N21-513 — ORIG APPROVAL _ PKG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-513

Trade Name: Enablex ER Tablets (7.5 mg/15mg)

Generic Name(s): (darifenacin hydrobromide)

Sponsor: Novartis Pharmaceuticals, Inc.

Agent:

Approval Date: December 22, 2004

Indication: Provides for extended release tablets for the treatment of overactive bladder

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APPLICATION NUMBER:

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21-513

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-513

Novartis Pharmaceutical Corporation
Attention: Lynne McGrath, MPH, Ph.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. McGrath:

Please refer to your December 3, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex® (darifenacin) 7.5 mg and 15 mg extended release tablets.

We also acknowledge receipt of your submissions dated May 14, 19, 24, and 28, June 16 and 21, August 27, September 15, 17, 28 and 30, October 1, 11, and 22, November 24, and December 1, 2, 8, 10, 14, 16, 17, 20 and 21, 2004.

The June 21, 2004, submission constituted a complete response to our October 2, 2003, action letter.

This amended new drug application provides for the use of Enablex® (darifenacin) 7.5 mg and 15 mg extended release tablets for the treatment of overactive bladder.

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 December 20, 2004 and the container label for the 7.5 and 15 mg blister tablet must be modified as agreed upon in your submission dated December 21, 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 21-513.**" 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 up to six months and are deferring pediatric studies for ages six months 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. These commitments are listed below.

1. Pediatric studies under PREA for the treatment of pediatric patients aged six months and older with detrusor overactivity associated with a known neurological condition (e.g., spina bifida).

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

Final Report Submission due: June 21, 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., Sr. Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-513

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-513

Novartis Pharmaceuticals Corporation
Attention: Lynn Fahey McGrath, MPH, Ph.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. McGrath:

Please refer to your new drug application (NDA) dated and received on December 3, 2002 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex (darifenacin hydrobromide), 7.5 and 15 mg extended release tablets, for the treatment of overactive bladder.

We also acknowledge receipt of your submissions dated December 10, 2002, January 20 and 24, February 6, 18, and 21, March 18 and 28, April 14 and 16, May 12, July 21, August 5, 11,19, 20, 21, and 29, and September 5, 10, 18, 19, and 23, 2003.

We have completed the review of this application as amended, and it is approvable under 21CFR314.125(3)(b)(2), which states that "the investigations required under section 505(b) of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling." Before this application may be approved, it will be necessary for you to address the following deficiencies:

Deficiency # 1. This application lacks sufficient information to conclude with assurance that darifenacin is not associated with clinically relevant Q-T interval prolongation when administered at a clinically relevant range of plasma concentrations. Such information is necessary prior to marketing approval in order to determine if the drug is safe for the full targeted population. Evidence from pre-clinical studies indicates that darifenacin has a direct effect on ventricular repolarization. This evidence comes from in-vitro HERG and [3H]-dofetilide binding studies, and from in-vivo dog studies. In the dog, Q-T prolongation was observed at a darifenacin plasma concentration of 357 ng/mL, which is roughly 5-6 times the mean peak plasma concentration attained in 4 subjects who took darifenacin 15mg and ketoconazole in Study 1035. Two studies in humans (Study 1007 and 1035) each revealed a mean between-group difference of 10 to 12 milliseconds when darifenacin 7.5mg, 15mg or 30mg was administered with ketoconazole versus when darifenacin was administered with placebo. Lack of placebo-alone and ketoconazole-alone groups in these two studies precludes a determination of the effect of darifenacin itself on the Q-T interval. While Study 1015 revealed no meaningful differences in changes in the Q-T interval between darifenacin 30mg or 60mg and placebo, this study did not include a positive control, and the maximum darifenacin plasma concentrations did not exceed concentrations that might be attained when a cytochrome P450 2D6 poor metabolizer is administered darifenacin 15mg and ketoconazole.

The following information is needed to address this deficiency:

Submit the results from a randomized, placebo-controlled study of darifenacin with the primary objective of determining the direct effect of darifenacin on the Q-T interval at a clinically relevant range of plasma concentrations. The study should include a dose of darifenacin that is sufficient to produce plasma concentrations that meet or exceed plasma concentrations that might be attained when a cytochrome P450 2D6 poor metabolizer is administered darifenacin 15mg and ketoconazole. This study should also include a positive control, such as moxifloxacin, in order to assure assay sensitivity and to provide a benchmark for comparison with Q-T effects of darifenacin. 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 female, preferably patients with overactive bladder (OAB), whose mean age is consistent with the age distribution of OAB patients in the community. The number of subjects should be sufficient to rule out a clinically important mean prolongation of the corrected Q-T interval by darifenacin. It is recommended that you submit a protocol for our review prior to initiating this study.

Deficiency # 2. Overall comments on labeling are deferred until data are available from the Q-T study. Submit draft labeling, updated to include the results of this study. In addition, darifenacin appears to be associated with the occurrence of urinary retention and constipation, and rarely, serious sequelae of these two adverse events. 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.

In addition, while not an approvability issue, we request that you commit to conduct a post-marketing study designed to assess the potential association of darifenacin with bone fracture. Of the 6,655 darifenacin-treated subjects (1462 person-years) in the overall darifenacin clinical development program, 16 had a bone fracture requiring hospitalization but there were no such reports in the 2,216 subjects who received placebo (329 person-years). While we acknowledge that some of these cases occurred during open-label trials, the application does not contain information sufficient to explain or to refute this discordance between groups.

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
10/2/03 11:29:34 AM

18 pages redacted from this section of the approval package consisted of draft labeling