have resolved on —

Torsade de pointes—

- Case# 5303764; ISR# 1652005-1; Mfr.# 95004635 (USA, 1995)—An 84-year-old male who had been taking digoxin and atenolol for a long time without any problems, started Ditropan (dose, dates unknown). At some point he was hospitalized for torsade de pointes. All drugs were stopped and the event was brought under control.

Findings / Conclusions: A total of eight cases of QT prolongation (five) or torsade de pointes (three) were retrieved for tolterodine and oxybutynin (four cases each). The cases involving tolterodine do not show a strong correlation for a QT effect as other factors are more likely involved (other medications, ischemia) and the fact that one case had a negative dechallenge and in another the event subsided even with the continuation of the drug. For oxybutynin, the cases are marginally better, but one involved an overdose and the others had minimal information, including one in which the patient was part of an unknown study undergoing serial ECG testing.

Based on the small number of postmarketing cases over the time frame these drugs have been available (5 years for tolterodine, 28 years for oxybutynin), the limited information in the reports related to the event, and confounding factors (underlying conditions and other drugs), we cannot establish the association between QT prolongation or torsade de pointes and these drugs.

Reviewer's Signature / Date: Ronald Wassel, Pharm.D. / October 17, 2003

Acting Division Director Signature / Date: Mark Avigan, M.D. / October 17, 2003

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/s/

Ronald Wassel
10/24/03 03:20:35 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
10/31/03 11:22:04 AM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products, HFD-580

From: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

CC: Jean King
Project Manager, Division of Reproductive and Urologic Drug Products, HFD-580

Date: September 26, 2003

Re: ODS Consult 02-0117-2; Vesicare 5 mg and 10 mg [Solifenacin Succinate Tablets] NDA 21-518

This memorandum is in response to the September 19, 2003 submission from the sponsor containing revised color mock-up container labels and carton labeling for Vesicare. Our consult, dated September 24, 2003 (ODS consult # 02-0117-1), reviewed the labels and labeling submitted on December 19, 2002. The sponsor had not received DMETS comments when they submitted the revised labels and labeling. The sponsor has not had an opportunity to address the majority of our comments and therefore comments from the September 24, 2003 review are still applicable. We also note the following additional concerns.

1. GENERAL COMMENTS

   a. The [redacted] is more prominent (color and size) than the strength and the established name. This detracts from the readability of the most important information on the main display panel. Revise accordingly.

   b. We note that the [redacted] is difficult to read. We recommend that you revised the color to improve readability.

2. CONTAINER LABELS (30 Count, 90 Count [redacted] Tablets)

3. CARTON LABELING (30 Count, 90 Count

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Alina Mahmud
9/26/03 03:50:24 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/26/03 04:20:17 PM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products, HFD-580

From: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

CC: Jean King
Project Manager, Division of Reproductive and Urologic Drug Products, HFD-580

Date: September 24, 2003

Re: ODS Consult 02-0117-1; Vesicare 5 mg and 10 mg [Solifenacin Succinate Tablets] NDA 21-518

This memorandum is in response to the July 31, 2003 request from your Division for a re-review of the proprietary name, Vesicare. In our consult, dated August 9, 2002 (ODS consult # 02-0117), DMETS did not have any objections to the use of the proprietary name Vesicare. Container labels, carton and package insert labeling were not reviewed in the initial review. However, these were submitted for review and comment in this cycle.

Since the initial Vesicare proprietary name review, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Vesicare.

In the review of the Vesicare container labels, carton and package insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

   a. DMETS cannot assess if the 5 mg and 10 mg strengths are clearly differentiated using the label and labeling provided (i.e., [illegible]). We recommend that a contrasting color, boxing, or other method be used to distinguish the two strengths.

   b. The word [illegible] olished name (e.g., Solifenacin Succinate Tablets). Revise accordingly.

   c. Since the [illegible] is unavailable for review, DMETS is unable to determine if the [illegible] is larger than one-third of the label.

2. CONTAINER LABELS (30 Count, 90 Count

d. Ensure there is a child-resistant closure (CRC) on the unit-of-use bottles containing 30 and 90 tablets.

3. CONTAINER LABELS

4. CARTON LABELING (30 Count, 90 Count

5. CARTON LABELING

6. PACKAGE INSERT LABELING

a. See General Comment 1-b.

b. DMETS questions why the adverse event blurred vision was
the occurrence of dry mouth and constipation was higher than that of blurred vision.

c. This section should also refer to the fact that Vesicare
the aforementioned statement also include "..

:. Additionally, should
'? Revise accordingly.

7. PATIENT PACKAGE INSERT

See General Comment 1-b and Comment 6-c.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name and it's associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Denise Toyer
9/24/03 07:07:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/25/03 08:12:16 AM
DRUG SAFETY OFFICE REVIEWER

Yamanouchi

DUPLICATE

Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

September 19, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
SEP 22 2003
FDR/CDER

N 000 BL
ORIG AMENDMENT

Ladies and Gentlemen:

Re: NDA 21-518
Vesicare® (solifenacin succinate) Tablets
NDA Amendment: Draft Labeling

Reference is made to the teleconference of September 16, 2003, between Jean King, Project Manager of your Division and Rudolph Lucek of Yamanouchi. During this discussion, it was agreed that draft labels and cartons should be submitted at this time. Therefore, we are herewith submitting draft color mock-ups of the proposed labeling (cartons, labels and trays). The attached document lists all of the documents provided. These documents are provided in hard copy only.

We consider the information contained in this submission to be **CONFIDENTIAL** and not to be disclosed to any person outside the Food and Drug Administration without prior notification and written consent of Yamanouchi Pharma America, Inc.

Please do not hesitate to contact the undersigned for any further information or clarification.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

for

Rudolph Lucek
Vice President, Drug Regulatory Affairs
Phone: (201) 909-3041
Fax: (201) 909-5244

Desk Copy: Ms. Jean King, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

Attachments
YM No. 2003-0221

55 Draft Labeling Page(s) Withheld

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: NDA 21-518, Requested Tradename- Vesicare
Generic: Solifenacin succinate 5 and 10 mg

Date of Application: December 19, 2002
Date of Receipt: December 19, 2002
PDUFA Date: October 19, 2003

Indication(s) requested:

Type of Application: Full NDA ___X___ Supplement _____
(b)(1) ___X___ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___X___ P_____
Resubmission after a withdrawal or refuse to file ___N/A___
Chemical Classification: (1,2,3 etc.) 1S
Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid ___X___ Waived (e.g., small business, public health) _____
Exempt (orphan, government) ____
Form 3397 (User Fee Cover Sheet) submitted: YES ___X___ NO _____
User Fee ID# 4355
Clinical data? YES ___X___ NO _____ Referenced to NDA#

Date clock started after UN N/A

User Fee Goal date: October 19, 2003

Action Goal Date (optional) October 17, 2003

- Does the submission contain an accurate comprehensive index? YES NO

- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO

  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? YES NO

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, ___ years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO N/A
  If no, for what ages and/or indications was a waiver and/or deferral requested:

  * The sponsor proposed pediatric clinical studies to be conducted with darifenacin and requested Division concurrence for deferral for submission of these pediatric studies and partial waiver for certain age groups.

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: 58, 135

End-of-Phase 2 Meeting? Date 9/19/2000 NO

If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date 7/1/2002 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?

YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO N/A

*This is not an application for an OTC product.

Advisory Committee Meeting needed? YES, date if known NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
- If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) package submitted? YES NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following: Not applicable

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

APPEARS THIS WAY
ON ORIGINAL

Filing Meeting Minutes

NDA: 21,518 **Drug:** Vesicare (solifenacin succinate)

Sponsor: Yamanouchi Pharma America

Date: February 3, 2003 **Time** 9:00 AM -- 10:00 AM

FDA/CDER/DRUDP Attendees:

Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
George Benson, M.D., Urology Medical Team Leader, DRUDP
Goudong Fang. M.D., Medical Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUPD
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUPD
Jean King, Project Manager, DRUDP
Lynnda Reid, Ph.D., Pharmacology/Toxicology Reviewer, DRUPD
Moo Jhong Rhee, Ph.D., Chemistry Team Leader, DRUPD
Roy Blay, DSI
Mike Welch, PH.D., Biometrics Team Leader

Issues Discussed:

On December 19, 2002, a new drug application (NDA) was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesicare (solifenacin succinate).

During this filing review meeting, the following issues were identified:

Clinical

The following are areas of concern and are major ongoing review issues:

- Safety concerns pertaining to QTc prolongation, hepatic toxicity, and drug-drug interactions as well as adverse events.

- It is noted that (1) a non-white patient population is not well represented in the two European clinical studies that were conducted outside the IND and (2) none of the data supporting the use of the 5 mg dose comes from pivotal trials in US sites.

Clinical Pharmacology and Biopharmaceutics

The following concerns will be the subject of detailed reviews in the Clinical Pharmacology and Biopharmaceutics section:

- We will review the information submitted to determine the appropriateness of granting a BIOWAIVER for the commercial formulation.
- We will ask the sposnor to electronically submit the information on Population/PK-PD (safety) so that we may evaluate the nature of QT prolongation (if any) with this drug.

- Additionally, we will ask the sposnor to submit the 400 mg QD ketoconazole interaction (currently ongoing) study results as soon as possible. This is a critical review issue along with the already submitted 200 mg QD ketoconazole interaction study results.
- We await the Full Hepatic Study report, which is expected at or before the 4-month update (as per pre-NDA minutes); interim report has been submitted with NDA.

Pharmacology/Toxicology

- No review issues noted at time of filing.

Chemistry

- No review issues noted at time of filing.

Statistics

- No review issues noted at time of filing.

Summary:

The above comments will be conveyed to the sponsor as a preliminary notice of potential review issues in the requisite 74-day letter. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. The sponsor will be informed that if they respond to these issues during this review cycle, we may not consider their response before we take an action on the application.

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/

Jean R. King
9/15/03 10:36:20 AM
CSO

Jean R. King
9/15/03 10:38:46 AM
CSO

15 Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Roger Fincher, M.D.
Urology Associates
12 East 5th Avenue
Spokane, Washington 99202

AUG 11 2003

Dear Dr. Fincher:

Between June 2 and 5, 2003, Mr. Carl A. Anderson, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #905-CL-014 entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study to Assess the Efficacy and Safety of Daily Oral Administration of 10 mg YM905 Versus Placebo in Male and Female Subjects with Overactive Bladder") of the investigational drug Vesicare® (solifenacin succinate) Tablets, performed for Yamanouchi Pharma America. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated June 26, 2003, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection Mr. Anderson presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not adhere to the protocol [21 CFR 312.60].

   a. Subject 032 was enrolled with an active urinary tract infection, an exclusion criterion.

   b. Subject 04 was enrolled although the subject had a history of urinary tract infections, an exclusion criterion.

   c. At least eleven study subjects had study visits outside of the protocol-required timeframes by four to eighteen days.

2. You did not report serious adverse events promptly to the Institutional Review Board (IRB) [21 CFR 312.66].

   a. Subject 026 had a stroke on — . The IRB was not notified of this serious adverse event until November 29, 2001.

   b. Subject 007 was treated for an infected leg and was hospitalized on — The IRB was not notified of this serious adverse event until August 22, 2001.

APPEARS THIS WAY
ON ORIGINAL

3. You did not maintain adequate and accurate records [21 CFR 312.62(b)] in that two subjects reported urinary tract infections that were not reported in the adverse events section of the Case Report Form.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Anderson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

/S/

for: Joseph Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

FEI: 3003996694
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__x__failure to adhere to protocol (5)
__x__inadequate and inaccurate records (6)
__x__failure to report adverse reactions (16)
Deficiency Codes: 5,6, and 16

cc:
HFA-224
HFD-580/Doc.Rm. NDA #21-518
HFD-580 Rev Div Dir
HFD-580/MO/ Fang
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File #010935
HFD-46 Blay
HFR-PA350/DIB/Corcoran
HFR-PA350/Bimo Monitor/Gripp
HFR-PA3540/Field Investigator/Anderson
GCF-1 Seth Ray

r/d: 8.8.03
reviewed: KMU: 8/8/03
f/t:ML:8/11/03
o:\blay\fincher.doc

Reviewer Note to Rev. Div. M.O.

33 subjects were randomized to the study with 30 subjects completing the study. Consent forms for all subjects were reviewed. Nineteen CRFs were reviewed in depth and compared with source data and the information reported to the FDA by the sponsor, including consent forms, inclusion/exclusion criteria, drug accountability, adverse event reporting, and patient diaries. Data at this site appear acceptable in support of the relevant submission.

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/s/

Joseph Salewski
8/19/03 09:20:36 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 4, 2003

TO: Dan Shames, M.D. Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Jean King, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Vesicare (solifenacin succinate), NDA 21-518

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Vesicare (solifenacin succinate), NDA 21-518. . It has been reviewed by our office and DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on December 19, 2002. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

3 Draft Labeling Page(s) Withheld

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/s/

Jeanine Best
8/4/03 11:01:44 AM
CSO

Toni Piazza Hepp
8/4/03 01:31:24 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 10 2003

Joel Kaufman, M.D.
1411 South Potomac, #140
Aurora, Colorado 80012

Dear Dr. Kaufman:

Between May 5 and 13, 2003, Ms. Martina Lagrange, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #905-CL-014 entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study to Assess the Efficacy and Safety of Daily Oral Administration of 10 mg YM905 Versus Placebo in male and Female Subjects with Overactive Bladder") of the investigational drug Vesicare® (solifenacin succinate) Tablets, performed for Yamanouchi Pharma America. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection Ms. Lagrange presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not obtain appropriate informed consent as required by 21 CFR 312.60 and 50.20 in that subjects 037 and 051 did not sign the most current approved consent form.

2. You did not adhere to the protocol as required by 21 CFR 312.60 in that:

   a. Subject 016 was enrolled and completed the study despite meeting exclusion criteria of having less than eight micturitions per day for three days during the Screening Period.

   b. Subject 024 was enrolled and completed the study despite taking a prohibited medication (Antivert, also known as meclizine hydrochloride).

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

APPEARS THIS WAY
ON ORIGINAL

We appreciate the cooperation shown Investigator Lagrange during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

/S/

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3001669170
Field Classification: VAI

Headquarters Classification:
_____1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:

__x__failure to obtain patient consent (2)
__x__failure to adhere to protocol (5)

Deficiency Codes: 2, 5

cc:
HFA-224
HFD-580/Doc.Rm. NDA #21-518
HFD-580/MO/ Fang
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File #09554
HFD-46 Blay
HFR-SW240/DIB/Miller
HFR-SW240/Bimo Monitor/Thompson
HFR-SW240/Field Investigator/Lagrange

r/d: 6.30.03
revised: rab/
reviewed:KMU:7/7/03
reviewed:aeh:
f/t:sg:7/7/03

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o:\blay\kaufman.doc

Reviewer Note to Rev. Div. M.O.

39 subjects were randomized to and completed the study. Consent forms for all subjects were reviewed. Thirteen CRFs were reviewed in depth and compared with source data and the information reported to the FDA by the sponsor, including consent forms, inclusion/exclusion criteria, drug accountability, adverse event reporting, and patient diaries. Data at this site appear acceptable in support of the relevant submission.

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/s/

Khin U
7/11/03 08:39:19 AM

Teleconference Minutes

NDA: 21,518 **Drug:** Vesicare (solifenacin succinate)

Sponsor: Yamanouchi Pharma America

Date: July 2, 2003 **Time** 2:00 PM – 2:30 PM

FDA/CDER/DRUDP Attendees:

Lynnda Reid, Ph.D., Pharmacology/Toxicology Reviewer, Division of Reproductive and Urologic Drug Products (DRUDP)
Jean King, Project Manager DRUDP

Yamanouchi Attendees:

Dr. Robert Desjardins	Chief Development Officer
Dr. Donna Tempel	VP, Project Management
Rudolph Lucek	VP, Regulatory Affairs
Susan Ridge	Director, Project Management
Dr. Ryuhel Fujimoto	Scientific Advisor, Non-clinical Safety
Dr. Katsuhiko Ishida	Scientific Advisor, Non-clinical Safety
—	Advisor
Dr. Koichiro Yuno	Associate Research Officer, Non-clinical Safety

Background: This teleconference was scheduled at the request of the sponsor to discuss the minutes of the Executive CAC meeting held on May 27, 2003 concerning Vesicare. The sponsor provided background information for the teleconference (received June 27, 2003).

Issues discussed/Decisions Made:

1. The Division and the sponsor discussed the material submitted June 27, 2003. The Division agreed that it was not necessary to include statistical analyses of the mouse or rat carcinogenicity studies; absolute raw numbers may be submitted as not to delay submission of the sponsor' response to the CAC.

   Sponsor's Response: Given this, the submitted timetable for discussion on today's call can be adjusted to earlier dates. Revised anticipated submission of absolute raw numbers for the mouse study will be July 28, 2003 and for the rat study, August 29. 2003.

2. The Division reiterated the CAC is most interested in knowing what treatment was given in the rat carcinogenicity study and that early mortality rates were the primary concern for the CAC reviewers.

   Sponsor Response: the Sponsor reported that no treatment and no infectious agents were administered.

The Division recommended that this information be included in the sponsor's characterization and conclusions of the anticipated response to the CAC. The Division also requested that the sponsor send a courtesy fax copy of response when submitted to NDA 21-518.

3. The Division asked for clarification as to why study 905-TX-031 (the second oral cancer study in mice) was not included in the NDA 21-518 submission.

   Sponsor Response: This study was initiated as a back up to the other carcinogenicity studies should there have been less than 20 mice that survived. The study was terminated early when acceptable survival rates were achieved in the first study.

   This was acceptable to the Division.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Lynnda Reid
7/15/03 03:52:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING ISSUES IDENTIFIED

NDA 21-518

Yamanouchi Pharma America, Inc.
Attention: Rudolph W. Lucek
Vice President
Drug Regulatory Affairs
Mack Centre IV
S. 61 Paramus Road
Paramus, NJ 07652

Dear Mr. Lucek:

Please refer to your December 19, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesicare (solifenacin succinate).

We have completed our filing review of your application and have identified the following issues:

Clinical

The following are areas of concern and are major ongoing review issues:

- Safety concerns pertaining to QTc prolongation, hepatic toxicity, and drug-drug interactions as well as adverse events.

- It has been noted that (1) a non-white patient population is not well represented in the two European clinical studies that were conducted outside the IND and (2) none of the data supporting the use of the 5 mg dose comes from pivotal trials in US sites.

Clinical Pharmacology and Biopharmaceutics

The following concerns will be the subject of detailed reviews in the Clinical Pharmacology and Biopharmaceutics section:

- We will review the information submitted to determine the appropriateness of granting a BIOWAIVER for the commercial formulation.
- Please electronically submit the information on Population/PK-PD (safety) so that we may evaluate the nature of QT prolongation (if any) with this drug.

- Additionally, please submit the 400 mg QD ketoconazole interaction (currently ongoing) study results as soon as possible. This is a critical review issue along with the already submitted 200 mg QD ketoconazole interaction study results.
- We await the Full Hepatic Study report, which is expected at or before the 4-month update (as per pre-NDA minutes); interim report has been submitted with NDA.

Pharmacology/Toxicology

No review issues noted at time of filing.

Chemistry

No review issues noted at time of filing.

Statistics

No review issues noted at time of filing.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, please call Jean King, M.S., R.D., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
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/s/

Daniel A. Shames
2/26/03 05:35:06 PM

Filing Meeting Minutes

NDA: 21,518 **Drug:** Vesicare (solifenacin succinate)

Sponsor: Yamanouchi Pharma America

Date: February 3, 2003 **Time** 9:00 AM – 10:00 AM

FDA/CDER/DRUDP Attendees:

Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)
George Benson, M.D., Urology Medical Team Leader, DRUDP
Goudong Fang. M.D., Medical Reviewer, DRUDP
DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUPD
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUPD
Jean King, Project Manager, DRUDP
Lynnda Reid, Ph.D., Pharmacology/Toxicology Reviewer, DRUPD
Moo Jhong Rhee, Ph.D., Chemistry Team Leader, DRUPD
Roy Blay, DSI
Mike Welch, PH.D., Biometrics Team Leader

Issues Discussed:

On December 19, 2002, a new drug application (NDA) was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesicare (solifenacin succinate).

During this filing review meeting, the following issues were identified:

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- We await the Full Hepatic Study report, which is expected at or before the 4-month update (as per pre-NDA minutes); interim report has been submitted with NDA.

Pharmacology/Toxicology

- No review issues noted at time of filing.

Chemistry

- No review issues noted at time of filing.

Statistics

- No review issues noted at time of filing.

Summary:

The above comments will be conveyed to the sponsor as a preliminary notice of potential review issues in the requisite 74-day letter. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. The sponsor will be informed that if they respond to these issues during this review cycle, we may not consider their response before we take an action on the application.

APPEARS THIS WAY
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/s/

George Benson
7/21/03 04:16:42 PM

RTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

ed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the de. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates nd on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

CANT'S NAME AND ADDRESS ph W. Lucek ouchi Pharma America, Inc. 61 Paramus Road Centre IV, 4th Floor s, NJ 07652	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-518 5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? ☒ YES ☐ NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: ☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: (APPLICATION NO. CONTAINING THE DATA).
ONE NUMBER *(Include Area Code)* 01) 909-3041	
CT NAME CARE® (solifenacin succinate)	6. USER FEE I.D. NUMBER 4355

APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS?** IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

VER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

ting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. nts regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Health and Human Services
Administration
Pike
0852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Vice President, Drug Regulatory Affairs	December 19, 2002

/01)

Created by: PSC Media Arts (301) 443-2454 EF

Financial Disclosure

BEST POSSIBLE COPY

10 Page(s) Withheld

Meeting Minutes

Date: July 1, 2002 **Time:** 10:00 – 11:30 PM **Location:** Parklawn; Conference Room "C"

IND: 58,135 **Indication:** Incontinence/Overactive Bladder

Drug Name: YM905 (solifenacin succinate)

Sponsor: Yamanouchi U.S.A., Inc.

Meeting Type: Pre-NDA Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Margaret Kober

FDA Attendees:
Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Zili Li, M.D. – Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader, DNDCII @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Clinical Pharmacology and Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Alex Jordan, Ph.D. – Pharmacology Team Leader, DRUDP (HFD-580)
Lynnda Reid, Ph.D. – Pharmacologist, DRUDP (HFD-580)
Mike Welch, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Margaret Kober, R.Ph. – Chief, Project Management Staff, DRUDP (HFD-580)

External Attendees:
Yamanouchi U.S.A.
I.Grimes, Ph.D. – Vice President, Statistician
R. Desjardins, M.D. – President, Research and Development
R. Lucek, B.S., M.S., M.B.A – Vice President, Regulatory Affairs
E. Wilford – Director, Project Management
S. Ridge – Director, Project Management
R. Fujimoto, D.V.M., Ph.D. – Scientific Advisor, Toxicology
N. Smith, M.D. – Medical Advisor
D. Tempel, Ph.D. – Vice President, Project Management

Yamanouchi Pharmaceuticals Co., Ltd.
K. Yasukawa, M.S. – Manager, Project Coordination Department
M. Asano, D.V.M., Ph.D. – Director, Project Coordination Department
T. Yoshinaga – International Regulatory Affairs Office

Yamanouchi Europe
T. Kos, Ph.D. – Project Leader
S. Bot – Regulatory Affairs

Consultants

Background:
The sponsor, Yamanouchi Pharma America, Inc, requested and was granted a Type-B Pre-NDA meeting to discuss with the Division of Reproductive and Urologic Drug Products (DRUDP) the clinical, non-clinical, and electronic submission aspects of the NDA for YM905 (solifenacin succinate), which is to be submitted in the 4th quarter of 2002.

Purpose of the Meeting: To discuss the clinical, nonclinical, and electronic submission issues and questions raised in the meeting package submitted by Yamanouchi, Pharma.

Discussion/Decisions Made:
General comments by discipline:
Clinical:
General clinical comments:

- The Division expressed significant concern related to preliminary evidence of QTc prolongation in two Phase 3 U.S. trials. The sponsor commented that similar results were seen in the two European Phase 3 trials. The sponsor acknowledged the Division's concern.
- The Phase 3 trials used a 3-day diary rather than a 7-day diary. The 7-day diary is preferred but the 3-day diary could be adequate. This will be a review issue.
- The two European Phase 3 trials were conducted outside the IND and the Division did not review those protocols.
- The clinical relevance of small changes in the micturition frequency and incontinence episode frequency (IEF) is a review issue.
- There were unexplained differences in the participation rates in the open-label extensions of the U.S. and European trials.

Comments related to the meeting package itself:

- Some of the sponsor's questions were non-specific in nature and some required a comprehensive review of all information. Therefore, the Division was unable to provide concurrence to all the sponsor's questions because a comprehensive review has never been the objective of a Pre-NDA meeting [21 CFR 312.47].
- The Division attempted to provide the sponsor with feedback or comments if major deficiencies were noted during review of this meeting package. However, lack such a comment should not be interpreted as the division's concurrence.
- Appropriate FDA and ICH guidance are currently available to the sponsor to address many of their questions. If the sponsor has a question regarding compliance with or interpretation of a specific requirement in the guidance, the Division will provide additional information.

Requests related to efficacy:

- In the NDA, please provide the following items related to the statistical analysis plan (SAP):
    - A list showing date of the first patient enrolled, date of last patient completed the last follow-up visit, date of SAP finalization, date of blind review of data, and date of breaking blind for each of the four pivotal studies.
    - A summary table showing the time and any significant change, addition or deletion to SAP for each of four pivotal studies. This includes, but not limited to, any change, addition or deletion made to the endpoint definition, analysis sets for main analysis, methods for handling of missing values and outliers and statistical testing procedures (including data transformation).
    - All original Phase 3 protocols and amendments to those protocols

- In the NDA, please provide the following items related to the primary efficacy analysis:
    - A table summarizing and comparing inclusion and exclusion criteria from four pivotal studies.
    - A table showing what percentages of endpoint visits in each of the four pivotal studies come from the first, second or third on-treatment visit by treatment groups (Appendix B-Table 1);
    - A table showing the distribution of the number of data points used to calculate mean number of micturition for each subject at baseline and endpoint visit by treatment groups (Appendix B-Table 2);

- In the NDA, please provide the following items related to clinical relevance of the efficacy results:
    - An exploratory "responder analysis" where a responder could be defined as having 50% reduction in micturition frequency from baseline at any given on-treatment visit. In this way, percentages of responders by treatment groups at each on-treatment visit could be compared.
    - An analysis of "consistent responders" (for example, those responding to treatment for all three visits).

- An analysis of the impact of baseline severity of overactive bladder on the subject's response to the treatment.

Requests related to safety:

- In the NDA, please provide the following information related to clinical adverse events:
  - A table similar to Table B for the "Primary AE Analysis" (page 251), showing study-specific results (not pooled data) from each of the four pivotal studies side by side (including tolterodine in European trials) or establish a hyperlink to the similar tables at clinical study reports.

  - A focused analysis of the impact of study dosing and treatment period on the occurrence of a few significant AEs. The sponsor should use time-adjustment whenever it is appropriate (e.g., person-year or life-table approach).

    The Division commented that the "Comprehensive AE Summary" (page 251), reflecting summary statistics on AEs pooled from all safety studies may be difficult to interpret because of a wide range of variations on study drug dosage (2.5 to 20 mg) and treatment period (4 week to 52 weeks). The Division reiterated that the sponsor should pay special attention to inter-study variability caused by the differences in treatment dosage, length of treatment or other non-random variables.

  - A special section in the ISS discussing (1) abnormal AST/ALT, (2) QT prolongation, (3) constipation requiring medical or surgical intervention, and (4) urinary retention requiring medical or surgical intervention.

  - For abnormal AST/ALT, please categorize abnormalities as follows: (1) any abnormal AST or ALT test, (2) any abnormal AST or ALT $\geq$3 times the ULN, (3) any abnormal AST or ALT $\geq$10 times the ULN; and (4) any abnormal AST or ALT with hyperbilirubinemia or jaundice.

Pharmacology:

- The CTD format is acceptable.
- Review of labeling is premature and will not be considered at this time.

Clinical Pharmacology and Biopharmaceutics:

The sponsor should provide the following additional information in the NDA submission:

- Exposure-response information (dose vs. efficacy/safety relationships and dose findings/selection information) *within* the CPB section.
- Full development of *in vitro* dissolution method and rationale for release specifications.
- Assurance that clinical and to-be-marketed formulations are appropriately linked/bridged (granting of biowaiver will be based on these results).

Additional OCPB comments:

- The ketoconozole interaction study did not use the maximal recommended dose of ketoconozole. This factor may have minimized the extent of the interaction.
- The preliminary Phase 3 results provide a signal of QT interval prolongation. The ongoing QTc trial may not be adequately designed to assess effect of drug on the QT interval at supratherapeutic concentrations and at concentrations seen after selected drug interactions. Sponsor reported that this trial was "clinically complete".

Questions:

Submission in General:

1. Does the Agency concur with the submission of the application in the format of the Common Technical document (CTD)?

   Answer:
   Yes. The Agency now is accepting NDA submission in CTD format.

2. Does the Agency concur that the filing will be made as a complete electronic submission? Are there any sections of the CTD submission that the Agency would like to receive in hard copy?

   Answer:
   Yes. The Agency is currently accepting marketing application in electronic format. However the Agency is NOT ready to receive eCTD at this time. The sponsor can adapt the CTD to our current process for electronic submission as described in Guidance for Industry: Submitting Marketing Applications According to the ICD-CTD format – General Consideration at www.fda.gov/cder/guidance/4707dft.pdf. The 1.1 volume should be submitted in hard copy for the archives.

3. Does the Agency concur with the proposed organization and content of the summaries of the following section of the CTD as outlined in this briefing package:
   Non-clinical
   Biopharmaceutical
   Pharmacokinetic
   Clinical

   Answer:
   Formats for non-clinical, biopharmaceutical, and pharmacokinetic are acceptable. For clinical, such a generalized assessment cannot be made at this time. The Division has no objection to the organization of any NDA submission as long as it is consistent with appropriate federal regulation and ICH guidance, and with the FDA guidance for industry regarding electronic submission and ICH-CTD format. If the sponsor has a specific question or issue regarding the compliance with or interpretation of ICH guidance or FDA's ICH-CTD format guidance, the division will address it or the sponsor could contact Dr. Randy Levin directly at 301-594-5411.

4. Does the Agency concur that the application content as outlined in the briefing package will be adequate to support the proposed labeling?

   Answer:
   The Division does not believe that it is an appropriate to make such an assessment at Pre-NDA meeting. This is a review issue.

Toxicology:

1. In the analysis of the 104-week carcinogenicity studies, the histopathologic evaluation will first be conducted on tissues from animals in the placebo and high dose drug group. If there is no evidence of carcinogenicity in the high dose animals, histopathologic evaluation of tissues from the lower dose animals will be omitted.

   Answer:
   The Sponsor has acknowledged receipt of the following response to this question sent on March 11, 2002:

   - Histological evaluation of tissues from only control and high dose treatment groups is acceptable provided you conduct histopathological examination of other dose groups under any of the following circumstances:

     a) If there are any macroscopic findings in the low and mid dose groups for a given tissue, you should examine that tissue for all of the dose groups.

     b) If an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, is found, you should examine the next lower dose group.

     c) If there is an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma, etc., see McConnell et al., JNCI 76:283, 1986), you should look at all relevant tissues for that dose level and the next lower dose level.

     d) If there is an excessive decrease in body weight or survival in the examined dose group, you should examine lower dose groups.

2. Datasets for the 104-week rodent carcinogenicity studies will be provided electronically in the initial filing. Specifically what information should be included in these datasets and what format should be used in assembling and submitting these data?

   Besides the 104-week carcinogenicity studies does the Agency request submission in the initial filing of electronic datasets for any other toxicology studies?

Answer:

- For the format needed for statistical analysis of the carcinogenicity studies please refer to the Division of Biometrics' guidance dated January, 1999.
- Electronic datasets should also be filed for any final study reports which have not been submitted to IND 58,135 and for all pivotal nonclinical studies (e.g., 26 week toxicology studies in mice and rats, 52 week toxicology study in dogs, genotox studies and reproductive and developmental studies in mice, rats and rabbits). Summary reports including summary tables should be submitted for all other nonclinical studies.
- Submission should also contain a list of all nonclinical studies submitted to IND 58,135. Please note the IND submission date, serial number and location for each study.
- In the 4-week and 13 week toxicity studies in dogs, YM905 induced ECG changes, e.g., A-V block, prolonged P-wave, and prolonged the PR, QRS and QT intervals. However, no cardiovascular effects were observed in the 52-week toxicity study at comparable doses and intervals. The Sponsor should include an explanation or hypothesis as to why similar effects were not observed in the 52-week study at the monitoring period corresponding to the shorter studies, e.g., weeks 12.

3. Tissue distribution studies in pigmented mice following a single dose of 3 mg/kg of ^{14}C YM905 indicated that levels of drug-related material decreased more slowly in the eye compared to other tissues. In the dog, ophthalmic and histopathologic examinations of the eye were normal following exposure to YM905 at doses from 3 to 25 mg/kg/day for 52 weeks.

   Yamanouchi believes that given the lack of adverse effects of YM905 on the eye in dogs following long-term exposure to high doses of YM905 no further studies are required. Does the Agency concur?

   Answer:
   No. The following data should be provided to more fully characterize any potential adverse ocular effects:
   - complete summary of any gross or histopathological ocular findings noted in the rodent carcinogenicity studies
   - drug binding study to determine if the drug binds to melanin and/or with any high affinity to specific areas of the eye
   - UV absorption spectrum for YM905

<u>Pharmacokinetics</u>

1. Does the Agency want Yamanouchi to submit SAS datasets for any of the pharmacokinetic studies, and if so, what studies?

   Answer:

The Division would like the sponsor to submit SAS datasets for all studies included in the NDA.

Clinical

1. Does the Agency concur with the proposed integrated Statistical Analysis Plan (ISAP) for the integrated analysis of efficacy and the integrated analysis of safety and with the specific proposals concerning the ISAP as outlined below?

   Answer:
   The plan appears to be acceptable, on its face, for the integrated analyses of efficacy and safety. However, the appropriateness and validity of ISAP will be assessed during the NDA review period. Responses to specific proposals concerning the ISAP are provided under clinical question 3 (efficacy) and section 4 (safety). The sponsor should also refer to the general comment section for more information.

2. Does the Agency concur that it will not be necessary to retrospectively collect financial disclosure statements from investigators who participated this Phase 2 study (905-CL-005)?

   Answer:
   Yes. [In the federal regulation, the covered clinical study is defined as "any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety" (21 CFR 54)].

3. Efficacy
   a. The primary support for the efficacy of YM905 will be derived from an analysis of the Phase 3 clinical studies (two Phase 3 IND studies conducted in the U.S. and two non-IND studies conducted in Europe). The result of each Phase 3 study will be individually reported and an integrated analysis of the four Phase 3 studies will also be conducted. Efficacy results for the two Phase 2 studies will be reported as individual studies and will not be integrated with Phase 3 efficacy results. Does the Agency concur?

      Answer:
      Yes. The division concurs. The Division reminds the sponsor that primary support for efficacy of YM905 will be derived from analyses of the individual Phase 3 studies.

   b. Datasets supporting the efficacy analysis will be provided for the four Phase 3 studies. Efficacy datasets for the supportive Phase 2 studies will not be provided in the initial submission but will be available on request. Does the Agency concur?

Answer:
Yes. However, we would encourage the sponsor to submit the Phase 2 datasets in the initial submission because it is likely that the Division will ultimately make such a request for these datasets. The Phase 2 studies used four different dosage strengths and the outcomes were assessed weekly. Therefore, those studies may provide clinically useful information that Phase 3 studies do not, such as treatment effect in relation to the time of the onset and to the dosage strength.

c. Yamanouchi will provide SAS datasets to conform to CDISC format for each of the four Phase 3 studies and, therefore, proposes that patient line listings will not be submitted in the application neither as an appendix to the Phase 3 final study reports nor will traditional Case Report Tabulations be included in the application. Analysis datasets will be provided as patient profile. Does the Agency concur?

Answer:
Yes. Datasets prepared as required under section K of Guidance to Industry: Providing Regulatory Submission in Electronic Format – NDA's are sufficient to meet FDA's CRT requirement and no patient line listings are necessary. A separate meeting may be needed to discuss the specific database structure.

d. We wish to confirm the definition, as presented below, of the full analysis set (FAS) that was discussed and agreed to at the End of Phase 2 Meeting of September 20, 2000. This definition was used in the Phase 3 clinical studies and will be used in the integrated statistical analysis plan.
   - Randomized subjects who took at least 1 dose of study drug in the double-blind treatment period
   - For whom baseline data and at least 1 on-treatment efficacy assessment are available.

Answer:
- The Division confirms this definition even though there is no evidence for such a discussion and agreement in the End-of-Phase 2 meeting minutes. We agree that this definition is consistent with the one used in the study protocols for the two US pivotal studies that were submitted one month after that meeting (IND 58,135, Serial No 014, October 18, 2000)..

- We remind the sponsor that the Division's acceptance of this definition does not guarantee validity of such an approach. Although ICH guidance allows for excluding randomized subjects from the full analysis set (FAS) under a limited number of circumstances, such exclusions should always be justified. We expect a discussion on the potential biases arising from specific exclusions.

e. We wish to confirm the definition, as presented below, of the primary efficacy parameter that was discussed and agreed to at the End of Phase 2 Meeting of

September 20, 2000. This definition was used in the Phase 3 clinical studies and will be used in the integrated statistical analysis plan.

- Mean change from baseline to endpoint visit in number of micturitions per 24 hours
- For the purpose of this analysis a micturition is defined as any voiding episode recorded by the subject onto a 3-day diary as "urinated" with or without "incontinence".

Answer:
The Division cannot confirm this definition. Although the primary efficacy endpoint was discussed, we could not find evidence that the exact definition of micturition was discussed during the EOP2 meeting. Nor could we find this definition in study protocols submitted under serial # 014. The Division defines a micturition as a "voluntary void".

f. We wish to confirm the definition, as presented below, of the secondary efficacy parameters that was discussed and agreed to at the End of Phase 2 Meeting of September 20, 2000. This definition was used in the Phase 3 clinical studies and will be used in the integrated statistical analysis plan.
   - Mean change from baseline to endpoint visit in:
     - Number of incontinence episodes per 24 hours
     - Mean volume voided per micturition
     - Number of urgency episodes per 24 hours
     - Number of nocturnal void episodes per 24 hours
     - Number of nocturia episodes per 24 hours

Answer:
No, The Division cannot confirm these definitions at this point. We note the difference between the secondary endpoints listed here and the ones submitted under the original study protocol (serial no 014). For example, we note that the descriptor "urge" has been deleted from the endpoint "number of incontinence episodes per 24 hours." We also note the addition of a new endpoint, "number of nocturnal void episodes per 24 hours." If amendments were made, it is important to document the time at which those secondary endpoints were finalized.

g. There will be no imputation of missing efficacy data. The last on treatment observation will be used as the endpoint observation. Does the Agency concur?

Answer:
Yes. However, the Division will have concerns over clinical significance of the study if a significant number of subjects do not have an assessment at the week 12 (final on-treatment visit) and/or the treatment and placebo groups have a different distribution regarding time of the final visit.

Safety

a. The integrated analysis of safety will be based on the integrated analysis of the safety date from the following studies…: (See page 7)
b. Primary analysis of adverse events will be based on the four Phase 3 studies in which patients with overactive bladder (OAB) were treated with YM905 for 12 weeks. The placebo-controlled Phase 2 studies will not included in this primary analysis. The primary analysis of adverse events will be used in the AE table display to be included in the package insert.

   A comprehensive analysis of AEs across all eight studies cited above will also be provided in the eCTD. This analysis will include Phase 2 data and also data from open-label uncontrolled studies. Does the Agency concur with the proposed safety analysis plan?

   Answer:
   - The Division agrees that integrated analysis of safety should focus on the eight studies listed in this Pre-NDA package.
   - The Division agrees that the primary analysis of adverse events will be based on the four Phase 3 studies and the Phase 2 studies will not included in this primary analysis.
   - The Division believes that a repeated display of AE frequency from the eight studies pooled has little clinical significance.
   - The Division cannot determine at this time what information will ultimately be used in creating the AE table for product labeling.

c. In study 905-CL-016 (US open-label, uncontrolled study of 1-year treatment period), Yamanouchi has selected an interim cut off date of June 1 for inclusion of data in the initial NDA filing because as of this time at least 100 patients will have one year of exposure to the 10 mg dose of YM905. The interim report will include data in exposure, AE and ECGs and will not include laboratory data. A presentation and analysis of laboratory data will be included in the final study report for study 016. Does the Agency concur?

   Answer:
   No. Analyses of laboratory data, particularly those concerning AST/ALT abnormalities must be included in the initial submission. In addition, we encourage the sponsor to select an interim cut-off date that is reasonably close to the anticipated NDA submission date (i.e., <6 months).

d. In the application Yamanouchi proposes to provide Case Report Forms only for patients who died, discontinued treatment because of an adverse event, or experienced a serious adverse event. Does the Agency concur or are there additional patients for which case report forms should be included in the application?
   Yamanouchi proposes to submit PDF images of the working copies of the CRFs hypertext linked to the DCFs. These CRFs were the actual CRFs used to construct the databases for analysis. Does the Agency Agree?

Answer:
Yes, the Division has no objection to the above-mentioned CRF submission plan. All CRFs should be available upon request.

e. Yamanouchi wishes to confirm the Agency's concurrence with the proposed plan for the investigation of the effect of YM905 on the QTc interval as outlined in Section 4.4.1.2 (Evaluation of Effects of YM905 on QTc) of this submission. Are there any additional data analysis that the Agency would requested at this time? Does the Agency want ECG recordings submitted in a digitalized format?

Answer:
No, the Division cannot concur with the proposed plan for assessing the effect of YM905 on the QTc interval. The Division reminds the sponsor that this will be a critical review issue for this NDA in light of the preliminary Phase 3 U.S study results.

f. A pharmacokinetic and safety study in patients with renal impairment will be included in the submission. Yamanouchi does not believe a study in hepatically impaired patients is necessary for the YM905 application; however, a study in this patient population will be ongoing at the time of NDA filing. Does the Agency concur?

Answer:
The Division would prefer the submission of the final report for the hepatic-impaired study at the time of NDA submission because this is a highly liver-metabolized drug. However, the Division would accept a summary report with the NDA and the final study report within 3 to 4 months of the original submission of the NDA.

g. Yamanouchi proposes that a separate integrated summary of safety (ISS) will not be included in Module 2 of this application. Yamanouchi believes that the presentation of safety data in the clinical written summary with support from the Integrated Analysis of Safety (Module 5) adequately addresses the required analyses and safety concerns. Does the Agency concur?

Answer:
Yes. If the sponsor could incorporate the information normally contained in ISS into the CTD summaries and overview as suggested by the FDA guidance to industry regarding ICD-CTD format, then this proposal is acceptable.

Pediatric patients

Yamanouchi wishes to confirm the agreement made with the Division at the end-of-phase 2 meeting (September 19, 2000) to defer studies in pediatric patients until after the filing of the NDA when a

Answer:
The sponsor will need to request a waiver or deferral (or some combination of the two) at the time of NDA submission. At this time, given preliminary concerns about QT prolongation, constipation and urinary retention, a deferral of pediatric studies would appear appropriate.

Biowaiver

1. Yamanouchi wishes to confirm the Agency's intent of October 24, 2001, to grant a biowaiver for conducting bioequivalence between the to-be-marketed and the clinical tablets subject to the results of testing to support a SUPAC-IR Level 1 change for composition, and a Level 3 change for site of manufacture and dissolution requirements as discussed in the SUPAC-IR Guidance.

   Answer:
   Granting of the biowaiver will be determined based on the results of the bridging studies that have been completed.

Electronic Submission (eCTD)

Question 1-5:

Answer:

- **For question #1 to 4:** As stated earlier, the Division does not wish to make a generalized assessment on the comprehensiveness and appropriateness of the sponsor's plan for electronic submission. All requirements for electronic submission have been clearly stated in FDA's guidance to industry. We do not expect any additional functionalities beyond those stated in the guidance. If the sponsor has more specific questions regarding electronic submission, please contact Dr. Randy Levin directly at 301-594-5411.
  For question #5: Sponsor's proposals are acceptable. As mentioned previously, a separate meeting may be needed to discuss the specific database structure.

Action Items:

- Fax meeting minutes within 30 days.

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

/s/

Mark S. Hirsch
7/31/02 01:54:01 PM

Teleconference Minutes

Date: January 17, 2002 **Time:** 10:00-10:45 AM, EST **Location:** PKLN; Chesapeake Room

IND 58,135 **Drug:** YM905 (solifenacin succinate) **Indication:** Overactive bladder (OAB)

Sponsor: Yamanouchi U.S.A., Inc.

Type of Meeting: Pre-NDA, CMC

Meeting Chair: Mark Hirsch, M.D., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Rudolph Lucek, Vice President, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Acting Director, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader for the Division of New Drug Chemistry 2 (DNDC 2) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, for DNDC 2 @ DRUDP (HFD-580)
Leslie Stephens, R.N., M.P.H. – Regulatory Project Manager, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Yamanouchi USA
Jane Aoyagi - Director, Regulatory Affairs
Robert Desjardins, MD - President, Research & Development
Rudolph Lucek - Vice President , Regulatory Affairs
Susan Ridge - Director, Research Operations
Mitsuhisa Sakurai - Scientific Advisor - CMC
Yamanouchi Pharmaceutical Co., Ltd
Yoshinori Kato - Assistant Manager, Chemical Technology Laboratories
Isao Sasaki, PhD - Manager, Drug Regulatory Affairs
Shoji Yokota - Manager, Novel Pharmaceutical Laboratories
Takashi Yoshino - Director, Quality Assurance Department
Yamanouchi Pharma Technologies
Tim Howes - Analytical Services
Consultants

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Meeting Objective: To discuss CMC aspects prior to NDA submission.

Background: YM905, an M_3-antimuscarinic compound, is being developed by Yamanouchi to treat overactive bladder. Previously, a CMC End of Phase 2 meeting was held on September 20, 2000. For the CMC pre-NDA meeting, the sponsor submitted a

briefing package, dated December 13, 2001, which included summaries of the drug substance and drug product information, as well as questions for the Division. Two additional questions were submitted in correspondence dated December 27, 2002, for the Division's consideration. The sponsor indicated that the NDA would be submitted electronically.

Discussion:

- the sponsor reported that:
  - the — will not be included in the to-be-submitted NDA
  - DRUDP's comments regarding — . were received, and a request for a future teleconference would be submitted
  - inclusion of information on the 5 and 10 mg film coated tablets in the NDA will be determined pending the analysis of the Phase 3 data
  - the NDA will be submitted electronically as a Common Technical Document

A. Drug substance Questions

1. **Does the agency concur with the compounds designated as starting materials for the synthesis of YM905 drug substance? The impurity profile and chemical characteristics of the compounds are well defined.**

- this is a review issue
- the information submitted is not sufficient to qualify — , as starting materials; please follow "Guidelines for submitting supporting documentation in drug applications for the manufacture of drug substances"
- the sponsor will submit data in support of the compounds designated as starting materials
- the sponsor indicated that that the compounds designated as starting materials are commercially available, and that there are several sources for each compound
- DRUDP requested that the sponsor submit information indicating that the compounds are also being used to manufacture other chemical products

2. **— , an enantiomer of YM905 has never been detected in any — scale batch. However, it may be preferable to control this enantiomeric compound in the specifications and we intend to set a criterion "NMT — " for — (the quantitation limit for the test method is —). The specification for — , diastereomers of YM905 drug substance, will be set for "NMT — YM905 (Lot K9059804), which contained — at a level of — and — at a level of — was used for the 26 weeks toxicology study in mice. The No Observed Adverse effect Level found in this study was — mg/kg/day. Since this dose level is 180 fold greater than the maximum recommended dose in humans (assuming a body weight of 60 Kg for man), it is considered that a sufficiently large amount of diastereomers were administered to mice to evaluate their toxicity in this stud. From this result, it has been concluded that both of these compounds have been qualified as non toxic for human at least up to a level of — Does the agency concur?**

- DRUDP agrees to have acceptance criterion for — as "NMT —
- the proposal to set an acceptance criteria "NMT — for impurities — which were present at levels, — respectively, in the drug substance, is a review issue; however, ICH-Q3A states that "if there is no safety concern, impurity specifications should be based on data generated on actual batches of the new drug substance allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the new drug

substance"; therefore, you should follow ICH-Q6A (Decision Tree # 1) to set the acceptance criteria for a specified impurity

- the sponsor indicated that the data on additional lots will be analyzed to meet the specifications recommended DRUDP

3. **In consideration of the amounts seen in all scale batches tested, which are defined as (NMT), in the ICH guideline, will be controlled by setting a specification limit of "NMT Additionally, in all batches tested, were either non detectable or found at very low levels. We, therefore, do not intend to include these solvents in the specifications for the drug substance if they are not detected in the validation batches. Does agency concur?**

- the proposed specification limit of "NMT is acceptable; however it is not acceptable to omit the specification limit for at this stage
- DRUDP recommends that you establish specifications for these ; however, if you accumulate justifiably sufficient data post approval, you may request the deletion of the specification

4. **are not included in the drug substance specifications because YM905 drug substance has were observed in a representative scale batch. We therefore, do not intend to include in the specifications for the drug substance if in the validation batches. Does the agency concur?**

- this is acceptable
- per discussion with a microbiologist, the specification is not required as long as the applicant demonstrates that the

5. **Particle size was not established as specification of YM905 drug substance based on the following rationale: 1) YM drug substance is during manufacture; 2) it is highly soluble in water: the solubility is more than 3) dissolution rate of YM905 tablets is independent of the particle size of YM905 drug substance used to prepare them. Does the agency concur?**

- this is acceptable (per ICH Q6A (decision tree # 3))

6. **, one of the starting materials in the synthesis of YM905 drug substance, has never been detected in any scale batch by the gas chromatography analysis (the detection limit is). We therefore, do not intend to include this compound as an impurity in the specifications for YM905 drug substance if it is not detected in the validation batches. Does agency concur?**

- this is not acceptable
- a specification for (a starting material) of NMT should be established; however, if sufficient historical data are accumulated, deletion of the specification may be requested
- historically sufficient data should be based on statistically significant number of batches, which you should determine and propose
- the sponsor will submit additional information

B. Drug product

1. **Related substances detected by — tests are not included (we will demonstrate that they do not increase significantly during the manufacturing process and storage period). Based on the following, does the agency concur?**
- deletion of related substances detected by — is not acceptable
- the HPLC chromatogram provided is not indicative of a good quantitation of the each impurities (at —
- a release specification "Total related substance detected by — NMT — should be established
- otherwise the proposal is acceptable
- the sponsor will collect data, and make the determination of accepting DRUDP's recommendations or submitting a rationale for their proposal

2. **The — methods for identification are not included based on the recommendations in Decision Tree # 5 of ICH Q6A. Does agency concur?**
- this is acceptable
- the rationale provided is acceptable per ICH Q6A (decision tree # 5); — — during manufacturing and during storage of the finished product

3. **— is not included (it is strongly presumed that the — of the tablet has no relation to the stability). Does the agency concur?**
- this is acceptable; — does not show any effect on the stability of the drug product

4. **Identification — and related substances detected by — should be omitted from the stability studies for the site specific batches and — production batches based on the results of the primary stability studies because these tests are not essential to assess the stability results. Does the agency concur with the proposed stability study protocols for the site specific batches and the first — production batches?**
- this is acceptable for identification — tests, but it is not acceptable for related substances detected by — see Question 1 for rationale
- the — time intervals in the stability study for — production batches must be included, as specified in the ICH-QIA guidance
- additional stability data may be submitted during the review period, but three months before the 10-month goal date
- the sponsor indicated that a — time point may be added
- the sponsor stated that the marketing group is proposing a 90-count bottle, instead of the the sponsor will conduct a container permeation test for the new supplier; the sponsor will bracket the testing protocol with 30-count bottles
- DRUDP recommends that the sponsor follow the guidance, and also, that the sponsor submit for review their bracket plan prior to the NDA submission

5. **Does the agency concur with the proposed expiration period of — for YM905 tablets based on the following results?**
   - **Stability studies for the primary stability batches having the same formulation as that of the marketed tablets — months of real time and — of accelerated stability at initial NDA filing, — of real time stability at NDA approval.**

- **Stability studies for the site specific batches ' — , of real time and accelerated stability at initial filing, — . of real time and — of accelerated stability at NDA approval.**
- this is a review issue
- the sponsor must demonstrate that the manufacturing processes and container/closure systems used in the site specific commercial batches and primary stability batches are comparable

Additional questions in the December 27, 2001 submission:

1. **The sponsor is requesting a categorical exclusion from preparing a complete environmental assessment based on the following rationale. Does the agency concur with the granting of the categorical exclusion?**

- a categorical exclusion from preparing environmental assessment is granted: ~ ppb (<1ppb)

2. **The CMC section of the CTD will be provided as an electronic submission, what degree of hyperlinking within Module 2 and between Module 3 CMC Summary and supporting data in Module 3 and or the Biopharmaceutic section of Module 5 would the Agency find helpful?**

- the sponsor is advised to follow the FDA guidance for industry "Regulatory submission in Electronic Format: General Considerations and Regulatory Submission in Electronic Format: New Drug Applications"
- for draft outline of the Quality Overall Summary for Module 2 and Format of Module 3, please follow "Guidance for Industry M4Q: The CTD-Quality

Additional questions:

1. **The sponsor is requesting agreement from the Division on the draft outline of the Quality Overall Summary for Module 2, and the format of Module 3 of the application.**

- the sponsor is advised to refer to the Guidance for industry M4Q: The CTD –Quality

2. **The sponsor is requesting agreement from the Division that the content of Module 3 will be adequate to support the manufacturing, processes and stability of the proposed drug product.**

- the sponsor is advised to refer to Guidance for industry M4Q: The CTD –Quality

Additional comments:

- the tentative dissolution acceptance criterion is too wide and should be tightened to reflect manufacturing capability; historical batches should be reanalyzed, and reasonable acceptance criteria should be proposed
- three copies of the Methods Validation package, in hard copy, should be submitted

Decisions made:

- the sponsor will not seek — ' in the NDA submission
- the sponsor will submit recently acquired CMC data in support of qualifying the starting materials for the synthesis of YM905 drug substance
- data on additional lots will be generated to establish the specifications for impurities (starting materials. — as recommended by DRUDP according to ICH-Q6A (Decision Tree # 1
- the NDA will include supporting data indicating that the drug substance lots are —
- the sponsor will add — time intervals in the "stability study for first three production batches, following ICH-QIA guidance
- the sponsor will consider the Division's recommendations on dissolution specifications, and submit a proposal based on more batches with higher acceptance derived from historical batch data

- the sponsor will provide a copy of the documents from USAN and WHO indicating that the solifenacin succinate was approved as an established name for YM 905

Action Items:

- attendee lists will be exchanged
- minutes will be sent to the sponsor in 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

Drafted: Farinas/January 22, 2002
Concurrence: Best Moore 1.25.02/Agarwal/ 1.31.02/Rhee 1.23.02/Hirsch 1.28.02
Finalized: Farinas 2.5.02

MEETING MINUTES

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/

Mark S. Hirsch
2/5/02 02:37:17 PM

Meeting Minutes

Date: September 19, 2000 **Time:** 1:00-2:30 PM, EST **Location:** Parklawn; Chesapeake Room

IND 58135 **Drug:** YM905 **Indication:** Overactive bladder

Sponsor: Yamanouchi

Type of Meeting: End of Phase 2, Clinical

Meeting Chair: Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., MGA, Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Daniel Shames, M.D. – Acting Deputy Director, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Mark Hirsch, M.D. – Acting Urology Team Leader, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Alexander Jordan, Ph.D. – Pharmacologist Team Leader, DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician, Division of Biometrics II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Michael Ortwerth, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., MGA – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Robert Desjardins, M.D. – Vice President, Research and Development, Yamanouchi, U.S.A.
Nobuyuki Izumisawa, D.V.M., Ph.D. – Toxicologist, Yamanouchi, U.S.A.
Imogene Grimes, Ph.D. – Vice President, Statistic and Data Management, Yamanouchi, U.S.A.
Susan Ridge – Asociate Director, Yamanouchi, U.S.A.
Donna Tempel, Ph.D. – Director, Research Operations, Yamanouchi, U.S.A.
Rudolph Lucek – Vice President, Regulatory Affairs, Yamanouchi, U.S.A.
Raan Krishna –Regulatory Affairs Manager, Yamanouchi Pharma Technologies, U.S.A.
Taisuke Ushida – Clinical Pharmacologist, Yamanouchi Pharmaceuticals, Tokyo
Kenji Yasukawa, M.S. – Manager, Project Promotion Group, Yamanouchi Pharmaceuticals, Tokyo
Tom Kos, Ph.D. – European Project Leader, Yamanouchi, Europe
Janine Laurencot-Roy – Project Director, Covance

Meeting Objective: To discuss future clinical development plan for YM905.

Background: YM905, an M_3-antimuscarinic compound, is being developed by Yamanouchi to treat overactive bladder. In the submission dated August 21, 2000, (Serial Number 009) the sponsor included summaries of the non-clinical findings, Phase 1 and Phase 2 programs, and proposal for the Phase 3 clinical program. The sponsor is also asking for deferral of a pediatric program

The submission also included a CMC meeting package, which stated that clinical trial materials used in the phase 2 studies showed an increase in the levels of an impurity, which is a and has been designated as Although several steps were taken to minimize the formation of , this impurity cannot be totally eliminated. Thus, the sponsor wants to relax the specifications for related substances and assay of YM905 for Phase 3 studies.

Discussion:

- the sponsor presented overhead projections outlining the Phase 3 Clinical Program, Protocol 905-CL-013 and Protocol 905-Cl-014, and listing the questions for discussion; copies of the overheads were provided to the attendees (see attached handout)
- in the proposed Protocol YM905-CL-013, the sponsor stated that the first exclusion criteria ("have an incidence of urinary incontinence <1 episode (on average) per 24 hours") should be reworded; the replacement wording should be "at least one episode in 24 hours, and include frequency, and or urgency"; patients who only have one episode of urgency will be accepted into the trial
- general Biopharmaceutics comments for the sponsor:
  - depending on the results of the mass balance study and if the drug is not contraindicated in hepatic-impaired patients, a separate study should address the effect of hepatic impairment on PK of this drug
  - the sponsor should clarify if the PGP or other potential oral drug-drug interaction has been explored
  - if clinical formulation is different form the to-be-marketed product formulation, then bioequivalence of the old and new formulation has to be ascertained

DRUDP provided the following responses to the questions listed in the sponsor's handout:

- Question 1: Are the proposed endpoints adequate to support the following indication statement?
  - should not be included in the indication statement
  - indication statement will be similar to that of other approved anticholinergic products for overactive bladder
  - review of data will determine indication statements
  - the sponsor indicated that will be removed from the proposed indication; however, will continue
- Question 2: Assuming both studies show significant reduction in micturition frequency, in order to include symptoms of urge incontinence and nocturia in the label, will it be adequate to: show a trend in the combined database, show statistical significance in the combined database, show statistical

significance in one of the two pivotal studies, or show statistical significance independently in each of the two pivotal studies?

- this is a review issue
- the sponsor clarified that the analysis of urge incontinence episodes will include only patients who were incontinent at baseline
- the sponsor also stated that Phase 3 studies will not include spinal cord injury patients nor neurogenic bladder patients

- Question 3: Does the Agency agree that these numbers will provide sufficient exposure to YM905 therapy to adequately characterize the safety of YM905 for the purpose of NDA review?
  - the proposed number of patients is barely adequate; DRUDP recommends increasing the number of patients enrolling in Phase 3 trials
  - DRUDP recommends conducting QT safety study, based on the findings of prolonged QT in two patients; the proposed QT study would be consulted to the CardioRenal Division for review and comments; DRUDP recommends conducting EKG measurements at C_{max}, and measuring of YM905 metabolites that may have an effect on the QT wave; DRUDP recommends that QTc studies include female patients and that a range of doses of YM905 be used; QT should monitored at steady state, considering the long t½ of the metabolite
  - DRUDP recommends that the sponsor include analysis of variance in the statistical plan
  - the sponsor indicated that a proposal for mass balance studies and QTc evaluation would be submitted
  - the sponsor stated that in order to preserve the heterogeneity of the population, only one randomization scheme was planned
- Question 4: Will the ongoing ketoconazole study, taken in conjunction with an in depth review of the clinical database (including the proposed population PK analysis), sufficiently address the potential for metabolic drug interactions between YM905 and concomitant medications?
  - data showing the results of a drug interaction between YM905 and Ketoconazole would be included in the label; implications for safety will also be considered
  - DRUDP recommends that sponsor include poor metabolizers in the pK studies
  - the sponsor indicated that the oral contraceptive study, scheduled to commence in October, will include female patients on combined oral contraceptives
- Question 5: Is the proposed subcore program adequate?
  - DRUDP recommends that sponsor follow the published Guidances on *in vitro* and *in vivo* metabolism
  - the sponsor stated that review of the data will determine if hepatic studies will be conducted
- Question 6: We are requesting to defer the pediatric program proposal until a review of data on safety and efficacy of YM905 in adults has been completed —
  Does the Agency agree?
  - DRUDP agrees with this proposal
- Question 7: Does the FDA have any advice on: Quality of Life instruments (e.g., King's, UUDI), Global Subject Assessment?
  - DRUDP prefers not to give advice on Quality of Life instruments; data collected by using Quality of Life instruments will not likely have a major impact on regulatory decisions in this clinical setting
- Question 8: If the data generated are sufficient to include frequency — in the label, we plan to include in labeling and in the promotional claim the following statement: —

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  - DRUDP does not agree
- Question 9: Are the completed and planned non-clinical studies sufficient to support the NDA?

- the studies submitted are sufficient

- Question 10: In all preclinical, toxicology and ADME reports the drug concentrations of YM905 are reported as the monosucinate. In all clinical reports the concentrations of YM905 have been reported as the free base. To allow comparison of YM905 concentrations between clinical and preclinical reports, we will: provide addenda to preclinical reports explaining the basis of the YM905 calculation and a conversion factor to convert YM905 monosuccinate levels to those of the free base. Does the Agency concur?
  - DRUDP agrees with this proposal

Action Items:

- Minutes will be faxed to the sponsor within 30 days

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Minutes Preparer

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Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
IND Arch:
HFD-580/DivFile

HFD-580/ Allen/Shames/Benson/ Hirsch/ Batra/ Jordan / Hoberman / Parekh / Chatterjee / Ortwerth/ Rumble

drafted: Farinas, 9.22.00
concurrence: /Shames 10.19.00/ Benson 10.24.00/ Hirsch 10.26.00/ Batra/ Jordan / Hoberman / Parekh 11.03.00/ Chatterjee /Ortwerth 10.19.00
final: Farinas, 11.03.00

MEETING MINUTES