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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-518

Trade Name:	VESIcare
Generic Name:	Solifenacin succinate
Sponsor:	Yamanouchi Pharma America, Inc.
Approval Date:	November 19, 2004
Indications:	Provides for the use of VESIcare (solifenacin succinate), 5 and 10 mg tablets, for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

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APPLICATION NUMBER:

21-518

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APPLICATION NUMBER:

21-518

APPROVAL LETTER(S)

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
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), 5 and 10 mg tablets.

We also acknowledge receipt of your submissions dated October 20 and 23, November 11, December 5 and 9, 2003; February 17, March 24, May 18, June 3 and 18, September 17, 21, 24 and 30, October 22 and 29, November 1, 8, 9, 12, 17, 18 and 19, 2004.

The May 18, 2004, submission constituted a complete response to our October 17, 2003, action letter.

This amended new drug application provides for the use of VESIcare (solifenacin succinate), 5 and 10 mg tablets, for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the attached labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed package insert and patient package insert. Additionally, the immediate container and carton labels must be identical to those submitted on November 18, 2004, and the carton labels must be modified as agreed upon in your submission dated November 19, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-518.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit the content of the labeling in electronic format as required by 21 CFR 314.50(l)(5) and in the format described at the following web site, http://www.fda.gov/oc/datacouncil/spl.html.

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 or deferred. We are waiving the pediatric study requirement for ages birth to four years and are deferring pediatric studies for ages five to 17 years for this application.

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 you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Reproductive and Urologic Drug Products (HFD-580) and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane

Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jean Makie, M.S., R.D., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

/S/

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-518

APPROVABLE LETTER(S)

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
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), 5 and 10 mg tablets.

We also acknowledge receipt of your submissions dated January 31, February 4 and 27, April 25, May 8, June 13, 16, 25, and 26, July 15, 18, 24, and 28, August 25 (2) and 29 (2), September 11, 19, and 22, and October 3 and 9, 15, and 16, 2003.

We have completed the review of this application as amended, and it is approvable. Before this application may be approved, it will be necessary for you to address the following deficiencies in investigations required under section 505(b) of the act to include adequate tests to demonstrate that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

Deficiency # 1. 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 population. 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 is needed 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 ECGs 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 recommend that you submit a protocol for our review prior to initiating this study.

Deficiency # 2. The current dissolution acceptance criterion — at 30 minutes) is unacceptable.

The following information is needed to address this deficiency:

Based on our Chemistry, Manufacturing, and Controls (CMC) teleconference held with you on October 16, 2003, we are now aware that you have produced — additional batches since the submission of your original NDA. Please submit additional dissolution data obtained at 20 minutes and 30 minutes from these — batches as part of your complete response.

Deficiency # 3. Labeling remains unresolved. Overall comments on labeling are deferred until data are available from the QT study.

The following information is needed to address this deficiency:

Submit revised draft labeling, updated to include the results of this 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. Additional risk management strategies, including emphasis on using the lowest effective dose for an individual patient, may be needed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission. Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Reproductive and Urologic Drug Products to discuss what steps need to be taken before the application may be approved. If you have any questions, please call Jean King, M.S., R.D., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

/S/ *[See appended electronic signature page]*

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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
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