CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-513

Administrative/Correspondence

PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

Patent and Exclusivity Information for ENABLEX™ (DARIFENACIN HYDROBROMIDE)

1.	Active Ingredient:	(*S*)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide
2.	Strengths:	7.5 and 15mg
3.	Trade Name:	ENABLEX™
4.	Dosage Form / Route of Administration:	Tablets / Oral
5.	Application Firm Name:	Pfizer Inc.
6.	NDA Number:	21-513
7.	Exclusivity Period:	5 Years
8.	Applicable Patent Numbers and Expiration Dates:	5,096,890 exp. March 13, 2010 6,106,864 exp. August 21, 2016

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

EXCLUSIVITY SUMMARY for NDA # NDA 21-513
Trade Name Requested Enablex
Generic Name Darifenacin hydrobromide
Applicant Name Novartis Pharmaceuticals HFD- 580
Approval Date December 23, 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__/

* The indicated disease/condition (Treatment of the involuntary loss or leakage of urine in women during physical exertion or activities such as laughing, coughing, sneezing, lifting, exercising- stress urinary incontinence(SUI))does not exist in children.

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

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

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: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 King, M.S., R.D.
Signature of Preparer Date

Title: Project Manager

{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

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

/s/

Margaret Kober
12/21/04 03:57:32 PM
signed for Daniel Shames

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

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-513

Supplement Type (e.g. SE5): N/A **Supplement Number:** N/A

Stamp Date: June 23, 2004 **Action Date:** December 23, 2004

HFD 580

Trade and generic names/dosage form: **Requested Tradename** - Enablex
Generic: Darifenacin hydrobromide
dosage form: 7.5 and 15 mg extended release tablets

Applicant: Novartis Pharmaceuticals

Therapeutic Class: 1S

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

ENABLEX Extended Release Tablets are indicated for the treatment of 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: not applicable to NDA 21-513

- ☐ **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 X **kg**____ **mo.**_____ **yr.** birth **Tanner Stage**_____
Max X **kg**____ **mo.** up to 6 **yr.**____ **Tanner Stage**_____

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

Note: Reason(s) for partial waiver: On September 30, 2004, the Sponsor submitted their pediatric development plan. The Sponsor requested a waiver for ages 0 up to 6 months because it would be impractical to study neurogenic OAB in very young infants. The Division concurs and grants this partial waiver.

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.

ction C: Deferred Studies

Age/weight range being deferred:

Min X **kg**____ **mo.** 6 **yr.**____ **Tanner Stage**_____
Max X **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**
- ☐ **X Formulation needed**

Other:

Note: Reason(s) for deferral: [illegible]

1

- [ ]
- [ ]

The Division grants a deferral in the conduct of pediatric studies in ages 6 months to 17 years of age.

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: Not applicable

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: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Margaret Kober
12/21/04 03:55:02 PM

NDA 21-513

Darifenacin — Oral Tablets

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(l)]

Pfizer 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.

Signature of Company Representative

November 11, 2002

Date

MEMORANDUM

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

DATE: December 22, 2004

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-513 Enablex Extended Release Tablets (darifenacin); Novartis

Darifenacin is a competitive muscarinic receptor antagonist. This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's approval action for darifenacin 7.5 mg and 15 mg extended-release tablets taken once daily for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. Novartis' submission dated June 21, 2004, represents a complete response to the Agency's October 2, 2003, approvable letter and adequately addresses our concerns regarding darifenacin effects on QT.

QT Prolongation

Both CYP3A4 and CYP2D6 are involved in darifenacin metabolism. Co-administration of 7.5 mg darifenacin with ketoconazole 400 mg, a potent inhibitor of CYP3A4, resulted in a 5-fold higher mean steady state exposure for CYP2D6 extensive metabolizers (EMs) and a 14-fold higher exposure for a CYP2D6 poor metabolizer (PM) compared to darifenacin plus placebo; co-administration of 15 mg darifenacin with ketoconozale 400 mg resulted in a 12-fold higher exposure for EMs and a 6-fold higher exposure for one PM compared to treatment with darifenacin plus placebo.

In the original NDA, the effect of darifenacin on rate-corrected mean QT change from baseline (using Fredericia's correction) was evaluated. The mean QTcF change from baseline in patients receiving 7.5 mg darifenacin plus placebo was 2 msec (95% CI: -12.5, 16.5) compared to 12 msec (95% CI: -2.9, 26.9) in patients receiving 7.5 mg darifenacin plus ketoconazole. For darifenacin 15 mg plus placebo, the mean QTcF change from baseline was -3 msec (95% CI: -17.6, 11.6) and for the combination of darifenacin 15 mg plus ketoconazole it was 10 msec (95% CI: -4.3, 24.3). Thus the change from baseline in QTcF of 10-12 msec appeared constant regardless of the darifenacin exposure in the combination. Novartis suggested that "the 10-12 msec QTcF effect with ketoconazole and darifenacin is solely due to the well known effect on QTc duration of ketoconazole alone". In a teleconference with Novartis held on September 22, 2003, DRUDP indicated that the literature evidence supporting the QT prolonging effects of ketoconozale was limited, that the effect of ketoconazole could not be assessed since there was no ketoconazole alone treatment group, and that the interpretation of a 10-12 msec QTc effect was problematic given the lack of placebo/placebo and active control groups. In addition, DRUDP expressed concerns that darifenacin was found to increase action potential duration in a dog study.

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 darifenacin doses that achieve exposures comparable to those produced by the darifenacin plus ketoconazole combinations, and that included placebo and active controls. The sponsor agreed to conduct Study DAR 328A 2302 and received Agency input on its design. A total of 179 healthy adults (44% male, 56% female) aged 18 to 65 were randomized to receive either placebo, darifenacin 15 or 75 mg, or moxifloxacin 400 mg active control. Subjects included both CYP2D6 PMs (18%) and EMs (82%). A dose of 75 mg darifenacin was evaluated to assess the exposure achievable in CYP2D6 PMs dosed with darifenacin 15 mg in the presence of potent CYP3A4 inhibitors. Neither darifenacin dose resulted in QTcF prolongation at any time during steady state. The placebo-subtracted, mean QTcF change from baseline to Day 6 was -1.6 msec for darifenacin 15 mg, -1.2 msec for darifenacin 75 mg, and +6.9 msec for moxifloxacin 400 mg.

Safety

In the 2003 approvable letter, the sponsor was requested to address serious sequelae of adverse events reported with use of darifenacin in labeling. Since the incidence of constipation on the 7.5 mg dose is lower than that on the 15 mg dose (15% vs. 21%), the current recommendation to begin dosing at 7.5 mg daily could minimize this concern somewhat. Note that the titration regimen (initial dosing at 7.5 mg for two weeks, then escalated to 15 mg) also resulted in a 21% incidence of constipation. Constipation leading to treatment discontinuation occurred in 0.6% and 1.2% of patients treated with darifenacin 7.5 mg and 15 mg, respectively. Interestingly, the incidence of dry mouth on the titration regimen was similar to that of 7.5 mg daily (19% vs. 20%), and was considerably lower than the incidence on 15 mg daily (35%). There were no cases of acute urinary retention requiring medical intervention in patients treated with darifenacin 7.5 or 15 mg. The patient package insert also addresses serious adverse events expected to occur with the use of anticholinergic agents such as darifenacin.

The daily dose of darifenacin should not exceed 7.5 mg in patients taking potent CYP3A4 inhibitors or in patients with moderate hepatic impairment. Darifenacin is not recommended for use in patients with severe hepatic impairment.

Phase 4 Studies

In the 2003 approvable letter, Novartis was requested to commit to conducting a phase 4 study to assess the potential association of bone fractures and darifenacin use. Upon careful re-review of the bone fracture cases in the NDA, DRUDP has determined that the events reported can be attributed to factors other than use of darifenacin. Consequently, Novartis will not be asked to conduct a phase 4 bone fracture study.

Tradename

The proposed tradename "Enablex" is acceptable to DRUDP and the ODE.

/S/

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

Not applicable. See Medical Team Leader Memo for signed concurrence.

12/22/04

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 22, 2004

To: Lynn McGrath, Ph.D.

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513: Approval Letter attached

Total no. of pages including cover: 26

Comments: see comment below.

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

Dear Lynne,

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

Sincerely

/S/

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

12/22/04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-513	Efficacy Supplement Type SE-	Supplement Number	
Drug: **darifenacin**		Applicant: Novartis	
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)	1S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	December 23, 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 10/2/03, pending)

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE (October 2, 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;9/16/02; 8/29/03; 9/23/04; 10/4/04; 11/18/04; 11/22/04)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X (VESIcare, 11/19/04)
❖ 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	X (received 12/21/04)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X (6/18/02)
• Pre-Approval Safety Conference (indicate date; approvals only)	X (10/21/04)
• 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, (10/2/03; 12/22/04)
❖ Clinical review(s) *(indicate date for each review)*	X (Review #1, 9/26/03; Review # 2, 12/20/04)
❖ 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 reviews)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	X (see ODS memo 11/3/04)
❖ 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 (2/26/03; 9/4/03; 2/26/04; 11/18/04)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (review # 1, 10/2/03; Review # 2, 12/20/04)
❖ 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
❖ CMC review(s) *(indicate date for each review)*	X (1/27/03; 9/25/03; 10/1/03; 10/2/03; 8/26/03; 11/3/04, 12/21/04)
❖ Environmental Assessment	
• 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)*	N/A
❖ Facilities inspection (provide EER report)	See Chemistry Review #1: **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (1/23/03; 9/17/03; no new issues in CR so now Review # 2 completed)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X 5/2/01
❖ CAC/ECAC report	X (7/5/01; 8/2/01)

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.

If 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).

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
12/22/04 10:10:22 AM

NOVARTIS

FACSIMILE TRANSMITTAL SHEET

TO:	FROM:
Ms. Jean Makie/Dr. Sarah Pope	Lynne Fahey McGrath, MPH, PhD
COMPANY: FDA Division of Reproductive and Urological Drug Products	DATE: 12/21/2004
FAX NUMBER: 301-827-4267	TOTAL NO. OF PAGES INCLUDING COVER: 3
PHONE NUMBER: 301-827-7270	SENDER'S REFERENCE NUMBER:
RE: NDA 21, 513 Reviser blister label	

☐ URGENT X FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Reference is made to the December 16, 2004 submission to NDA 21, 513. This submission contained the final carton and container labels. On December 21, 2004, Dr. Sarah Pope identified a minor inconsistency in the label for the 7.5 and 15 mg blister tablet. The submitted blister had the words **"Extended-Release Tablet"** printed on the label with capital letters on all words. We have now changed this blister label to read, **"Extended-release tablet"** to be consistent with the PI and all other carton and container labels. The two new blister labels are attached to this fax and will be sent via e-mail.
We also commit to submit this change officially to the NDA.

Kindest regards

/S/

Lynne Fahey McGrath, MPH, Ph.D
Director, Drug Regulatory Affairs
Novartis Pharmaceutical Corporation

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

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

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

10 Pages Redacted of
Deliberative Process
§ 552(b)(5)

Lynne Fahey McGrath, MPH, PhD
Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corpoation
One Health Plaza
East Hanover, N.J. 07936-1080
Tel: 862 778 5139
fax: 973-781-3966
lynne.mcgrath@pharma.novartis.com

December 20, 2004

Attention: Daniel Shames, MD
Division of Reproductive and Urological
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA #21, 513

Enablex® (darifenacin)

Amendment to a Pending Application

Labeling Revised PI and PPI and Postmarketing Commitments

Dear Dr. Shames,

Reference is made to the comments and revisions to the Package Insert and Patient Information received from FDA by fax on December 17, 2004. Novartis has reviewed the Division comments. Further reference is made to the December 17, 2004 sent by Novartis to FDA indicating agreement with the changes proposed by FDA. At this time it appears there are no more issues regarding labeling of this product.

This submission provides the revised PI and PPI containing the revisions proposes on December 17, 2004. In addition to the changes suggested by the FDA we have made minor formatting and punctuation changes.

Further reference is made to the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA). Novartis agrees to the following postmarketing study commitments:

1. Pediatric studies under PREA for the treatment of pediatric patients aged six months and older with detrusor over activity 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.

In addition, Novartis acknowledges that the status of these postmarketing studies shall be reported annually according to 21 CFR 314.81 and that the submission of the final reports for these studies is due by June 21, 2009.

We look forward to working with the Division on the design of these studies. As detailed in the September 30, 2004 submission to FDA, pursuant with Section 505A of the Federal Food, Drug and Cosmetic Act, Novartis Pharmaceuticals proposes to discuss and reach agreement on the design of the studies described in this

submission to obtain a Written Request for pediatric studies from the Division for the purpose of obtaining Pediatric Exclusivity.

This notification is submitting in accordance with the guidance for industry entitled:

Providing Regulatory Submissions in Electronic Format – NDAs (January 1999).

The relevant technical details of the electronic portions of this submission are as follows:

- Submission size: MB
- Electronic media: one compact disk
- Network Associates Incorporated VirusScan© version 7.1.0 (formerly known as the McAfee VirusScan). The submission is virus free.

If you have any questions or concerns regarding this submission you can call me at (908) 432-9605 or (862) 778-5139.

Sincerely,

Lynne Fahey McGrath, MPH, Ph.D

MEMORANDUM

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

Date: December 15, 2004

From: Suresh Kaul, MD, MPH
Medical Officer
Division of Reproductive and Urologic Drug Products
(HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-513 (study 1001, 1002 and 1041)

I have reviewed the financial disclosure information submitted by Novartis Pharmaceuticals Corporation in support of their NDA 21-513 for Enablex (Darifenacin).

The pivotal studies were conducted to assess the safety and efficacy of Enablex (Darifenacin) for the treatment of patients with overactive bladder with symptoms of urge incontinence, urgency and frequency. The number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	**Study Status**	**Financial Disclosure Review**
Study 1001 Darifenacin 15mg oral once daily in patients with symptoms of OAB. A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel group Study conducted in the US.	Completed	Appropriate documentation and financial disclosure submitted

Study Number/Title	Study Status	Financial Disclosure Review
Study 1002 Darifenacin 7.5 and 15mg oral once daily in patients with symptoms of OAB. A (Non-US) Multi-Center, Randomized, Double-Blind, Placebo-Controlled, dose response study.	Completed	Appropriate documentation and financial disclosure submitted
Study 1041 Darifenacin 7.5 and 15mg oral once daily in patients with symptoms of OAB. A (Non-US) Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel group study.	Completed	Appropriate documentation and financial disclosure submitted

Documents Reviewed:

- Financial Certification Information (Form FDA 3454) submitted March 3, 2003.

There were a total of 1319 investigators listed in all the studies. Nineteen of the listed investigators had financial information to disclose. Completed Form 3455 was reviewed for each of these investigators. All independent grants associated with these investigators were found to have been paid directly to the institution rather than to the individual investigators per sponsor's submission.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of any of the pivotal trials for NDA 21-513.

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

/s/

Suresh Kaul
12/15/04 03:08:59 PM
MEDICAL OFFICER

NOVARTIS

FACSIMILE TRANSMITTAL SHEET

TO: Ms. Jean Makie	FROM: Lynne Fahey McGrath, MPH, PhD
COMPANY: FDA Division of Reproductive and Urological Drug Products	DATE: 12/20/2004
FAX NUMBER: 301-827-4267	TOTAL NO. OF PAGES INCLUDING COVER: 22
PHONE NUMBER: 301-827-7270	SENDER'S REFERENCE NUMBER:
RE: NDA 21, 513 PPI/PI and Post approval Commitment	

☐ URGENT X FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:
Please find attached revised PI and PPI based on FDA comments.
We are in agreement with these changes.
Cover letter describes PI/PPI revisions and also acceptance of post-approval commitment

Lynne Fahey McGrath, MPH, PhD
Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corpoation
One Health Plaza
East Hanover, N.J. 07936-1080
Tel: 862 778 5139
fax: 973-781-3966
lynne.mcgrath@pharma.novartis.com

December 20, 2004

Attention: Daniel Shames, MD
Division of Reproductive and Urological
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA #21, 513

Enablex® (darifenacin)

Amendment to a Pending Application

Final Draft Labeling
PI and PPI and Postmarketing Commitments

Dear Dr. Shames,

Reference is made to the comments and revisions to the Package Insert and Patient Information received from FDA by fax on December 17, 2004. Novartis has reviewed the Division comments. Further reference is made to the December 17, 2004 sent by Novartis to FDA indicating agreement with the changes proposed by FDA. At this time it appears there are no more issues regarding labeling of this product.

This submission provides the revised PI and PPI containing the revisions proposes on December 17, 2004. Clean copies (without marked revisions) of the PI and PPI are also included. In addition to the changes suggested by the FDA we have made minor formatting and punctuation changes.

Further reference is made to the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA). Novartis agrees to the following postmarketing study commitments:

1. Pediatric studies under PREA for the treatment of pediatric patients aged six months and older with detrusor over activity 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.

In addition, Novartis acknowledges that the status of these postmarketing studies shall be reported annually according to 21 CFR 314.81 and that the submission of the final reports for these studies is due by June 21, 2009.

We look forward to discussions with the Division regarding the design of these studies. As detailed in the September 30, 2004 submission to FDA, pursuant with Section 505A of the Federal Food, Drug and Cosmetic Act, Novartis Pharmaceuticals

proposes to discuss and reach agreement on the design of the studies to obtain a Written Request for pediatric studies from the Division for the purpose of obtaining Pediatric Exclusivity.

This notification is submitting in accordance with the guidance for industry entitled:

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The relevant technical details of the electronic portions of this submission are as follows:

- Submission size: MB
- Electronic media: one compact disk
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If you have any questions or concerns regarding this submission you can call me at (908) 432-9605 or (862) 778-5139.

Sincerely,

Lynne Fahey McGrath, MPH, Ph.D

Addendum:
A print copy of the carton and container labels submitted December 16, 2004 are also included in the paper submission.

NOVARTIS

Enablex® (darifenacin)

NDA No. 21-513

Labeling History

Author(s):	Lynne Fahey McGrath, MPH Ph.D
Document type:	Labeling History
Document status:	*Final*
Release date:	20 December 2004
Number of pages:	4

Table of contents

Labeling History

Original labeling was submitted with the NDA 21, 513 on December 3, 2002. On August 25, 2003, Novartis proposed changes to the carton and container labels changing the name from Pfizer to Novartis. Further revisions to the carton and container label were submitted on June 21, 2004 as part of the Complete Response to the Oct 2, 2003 approvable letter. The layout and color of the label and addition of the revised ENABLEX logo were included. On October 22, 2004 the carton and container labels were revised to address comments received by Dr. Moo-Jhong Rhee, Chemistry Team Leader, DRUDP, on July 12, 2004 and October 14, 2004. On November 24, 2004 a carton and container labels including additional changes, specifically the relocation of dose information on the carton and container labels, requested by Sarah Pope and the Chemistry Team at DRUDP were submitted. A December 2, 2004 submission included carton and container labels revised to address the comments on the size and placement of the logo received November 30, 2004. The submission dated December 8, 2004 included revisions to the PI based on comments received by the FDA Division of Reproductive and Urological Drug Products on November 30, 2004. The December 10, 2004 submission provided revisions to the PPI received from the Division on December 3, 2004. The December 14, 2004 submission included final revisions to the carton and container label proposed by FDA on December 6, 2004. This submission included revisions to the PI and PPI suggested in the December 14, 2004 fax. On December 17, 2004 FDA faxed additional revisions to PI and PPI submitted on December 16, 2004. Novartis faxed a letter to FDA on December 17, 2004 indicating that they agreed with all these changes. There appears to be no more issues with the labeling.

1 Proposed Labeling Changes

The current submission contains the revised PI and PPI for which Novartis and FDA have agreed upon. The following changes suggested by FDA have been made:has made changes to the PI and PPI as suggested by FDA in the December 14, 2004 fax. These include:

Clinical Studies: Add "CI" after 95% on Y-axis of figures 2a, b, and c. In addition, lighten the lines on the graph.

Adverse Events: The revision to the statements on acute urinary retention and constipation proposed by FDA have been accepted. The revised versions of the PI reflect these comments.

Minor formatting changes have also been made to both the PI and PPi for consistency with the Novartis labeling format.

The revised PI identifying these changes is in the file proposed.doc and proposed.pdf. The revised PPI is in the file PPI.doc and PPI.pdf.

2 Last Approved Labeling

No approved labeling exists for Enablex. The original NDA for this product was submitted to the FDA Division of Reproductive and Urological Drug Products (HFD-580) on December 3, 2002 by Pfizer, Inc. with draft labeling. The action date for the NDA is October 3, 2003. On April 23, 2003 NDA 21, 513 was transferred to Novartis Pharmaceutical Corporation.

Therefore, no "approved.pdf" or "current.pdf" files exist for this submission.

3 History of Changes

No approved labeling exists for Enablex. The original NDA for this product was submitted to the FDA Division of Reproductive and Urological Drug Products (HFD-580) on December 3, 2002 with draft labeling. Revisions to the proposed package insert was submitted on August 11, 2003.

4 Pending Supplements

The Complete Response to the approvable letter was submitted as a supplement on June 21, 2004.

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 17, 2004

To: Lynn McGrath, Ph.D.

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513: Division comments/revisions to Sponsor proposed PI and PPI

Total no. of pages including cover: 23

Comments: see comment below.

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

Dear Lynn,

Please find attached revised package insert (PI) and patient package insert (PPI) labeling from the Division.

Sincerely,

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 14, 2004

To: Lynn McGrath, Ph.D.

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513: Division comments/revisions to Sponsor proposed PI and PPI

Total no. of pages including cover: 23

Comments: see comment below.

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

Dear Lynn,

Please find attached revised package insert (PI) and patient package insert (PPI) labeling from the Division.

Sincerely,

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

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

ADMINISTRATIVE REVIEW OF NDA ACTION PACKAGE
OFFICE OF DRUG EVALUATION III

NDA: 21-513
Drug: Enablex (darifenacin) Extended Release Tablets
Classification: 1S
Sponsor: Novartis
Project Manager/CSO: Jean Nakie

Reviewer: Maria Walsh
Review Date: 12/15/04

Review Cycle 2
Date Submitted: 6/21/04
Date Received: 6/23/04
Goal Date: 12/23/04
Extended Goal Date: N/A
Proposed Action: AP

	STATUS	COMMENTS
ACTION LETTER	Draft	Add statement that sponsor need not [ ]
EXCLUSIVITY CHECKLIST	Draft	Draft exclusivity checklist in action package.
DEBARMENT STATEMENT	Complete	Sponsor's debarment certification in action package.
PEDIATRIC PAGE	Complete	[ ] Partial waiver for 0-6 months; Deferral for 6 mos-17 years.
TRADE NAME REVIEW	Complete	Acceptable (see Cycle 1 final DMETS review dated 9/16/02).
DSI AUDITS	Complete	Clinical audits completed in Cycle 1; Biopharm audits not requested.
FACILITY INSPECTIONS	Complete	Acceptable on 8/24/04 (see Cycle 2 final CMC review dated 11/3/04, page 21).

REVIEWS	STATUS	COMMENTS
DIV. SUMMARY REVIEW	Pending	
CLINICAL	Draft	Cycle 2 draft clinical review in action package.
SAFETY UPDATE	Draft	Covered in Cycle 2 draft clinical review.
FINANCIAL DISCLOSURE	Complete	See cycle 1 clinical review dated 9/26/03, page 21.
STATISTICAL	Complete	Cycle 2 final review dated 11/18/04 in action package.
BIOPHARM	Draft	Cycle 2 draft biopharm review in action package.
CMC	Draft	Cycle 2 final CMC review dated 11/3/04 in action package; Cycle 2 final ONDC review dated 12/13/04 in action package. Second cycle 2 CMC draft review addressing carton/container labeling issues in action package.
EA	Complete	Claim of categorical exclusion acceptable (see Cycle 1 final CMC review dated 9/25/03, page 112).
MICRO (validation of sterilization)	N/A	
STABILITY (stats)	N/A	
PHARM/TOX	Pending	Revisions to Cycle 2 review in progress per Ken Hastings' e-mail of 12/9/04 (attached).
CAC (stats)	Complete	See final stats review of IND 45,457 dated 5/2/01.
CAC/ECAC REPORT	Complete	See final report dated 7/5/01 and addendum dated 8/2/01

Labeling: FDA revisions faxed to sponsor 11/30/04. Negotiations pending.

Postmarketing Commitments: In AE letter dated 10/2/03, sponsor was requested to conduct a study to assess the potential association of bone fracture with use of Enablex. However, Cycle 2 draft clinical review ruled out possible association. FDA to withdraw request for post-marketing commitment to conduct this study.

Advisory Committee Meeting: N/A

Comments:

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
12/21/04 03:06:18 PM
CSO

Margaret Kober
12/21/04 04:01:29 PM
CSO
signed for Maria Walsh

Lynne Fahey McGrath, MPH, PhD
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corpoation
One Health Plaza
East Hanover, N.J. 07936-1080
Tel: 862 778 5139
fax: 973-781-3966
lynne.mcgrath@pharma.novartis.com

December 10, 2004

Attention: Daniel Shames, MD
Division of Reproductive and Urological
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA #21, 513

Enablex® (darifenacin)

Amendment to a Pending Application

Revised PPI Draft Labeling

Dear Dr. Shames,

Reference is made to the comments and revisions to the Patient Information Leaflet received from FDA on December 3, 2004. Novartis has reviewed the Division comments and propose the attached PPI dated December 10, 2004 for your review.

This notification is submitting in accordance with the guidance for industry entitled:

Providing Regulatory Submissions in Electronic Format – NDAs (January 1999).

The relevant technical details of the electronic portions of this submission are as follows:

- Submission size: MB
- Electronic media: one compact disk
- Virus scan: Network Associates Incorporated VirusScan© version 4.50 (formerly known as the McAfee VirusScan). The submission is virus free.

If you have any questions or concerns regarding this submission you can call me at (908) 432-9605 or (862) 778-5139.

Sincerely,

Lynne Fahey McGrath, MPH, Ph.D

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

NOVARTIS

May 24, 2004

Author(s):	Lynne Fahey McGrath, MPH, Ph.D.
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3 pages redacted from this section of the approval package consisted of draft labeling

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2004

To: Lynn McGrath, Ph.D.

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513: CMC comments for carton labels

Total no. of pages including cover: 1

Comments: see comment below.

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

Dear Lynn,

As I mentioned in my voice message left today at 2:45 PM, the CMC reviewer had the following comments to convey regarding your recently-submitted container/carton labels:

The phrase "Extended-release tablet" should not be separated in the purple-shaded area. Instead, the labels should be revised so that the "Extended-release tablets" phrase is directly beneath the approved USAN name (darifenacin) in the white area of the label. Additionally, the "Extended-release tablets" phrase should appear in an identical size and font as is used for the approved USAN name. The "Extended-release tablets" phrase should be left-justified with the trade name and the approved USAN name.

Please submit revised color mock-ups as soon as feasible.

Sincerely,

/S/

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

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/s/

Jean Makie
12/6/04 02:54:25 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2004

To: Lynn McGrath, Ph.D.

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513: Division comments/revisions to Sponsor proposed PPI

Total no. of pages including cover: 5

Comments: see comment below.

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

Dear Lynn,

Please find attached revised patient package insert (PPI) labeling from the Division.

Sincerely,

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

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2004

To: Lynn McGrath, Ph.D.

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513: Division comments/revisions to Sponsor proposed PI

Total no. of pages including cover: 21

Comments: see comment below.

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

Dear Lynn,

In follow-up to my telephone call today, please find attached revised package insert (PI) labeling from the Division.

Sincerely,

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

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

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

DATE: November 2, 2004

TO: Daniel Shames, MD, Director
Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

FROM: Claudia B. Karwoski, Pharm.D., Scientific Coordinator (detail)
Office of Drug Safety, HFD-400

DRUG: Enablex® (darifenacin)

NDA #: 21-513

APPLICANT: Novartis

SUBJECT: Review of Proposed Risk Management Plan (RMP) submitted September 15, 2004

PID #: D040625

Overall, the Enablex® (darifenacin) Risk Management Plan[1], as submitted on September 15, 2004 does not appear to differ substantially from a typical new product labeling and routine passive post-marketing safety surveillance.

Enablex® is a selective muscarinic M3 receptor antagonist targeted at the treatment of overactive bladder (OAB). The Enablex® clinical development program included over 7000 patients exposed to doses up to 5 times its recommended therapeutic dose of 7.5 and 15 mg in 97 completed studies. The sponsor states in their submission that one-year long-term data is already available, and a 2-year open label study is ongoing. The most common adverse events observed were dry mouth, constipation and dyspepsia.[2] Acute urinary retention and severe constipation, two safety concerns expressed in the original clinical review[3], were felt by the current DRUDP medical officer and team leader to be recognized adverse events of all

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[1] Referred to a Risk Minimization Action Plan (RiskMAP) per Draft Guidance to Industry:Development and Use of Risk Minimization Action Plans (RiskMAP) http://www.fda.gov/cder/guidance/5766dft.pdf
[2] Enablex® Draft Risk Management Plan (NDA 21-513, September 13, 2004); Section 3.2.3: pg 7.
[3] Li, Z. Clinical Review of NDA 21-513 Enablex®; September 26, 2003.

drugs in this class[4].

Novartis states that the clinical program has resulted in a good understanding of the potential benefits and risks associated with Enablex® use. Based on this understanding, the sponsor's proposed risk management plan focuses primarily on [ ] the drug to maximize benefits and minimize potential risks and [ ] such that any new risk or benefit will be identified and communicated in a timely fashion.

The Enablex® proposed risk management plan has two elements:

[ ]

The sponsor's stated goal of the risk management plan is to:

- [
-
-
-]

The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. The measures proposed by the sponsor seem reasonable but would appear to be routine given the potential risk. A separate Patient Package Insert (PPI) consult was performed by the ODS Division of Surveillance, Research and Communication Support (DSRCS). Should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

/S/

Claudia B. Karwoski, Pharm.D., Scientific Coordinator (detail)
Office of Drug Safety, HFD-400

[4] Enablex (darifenacin hydrobromide) 4 month status meeting, October 21, 2004.

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/s/

Mary Dempsey
11/2/04 03:53:35 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
11/3/04 11:22:27 AM
DRUG SAFETY OFFICE REVIEWER

5600 Fishers Lane, Rockville, Maryland 20857

Food & Drug Administration
Division of Reproductive and Urologic Drug Products

Fax

To: Lynn McGrath From: Jean Makin

Fax: 973-781-3966 Pages: 5

Phone: Date: 10/21/04

Re: 10/14/04 minutes CC:

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

• Comments:

Hi Lynn -

CMC minutes attached. Please see them - would you let me know when we can expect update?

Thank you - Jean

Division of Reproductive and Urologic Drug Products
Industry Teleconference Meeting Minutes

Date: October 14, 2004 **Time:** 11:00 – 11:30 AM **Location:** Room 18B-37

NDA: 21-513 **Drug:** Enablex™ (darifenacin)

Sponsor: Novartis Pharmaceuticals, Inc.

Indication: Treatment of overactive bladder

Type of Meeting: Guidance

Meeting Chair: Sarah Pope, Ph.D.

Meeting Recorder: Jean Makie, M.S., R.D.

FDA Attendees:

Sarah Pope, Ph.D. – Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Jean Makie, M.S., R.D., – Project Manager, DRUDP (HFD-580)

Novartis Pharmaceuticals Attendees:

Lynne Fahey McGrath, Ph.D. – Associate Director, Regulatory Affairs
Ken Kopec, Ph.D. – Chemistry, Manufacturing, and Controls (CMC
Maria Tolerico, Director, Regulatory Affairs for labeling

Background:

The Division requested a teleconference to discuss remaining CMC review issues.

Discussion:

Item 1
The previous container/carton labeling included bottle labels for 100-count bottles, while the most updated container/carton labels include bottle labels for 90-count bottles. Please clarify the discrepancy.

Sponsor Response: The Sponsor stated they will review previous submissions to determine if this information has been submitted and if so, will inform the Division of electronic location and date. If the information was not previously submitted, the Sponsor will submit a justification summary.

Item 2
For the unit dose label on the 100-tablet unit dose (for institutional use only), place the strength "7.5 mg per tablet" below the established name (similar to the professional sample unit-dose label).

Sponsor Response: The Sponsor agreed and will submit changes on final colored mock-ups.

Item 3
The Sponsor was asked for an update regarding the approval of "darifenacin" as an alternate USAN name. The Sponsor was asked to submit a copy of the USAN approval letter for darifenacin hydrobromide, and the Sponsor was advised to submit a USAN approval letter for darifenacin, if/when obtained.

Sponsor Response: The Sponsor explained that they applied for an expedited review of the USAN name on September 9, 2004 after USAN agreed to review the proposed name "darifenacin." They were informed that it would take 3-4 months. However, the Sponsor will contact their legal department to get clarity on that date. The Sponsor also agreed to submit a copy of the USAN approval letter for darifenacin hydrobromide, and will submit the USAN approval letter for darifenacin, if/when obtained.

Item 4
As a pro-active measure, the Sponsor was asked to submit two versions of the container/carton labels incorporating "darifenacin" and "darifenacin hydrobromide" as the established name on separate sets. The goal of the submission is to have both container/carton labeling schemes on file, in the event that USAN approval of "darifenacin" as an alternate name is delayed.

Sponsor Response: The Sponsor agreed.

Item 5

[ ]

Division Response: Following the teleconference, Ms. Makie conferred with Corrinne Kulick, Pharm.D., BCNSP of DDMAC. [

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/s/

Moo-Jhong Rhee
10/20/04 02:37:04 PM
I concur

5600 Fishers Lane, Rockville, Maryland 20857

Food & Drug Administration
Division of Reproductive and Urologic Drug Products

Fax

To: Lynn McGrath From: Jean Mahan

Fax: 973-781-3966 Pages: 4

Phone: Date: 10/13/04

Re: 9/17/04 Cmte minutes CC:

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

• Comments:

APPEARS THIS WAY
ON ORIGINAL

Division of Reproductive and Urologic Drug Products
Industry Teleconference Meeting Minutes

Date: September 17, 2004 **Time:** 11:00 – 11:30 PM **Location:** Room 18B-37

NDA: 21-513 **Drug:** Enablex™ (darifenacin)

Sponsor: Novartis Pharmaceuticals, Inc.

Indication: Treatment of overactive bladder

Type of Meeting: Guidance

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Meeting Recorder: Albert Perrine

FDA Attendees:

Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Sarah Pope, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Albert Perrine – Project Manager, DRUDP (HFD-580)

Novartis Pharmaceuticals Attendees:

Lynne Fahey McGrath, Ph.D. – Associate Director, Regulatory Affairs
Ken Kopec, Ph.D. – Chemistry, Manufacturing, and Controls

Background:

Novartis Pharmaceuticals requested a guidance teleconference to discuss item number 9 included in the July 12, 2004, information request letter, in which the Division suggested that Novartis express the dosage strength of the product in relationship to the active moiety (darifenacin) only on all container and carton labels.

Discussion:

Novartis:USAN has reviewed and approved the name darifenacin hydrobromide for the product. After receiving your letter dated July 12, 2004, we asked USAN to review the name darifencin only when referring to the product. The consult was sent to USAN approximately two weeks from today and they have agreed to re-review the name. Our concern is that throughout all of our trials, we have referred to the product as darifenacin hydrobromide.

DRUDP: We understand your concerns. If, however, the strength of the product is based on the freebase, you should only use the name darifenacin. On the other hand, if the clinical trials were done with strengths based on salt, then salt will be used as an established name. If you wish to indicate the amount of hydrobromide in the tablet, you could put an * with a footnote that xx mg darifenacin hydrobromide is used to provide x mg of darifenacin.

Novartis: How can FDA distinguish between salts?

DRUDP: This can be done by using an * to indicate the amount of hydrobromide salt used.

Agreements:

Novartis agreed to comply with FDA policy regarding USAN name to use Enablex (darifenacin) on all labeling of the product if it is approved by USAN. They will also forward to the Division USAN's report.

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/s/

Moo-Jhong Rhee
10/13/04 10:12:57 AM

MEMORANDUM

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

DATE: October 4, 2004

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

VIA: Jean Makie, 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 of Patient Labeling for Enablex (darifenacin hydrobromide), NDA 21-513

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Enablex (darifenacin hydrobromide), NDA 21-513. 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 June 21, 2004. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

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.

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/s/

Jeanine Best
10/4/04 09:52:59 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/4/04 12:23:30 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

9/23/04

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

DATE RECEIVED: July 19, 2004	**PDUFA DATE:** December 23, 2004 **DESIRED COMPLETION DATE:** November 1, 2004	**ODS CONSULT #:** 02-0006-2

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

THROUGH: Albert Perrine
Project Manager
HFD-580

PRODUCT NAME: **Enablex** (Darifenacin Hydrobromide Extended-release Tablets) 7.5 mg and 15 mg **NDA: 21-513**	**NDA SPONSOR:** Novartis Pharmaceuticals, Corporation

SAFETY EVALUATOR: Linda Y. Kim-Jung, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Enablex. DMETS considers this a final decision. However, if the approval of the NDA is delayed beyond 90 days the firm should be notified that this name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.
2. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review.
3. DDMAC finds the proprietary name Enablex unacceptable from a promotional perspective. See page 3 for further details. Please contact Debie Tran at 301-827-2828 to discuss further.

/S/

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Carol Holquist, RPh
Director,
Division of Medication Errors and Technical Support
Office of Drug Safety

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 8, 2004

NDA # 21-513

NAME OF DRUG: Enablex
(Darifenacin Hydrobromide Extended-release Tablets) 7.5 mg and 15 mg

NDA HOLDER: Novartis Pharmaceutical Corporation

*****NOTE: This review contains proprietary and confidential information that should not be released to the public. *****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products, to re-review the proprietary name Enablex regarding potential name confusion with other proprietary and established drug names. In our consult, dated August 29, 2003 (ODS consult #02-0006-1), DMETS did not have any objections to the use of the proprietary name Enablex. Revised container labels, carton and package insert labeling were provided for review and comment.

PRODUCT INFORMATION

Enablex is the proposed proprietary name for Darifenacin Hydrobromide Extended-release tablets. Enablex is an M_3 selective receptor antagonist, developed for the treatment of overactive bladder. It will be available as 7.5 mg and 15 mg extended-release tablets. The proposed dose is 7.5 mg daily, which may be increased to 15 mg daily. Enablex will be marketed in bottles of 30, 90, —— tablets.

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 "Enablex" 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

[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/main/trademarks.htm
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

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

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Enablex." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include 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. Since that review, DMETS has identified four additional proprietary names: [redacted] and [redacted] as having potential sound-alike confusion with Enablex, Embrex 600 as having potential look and sound-alike confusion with Enablex, and Engerix B as having potential look-alike confusion with Enablex. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC found the proprietary name Enablex unacceptable from a promotional perspective.

[redacted]

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
[redacted]			
[redacted]	[redacted]	[redacted]	S/A
[redacted]	[redacted]	[redacted]	S/A
Embrex 600	Multivitamins with Calcium and Iron Table	One tablet daily.	L/A
Engerix B	Hepatitis B Vaccine, Recombinant, Injectable Adult: 20 mcg hepatitis B surface antigen/mL Pediatric: 10 mcg hepatitis B surface antigen/0.5 mL	20 mcg/mL IM at 0, 1, and 6 months.	L/A

* Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)
This review contains proprietary and confidential information that should not be released to the public. These names are pending approval.

B. PHONETIC and ORHTOGRAPHIC COMPUTER ANALYIS (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 though the phonetic algorithm. The phonetic search modules return 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. All names considered to have significant phonetic or orthographic similarities to Enablex were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Enablex, the primary concerns raised were related to the potential for confusion with [redacted] *** and the currently marketed products Embrex 600 and Engerix B. [redacted] was reviewed by DMETS on September 24, 2002 and found unacceptable from a safety perspective. The drug was however, approved under an alternate name of Xifaxan on May 25, 2004. Therefore, [redacted] will not be discussed in this review. Upon further review, the IND, [redacted] ***, was not reviewed due to a lack of convincing sound-alike similarities with Enablex. Additionally, [redacted] and Enablex do not have overlapping product characteristics such as the dosage forms, strengths, and route of administration. Moreover, since Enablex is available in two different strengths and [redacted] is dosed by the patient's weight, a prescriber would have to write the strength of the product when prescribing, further differentiating [redacted] from Enablex.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Enablex.

1. Embrex 600 is a chewable prenatal vitamin drug product. Embrex 600 and Enablex share similar letters in their suffixes, (B, E, X) which contributes to the look-alike similarity between the two names. Additionally, the numerical modifier "600" could potentially be omitted on an order, increasing the look-alike similarities with Enablex. However, the beginning portion of the names, "Emb" and "Ena" are orthographically and phonetically different. The additional upstroke of the letter "l" in Enablex helps to distinguish the name from Enablex. Moreover, since Enablex is available in different strengths (7.5 mg and 15 mg), a prescriber would have to write the strength of the product when prescribing, further differentiating Embrex 600 from Enablex. Thus, the potential for confusion between the two names is minimal.

Embrex 600 Enablex

2. Engerix B could potentially have look-alike similarity with Enablex. Engerix B is a recombinant hepatitis b vaccine. The usual adult dose is 20 mcg/mL intramuscularly at 0, 1, and 6 months interval. Engerix B is available in a single-dose vial of 20 mcg /mL (adult formulation) and in a single dose vials and prefilled syringes of 10 mcg/0.5 mL (pediatric/adolescent formulation). Both names start with the letters, "En-" and ends with the letter, "x" which contributes to the look-alike similarity between the two names. Additionally, the letter modifier, "B" of Engerix B could be omitted on an order contributing to the look-alike similarity. However, the downstroke of the letter "g" in Engerix B and the upstroke of the letter "b" in Enablex helps to differentiate between the two names. Moreover, the two products have different dosage forms (injectable vs. tablets), strengths (20 mcg/mL vs. 7.5 mg and 15 mg), and route of administration (intramuscular vs. oral). Additionally, since both products are available in different strengths, a prescriber would have to write the strength of the product when prescribing. Moreover, Engerix B is administered by a healthcare professional and most likely to occur in a hospital, clinic/Dr.'s office setting. The orthographic differences and different product characteristics helps to minimize the potential for confusion between Engerix B and Enablex.

Enablex Engerix B

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

We note that the sponsor adequately addressed most of DMETS' label and labeling comments included in the August 29, 2003 review. However, DMETS has identified the following additional areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

Currently, the expression of the established name and the strength in relationship to active moiety in the product on the container label, carton and insert labeling (including Information for the Patient) are presented inconsistently. The strength of this product is based on the active moiety, Darifenacin, and not the salt, Darifenacin Hydrobromide.

To ensure consistency throughout the entire container label, carton and insert labeling (including Information for the Patient) of the product, revise all labels and labeling so that the established name and strength appear in one of the following formats consistently.

1	Enablex (Darifenacin Extended-release Tablets) 7.5 mg
2	Enablex (Darifenacin Hydrobromide Extended-release Tablets) equivalent to7.5 mg of Enablex
3	Enablex (Darifenacin Extended-release Tablets). 8.929 mg * * Each extended-release tablet contains darifenacin hydrobromide equivalent to 7.5 mg darifenacin.

Please note DMETS prefers option 1 because this nomenclature is consistent with USP recommendations on "labeling of salts of drugs".

B. CARTON LABELING

See General Comment.

C. CONTAINER LABEL

1. See General Comment.

2. For the unit dose label of 100 Tablets Unit Dose (for institutional use only), place the strength, "7.5 mg per tablet" below the established name (like the professional sample unit-dose label).

D. PACKAGE INSERT LABELING

1. See General Comment.

2. Under How Supplied section of Enablex 7.5 mg, add bottle of 30 tablets.

E. INFORMATION FOR THE PATIENT LABELING

See General Comment.

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Enablex. DMETS considers this a final decision. However, if the approval of the NDA is delayed beyond 90 days the firm should be notified that this name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review.

3. DDMAC finds the proprietary name Enablex unacceptable from a promotional perspective.
[redacted] See page 3 for further details. Please contact Debie Tran at 301-827-2828 to discuss further.

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/

Linda Y. Kim-Jung, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Linda Kim-Jung
9/23/04 01:36:03 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/24/04 11:51:47 AM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director of DMETS

16 Pages Redacted of
Deliberative Process
§ 552(b)(5)

American Medical Association
515 North State Street, 8th Floor
Chicago, Illinois 60610

Phone: 312-464-4906
Telefax: 312-464-4023
sandra_van_laan@ama-assn.org
www.ama-assn.org/go/usan

Sandra Van Laan
Council Assistant Secretary
USAN Program

September 29, 2004

CTRY:	☐ NF ☐ CTM ☐ INT		
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		P/L	TS
CL:			
Prison ☐	CONFLICT: ☐ active ☐ passive No.: other TM:		

RR-29

Novartis Pharma AG
Corporate Intellectual Property
Lichtstrasse 35
CH-4002 Basel
Switzerland

Attn.: Andreas Hohenberger
Trademark Attorney

Dear Mr. Hohenberger:

It is my pleasure to inform you that the USAN Council adopted *darifenacin* as the United States Adopted Name for UK 88525, Novartis Pharma's product intended for the treatment of overactive bladder.

Please review this information for accuracy, initial, and return the statement to me within 60 days of the date listed above. After December 1, 2004, the information on *darifenacin* will be scheduled for posting on the homepage of the USAN Web site (www.ama-assn.org/go/usan). At that time, the same information will be forwarded to the United States Pharmacopeial Convention, Inc., for publication in the USP Dictionary of USAN and International Drug Names.

You may mail, fax, or e-mail any changes or comments regarding the publication of *darifenacin* to me any time before December 1, 2004.

Sincerely,

Sandra Van Laan

Sandra Van Laan
Assistant Secretary
USAN Council

N04
80

September 29, 2004

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

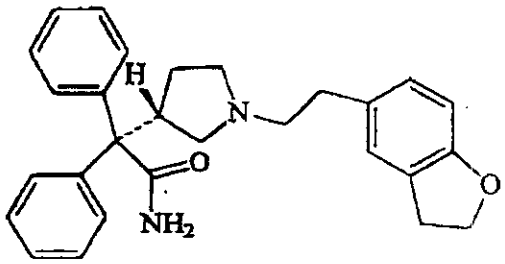
USAN (RR-29)	DARIFENACIN
PRONUNCIATION	dar ee fen' a sin
THERAPEUTIC CLAIM	treatment for an overactive bladder

CHEMICAL NAMES

1). 3-pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3*S*)-

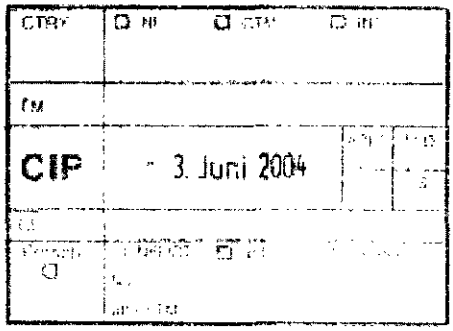
2). (*S*)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-3-pyrrolidineacetamide

STRUCTURAL FORMULA



MOLECULAR FORMULA	$C_{28}H_{30}N_2O_2$
TRADEMARK	Unknown as yet
MANUFACTURER	Novartis, International AG
CODE DESIGNATION	UK-88525
CAS REGISTRY NUMBER	133099-04-4
WHO NUMBER	7153

SVL



American Medical Association
515 North State Street
Chicago, Illinois 60610

Telefax 312-464-4028
stephanie_shubat@ama-assn.org

STEPHANIE C. SHUBAT, Associate Secretary
312-464-5352

May 26, 2004

OO-85
Novartis Pharma AG
Corporate Intellectual Property
Lichtstraße 35
CH-4002 Basel
Switzerland

Attn.: Andreas Hohenberger
Trademark Specialist

Dear Mr. Hohenberger:

It is my pleasure to inform you that the USAN Council adopted *darifenacin hydrobromide* as the United States Adopted Name for UK 88525-04 (hydrobromide), a product designed for the treatment of overactive bladder.

Please review this information for accuracy, initial, and return the statement to me within 60 days of the date listed above. Irregardless, after August 1, 2004, the information will be scheduled for posting in the "What's New" section of the USAN web site (www.ama-assn.org/go/usan). At the same time, the information on *darifenacin hydrobromide* will be submitted to the United States Pharmacopeial Convention, Inc., for publication in the *USP Dictionary of USAN and International Nonproprietary Names*.

You may mail, fax, or e-mail any changes, regarding the publication of *darifenacin hydrobromide* to me at any time before August 1, 2004

Sincerely,

Stephanie C. Shubat

Stephanie C. Shubat
Associate Secretary,
USAN Council

enclosure: N04/63

May 26, 2004

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

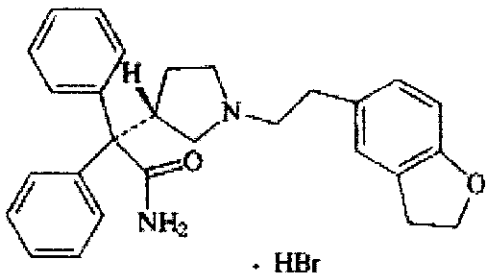
USAN (QQ-85)	DARIFENACIN HYDROBROMIDE
PRONUNCIATION	dar ee fen' a sin
THERAPEUTIC CLAIM	Treatment for an overactive bladder

CHEMICAL NAMES

1). **3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, monohydrobromide, (3*S*)-**

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

STRUCTURAL FORMULA



· HBr

MOLECULAR FORMULA	$C_{28}H_{30}N_2O_2 \cdot HBr$
MOLECULAR WEIGHT	507.5
TRADEMARK	Enablex™
MANUFACTURER	Novartis, International, AG
CODE DESIGNATION	UK-88525-04 (hydrobromide)
CAS REGISTRY NUMBER	133099-07-7
WHO NUMBER	7153

SCS

NOVARTIS

October 22, 2004

Attention: Daniel Shames, MD
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA #21, 513

Enablex® (darifenacin)

Response to Information Request

Dear Dr. Shames,

Reference is made to the 14 October 2004 teleconference with the Division of Reproductive and Urological Drug Products to discuss chemistry revisions to the carton and container labels. Specifically, Dr. Sarah Pope had discussed the following three issues:

1. Please explain the change from — count to 90 count bottles.

Response: This was first described in the "Labeling History" document submitted on June 21, 2004 with the Complete Response to the Oct 2, 2003 Approvable Letter. As you indicated this was not detailed as a change to the carton and container labels, but was described as a change to the "How supplied section" of the prescribing information. The carton and container labels submitted on June 21, 2004 did contain this change. The change was made to accommodate mail-order requests to pharmacies which are commonly asked to provide 3-month supplies. Therefore, 90 tablet bottles would facilitate supply to patients availing themselves of this low cost option. This change is now described in the attached *history.pdf* document.

2. Please place the dose under the established name.

Response: This requested change has been made on all relevant carton and container labels, and can be viewed in the attached files *carton. pdf* and *container.pdf*.

3. **Although the FDA had recommended on 17 September 2004 that they would prefer Novartis use "darifenacin" as the established name, this had not been confirmed as a USAN name. Therefore, FDA had requested that Novartis submit two sets of carton and container labels with both the established name "darifenacin" and "darifenacin hydrobromide." If prior to approval Novartis receives confirmation of the established name, "darifenacin", then this name may be used.**

Response: Novartis has received confirmation that darifenacin has been adopted by USAN council. The confirmation letter is attached as USAN_01.pdf. In addition, the STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL is attached as USAN_02.pdf. In addition, confirmation of the USAN name for "darifenacin hydrobromide" are attached as USAN_03 and USAN_04. Based on the receipt of these letters, Novartis is now able to follow the FDA recommendation to use "darifenacin" as the established name. Therefore, carton and container labels with "darifenacin" and not "darifenacin hydrobromide" are included in this submission in attached files labeled *carton. pdf* and *container.pdf*.

This notification is submitting in accordance with the guidance for industry entitled:

Providing Regulatory Submissions in Electronic Format – NDAs (January 1999).

The relevant technical details of the electronic portions of this submission are as follows:

Submission size: 6.5 MB

Electronic media: one compact disk

Virus scan: Network Associates Incorporated VirusScan© version 4.50 (formerly known as the McAfee VirusScan). The submission is virus free.

If you have any questions or concerns regarding this submission you can call me at (908) 432-9605 or (862) 778-5139.

Sincerely,

Lynne Fahey McGrath, MPH, Ph.D

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: 13 September 2004

To: Lynne Fahey McGrath, MPH, Ph.D. Associate Director, Drug Regulatory Affairs	**From:** Albert Perrine RN, BSN Project Manager
Company: Novartis Pharmaceutical Corporation	Division of Reproductive and Urologic Drug Products
Fax number: (973) 781-3966	**Fax number:** (301) 827-4267/4272
Phone number: (862) 781-3966	**Phone number:** 301-827-7511

Subject: 45 Day Information Request Letter.

Total no. of pages including cover: 4

Comments:

Document to be mailed: X YES NO

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-513

INFORMATION REQUEST LETTER

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 hydrobromide) 7.5 mg and 15 mg extended release tablets.

We are reviewing your Complete Response dated June 21, 2004, received June 23, 2004, and have the following requests and recommendation:

1. As discussed with Albert Perrine, Project Manager, in a brief final safety update, that should be submitted by September 23, 2004, provide us with the verified serious adverse events (SAEs) for the reporting period of July 31, 2003, through December 18, 2003.

2. On page 5383, Table 1.1, clarify if time-averaged or time-matched baseline QT/QTc values were employed for each study endpoint (E_tmax, E_mean, and E_max). If time-averaged baseline values were employed to calculate the change in QT/QTc at pK tmax (E_tmax), provide additional data comparing day 6 QT/QTc_tmax to the corresponding time-matched baseline values. For calculating the mean change from baseline (E_mean), provide clarification whether time-averaged baseline values (mean over 24 hours) were employed for comparison. If not, provide this analysis for review. Additionally, include non-baseline subtracted QT/QTc intervals for each of the four treatments on day 6.

3. During the February 13, 2004, teleconference you agreed to conduct a comparison of exposure results from the QT study and from the studies submitted in the original NDA in order to verify EM and PM exposure. Please confirm whether or not these data are in your complete response.

4. Provide the raw data collected from study DAR 328A2302, your thorough QT study, in SAS transport file format. We specifically would like the following columns of data: Subject Identification, Treatment, Dose, Day of Sample, Nominal Time of Sample, Measured Time of Sample, QT, QTcF, RR interval, Plasma Concentration of Drug, Plasma Concentration of Metabolite(s), Gender of Subject, and CYP Classification (EM vs. PM).

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Margaret Kober
9/9/04 12:13:50 PM
Chief, Project Management Staff

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

Foreign Labeling

Not applicable for this application.

/S/
9/3/03

Lynne Fahey McGrath, MPH, PhD
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corpoation
One Health Plaza
East Hanover, N.J. 07936-1080
Tel: 862 778 5139
fax: 973-781-3966
lynne.mcgrath@pharma.novartis.com

August 27, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA #21, 513

Enablex® (darifenacin hydrobromide)

Extended Release Tablets
Prior Approval Amendment

Dear Sirs:

Reference is made to the July 12, 2004 comments from Dr. Moo-Jhong Rhee requesting revisions to the carton and container labels. All comments regarding these labels are addressed in this submission. Please review the Label History document for details on these changes. Comments from Dr. Rhee regarding the Package Insert have been taken under advisement and will be included in a subsequent submission of the PI.

Please note, this submission also includes container labels for [redacted] Again, the comments from Dr. Rhee have been included in these labels.

[redacted]

as

This notification is submitting in accordance with the guidance for industry entitled:

Providing Regulatory Submissions in Electronic Format – NDAs (January 1999).

The relevant technical details of the electronic portions of this submission are as follows:

- Submission size: 2.64 MB

- Electronic media: one compact disk
- Virus scan: Network Associates Incorporated VirusScan© version 4.50 (formerly known as the McAfee VirusScan). The submission is virus free.

If you have any questions or concerns regarding this submission you can call me at (908) 432-9605 or (862) 778-5139.

Sincerely,

Lynne Fahey McGrath, MPH, Ph.D

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

7/23/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-513

Novartis Pharmaceuticals Corporation
Attention: Lynne 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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex™ (darifenacin hydrobromide) 7.5 and 15 mg extended release tablets.

We also refer your May 14, 2004, correspondence, received May 17, 2004, requesting a pre-submission of a Complete Response meeting to discuss the results of your QT study and to receive guidance related to the pediatric deferral process.

Based on the submission of your Complete Response, dated June 21, 2004, received June 23, 2004, we have reconsidered your request for a meeting and now conclude that a meeting at this time is unnecessary. The Division believes that it would be more beneficial to you that we continue with the review of your Complete Response. If, at any time during the review period, we have any questions or comments, we will notify you in a regulatory letter or schedule a meeting that is convenient for both parties.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Margaret Kober
7/23/04 10:27:35 AM
Chief, Project Management Staff

7/8/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-513

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

Dear Dr. McGrath:

We acknowledge receipt on June 23, 2004, of your June 21, 2004, resubmission to your new drug application (NDA) for Enablex™ (darifenacin hybromide) 7.5 mg and 15 mg extended release tablets.

We consider this a complete, class 2 response to our October 2, 2003, approvable letter. Therefore, the user fee goal date is December 23, 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 or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until June 19, 2009. However, in the interim, please submit your pediatric drug 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,

/S/

{See appended electronic signature page}

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

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

/s/

Margaret Kober
7/8/04 11:45:05 AM
Chief, Project Management Staff

NDA 21-513

Supervisory Medical Officer's Memorandum: Response to Approvable

Date received: June 23, 2004
Memo draft completed: December 22, 2004

Drug product (tradename): ENABLEX®
Drug product (established name): darifenacin
Dose: 7.5 mg and 15mg once daily
Route: extended release tablets
Indication: Treatment of Overactive Bladder (OAB)

Sponsor: Novartis Pharmaceuticals Corporation
Related INDs/NDAs: IND #45,457

I. Executive summary:

The purpose of this medical team leader's memo is to provide a regulatory recommendation for NDA 21-513. I recommend that ENABLEX Extended-release tablets be approved for the indication of treatment of overactive bladder (OAB). The efficacy and safety information submitted in the original NDA and in this Response supports approval. The benefits of the drug appear to outweigh the known risks, and the product is considered safe and effective as labeled. The sponsor's Response to the October 2, 2003 Approvable deficiencies is adequate. There are no unresolved issues for this NDA.

II. Clinical results in brief:

1. Efficacy

The original medical officer's review and the original medical team leader's memo provided a comprehensive summary of the efficacy results for ENABLEX. Nevertheless, the basic efficacy results are shown here again:

ENABLEX was evaluated in three randomized, fixed-dose, placebo-controlled, multicenter, double-blind, 12-week studies (Studies 1002, 1041 and 1001) and one randomized, double-blind, placebo-controlled, multicenter, dose-titration study (Study 1047). Studies 1002 and 1041 were conducted completely outside the U.S. Studies 1001 and 1047 had U.S. centers. For study eligibility in all four studies, patients with symptoms of overactive bladder for at least six months were required to demonstrate at least eight micturitions and at least one episode of urinary urgency per day, and at least five episodes of urge urinary incontinence per week. The majority of patients were white (94%) and female (84%), with a mean age of 58 years, range 19 to 93 years. 33% of patients were >65 years of age. These characteristics were well balanced across treatment groups. The study population was inclusive of both naïve patients who had not received prior pharmacotherapy for overactive bladder (60%) and those who had (40%).

Table 1 shows the efficacy data collected from the 7- or 14-day voiding diaries in the three fixed-dose placebo-controlled studies in which 1059 patients were treated with placebo, 7.5 mg or 15 mg once daily ENABLEX for 12 weeks. The table demonstrates that there was statistically significant decreases in the primary endpoint, change from baseline in average weekly urge urinary incontinence episodes in all three studies. Data is also shown for two other clinically important secondary endpoints: change from baseline in the average number of micturitions per day (urinary frequency) and change from baseline in the average volume voided per micturition.

Table 1: Difference Between ENABLEX® (7.5 mg, 15 mg) And Placebo For The Week 12 Change From Baseline (Studies 1041, 1002 And 1001)

	Study 1041			Study 1002			Study 1001	
	ENABLEX® 7.5 mg	ENABLEX® 15 mg	Placebo	ENABLEX® 7.5 mg	ENABLEX® 15 mg	Placebo	ENABLEX® 15 mg	Placebo
No. of Patients Entered	229	115	164	108	107	109	112	115
Incontinence Episodes per Week								
Median Baseline	16.3	17.0	16.6	14.0	17.3	16.1	16.2	15.5
Median Change from Baseline	-9.0	-10.4	-7.6	-8.1	-10.4	-5.9	-11.4	-9.0
Median Difference to Placebo	-1.5 *	-2.1 *	-	-2.8 *	-4.3 *	-	-2.4*	-
Micturitions per Day								
Median Baseline	10.1	10.1	10.1	10.3	11.0	10.1	10.5	10.4
Median Change from Baseline	-1.6	-1.7	-0.8	-1.7	-1.9	-1.1	-1.9	-1.2
Median Difference to Placebo	-0.8 *	-0.9 *	-	-0.5	-0.7 *	-	-0.5	-
Volume of Urine Passed per Void (mL)								
Median Baseline	160.2	151.8	162.4	161.7	157.3	162.2	155.0	147.1
Median Change from Baseline	14.9	30.9	7.6	16.8	23.6	7.1	26.7	4.6
Median Difference to Placebo	9.1 *	20.7 *	-	9.2	16.6 *	-	20.1 *	-

* Indicates statistically significant difference versus placebo ($p<0.05$, Wilcoxon rank-sum test)

Table 2 below shows the efficacy data from the dose-titration study (Study 1047) in 395 patients who initially received 7.5 mg ENABLEX or placebo daily with the option to increase to 15 mg ENABLEX or placebo daily after 2 weeks. This table demonstrates statistically significant differences between drug and placebo for all three endpoints.

Reviewer's comment: It is clear from the results of these four clinical studies that Enablex provides clinically relevant improvement in the signs and symptoms of OAB at the 7.5mg and 15 mg fixed doses, and when using a dose up-titration regimen.

The only other efficacy issues of note were the following:

1. Treatment effect was seen across subgroups. However, the non-Caucasian subgroup accounted for only approximately 5% of all enrolled patients. There is no reason to assume that symptomatic relief would be different in this group.
2. There was evidence of efficacy in both young and older patients.
3. There was evidence of efficacy in both men and women, although the effect of the 7.5mg dose was less robust in men.
4. The treatment effect was seen as early as 2 weeks after initiating therapy and was consistent for the 12 weeks of the pivotal trials.
5. A dose of 3.75mg was not sufficient to relieve symptoms. A dose of 30mg showed numeric increase in symptom relief, but was associated with an increased incidence of side effects.
6. The reviewer believes that efficacy data from non-U.S. populations is applicable to the U.S. population.

Table 2: Difference Between ENABLEX® (7.5 mg/15 mg) And Placebo For The Week 12 Change From Baseline (Study 1047)

	ENABLEX® 7.5 mg / 15 mg	Placebo
No. of Patients Treated	268	127
Incontinence Episodes per Week		
Median Baseline	16.0	14.0
Median Change from Baseline	-8.2	-6.0
Median Difference to Placebo	-1.4*	-
Micturitions per Day		
Median Baseline	9.9	10.4
Median Change from Baseline	-1.9	-1.0
Median Difference to Placebo	-0.8 *	-
Volume of Urine Passed per Void (mL)		
Median Baseline	173.7	177.2
Median Change from Baseline	18.8	6.6
Median Difference to Placebo	13.3 *	-

* Indicates statistically significant difference versus placebo ($p<0.05$, Wilcoxon rank-sum test)

2. Safety

2.1 Effect of Darifenacin on the QT Interval

On October 2, 2003, the Approvable action letter issued by the Division requested that sponsor submit the results from a prospective, randomized, double-blind, "thorough" QT study including both positive and placebo controls, to evaluate the effect of darifenacin on cardiac repolarization at therapeutic and supratherapeutic drug concentrations. The reviewer herein provides a brief summary of the rationale for this request, the design and results of the study, and conclusions of the study.

2.1.1 Background for the QT issue

The original NDA contained a large amount of information related to the effect of darifenacin on cardiac conduction. Yet, the Division found that data insufficient. First, there was evidence from pre-clinical studies that darifenacin might prolong the QT interval. This evidence came from HERg channel and dofetile-binding studies and in vivo dog assessments. Second, human studies were concerning in that they also appeared to demonstrate a possible prolongation of the QT interval. For example, Studies 1007 and 1035 were drug interaction studies which employed darifenacin doses of 30mg (Study 1007), or 7.5 and 15mg (Study 1035) in combination with ketoconazole or with placebo. The results of these two studies demonstrated a mean difference between darifenacin+ketoconazole and darifenacin+placebo of approximately 10-12 msec, regardless of darifenacin dose.

The sponsor argued that the results of these drug interaction studies actually should be interpreted as a direct effect of ketoconazole on the QT, not an effect of darifenacin on QT. Sponsor provided literature to support this assertion. Nevertheless, the Division concluded that these two studies might actually implicate darifenacin. Even if these studies did not directly confirm an effect of darifenacin on the QT, the Division believed strongly that the studies could not rule out such an effect. Neither contained a positive control group for QT prolongation, nor a placebo-placebo group. Neither had multiple ECGs at baseline or at around the time of maximum darifenacin concentration. The number of patients included in the QT analysis was actually very small and was less than the total number enrolled.

The sponsor provided two additional pieces of evidence to exonerate darifenacin. First, sponsor presented a pooled analysis of QT data from 964 darifenacin-treated subjects and 261 placebo-treated subjects from four studies (Study 137-684, A1371002, A1371007 and A1371015). From this data, the sponsor concluded that there was no evidence to associate darifenacin with any statistical or clinically relevant increase in the QT interval. In this analysis, the percentage of subjects with a maximum individual increase in QTcF from baseline of >30 msec or >60msec was the same for darifenacin and placebo. Again, the Division found this piece of evidence deficient. The pooled analysis lacked a comparison with a positive control. It was also not clear how sponsor selected the studies for the pooled analysis. Some of the studies specifically excluded users of concomitant potent inhibitors of CYP 3A4, thereby limiting maximal potential systemic darifenacin exposure.

Finally, the sponsor submitted the results from Study 1015, a Phase 1 study evaluating the safety, tolerability and pK of darifenacin at doses of 30mg, 60mg and placebo daily for 14 days. Results from an analysis of QT data at baseline and at Day 14 showed no apparent difference between groups. Again, the Division concluded that this study was not sufficient to rule out an independent effect of darifenacin. The Division argued that there was no positive control to document assay sensitivity. Further, ECGs were done only once at baseline and once at Hour 4 after dosing on Day 14. Finally, it was not clear that 60mg provided high enough systemic darifenacin exposure; for example, in the case of a CYP 2D6 poor metabolizer taking a potent 3A4 inhibitor.

Therefore, based on these data, the Division went ahead and issued an Approvable letter which included the inability to rule out an effect on QT as the major Approvable deficiency. The sponsor and Division held several discussions after the action in order to come to agreement on a protocol for the thorough QT study. With the agreement with the Division, the sponsor conducted this "thorough" QT study and submitted the results in this Response to Approvable.

2.1.2. Design, Results, and Conclusions from the Thorough QT Study

QT Study Design

This was a single-center, double-blind, placebo and active-controlled, randomized, and parallel-arm design, multiple-dose trial. Enrollment was stratified by cytochrome P450 CYP2D6 metabolic status, by age and by gender, with CYP 2D6 status taking priority in the event of randomization difficulties. Subjects were randomized to receive placebo, moxifloxacin (Avelox® 400 mg) or darifenacin (15 or 75 mg) for 6 days. Serial digitized ECGs were collected in triplicate at 13 pre-specified time points on Day -1 and on Day 6. Blood samples were collected on Day 2-5 for trough measurements to verify attainment of steady-state. Blood collections were time matched to ECG on Day 6 to assess the relationship between darifenacin maximal concentrations and QTcF interval.

The trial included one day of placebo run-in (Day -1) and 6 days of study drug treatment. 188 subjects were enrolled and all completed the trial. ECG data analysis was conducted on 179 of the 188 completed subjects as 8 subjects (#5174, #5181, #5191, #5230, #5239, #5241, #5252 and #5253) had multiple artifact recordings on either Days -1 or 6 and the Day 6 flash card (containing ECG data) for 1 (5236) subject was lost.

The study was powered to detect a difference of 5 milliseconds between the darifenacin groups and placebo in the mean change from baseline to Tmax in QTcF, based upon a two-sided t-test at a 5% significance level. The primary endpoint in this study was the change from baseline to Day 6 in QTcF_tmax, where QTcF_tmax is the QTcF at the PK sampling time corresponding to the maximum plasma darifenacin concentration. The secondary endpoints were QT/QTc mean change-from-baseline to Day 6 (all 24-hour collection points taken into consideration), and the change from baseline to the mean maximum QT/QTc interval on Day 6.

Darifenacin 15 mg is the maximum recommended dose and represents the "therapeutic dose" in this QT study. Darifenacin 75 mg (5X the maximum recommended dose) represents the "supratherapeutic dose". The 75mg dose was selected because it would allow for reasonable assessment of change in QT interval with change in darifenacin serum concentrations, and it was expected to achieve systemic darifenacin exposure comparable to that observed in CYP2D6 poor metabolizers (PMs) taking 15 mg darifenacin in combination with ketoconazole.

The actual pharmacokinetics observed in this study in poor CYP 2D6 metabolizers in the 75mg group was, in fact, comparable to that observed in three CYP 2D6 poor metabolizers administered 15mg in combination with ketoconazole. Specifically, the mean Cmax and AUC in the 75mg group in 7 poor metabolizers was **68.5 ng/mL** and 1219ng•hr/mL, respectively. In the 5 females poor metabolizers given 75mg, the mean Cmax and AUC was higher, **84.5 ng/mL** and 1487 ng•hr/mL, respectively. According to Figure 3 of Dr. Apparaju's final report, the Cmax values for some patients in the 75 mg group reached up to **130 ng/mL**. In the original NDA, the Cmax and AUC for one poor metabolizer who received 7.5mg + ketoconazole was 55.4 ng/mL and 939 ng•hr/mL, respectively. The Cmax and AUC for one poor metabolizer who received 15 mg + ketoconazole was 58.9 ng/mL and 931 ng•hr/mL, respectively. Finally, in the original NDA, there were two CYP 2D6 poor metabolizers who were given 30mg + ketoconazole for three days, then 15mg + ketonazole for 3 days. In those two subjects (#013 and #014 of Study 1007), the Cmax values were 115 ng/mL and 79.9 ng/mL .

These results are depicted graphically in Figure 1 below. The figure is derived from Dr. Apparaju's primary clinical pharmacology review.

Reviewer's comments:

1. As an additional precaution, the label states that the maximum recommended dose in patients taking concomitant potent 3A4 inhibitors is 7.5 mg, not 15 mg.

2. The incidence of dry mouth in the 75mg group was approximately 50%. Blurry vision was reported in 4%. Therefore, it is anticipated that concentrations above those achieved with 75 mg would be difficult to tolerate due to systemic anticholinergic effects.

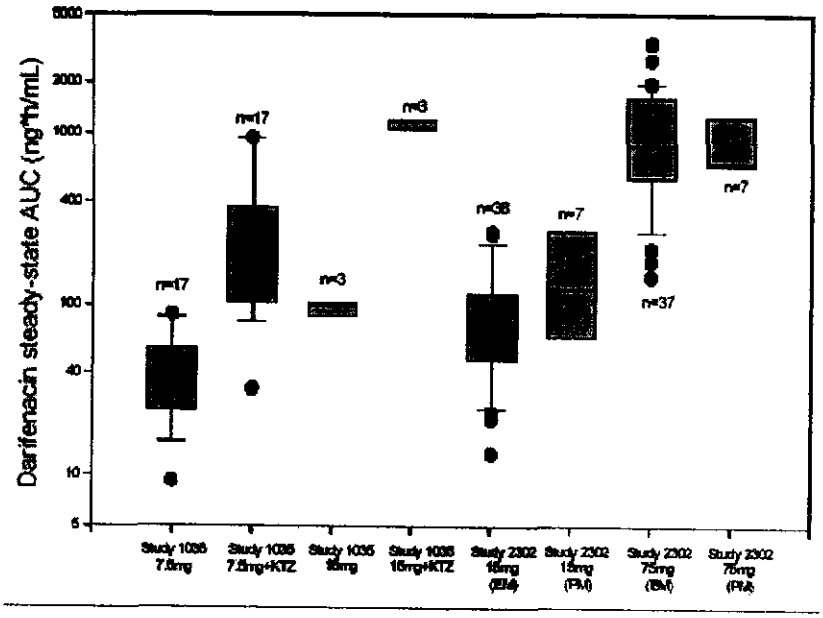


Figure 1: Darifenacin systemic exposure following the administration of 7.5 mg and 15 mg doses with ketoconazole in Study 1035 and 15 mg & 75 mg doses in Study 2302 (QT study). The exposure achieved with 75 mg darifenacin dose in study 2302 (QT study) was comparable to the highest exposure observed following administration of 15 mg darifenacin with ketoconazole.

QT Study Results

Aside from the primary central tendency analysis (change-from-baseline to Tmax on Day 6), the following additional analyses were conducted:

- Mean maximum change from baseline on Day 6
- Mean change from baseline (averaged over the 24-hour collection period) on Day 6
- Various categorical analyses

Table 3 provides results for the primary endpoint, change from baseline in QT/QTc at Tmax.

Table 3: Mean QT Interval Change from Baseline to Tmax on Day 6 - with Placebo Subtracted

Interval (msec)	Darifenacin 15 mg	Darifenacin 75 mg	Avelox® 400mg
QT	-4.9	-8.2	20.5
QTcF	-0.4	-2.2	11.6
QTcB	2.5	2.0	6.4

Table 4 provides results for a secondary analysis of QT data, mean change from baseline in QT/QTc (over the 24-hour collection period) on Day 6.

Table 4: Mean QT Change from Baseline to Day 6 (Mean Over the 24-Hour Collection Period) – with Placebo-Subtracted

Interval (msec)	Darifenacin 15 mg	Darifenacin 75 mg	Avelox® 400 mg
QT	-4.0	-0.1	9.3
QTcF	-1.6	-1.2	6.9
QTcB	0.2	-1.2	5.8

It is clear that Avelox ® (moxifloxacin) significantly prolonged the QT/QTc intervals, indicating that this study was capable of detecting a small increase in the QT interval. For moxifloxacin, the mean, placebo-subtracted change in QTcF from baseline to Tmax on Day 6 was +11.6 msec (Table 3). The mean, placebo-subtracted change in TcF from baseline to Day 6, averaged over the 24-hour collection period, was +6.9 msec (Table 4).

In contrast, darifenacin did not result in an increase in QT interval compared to placebo at either the therapeutic or supratherapeutic dose strengths administered for 6 consecutive days. For 15mg, the mean, placebo-subtracted change in QTcF from baseline to Tmax on Day 6 was –0.4 msec, and for 75mg this value was –2.2 msec (Table 3). When baseline was compared to the mean of the 24-hour collection period on Day 6, the mean placebo-subtracted change-from-baseline was -1.6 msec for QTcF for darifenacin 15mg, and -1.2 msec for darifenacin 75 mg.

> **Reviewer's comment**: Although not provided in Tables 3 or 4, the 90% confidence intervals for the difference from placebo (QTcF_Tmax) for both doses confirm the lack of QT prolongation for darifenacin. They are (-4.1, 3.2 msec) for darifenacin 15mg and (-6.6, 3.2 msec) for darifenacin 75 mg.

QT correction for RR is necessary in "thorough" QT studies in order to adjust absolute QT values for increase in heart rate. According to the sponsor and the clinical pharmacology reviewer, in this study, the Bazett's method resulted in over-correction, but the Fridericia's method was adequate. When the changes-from-baseline in heart rate were computed for the 24-hour duration on Day 6, the 15 mg and 75 mg doses of darifenacin resulted in mean increases of 8.4 ± 2.9 and 6.6 ±2.8 beats per minute (bpm), respectively. Placebo and moxifloxacin demonstrated increases from baseline in heart rate of 5.3 ± 2.4 and 3.3 ± 1.0 bpm, respectively.

> **Reviewer's comment**: The effect of darifenacin 75 mg on heart rate was fairly small compared to placebo, even at five times the maximum recommended dose.

Categorical analyses of the QT data were also conducted. One of these is depicted in Table 5.

Table 5: Number(%) Subjects with Change from Baseline for QTcF >30 msec or >60 msec

Treatment	>30 msec N(%)	>60 msec N(%)
Darifenacin 15 mg	8 (17%)	0
Darifenacin 75 mg	8 (19%)	0
Avelox 400 mg	18 (39%)	2 (4%)
Placebo	9 (20%)	0

Finally, sponsor reports that there were no subjects with QTcF >480 msec while on treatment. There were two subjects, one in the darifenacin 75 mg group and one in Avelox 400 mg group with a reported QT interval >450msec. However, the subject in darifenacin group had a higher baseline QT of 455 msec with a Day 6 value of 469 msec. When Fridricia's correction was used, there were two subjects in the high dose darifenacin group with QTcF >450 msec and none in the other groups. It is possible that this reflects the higher baseline QTcF vales in the 75 mg group compared to the other groups.

QT Study Conclusion

Multiple dose treatment for 6 days with therapeutic (15 mg) or supratherapeutic (75 mg) doses of darifenacin was not associated with QT/QTc interval prolongation. Assay sensitivity was clearly demonstrated. The concentrations attained in poor CYP 2D6 metabolizers taking 75mg were comparable to those attained in poor CYP 2D6 metabolizers taking 7.5mg or 15mg with the potent CYP 3A4 inhibitor ketoconazole 400mg daily.

2.2. Urinary Retention and Constipation

Darifenacin is a potent muscarinic receptor antagonist. The sponsor purports that darifenacin has a greater in vitro affinity for the M3 subtype receptor than for M1, M2, M4 or M5 (9 and 12-fold greater affinity for M3 compared to M1 and M5, respectively, and 59-fold greater affinity for M3 compared to both M2 and M4). It is important for the reader to understand that M3 receptors are involved in contraction of human bladder and gastrointestinal smooth muscle, saliva production, and iris sphincter function. Therefore, adverse drug effects such as dry mouth, constipation, urinary retention and accommodation disturbance may be mediated through effects on M3 receptors in these organs.

In human trials, there were reports of some antimuscarinic side effects similar to those recognized for the class. For example, dry mouth, constipation, and urinary hesitancy/retention were reported frequently. Visual disturbance was reported as an adverse event infrequently at the recommended doses, but more frequently (approximately 4%) in subjects administered 75mg for 6 consecutive days. In a small number of cases, urinary retention and constipation was actually reported as serious adverse events. In the Approvable letter, the sponsor was advised to describe the serious events of constipation and urinary retention in the label in a clear manner with appropriate cautionary guidance to the prescriber and patient. In the Complete Response, the sponsor provided a review of these two adverse events and incorporated specific language into the label in the Precautions and Adverse Reactions sections. Herein the reviewer provides a brief overview of these two specific adverse events.

2.2.1. Urinary Retention

From the NDA safety database, a total of 49 (0.7%) darifenacin-treated subjects, 2 (0.1%) placebo-treated subjects, and four (0.5%) subjects treated with an active comparator reported an adverse event coded as urinary retention. However, detailed review of these cases revealed that only sixteen of the 49 darifenacin cases were actually "acute urinary retention" (AUR), as generally recognized in the urologic community. The remaining 33 cases were reported as the sensation of incomplete bladder emptying that required neither catheterization nor intervention.

Of the 16 darifenacin cases that were considered to reflect acute urinary retention, only seven (0.11%) were reported as an SAE, as follows:

- One case was reported in a 62 year old male patient with BPH taking part in an IBS (irritable bowel syndrome) study.

- One case was reported in a healthy 76 year old male with BPH taking part in a healthy volunteer study.
- One case was reported in a 75 year old male patient with detrusor hyperreflexia secondary to stroke.
- The remaining four serious cases were reported in OAB studies, but all four occurred in patients taking a daily dose of 30mg. In one of these, an 83 year old Japanese woman with OAB was found to have acute renal failure and bilateral hydronephrosis as a consequence of acute urinary retention.

Of the remaining nine cases, none were reported as serious adverse events. Six of these cases occurred in patients taking 30mg daily. Only three occurred in OAB patients taking the recommended doses, as follows:

- An 80 year old female had AUR after pre-planned hand surgery and required bladder catherization for 1 day.
- A 74 year old Japanese male with BPH had AUR and required bladder catheterization for 2 days.
- A 41 year old female with childhood enuresis, recurrent UTIs, and history of detrusor instability *and urinary outflow obstruction* had dry mouth, dry eyes and AUR. The AUR required only a single emptying of the bladder by straight catheterization (not an indwelling catheter).

Reviewer's comment: The first Precaution in the label is in regard to the potential for urinary retention, especially in those patients with pre-existing bladder outlet obstruction (e.g. men with BPH). In addition, the Adverse Reactions section contains a full paragraph on these specific events. In addition, the dosing strategy (7.5mg starting dose and 15 mg maximum) is expected to minimize this risk. Therefore, the issue of urinary retention has been handled properly and does not preclude approval

2.2.2. Constipation

According to the sponsor, there have been 7,258 subjects treated with darifenacin, 2343 subjects treated with placebo, and 887 subjects treated with an active comparator included in all phase 1, 2 and 3 trials combined.

There were 6 cases of constipation reported as serious adverse events among darifenacin-treated patients (0.083%), 1 among placebo-treated patients (0.043%) and none among patients treated with an active comparator. All 6 cases were classified as treatment-related by the investigators.

Of these six cases, two occurred at doses in excess of the maximum recommended dose, including one healthy volunteer exposed to 60 mg in Study A1371015 (Subject 1130-88) and one OAB patient taking 30mg daily. Two other cases were reported in patients taking part in studies for treatment of Irritable Bowel Syndrome (Study 137351 Subject 2670240 and Study 137356 Subject 1010750). A fifth case was reported in a patient taking part in a study for the treatment of Benign Prostate Hyperplasia (Study A1371026 Subject 0441-51).

Reviewer's comment: In none of these 5 SAE cases was surgical intervention required. These cases were categorized as serious only because they were hospitalized for investigations to rule out more serious etiologies of their constipation.

Therefore, of all 6 cases of constipation as a serious adverse event, only one was in an OAB patient taking the recommended doses. This patient complained of nine months of chronic constipation of moderate severity. She was hospitalized briefly to undergo investigation by colonoscopy. She was released from the hospital promptly without further intervention.

In addition, in the recent thorough QT study, where doses of 15mg and 75mg were administered for 6 consecutive days to healthy volunteers, the reported incidences of constipation were 6.4% and 19.6%, respectively, compared to 2.1% for placebo. None of these events were classified as serious.

> **Reviewer's comment:** The second Precaution in the label describes risk of decreased gastrointestinal motility, especially in susceptible patients. The Adverse Reaction section lists constipation as the second most common adverse event and also contains a separate paragraph for the 6 SAE cases. I believe this issue is handled sufficiently.

2.3. Bone Fractures

The medical review of the original NDA revealed 16 cases of bone fracture reported as SAE's in all darifenacin-treated subjects versus no such reports in those patients treated with placebo. Most of these occurred in open-label, uncontrolled safety extensions. Still, there appeared to be a possible imbalance in the overall, exposure-adjusted incidence between darifenacin and placebo. Therefore, a more detailed review of this issue was undertaken during this review cycle by sponsor and by the Division.

As per the most recent safety data submission, there have been a total of 18 bone fracture cases reported as SAE's among the 7,258 darifenacin-treated patients across the entire clinical program, representing an overall incidence of 0.25% and an exposure-adjusted incidence of 0.82 cases per 100 patient-years. There have been no SAE bone fractures reported in placebo-treated (N= 2343) patients. When the exposure-adjusted incidence of SAE bone fracture was compared between drug and placebo, the difference was not statistically significant ($p = 0.11$) and the 95% confidence intervals for the groups overlapped (95% CI for darifenacin = 0.50, 1.34; versus 95% CI for placebo = 0.00, 1.03).

Ten of the 18 darifenacin cases (56%) occurred in open-label, uncontrolled trials (in Studies 311, 1010, 1017, and 1042). Cases were reported in patients taking all four doses: 3.75mg, 7.5mg, 15mg, and 30 mg, with no apparent dose relationship. The amount of exposure prior to the event (number of days of treatment) was also widely distributed, without any pattern of clustering at the beginning of treatment or increase in number of events over time.

Reflecting the composition of the study populations, 12 of the 18 cases were in females. Eight of the eighteen cases were in patients 65 years of age or older and two cases were in patients 75 years of age or older. The increased frequency in older patients is consistent with observations in general population and demographics of the OAB population.

Nearly all of these cases were reported from study sites outside of North America. Out of 2074 subjects in North America who were exposed to darifenacin, there was one case of SAE fracture. The incidence of 0.18 cases per 100 subject-years in North America was near 5-fold lower than the worldwide reported incidence of 0.82 per 100 subject-years. The geographic disparity in the fracture SAE reporting rate appears to reflect a geographic difference in medical care. Whether an adverse event of fracture was coded as an SAE might have been influenced by geographical differences in hospital admission policies.

In this review cycle, when all serious adverse events of accidental bone fracture were examined and adjusted for the amount of exposure, the confidence intervals for the darifenacin and placebo exposure-adjusted incidences overlapped and the p-value was not significant. This suggests that there is no independent contribution of darifenacin to SAE bone fractures.

In addition, when each case of SAE bone fracture was reviewed individually, there were reasonable alternative etiologies for each (see Table 6 below).

Table 6. All cases of SAE bone fracture in darifenacin-treated patients

Study	Subject ID	Age	M/F	Dose	Day #	Event	Causality (Investigator)	Country
305	00550108	73	F	7.5 mg	80	Fracture lumbar spine	"Suspected osteoporosis"	Sweden
305A	01145066	28	M	15 mg	218	Compression fracture lumbar spine	"Road traffic accident"	France
311	00260016	55	F	15 mg	61	Broken left wrist	Slipped on ice	UK
311	03010192	46	F	30 mg	40	Fracture pelvis	Fell down stairs (Multiple sclerosis)	UK
356	03110245	25	F	3.75 mg	53	Nose fracture; neck injury	"Traffic accident"	Sweden
1001	5060839	89	F	30 mg	8	Fracture right ankle	Slipped on wet kitchen floor	US
1002	0456810	44	F	15 mg	54	Fracture 12th thoracic vertebra/liver injury	Thrown from horse	Sweden
1010	10280002	32	M	30 mg	8	Fracture hip and right distal radius	Motorcycle accident	Spain
1013	10590341	70	M	30 mg	75	Fracture right femur	"Heavy alcohol intake"	Norway
1017	50817068	70	M	7.5 mg	107	Fracture right hip	"Got drunk and fell from a window"	Japan
1017	50777016	65	F	15 mg	39	Compression fracture	"Accidental fall"	Japan
1017	51327127	83	F	15 mg	12	Fracture right tibia and fibula	Electric wheelchair fell down at home	Japan
1041	11260128	55	F	3.75 mg	11	Fracture left tibial plateau	"Attacked by a dog"	Australia
1041	04610481	68	M	7.5 mg	54	Fracture right distal radius	"Transient cerebral ischemia"	Denmark
1042	1140410223	68	F	7.5 mg	69	Fracture hip	"Fell"	Poland
1042	1141410193	46	M	7.5 mg	99	Fracture right leg	"Accident" (paraplegic)	Poland
1042	04520311	41	F	15 mg	424	Fracture right ankle	Post-poliomylelitis	Israel
1042	1175410389	58	F	7.5 mg	340	Fracture right hand bone	"Had an accident"	

Dr. Kaul's primary medical review contains patient narratives for each of these 18 cases. A case-by-case analysis demonstrates an alternative reason for each case without evidence of relationship to darifenacin. There were no reports of dizziness, blurred vision, sleepiness or somnolence in any of the accident cases. Nor is there is any reason to believe that darifenacin has a direct effect on bone.

Finally, the sponsor informed the Division that when all adverse events of fracture were combined (including both serious and non-serious events), then the absolute incidences were 0.4% for darifenacin and 0.3% for placebo. In this analysis, the exposure-adjusted incidences

were actually higher for placebo: 1.25 cases per 100 patient-years for darifenacin, versus 2.00 cases per 100 patient-years for placebo. In addition, an additional analysis of adverse event reports of "accidental fall" or "accidental injury" (combined) again revealed a higher exposure-adjusted incidence for placebo. For this analysis the absolute incidences were 1.9% and 1.2% for darifenacin and placebo, respectively, but the exposure-adjusted incidences were 5.59 cases per 100 patient-years for darifenacin and 7.14 cases per 100 patient-years for placebo.

Reviewer's comment: The reviewer concludes that no linkage has been shown between these SAE bone fracture cases and darifenacin. This decision is based on:

- the case-by-case review showing reasons other than drug for these cases as well as the lack of evidence for relationship to darifenacin in any given case,
- the lack of statistical evidence for a difference between groups
- additional analysis of all bone fracture cases (serious and non-serious) and all acidental fall/injury cases.

Therefore, at this time, no specific phase IV study is deemed necessary. ODS/DDRE and sponsor are aware of the issue and will continue to monitor for this specific adverse event using the best available pharmacovigilance methods.

2.4. General Safety

The sponsor submitted a comprehensive Safety Update with this Response indicating that the overall exposure to darifenacin was large. A total of 7,363 patients and volunteers were treated with doses of darifenacin from 3.75 mg to 75 mg once daily. The safety of ENABLEX was evaluated in Phase II and III controlled clinical trials in a total of 8,830 patients, 6001 of whom were treated with ENABLEX. In all long term trials combined, 1,216 and 672 patients received treatment with ENABLEX for at least 24 and 52 weeks, respectively.

The sponsor also submitted safety results from the long-term, open-label safety study 1042.

In terms of overall safety, including serious and routine adverse events, the safety profile for darifenacin was consistent with its pharmacologic properties as a potent muscarinic antagonist. The overall safety profile was comparable to other drugs in this class. The safety update and data from the open-label, long-term study revealed no new concerns or new findings. There was no substantial change in the routine or serious adverse events nor in the reasons or frequency of premature discontinuation due to adverse events, since the original NDA.

For the entire NDA, there were 4 deaths, including patients with metastitic malignant melanoma, suicide, adenocarcinoma and hepatic failure. None of these were judged related to study medication by the investigators.

In all placebo-controlled trials combined, the incidence of serious adverse events for 7.5 mg, 15 mg and placebo was similar. The only exceptions were for the events urinary retention, constipation and bone fracture as SAE's. These three issues have been discussed in great detail in the previous two sections of this memo. At the recommended doses and with the approved labeling, the former two issues should not pose a public health hazard. The bone fracture issue has been satisfactorily resolved by additional analysis of data and of the individual cases. There were very few reported cardiovascular serious adverse events in this program.

The discontinuation rates due to adverse events in the 12-week pivotal studies were low, especially for the 7.5mg dose. For example, in all three pivotal fixed-dose studies combined, the discontinuation rates due to adverse events were 2.6%, 1.5%, and 5.1% for placebo, 7.5mg and

15mg, respectively. In the 12-week, dose-titration trial, the incidence of discontinuations due to AE's was somewhat higher: 3.1% and 6.7%, for placebo and for ENABLEX, respectively. The incidences of discontinuation due to dry mouth and constipation were actually very low. Study discontinuation due to dry mouth occurred in 0%, 0.9%, and 0% of patients treated with ENABLEX 7.5 mg daily, ENABLEX 15 mg daily and placebo, respectively. Study discontinuation due to constipation occurred in 0.6%, 1.2%, and 0.3% of patients treated with ENABLEX 7.5 mg daily, ENABLEX 15 mg daily and placebo, respectively.

Finally, in terms of routine adverse events, the safety profile is consistent with a potent antimuscarinic. Adverse events were reported by 54% and 66% of patients receiving 7.5 and 15 mg once daily ENABLEX extended-release tablets, respectively, and by 49% of patients receiving placebo. In the pivotal studies, the most frequently reported adverse events were dry mouth and constipation. As stated in the label, the majority of adverse events in ENABLEX-treated subjects were mild or moderate in severity and most occurred during the first two weeks of treatment. Table 7 below shows the all-causality adverse events reported by at least 2% of darifenacin-treated patients in the fixed-dose studies.

Table 7: Incidence Of Adverse Events* Reported In ≥2.0% Of Patients Treated With ENABLEX And More Frequent With ENABLEX Than With Placebo In Three, Fixed-Dose, Placebo-Controlled, Phase III Studies (Studies 1041, 1001, and 1002)

Body System	Adverse Event	Percentage of subjects with adverse event (%)		
		ENABLEX® 7.5 mg N = 337	ENABLEX® 15 mg N = 334	Placebo N = 388
Digestive	Dry Mouth	20.2	35.3	8.2
	Constipation	14.8	21.3	6.2
	Dyspepsia	2.7	8.4	2.6
	Abdominal Pain	2.4	3.9	0.5
	Nausea	2.7	1.5	1.5
	Diarrhea	2.1	0.9	1.8
Urogenital	Urinary Tract Infection	4.7	4.5	2.6
Nervous	Dizziness	0.9	2.1	1.3
Body as a Whole	Asthenia	1.5	2.7	1.3
Eye	Dry eyes	1.5	2.1	0.5

*Regardless of causality

Some adverse events were reported at an incidence less than 2% but ≥1% and are still potentially clinically relevant. These include: accidental injury, abnormal vision, dry skin, rhinitis, arthralgia, vomiting, peripheral edema, weight gain, rash, pruritus, urinary tract disorder and vaginitis.

Finally, the dose-titration trial revealed a similar pattern of routine adverse events and is shown in Table 8 below.

Table 8: Number (%) Of Adverse Events* Reported In >3% Of Patients Treated With ENABLEX And More Frequent With ENABLEX Than Placebo, In The Placebo-Controlled, Dose-Titration, Phase III Study (Study 1047).

Adverse Event	ENABLEX®7.5 mg/15 mg N = 268	Placebo N = 127
Constipation	56 (20.9%)	10 (7.9%)
Dry Mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary Tract Infection	10 (3.7%)	4 (3.1%)
Accidental Injury	8 (3.0%)	3 (2.4%)
Flu Syndrome	8 (3.0%)	3 (2.4%)

*Regardless of causality

III. Relevant issues from other disciplines

1. Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

In their original review of the NDA, OCPB concluded:

> *"From the viewpoint of the Office of Clinical Pharmacology and BioPharmaceutics, the Human Pharmacokinetics and BioPharmaceutics section of NDA 21-513 is acceptable."*

Nevertheless, Myong-Jin Kim commented that the available QT information was limited by several deficiencies, including lack of positive control group, inadequate number of placebo-alone subjects, inadequate frequency of ECG measurements, and lack of ketoconazole- alone arm.

> **Reviewer's comment**: These issues have been successfully resolved by conducting an appropriate "thorough" QT study. For detailed results of this study, the reader is referred to the Clinical Safety section of this memo, to Dr. Kaul's primary medical officer's review, and to Dr. Apparaju's primary clinical pharmacology review.

Also, Dr. Kim commented that "*The Clinical Division has recommended that the sponsor conduct an adequate and well-controlled (Phase IV) clinical investigation to confirm the effectiveness of darifenacin for the treatment of overactive bladder in an appropriate non-Caucasian population.*"

> **Reviewer's comment**: There is no reason to believe that efficacy or safety will be different in non-Caucasian patients in the United States. OAB symptoms are expected to be similar across ethnic and racial subgroups. There is no pharmacological or clinical rationale to believe that the response to the darifenacin 7.5mg/15mg dose-titration regimen would differ significantly in non-Caucasians versus Caucasians. Further, safety data is currently available in over 7,000 patients who have taken Enablex, including

approximately 600 patients for at least one year and many at higher than recommended doses. The patients studied in North America include some non-Caucasian patients, albeit only approximately 5% of those enrolled. Therefore, this reviewer does not recommend a Phase 4 study in non-Caucasians.

In her original review, Dr. Kim noted several important issues concerning the clinical pharmacology of darifenacin. These comments are repeated here because of their clinical importance:

1. Absorption of darifenacin is rapid. In the proposed extended-release (ER) formulation, the rate of absorption is limited by the rate of release from the tablet matrix. The maximum plasma concentration values for this extended-release tablet occur at around 7-8 hours after dosing.

2. There is low oral bioavailability, as a consequence of extensive first-pass metabolism by the liver.

3. Ingestion of food has little effect on overall pharmacokinetics, therefore darifenacin may be taken without regard to food.

4. Darifenacin is 98% bound to plasma proteins, primarily alpha-1-acid glycoprotein.

5. The estimated half-life is around 12-18 hours. Steady-state is reached around Day 6.

6. Metabolism is mediated by both CYP 2D6 and CYP 3A4 enzymes. The contribution of CYP 2D6 is less at higher doses and at higher concentrations. Approximately 7% of Caucasians and approximately 2% of African-Americans are poor metabolizers of CYP 2D6 substrates

   Reviewer's comment: See also Item 12 of this list.

7. Darifenacin pharmacokinetics are dose-dependent. Dose-dependency appears to be related to saturation of CYP 450 3A4 metabolism in the gut wall at higher doses, combined with a reduction in the overall contribution of CYP 450 2D6 to metabolism at steady-state.

8. About 60% of a radio-labeled dose is recovered in the urine and 40% in the feces. Only approximately 3% is excreted unchanged.

9. Darifenacin exposure is slightly lower in males than in females. At steady-state, AUC is approximately 28% lower in males than in females. No dose adjustment is recommended based upon gender due to this modest difference.

10. Darifenacin exposure is slightly higher in the elderly than in the younger population. At steady-state, exposure in older volunteers is approximately 12-19% greater than in younger volunteers. Estimated clearance is reduced by approximately 6% per decade. No adjustment in dose is recommended based upon this modest difference.

11. There were insufficient numbers of non-whites to assess differential pharmacokinetics by race.

12. In poor metabolizers for CYP 2D6 substrates, total exposure (AUC) for 7.5mg and 15mg is 164% and 99% higher, respectively, compared to CYP 2D6 extensive metabolizers. Corresponding values for mean peak concentrations (Cmax) were 145% and 89% for the 7.5mg and 15mg doses, respectively.

    As noted in these differences between 7.5mg and 15 mg, differences in exposures between EM and PM populations decrease with increasing dose. In addition, there is considerable inter-subject variability in darifenacin plasma concentrations, which causes a high degree of overlap between individual patient exposures in EMs and PMs. Finally, when 2D6 metabolizer status was examined in the pop pK/pD analysis of the pivotal trials, there was only a small effect on clinical safety. For example, in OAB fixed-dose, phase 3 trials, the rates of discontinuation due to adverse events were 0.4% and 1.3% in EMs treated with 7.5mg and 15mg, respectively, versus 1.6% and 4.8% in PMs treated with 7.5mg and 15mg, respectively.

    Taking all this data into consideration, no dose adjustment is recommended for CYP 2D6 EM versus PM status.

    > **Reviewer's comment**: The reader should be aware that the initial recommended dose is 7.5mg and that dose can be up-titrated to 15mg after two weeks, as dictated by individual clinical response. This recommended dosing regimen is intended to minimize adverse reactions in all patients, but especially for those with expected increased exposure, such as the 7% of Caucasians and 2% of African-Americans who are latent CYP 2D6 poor metabolizers.

13. There is no effect of renal insufficiency on pharmacokinetics of darifenacin. No dose adjustment is recommended for patients with renal insufficiency.

14. Mild hepatic impairment did not alter darifenacin pharmacokinetics. However, steady-state exposure was increased by 168% in those with moderate liver impairment compared to normals. After adjusting for lower protein binding in the liver-impaired, that increase is even greater, approximately 300 to 370% higher than in normals. Therefore, the maximum recommended dose in subjects with moderate hepatic impairment is 7.5 mg. Finally, subjects with severe hepatic impairment were not studied. Therefore, treatment with darifenacin is not recommended in those patients with severe hepatic impairment.

15. Darifenacin pharmacokinetics are altered by the following concomitant drugs:

    a. With ketoconazole 400mg qd, the increase in Cmax and AUC was approximately 5x and 5x, respectively for 7.5mg, as compared to 10x and 11.6x for 15mg, respectively.
    b. With erythromycin 500mg BID and with fluconozole 200 mg qd, the increases in Cmax and AUC (for 30mg) are approximately 2-fold.
    c. With cimetidine 800mg BID, the increases in Cmax and AUC are only 1.42 fold and 1.34 fold, respectively.
    d. With paroxetine 20mg qd, the increases in Cmax and AUC are only 1.33 fold and 1.36 fold, respectively.

    Therefore, in patients taking potent 3A4 inhibitors (such as ketoconozole, itraconozole, ritonavir, nelfinavir, clarithromycin and nefazadone) the maximum recommended daily dose is 7.5mg

16. The pharmacokinetics of the following drugs are altered by darifenacin:

a. The Cmax and AUC of desipiramine is increased by approximately 2.6 fold each.
b. The Cmax and AUC of imipramine is increased by approximately 1.6 fold each.

Reviewer's comment: Based upon this potential for darifenacin to increase exposure of concomitant CYP 2D6 substrates, the labeling recommends caution when darifenacin is used with CYP 2D6 substrate medications which have a narrow therapeutic index.

17. Bioequivalence was established between the Phase 3 research formulation and the to-be-marketed formulation.

OCPB also conducted a review of the thorough QT study that was submitted as the major part of the Response to Approvable. The overall conclusion by OCPB was:

> *"Multiple dose treatment (for 6 days) with therapeutic (15 mg) or supra-therapeutic (75 mg) doses of darifenacin was not associated with QT/QTc interval prolongation."*

Finally, the clinical pharmacology team successfully completed their labeling negotiations during this review cycle. Final minor edits were on December 16, 2004 and these were completely accepted by sponsor.

2. Chemistry, Manufacturing and Controls (CMC)

The original chemistry review for this NDA by Allan Fensalau concluded:

> *"All product quality issues that relate to the safety and efficacy of this drug have been adequately addressed to support a recommendation to approve this NDA."*

The only issue of note in the original review was in regard to specific revisions to the package insert and container/carton labeling.

Chemistry conducted another review of the application during this second cycle, including a review of revised container/carton labeling, an extended expiry date (36 months), the established (USAN) name, and confirmation of manufacturing site acceptability. In her final review dated December 21, 2004, Sarah Pope concluded:

> *"From a Chemistry, Manufacturing and Controls standpoint, this NDA can be approved. Final labeling issued ...have been resolved. There are no outstanding CMC deficiencies for this application.'"*

Issues of note from this review included the following: 36 month's expiry was granted, the established name was set as "darifenacin" (not darifenacin hydrobromide), and the manufacturing sites were still acceptable. The final Chemistry memo on December 22, 2004 documents that all final negotiated labeling, including container/carton, Package Insert, and PPI are acceptable.

3. Pharmacology/Toxicology (P/T)

Pharmacology conducted a comprehensive review of the original NDA. In her final supervisory memo, Suzanne Thornton concluded:

"The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues."

In her extensive original P/T review, the primary reviewer, Laurie McLeod agreed with approval of the NDA but raised a concern regarding a pre-clinical signal for QT prolongation. Some key findings in her review in regard to QT were:

1. Darifenacin competitively displaced 3-H-dofetilide hERG receptors with an IC50 value of 1.1 x 10-6 M (550 ng/mL) and an IC10 of about 1 X 10-7M (50ng/mL).

2. Using whole cell patch clamp technique which examines the effect on the hERG potassium current, the parent compound exhibited an IC50 of 77nM (39.1 ng/mL).

3. In an in vivo dog study, at a plasma darifenacin concentration of 10.7 ng/mL there was a 7% increase in the QT interval. At a concentration of 43.2 ng/ml, there was a 16% increase in the QT interval.

Reviewer's comment: One of the major reasons for conducting the "thorough QT study" prior to approval was this pre-clinical data. The "thorough QT study" has definitively shown no QT prolongation after a 6-day course of darifenacin 75 mg, even in poor metabolizers of CYP 2D6. The mean maximum plasma concentration was actually 68.5 ng/mL in these poor metabolizers and in fact, in female poor metabolizers, the mean maximum plasma concentration attained after 75 mg was 84.5 ng/mL. Some poor metabolizers actually attained maximum plasma concentrations up to 130 ng/mL. Thus, no QT prolongation was seen in the thorough QT study at a clinically meaningful range of concentrations, and at concentrations that exceed plasma concentrations in dogs that were previously concerning.

On December 13 and December 17, 2004, Drs. McLeod and Reid, respectively, agreed with final labeling.

4. Biometrics

At the time of the original NDA review, Biometrics conducted a detailed review of the efficacy results from the pivotal trials. During this second review cycle, Biometrics conducted an additional review of the results from the "thorough QT study" from a statistical perspective. In addition, Biometrics provided recommendations for overall product labeling (especially for the Clinical Studies section).

In her original review of the efficacy data from the pivotal trials, Sonia Castillo concluded:

"The effectiveness of darifenacin 7.5mg and 15mg in decreasing the number of incontinent episodes per week and the effectiveness of darifenacin 15mg in decreasing the number of micturitions per day has been demonstrated. The effectiveness of darifenacin 7.5mg in decreasing the number of micturitions per day is demonstrated in one study but a second study did not reach statistical significance (p=0.066)"

Reviewer's comment: I have no reservations in approving the 7.5mg dose, based upon its demonstration of effectiveness for the primary endpoint in all three trials and for secondary endpoints in multiple trials. Perhaps more importantly, the low dose affords

users and prescribers the ability to titrate Enablex safely. It is an important element in the overall risk/benefit equation for Enablex

In her review of the "thorough QT study", Dr. Castillo concluded:

> *"The Sponsor has conducted the study as recommended by the Division and the QT results in Table 4-5 on page 14 of the submission, (shown below), have been re-calculated and verified by the statistical reviewer. In general, these results for the QTcF show that Avelox 400mg has a QT prolongation effect, and that the upper bounds for the 90% confidence interval for the difference from placebo are 3.2 mm for darifenacin 15mg and 2.2 mm for darifenacin 75 mg."*

There are no other issues of note in the Biometrics review. Dr. Welch agreed to final labeling on December 16, 2004.

5. Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS)

ODS/DMETS consultation was obtained at the time of the original NDA review and again during this cycle. On both occasions, DMETS had "*no objection*" to the use of the proprietary name "ENABLEX".

In the DMETS final memo from Denise Toyer, DMETS made the following comments about the tradename:

1. DMETS had originally identified two other tradenames with potential "sound-alike" risk. These included: [ ] These two names were associated with unapproved drugs. [ ] was approved on May 25, 2004 under the tradename "XIFAXAN", therefore, this was no longer an issue. After re-review, the second name, [ ] was no longer considered a convincing sound-alike. Further, the two drugs do not have overlapping product characteristics.

2. DMETS had originally identified two tradenames with potential "look-alike" risk. These included: "EMBREX 600" and "ENGERIX". Both were felt to have "minimal risk". For Embrex 600, a chewable prenatal vitamin, the dosage strength of 600mg would differentiate it from Enablex. In addition, the "L" in Enablex was considered to be a differentiating element. For Engerix, a recombinant hepatitis B vaccine, the orthographic differences and differences in product administration and dosage form were believed to be sufficient differentiating elements.

3. DDMAC continued to find the proprietary name Enablex "unacceptable from a promotional perspective", [ ]

   Reviewer's comment: This reviewer finds the tradename fully acceptable despite reservations expressed by DDAMC.

DMETS also had several comments in regard to the carton/container labels, including:

1. "We note that sponsor adequately addressed most of the DMETS' label and labeling comments included in the August 29, 2003 review".

2. Revise the container/carton and package insert so that the established name and strength appear consistently in one of three acceptable formats (as described in their review).

   Reviewer's comment: In conjunction with our Chemistry reviewers, the Division successfully negotiated acceptable container/carton labeling including all DMETS comments. In addition, sponsor agreed to make the "star logo" smaller and to move it away from the tradename. Finally, sponsor agreed to keep the tradename, established name, and dosage form all on the same color background in accordance with Chemistry recommendations.

6. Division of Scientific Investigations (DSI)

Consultation was originally obtained from DSI for the purpose of conducting routine clinical site inspections of the pivotal trials. After consulting with the Division, DSI agreed to conduct routine overseas inspections of the pivotal Studies 1002 and 1041. During the first cycle, DSI concluded:

> *"The data submitted in support of this NDA by Drs. Karjka and Rechberger appear acceptable".*

Clinical site inspection was not considered necessary and was not requested for the "thorough QT study".

7. Division of Drug Marketing, Advertising and Communications (DDMAC)

Consultation was obtained from DDMAC for the purpose of reviewing the proposed drug labeling. Corrine Kulick of DDMAC provided a detailed review of the proposed ENABLEX label. Each of the DDMAC labeling comments was carefully reviewed by the Division. Those that required action were enacted through successful labeling negotiations with the sponsor during the months of November and December 2004.

Reviewer's comment: One issue is of note: DDMAC questioned [redacted] This decision is consistent with the Division's policy for drugs in this indication, [redacted]

8. Office of Drug Safety/Division of Surveillance, Research, and Communication Support (ODS/DSRCS)

Consultation was obtained from ODS/DSRCS for the purpose of reviewing the proposed patient package insert (PPI). On October 4, 2004, Jeanine Best provided a final review of the PPI including detailed re-formatting, re-wording and other revisions. Sponsor was amenable to all revisions proposed by DSRCS. Therefore, the PPI is considered fully resolved.

9. Division of Cardio-Renal Drug Products (DCRDP)

Consultation was obtained from DCRDP in order to "audit" the electronic annotated ECGs submitted in support of the "thorough" QT study. On October 14, 2004, Norman Stockbridge concluded:

"The quality of the records is generally quite satisfactory. In general, the ends of the T waves were marked close to where most observers would likely have placed them."

No other issues were of note in the DCRDP consultation report.

10. Office of Drug Safety/Division of Drug Risk Evaluation (ODS/DDRE)
Consultation was obtained from DDRE to review the potential for post-marketing drug risk and the need for any additional risk management measures to minimize such risk. On November 3, 2004, Claudia Karwoski provided formal consultation from DDRE, concluding:

"The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which an RMP to minimize risk would be normally associated. The measures proposed by the sponsor seem reasonable but would appear to be routine given the potential risk. A separate PPI consult was performed by ODS/DSRCS. Should the review Division wish ODS to review any proposed Phase IV protocols or epidemiological studies, please provide a consult request."

There were no other issues of note in the DDRE consults, except to emphasize that sponsor's proposed postmarketing risk management plan *"focuses primarily on assuring proper use of the drug to maximize benefits and minimize potential risks and on enhancing pharmacovigilance such that any new risk (or benefit) will be identified and communicated in a timely fashion"*.

Reviewer's comment: Based upon the known risks of this drug, which include routine antimuscarinic side effects, constipation, and urinary retention, this plan is acceptable. Based upon our detailed review of each bone fracture case, showing alternate etiologies for most cases, and no statistical difference between drug and placebo groups for this event, the reviewers conclude that routine postmarketing pharmacovigilance is sufficient to monitor for this issue. In my opinion, there are no unresolved issue related to DDRE.

IV. Other relevant issues

1. Financial Disclosure
As part of the original NDA, Dr. Li reviewed the financial disclosure information from the required trials (including the pivotal trials). At that time, he concluded:

"Financial disclosure was made from all required studies. The disclosure appears adequate and no evidence suggest that financial relationship had any impact on the study findings."

During the second cycle, Dr. Kaul also reviewed the financial disclosure material for Studies 1001, 1002 and 1041. He stated that of 1319 investigators, only 19 had any financial information to disclose. He reviewed the information provided for all of these. In all instances, adequate documentation had been submitted to comply with 21 CFR 54; that is, there was no disclosure of financial interests that could bias the outcome of the pivotal trials for this NDA.

2. Pediatrics
On September 30, 2004, Sponsor proposed an extensive pediatric development program for ENABLEX for the treatment of children with detrusor overactivity associated with a neurological

condition (e.g. spina bifida) and for children with overactive bladder of undetermined etiology. In accordance with PREA regulations, a Phase 4 commitment will appear in the action letter, with the following stipulations:

1. Conduct 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. Conduct pediatric studies under PREA for the treatment of overactive bladder (of undetermined etiology) in pediatric patients six to 11 years old and adolescents for ages 12 to 17 years old.

The Division and Sponsor have agreed to meet in the near future for the purpose of reaching further agreement on the proposed pediatric protocols and pediatric formulation(s).

3. Phase 4 commitments

No Phase 4 commitments are considered necessary at this time and none are being requested (other than those required to meet PREA pediatric regulations). After a detailed review of each accidental fracture case, reasonable alternate explanations exist for virtually every case. Further, there is insufficient statistical evidence to link the cases of accidental fracture to treatment with ENABLEX. Therefore, no Phase 4 commitment is being requested for this issue. The Division will continue to monitor for this adverse event in conjunction with the Office of Drug Safety (ODS) using post-marketing pharmacovigilance techniques. The Office of Drug Safety/ Division of Drug Risk Evaluation was made aware of this particular concern and voiced no objections to this plan.

V. Medical team leader's summary statement

ENABLEX is considered safe and effective for the treatment of overactive bladder with symptoms of urgency, frequency and urge urinary incontinence. The drug was effective in reducing incontinence episode frequency in four separate phase 3 trials. The adverse event profile is comparable to other antimuscarinic drugs. There is no evidence of cardiovascular side effects; in fact, effect on heart rate is small even at high plasma concentrations. There is no evidence of QT prolongation at a wide range of clinically relevant exposures. A comprehensive review of all 18 accidental fractures in patients taking darifenacin revealed alternative causes for the injury in most cases. There was no statistically significant difference between darifenacin and placebo for accidental fracture. Overall, therefore, ENABLEX is safe and effective and should be approved. It offers another option for patients and prescribers in the management of overactive bladder .

Mark S. Hirsch M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Arch NDA 21-513
cc: HFD-580/Div File
HFD-580/DShames/SKaul/JMakie

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/s/

Mark S. Hirsch
12/22/04 01:13:18 PM
MEDICAL OFFICER

Daniel A. Shames
12/22/04 01:32:36 PM
MEDICAL OFFICER

4/23/04

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, PhD
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. McGrath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex™ (darefenacin hydrobromide) 7.5 mg and 15 mg extended release tablets.

We have reviewed your February 4, 2004, submission wherein you provided your proposal for the safety update to be included in your complete response. Your proposed plan is generally acceptable, but we offer the following comments and recommendations:

1. The proposed cut-off date of July 31, 2003, for study 2301/1042 is acceptable.
2. Submit an additional safety update in table format comparing the incidences of adverse events (AEs) in the original NDA to the incidences of AEs reported in the period covered by the safety update.
3. A final brief safety update is due three months prior to the action date.
4. We require case report forms for all new serious adverse events (SAEs) and deaths.
5. We encourage you to request a Pre-submission of a Complete Response Meeting. In this meeting, you are expected to discuss your completed controlled QT study, labeling issues related to severe constipation and urinary retention, chemistry labeling concerns, and plans for your Postmarketing studies concerning bone fractures.

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

Sincerely,

/S/

{See appended electronic signature page}

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
4/23/04 07:34:45 AM
Chief, Project Management Staff

IND 45,457

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 1, 2004

To: Lynn McGrath

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: IND 45,457: 2/13/04 teleconference minutes

Comments: Minutes are attached for your reference.

Document to be mailed: YES NO

Teleconference Minutes

IND: 45,457 **Drug:** Darifenacin hydrobromide

Sponsor: Novartis Pharmaceuticals

Date: February 13, 2004 **Time** 2:00 – 2:10 PM

FDA/CDER/ Division of Reproductive and Urologic Drug Products (DRUDP) Attendees:
Meeting Chair: Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Reviewer, DRUDP
Meeting Recorder: Jean Makie, M.S., R.D., Project Manager, DRUDP

Novartis Attendees:
Dr. Lynne McGrath, Regulatory
Dr. Andrej Skerjanic, Clinical Pharmacology
Dr. Damayanthi Devineni, Clinical Pharmacology
Louise Rowe, Project Management

Background: This teleconference was held at the request of the sponsor to clarify the following comment provided by the Division during the January 23, 2004 teleconference with the sponsor:

Division Comment #5: The Division stated the following clinical pharmacology recommendations:

- The sponsor should verify the classification of PMs used in the previous studies submitted to this NDA, given an observed discrepancy of phenotype results that were not confirmed by genotype in the ongoing QT study.
- The sponsor should consider this verified information regarding EM/PM exposure for inclusion in the label.

Sponsor Response: The sponsor agreed.

Issues Discussed: The Division reiterated that it is usual Agency practice to include confirmatory data in product labeling when a drug is metabolized via different pathways. The Division clarified that the above comments were made to make the sponsor aware of this practice. Because the sponsor will be submitting new exposure data for poor metabolizers (PMs) and extensive metabolizers (EMs) from the currently ongoing thorough QT study, the Division also informed the sponsor that a comparative review will be completed between these exposure results and the exposure information provided in the original NDA 21-513 submission when the sponsor submits their Complete Response to an Approvable Action.

Sponsor Response: The sponsor acknowledged this clarification. The sponsor also agreed that they would perform a complete review to verify exposure data for all PM and

EM subjects studied in the previously submitted drug-drug interaction study, and those results from the ongoing QT study.

Action Items:

1. The Division will provide minutes of this teleconference within 30 days.

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/s/

Ameeta Parekh
3/2/04 08:27:49 AM

1/22/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,457

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Lynn McGrath, Ph.D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. McGrath:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for darifenacin UK-88,525.

We also refer to your submission (serial # N-181), dated December 11, 2003, which contained Amendment 1 to protocol CDAR328A2302 entitled "A Double Blind, Double Dummy, Parallel Group, Placebo, And Active Controlled, Multiple-Dose Study to Evaluate the Effects of Darifenacin on Cardiac Safety in Poor and Extensive CYP2D6 Substrate Metabolizers."

We have completed the review of this amendment. The protocol appears adequate to generate data towards resolving the approvable deficiency for NDA 21-513. The following are additional review comments. Your response to these is requested.

1. Provide analyses of the difference in change-from-baseline for the each darifenacin dose (and moxifloxacin) compared to placebo using separate t-tests or separate ANCOVA procedures. For each comparison, provide the two-sided 95% confidence intervals.

2. The intent of the proposed hypotheses testing procedures (Section 2.2.1-2) is unclear. For each comparison to placebo, the hypothesis test should be stated as in the below example for the darifenacin high dose.

> Let Δ_{75} = the difference in the change from baseline between darifenacin 75 mg qd and placebo. The hypothesis of interest is as follows: H_0: $\Delta_{75} \geq 10$ msec vs. H_1: $\Delta_{75} < 10$ msec, or alternatively, the null hypothesis is rejected if the upper bound of the two-sided 95% confidence interval is less than 10 msec.

3. In your Complete Response to Approvable submission, provide the raw data for QT and RR for each of the three ECGs extracted at each time-point for each patient.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Daniel A. Shames
1/22/04 03:17:03 PM

IND 45,457

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

FACSIMILE TRANSMITTAL SHEET

DATE: January , 2004

To: Lynn McGrath

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: IND 45,457: 1/15/04 teleconference minutes

Comments: Minutes are attached for your reference.

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

Teleconference Minutes

IND: 45,457 **Drug:** Darifenacin hydrobromide

Sponsor: Novartis Pharmaceuticals

Date: January 15, 2004 **Time** 2:30 – 3:30 PM

FDA/CDER/ Division of Reproductive and Urologic Drug Products (DRUDP) Attendees:
Meeting Chair: Mark Hirsch, M.D., Urology Team Leader, DRUDP
Leslie Kenna, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP
Meeting Recorder: Jean Makie, M.S., R.D., Project Manager, DRUDP

Novartis Attendees:

Dr. Lynne McGrath, Regulatory
Dr. Yibin Wang, Biostatistics
Ms. Denise Barrilla, Clinical Pharmacology
Dr. Andrej Skerjanic, Clinical Pharmacology
Dr. Melton Affrime, Clinical Pharmacology
Dr. Martin Bedigian, Clinical
Dr. Vanaja Ragavan, Clinical
Dr. Damayanthi Devineni, Clinical Pharmacology

Background: This teleconference was held to discuss the sponsor's draft protocol amendment to study DAR328A2302, which was sent via facsimile to the Division on January 13, 2004. This proposal informed the Division that the sponsor has screened 1612 subjects for CYP2D6 metabolic status. Nineteen of these subjects were phenotypically and genotypically identified as CYP2D6 poor metabolizers (PM), less than the goal for recruitment. The proposal outlined an alternative approach to study randomization that controlled for priority placement of subjects into the darifenacin 15 mg and 75 mg groups and replacing PMs with extensive metabolizers (EM).

Issues Discussed: The Division provided the following comments regarding the sponsor's draft protocol amendment.

Division Comment: The Division stated that the sponsor's proposal is not acceptable because of the inequitable distribution of these patients into the four different treatment arms. This proposal would call into question the consistency of baseline patient characteristics across the four randomized, parallel-arm treatment groups. The Division would not recommend changing the protocol in this way.

Sponsor Response: The sponsor stated that they also had considered this potential design problem. Still, they believed that there is essentially no difference between PM and EM (extensive metabolizers) when administered 75 mg darifenacin, based on results of studies using 60 mg darifenacin.

Division Response: The impact of CYP2D6 metabolic status at high darifenacin doses remains a review issue.

Sponsor Response: The sponsor acknowledged the Division's recommendation not to revise the protocol as proposed. As an alternative means to resolve this issue, the sponsor requested the Division consider allowing subjects who are determined to be PMs by phenotype, but not confirmed by genotype, be enrolled and classified as PMs into the study. The sponsor has accrued 13 such patients.

Division Comment: The Division requested the following information be submitted to allow further evaluation of the sponsor's request to modify the definition of PM subjects enrolled in this study:

- Methodology for determination of metabolic status of study subjects.
- Detailed listings of subjects identified as phenotypically poor metabolizers (including results of genotyping).
- A written response to the Division's question regarding the rationale for the observed genotype-phenotype discordance.
- A revised protocol amendment for study DAR328A2302.

Action Items:

1. The sponsor will submit the methodology of CYP2D6 phenotype using dextromethoraphan as a substrate to determine PM status.
2. The sponsor will submit the methodology used to determine PM status by genotype.
3. The sponsor will submit the line listings of the phenotype and genotyping results for the 19 patients identified as PMs by phenotype and genotype, as well as the additional 13 patients identified as PMs by phenotype, but not confirmed by genotype.
4. The Division will provide minutes of this teleconference within 30 days.

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/s/

Mark S. Hirsch
2/9/04 01:15:38 PM

IND 45,457

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

FACSIMILE TRANSMITTAL SHEET

DATE: January , 2004

To: Lynn McGrath

Company: Novartis Pharmaceuticals

Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: IND 45,457: 1/23/04 teleconference minutes

Comments: Minutes are attached for your reference.

Document to be mailed: **YES** NO

Teleconference Minutes

IND: 45,457 **Drug:** Darifenacin hydrobromide

Sponsor: Novartis Pharmaceuticals

Date: January 23, 2004 **Time** 9:30 – 10:30 AM

FDA/CDER/ Division of Reproductive and Urologic Drug Products (DRUDP) Attendees:

Meeting Chair: Mark Hirsch, M.D., Urology Team Leader, DRUDP
Leslie Kenna, Ph.D., Clinical Pharmacology Reviewer, DRUDP
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Reviewer, DRUDP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP
Meeting Recorder: Jean Makie, M.S., R.D., Project Manager, DRUDP

Novartis Attendees:

Dr. Lynne McGrath, Regulatory
Dr. Yibin Wang, Biostatistics
Ms. Denise Barrilla, Clinical Pharmacology
Dr. Andrej Skerjanic, Clinical Pharmacology
Dr. Melton Affrime, Clinical Pharmacology
Dr. Martin Bedigian, Clinical
Dr. Vanaja Ragavan, Clinical
Dr. Damayanthi Devineni, Clinical Pharmacology

Background: This teleconference was held to discuss the sponsor's revised draft protocol amendment to study DAR328A2302, which was sent via facsimile to the Division on January 16, 2004. This teleconference was also a continued discussion from the teleconference held with the sponsor on January 15, 2004.

The revised amendment requested the Division's concurrence to permit the inclusion of phenotypically identified CYP2D6 poor metabolizers (PMs), in addition to the 19 PM subjects previously identified via phenotype and genotype testing. The amendment also provided additional information regarding the methodology for the determination of metabolic status of subjects; a detailed listing of subjects identified as poor metabolizers (including results of genotyping); and a response to the Division's question regarding the rationale for the heterozygous genotypes to predict poor metabolizers.

The Division provided the following comments regarding the sponsor's January 16, 2004 amendment.

Division Comment #1: The Division stated that, if the sponsor's attempts to identify enough subjects in this category do not provide the recommended number of PMs (20%

or 36 subjects), the sponsor may include some intermediate metabolizers as identified by the dextromethoraphan test. However, the sponsor should realize the risk of completing the study with fewer high exposure representations.

Therefore, the Division concurred that the protocol amendment to include subjects who were identified as poor metabolizers (PMs) phenotypically, but not confirmed by genotyping, was acceptable. However, the inclusion of Patient #057 is not acceptable to the Division because the metabolic ratio (MR) results from the phenotype study for this patient were unavailable. Therefore, the Division granted permission to the sponsor to enroll the remaining 12 phenotypically identified PMs.

Sponsor Response: The sponsor agreed to enroll those 12 patients found acceptable by the Division as additional PMs.

Division Comment #2: The Division asked the sponsor to clarify how these 31 PM patients will be randomized into the four treatment arms.

Sponsor Response: The sponsor stated that the 31 PM patients will be randomized evenly into each of the four dosing groups, although the proposed stratification into the sponsor's defined eight cohorts may not be achieved.

Division Comment #3: The Division restated that it is primarily interested in even randomization to four treatment groups, and not the specific cohort delineations proposed by the sponsor.

Division Comment #4: With regard to enrolling 20% PM subjects, the Division stated that 32 PM subjects would be acceptable if the sponsor has not identified the expected 36 PM subjects. The Division reiterated that a goal of conducting this QT study is to maximize exposure to darifenacin. The Division acknowledged the sponsor's opinion that the current proposed amendment may achieve this goal. However, the Division stated that the sponsor may be assuming some risk to provide the necessary results if very high exposures are not attained. The Division will, therefore, review all of the exposure data submitted from this study in an effort to evaluate a linear or continuous drug exposure response.

Sponsor Response: The sponsor stated that one additional PM patient was identified from results of screening 200 patients. Additional subjects were recently screened; however, the results were not yet available as of this teleconference.

Division Comment #5: The Division stated the following clinical pharmacology recommendations:

- The sponsor should verify the classification of PMs used in the previous studies submitted to this NDA, given an observed discrepancy of phenotype results that were not confirmed by genotype in the ongoing QT study.
- The sponsor should consider this verified information regarding EM/PM exposure for inclusion in the label.

Sponsor Response: The sponsor agreed.

Division Comment #6: The Division asked the sponsor to verify the dose of dextramethoraphan used in the phenotype study. Based on the review of the January 16, 2004 submission, it appears that a 60 mg dose was administered, when the protocol stated a 30 mg dose of dextramethoraphan would be used.

Sponsor Response: The sponsor stated that a 60 mg dose of dextramethoraphan was actually given to the subjects. The sponsor agreed to submit a revised protocol to reflect the actual procedures used in the conduct of this study.

Action Items:

1. The sponsor will submit a protocol amendment for the conduct of the phenotype study.
2. The Division will provide minutes of this teleconference within 30 days.

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/s/

Mark S. Hirsch
2/9/04 01:13:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 2 2003

Prof Kazimierz Krajka
Klnika Urologii Akademii
Medycznej W Gdansku
Ul Kieturakisa 1
Gdansk
80-742
Poland

Dear Dr. Krajka:

Between July 28 and August 1, 2003, Mr. Kenneth Merritt and Dr. Roy Blay, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # A1371002 entitled: "A Phase III multicentre, double-blind, randomised, placebo-controlled, dose response study of darifenacin in subjects with overactive bladder (urge urinary incontinence)" of the investigational drug Enablex® (darifenacin hydrobromide) Tablets, performed for Novartis Pharmaceuticals Corporation. 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. We provide these comments based on our review of the establishment inspection report, the documents submitted with that report, and the Form FDA 483, Inspectional Observations issued to you at the conclusion of the inspection. 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 temperature logs were not maintained for study drug storage for approximately four months prior to July 2000. Also, calibration records for the EKG equipment used for additional safety testing in this study were not maintained.

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 Merritt and Dr. Blay 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: 3004028647

Field Classification: VAI

Headquarters Classification:
____ 1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiency code: 06

Deficiencies noted:
__x__inadequate and inaccurate records (06)

cc:
HFA-224
HFD-580/Doc.Rm. NDA# 21-513
HFD-580/Review Div.Dir./Shames
HFD-580/MO/Li
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File # 010984
HFD-/47 GCP Reviewer/Blay
HFR-SE340/DIB/Lewis
HFR-SE350/BIMO Monitor/Abel
HFR-SE350/Field Investigator/Merritt
HFC-134 Kadar (for foreign only)
GCF-1 Seth Ray

r/d: (Blay):9/23/03
reviewed: JPS 10/7/03
f/t: sg:10/9/03

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Reviewer Note to Rev. Div. M.O.
35 subjects were randomized to the study. Inclusion/exclusion criteria were met appropriately. The primary efficacy variable (average number of micturitions per week) was recalculated from CD copies of the original electronic diary records and confirmed for 18 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 11:22:21 AM

MEMORANDUM

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

DATE: October 2, 2003

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-513 Enablex Extended Release Tablets (darifenacin hydrobromide); Novartis

Darifenacin hydrobromide 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 darifenacin 7.5 mg and 15 mg once daily doses for the treatment of overactive bladder. Before this application may be approved it will be necessary for the sponsor to address the following deficiency:

Approvability Issue: QT Prolongation

Both CYP3A4 and CYP2D6 are involved in darifenacin metabolism. Co-administration of 7.5 mg darifenacin with ketoconazole 400 mg, a potent inhibitor of CYP3A4, resulted in a 5-fold higher mean steady state exposure compared to darifenacin plus placebo; co-administration of 15 mg darifenacin with ketoconozale 400 mg resulted in a 12-fold higher exposure compared to treatment with darifenacin plus placebo. In addition, steady state darifenacin exposure in the subgroup of CYP2D6 poor metabolizers was higher than in extensive metabolizers, however inter-subject variability resulted in considerable overlap between the ranges of exposures seen in extensive and poor metabolizer patient subgroups.

The rate-corrected mean QT change from baseline (using Fredericia's correction) in patients receiving 7.5 mg darifenacin plus placebo was 2 msec (95% CI: -12.5, 16.5) compared to 12 msec (95% CI: -2.9, 26.9) in patients receiving 7.5 mg darifenacin plus ketoconazole. For darifenacin 15 mg plus placebo, the mean QTcF change from baseline was -3 msec (95% CI: -17.6, 11.6) and for the combination of darifenacin 15 mg plus ketoconazole it was 10 msec (95% CI: -4.3, 24.3). Thus the change from baseline in QTcF of 10-12 msec appeared constant regardless of the darifenacin exposure in the combination. Novartis suggests that "the most plausible explanation for this finding is that the 10-12 msec QTcF effect with ketoconazole and darifenacin is solely due to the well known effect on QTc duration of ketoconazole alone". In a teleconference with Novartis held on September 22, 2003, DRUDP indicated that the literature evidence supporting the QT prolonging effects of ketoconozale was limited, that the effect of ketoconazole could not be assessed since there was no ketoconazole alone treatment group, and that the interpretation of a 10-12 msec QTc effect was problematic given the lack of placebo/placebo and positive control groups. In addition, DRUDP expressed concerns that darifenacin was found to increase action potential duration in a dog study.

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 darifenacin doses that achieve exposures comparable to those produced by the darifenacin plus ketoconazole combinations, and that includes placebo and positive controls. Given that darifenacin is likely to be prescribed to older female patients, many of whom may be co-prescribed 3A4 inhibitors, we believe submission of the data from this QT study is required pre-approval so that product labeling can include dosing recommendations for darifenacin when co-administered with 3A4 inhibitors.

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 serious sequelae of adverse events reported with use of this product, e.g., urinary retention and constipation. Additional risk management strategies may be needed.

Phase 4 Studies

Novartis will be requested to conduct a phase 4 study to assess the potential association of bone fractures and darifenacin use. In the NDA, an unexpected excess number of bone fractures was reported in darifenacin-treated patients compared to placebo-treated patients. There are no plausible explanations for this finding at this time.

Tradename Review

The proposed tradename "Enablex" is acceptable.

/S/

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

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/s/

Julie Beitz
10/2/03 11:25:05 AM
DIRECTOR

This review was amended to remove an erroneous reference to "duloxetine".

NDA 21-513

Supervisory Medical Officer's Memorandum: New NDA

Date submitted: December 3, 2002
Date received: December 3, 2002
Memo completed: October 2, 2003

Drug: darifenacin hydrobromide
Tradename: Enablex™ extended release tablets
Dosage strength: 7.5mg and 15mg
Indication: Treatment of overactive bladder

1. Executive Summary: The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on this NDA. I recommend that the NDA receive an **approvable** action. My rationale for this decision is as follows: The NDA contains substantial evidence that the product, darifenacin hydrobromide, is effective for the treatment of overactive bladder. The NDA also contains the required ICH guidance criteria for safety exposure and in general, the safety concerns with darifenacin are similar to those for the class of anti-muscurinics. However, there is insufficient information to determine the effect of darifenacin on the QT interval. The NDA deficiency and resolution item are described herein:

NDA Deficiency

There is evidence from pre-clinical studies that darifenacin has a direct effect on ventricular repolarization. This evidence comes from the both in-vitro HERG and [3H]-dofetilide binding studies and in-vivo dog studies. Studies in humans have also assessed the effect of darifenacin on the QT interval. In two of these (Study 1007 and 1035) there was a consistent difference of approximately 12 milliseconds between groups when darifenacin 7.5mg, 15mg or 30mg was administered with ketoconazole versus when darifenacin was administered alone. Due to limitations in the designs of these studies (the lack of a placebo alone group, the lack of a ketoconazole alone group, and the lack of multiple EKGs at baseline and at endpoint), it is not possible to ascertain whether darifenacin itself was associated with this 12 millisecond prolongation of the Q-T interval or whether the darifenacin effect is either smaller or greater than 12 milliseconds.

The potential effect of darifenacin on the QT interval was also assessed in a randomized, placebo-controlled study of 30mg and 60mg. In this study (Study 1015), there were no meaningful differences between darifenacin and placebo in changes in the Q-T interval. However, the design of this study was deficient in that it did not include a positive control and maximum darifenacin plasma concentrations attained did not exceed those that might be attained when a poor metabolizer of CYP 2D6 is administered darifenacin 15mg and ketoconazole. The lack of a positive control does not allow for the ascertainment of whether the study was sensitive to pick up small

positive changes in the QT interval and just as importantly, does not allow a "benchmark" for which to compare the effect of darifenacin alone.

Therefore, in sum, this application lacks sufficient information to conclude with assurance that darifenacin is not associated with a clinically relevant effect on prolonging the Q-T interval when administered at a clinically relevant range of blood concentrations. Such is considered necessary prior to marketing approval of this product because:

a. *There is a strong pre-clinical signal.*
b. *There were mean differences in QT interval changes between treatment groups in Studies 1007 and 1035 of approximately 12 milliseconds.*
c. *The post-marketing use of darifenacin is expected to be widespread and diverse (e.g. perhaps millions of patients in the United States).*
d. *There are several currently available agents for the treatment of overactive bladder.*
e. *There is no demonstrated significant benefit of darifenacin over other currently available agents.*
f. *Prolongation of the QT interval has been associated with induction of latent ventricular arrythmia and cardiac death.*

Resolution item for the NDA deficiency

A thorough QT study, with active control, must be conducted. Details for the design of such a study can be found in the medical officer's review and in the action letter. The results from such a study should be submitted in the Complete Response to this approvable action.

Other items that require resolution

Labeling still must be reviewed and agreed-upon. In that regard, the occurrence of urinary retention and constipation and potential serious sequalae associated with these events should be included in the revised labeling. Although the incidence of acute urinary retention was low (0.2%) in subjects treated with darifenacin in the three pivotal Phase 3 trials, one female subject treated with darifenacin developed acute renal failure secondary to urinary retention and another six patients developed acute urinary retention requiring some medical intervention. In addition, seven subjects in the Phase 3 trials reported severe constipation and of those, all remained constipated at the end of the study despite anti-constipation treatment. Finally, three serious adverse events were constipation-related. The approved labeling must describe these events and provide some guidance to physicians and patients on management and prevention.

Finally, though not an approvable issue, the clinical review team is requesting a *Phase 4 commitment*. We request that the sponsor commit to conducting a controlled post-marketing safety study designed to determine whether darifenacin is associated with bone fracture. Evidence from the NDA suggests a possible association. For example, of 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). At present, the application does not contain information sufficient to explain or to refute this discordance between groups.

2. Scientific and Regulatory Background

The term "overactive bladder" (OAB) refers to a symptomatic condition that includes urinary urgency, urinary frequency, and urge urinary incontinence. A patient may manifest any or all of these three cardinal symptoms. The vast majority of patients with OAB are middle-aged women, although OAB can occur in men too. However, when OAB symptoms occur in men they are often associated with some degree of bladder outlet obstruction due to benign prostatic hypertrophy. OAB symptoms are also reported by some children who have previously attained continence. There can be no doubt that OAB symptoms are troublesome, annoying and can profoundly affect the quality of an individual's life. The inability to defer voiding impacts a given individual by impeding everyday and special activities and by undermining self-confidence and self-image. It is estimated that up to 16 million Americans suffer from OAB symptoms. The public health impact, in terms of economic costs for sanitary materials and days away from work, as well as institutionalization of the incontinent elderly cannot be underestimated.

Currently, the mainstay of management of OAB symptoms is anticholinergic medication and "bladder training". Bladder training refers to behaviorial techniques used to lessen the overall impact of OAB. This includes more frequent volitional voiding episodes so as to keep the bladder less full, voiding prior to bedtime, biofeedback-type techniques meant to prolong the time from first desire to void to actual voiding, and limitations on fluid intake. While these techniques can help, they do not fully manage the condition in the majority of patients. Anticholinergic medications, including oxybutynin and tolterodine, are widely used to dampen the involuntary bladder muscle contractions that lead to the symptoms of OAB. These are of known benefit, but their benefit is limited by tolerabilty issues. These include such anticholinergic adverse reactions as dry mouth, dry eyes, inability for vision to accommodate, constipation, heat intolerance, tachycardia, and urinary retention.

Darifenacin was developed by Pfizer Pharmaceuticals and the NDA was transferred during the review to Novartis. Pfizer hoped that darifenacin might offer an effective treatment for OAB with better tolerability than currently available agents, based upon its selectivity for the M3 muscurinic receptor. The IND (#45,457) was submitted on June 3, 1994. An End-of-Phase 2 meeting was help on June 1, 1996. A Pre-NDA meeting was help on June 18, 2002. The NDA was submitted in December of 2002. During the development of darifenacin, the major issue was the choice of dosage strength and the development of the controlled release formulation. [redacted]

However, based upon tolerability issues at that dose, as well as the observation of drug interaction potential, the sponsor eventually saw the need to lower the recommended doses to 7.5mg and 15mg.

3. Clinical Efficacy

In summary, the NDA contains evidence that darifenacin is effective in the treatment of OAB. The evidence comes from three pivotal Phase 3 studies (Studies 1002, 1041 and 1001) and a fourth Phase 3 supportive trial (Study 1047). All three pivotal trials were similar in design and procedures and were consistent with the Division's expectations in regard to OAB trials. These were randomized, placebo-controlled, fixed-dose, parallel-arm design studies. Each study had a no-treatment or single-blind placebo run-in and a 12-week treatment period. Studies 1002 and 1041 were conducted outside the U.S., while studies 1001 and 1047 had U.S. centers. Study 1047 was the only dose-titration study, whereas the others were fixed-dose. The endpoints in these studies were appropriate and included the following:

> Primary endpoint: change from baseline in average number of weekly incontinence episodes
>
> Secondary endpoints: change from baseline in the average number of daily micturition episodes, change-from baseline in the daily episodes of urgency, and change-from-baseline in average volume voided per micturition (among others).

According to the Biometrics review, the statistical analysis plans for these studies were all appropriate. Patient entry criteria included adult patients with OAB symptoms for at least 6 months. Patients were required to demonstrate all three major symptom components of OAB at baseline, as follows:

1. Incontinence (>10 [Studies 1001 and 1002] or >5 incontinence episodes per day [Study 1041]),
2. Excessive micturition frequency (>8 per day), and
3. Excessive urinary urgency (>1 urgency episode per day).

Thus, the entry criteria, as listed in the primary MO's review (see Appendix) are considered acceptable.

Table 1 below, as extracted from the primary medical officer's review, demonstrates the efficacy results for the primary efficacy endpoint in each of the 3 pivotal trials:

Table 1. Change in number of incontinence episodes per week from baseline to Week 12 in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Incontinence Episodes Per Week	Study 1002		
	Darifenacin 7.5mg (N=108)	**Darifenacin 15mg (N=106)**	**Placebo (N=108)**
Median Baseline	14.0	17.3	16.1
Median Change from Baseline	-8.1	-10.4	-5.9
Median Difference from Placebo	-2.8	-4.3	--
P value	0.007	<0.001	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	**Darifenacin 15mg (N=115)**	**Placebo (N=163)**
Median Baseline	16.3	17.0	16.6
Median Change from Baseline	-9.0	-10.4	-7.6
Median Difference from Placebo	-1.5	-2.1	--
P value	0.01	0.02	--
	Study 1001		
	Darifenacin 7.5mg	**Darifenacin 15mg (N=109)**	**Placebo (N=113)**
Median Baseline	--	16.2	15.5
Median Change from Baseline	--	-11.4	-9.0
Median Difference from Placebo	--	-2.4	--
P value	--	0.049	--

Source data: Table 11 of 2.7.3 Summary of Clinical Efficacy or Table 5.1.3 of Individual Study Report
N: number of subjects included in the analysis
LOCF: Last observation carry forward
FAS: Full Analytical Set

Reviewer's comment: It is notable that in Study 1001, the pre-defined statistical "bar" of p<0.025 was not attained for the primary endpoint. The actual p-value attained was 0.049. In this study, multiple comparisons were made between treatment groups, including one for an active-comparator group. Based upon the need to adjust for these comparisons, the requisite p-value was smaller than the usual p<0.05. Nevertheless, while the predefined level of statistical significance was not achieved in Study 1001, the clinical review team notes that p-value was still small (0.049). Compared to the results of other two studies, it appears likely that the reason for not achieving per-protocol statistical significance in Study 1001 was a high placebo response rather than a lower treatment effect.

Table 2 below presents the efficacy results for the critical secondary efficacy endpoint, micturition frequency, from the three pivotal studies.

Table 2. Change in average number of daily micturitions from baseline to Week 12 in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Number of Micturitions Per Day	Study 1002		
	Darifenacin 7.5mg (N=107)	Darifenacin 15mg (N=106)	Placebo (N=108)
Median Baseline	10.3	11.0	10.1
Median Change from Baseline	-1.7	-1.9	-1.1
Median Difference from Placebo	-0.5	-0.7	--
P value	0.066	<0.005	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	Darifenacin 15mg (N=115)	Placebo (N=163)
Median Baseline	10.1	10.1	10.1
Median Change from Baseline	-1.6	-1.7	-0.8
Median Difference from Placebo	-0.8	-0.9	--
P value	<0.001	<0.001	--
	Study 1001		
	Darifenacin 7.5mg	Darifenacin 15mg (N=109)	Placebo (N=114)
Median Baseline	--	10.5	10.4
Median Change from Baseline	--	-1.9	-1.2
Median Difference from Placebo	--	-0.5	--
P value	--	0.076	--

Source data: Table 20 of 2.7.3 Summary of Clinical Efficacy or Table 5.2 3 of Individual Study Reports
N: number of subjects included in the analysis
LOCF: Last observation carry forward
FAS: Full Analytical Set

The results for the critical secondary endpoints provide support for the primary endpoint. In Studies 1002 and 1041, the results for the "micturitions" endpoint were statistically significant. In Study 1002, the p-value achieved in the 7.5mg dose group was 0.066, marginally above the level required for statistical significance. Further, in Study 1001, the p-value achieved for the 15mg dose group was similar (0.076).

> *Reviewer's comment: Taking all the efficacy data into consideration, including the relative importance of the three symptoms outcomes, the strength of statistical evidence, and the direction of the treatment effect in the three pivotals and one supporting study, the clinical team concludes that the evidence supports the effectiveness of darifenacin (7.5mg and 15mg qd) for the treatment of overactive bladder. We acknowledge the lack of statistical significance for the micturition endpoint for the 7.5mg group in 1002 and the 15mg dose group in Study 1041.*

The results for the "urgency" endpoint in the three pivotals was similar, as follows:

Table 3. Change in average number of daily episodes of urgency from baseline to Week 12 in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Number of Episodes of Urgency Per Day	Study 1002		
	Darifenacin 7.5mg (N=107)	Darifenacin 15mg (N=106)	Placebo (N=108)
Median Baseline	8.5	8.6	8.1
Median Change from Baseline	-1.8	-2.3	-1.2
Median Difference from Placebo	-0.5	-1.1	--
P value	0.196	0.013	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	Darifenacin 15mg (N=115)	Placebo (N=163)
Median Baseline	7.7	8.0	8.3
Median Change from Baseline	-2.0	-2.0	-0.9
Median Difference from Placebo	-0.9	-0.9	--
P value	0.001	0.005	--
	Study 1001		
	Darifenacin 7.5mg	Darifenacin 15mg (N=109)	Placebo (N=113)
Median Baseline	--	8.6	8.5
Median Change from Baseline	--	-2.6	-1.9
Median Difference from Placebo	--	-0.7	--
P value	--	0.061	--

Source data: Table 30 of 2.7.3 Summary of Clinical Efficacy or Table 5.2.3 of Individual Study Reports
N: number of subjects included in the analysis
LOCF: Last observation carry forward
FAS: Full Analytical Set

Reviewer's comment: The review team again acknowledges the lack of statistical significance for this endpoint in the 7.5mg dose group in Study 1002 and for the 15mg dose group in Study 1001. Again, in 1001, the p-value is small (0.061). These minor inconsistencies do not affect the team's overall decision regarding effectiveness given the weight of the current evidence.

Treatment effect appeared to be consistent across subgroups with the acknowledgement that non-white patients constituted <5% of all enrolled patients. Further, there appeared to be effectiveness in the young and elderly, as well as in men and women. The drug demonstrated the most robust efficacy in older women. In fact, the 7.5mg dose did not demonstrate statistical significance for the primary endpoint in men. Such may be an issue if the 15mg dose were not to be approved for some other reason.

The sponsor argued that a dose-titration paradigm would be optimal in the management of OAB and proposed such for the label (all start with 7.5mg and advance to 15mg if sufficient efficacy is not attained and safety allows). Clinically, this was supported by evidence from Study 1047, the only dose-titration Phase 3 trial. In Study 1047, all subjects started on 7.5mg daily (or 7.5mg placebo) with an upward option to 15 mg

daily (or 15mg placebo) after 2 weeks of treatment. A total of 269 and 129 subjects were enrolled into darifenacin 7.5/15mg and placebo groups, respectively. The demographic and baseline characteristics of the subjects and efficacy assessment of this study were similar to that in Study 1001. The results from 1047 showed that darifenacin 7.5mg/15mg was associated with a median improvement of 1.4 episodes per week in number of incontinence episodes per week and the treatment effect was statistically significant at p =0.035 level. This result was verified by our colleguc in Biometrics in her statistical review of this NDA.

> *Reviewer's comment: The results of Study 1047 support the dose-titration paradigm. Clinically, the dose-titration paradigm is very reasonable and optimizes safety and efficacy.*

The only other efficacy issues are the following:

1. The sponsor has not supported [redacted]
2. The treatment effect is seen as early as 2 weeks.
3. A dose of 3.75mg dose not appear to be effective, while a dose of 30mg provides numerically greater reduction in symptoms than the to-be-marketed doses.
4. There is no reason to believe that the results from studies conducted outside the U.S. are not applicable to the U.S. for this inidication.

4. Clinical Safety

4.1 Exposure

The NDA contains sufficient safety information in terms of overall exposure to darifenacin. As of 11 October 2002, a total of 6,655 subjects were exposed to at least one dose of darifenacin. Doses studied ranged from 3.75mg up to 60mg. In the Phase 3 OAB trials 1002, 1041 and 1001, a total of 1069 patients received darifenacin. In all Phase 2 and 3 placebo-controlled OAB trials (as of the abovementioned cut-off date), a total of 1833 patients received darifenacin. In all Phase 2 and Phase 3 trials for both OAB and irritable bowel syndrome, a total of 5,398 patients received darifenacin. Finally, a total of 601 and 363 subjects were exposed to the maximum recommended or higher dose of darifenacin for at least 6 months and 12 months, respectively.

4.2. Demographics

In the Phase 3 OAB trials, approximately 85% of the darifenacin-treated population was female, approximately 96% were Caucasian, and the mean age was approximately 57 years (range 22-85 years).

> *Reviewer's comments: Due to the limited number of non-whites, subgroup analysis by race is not meaningful for these studies. However, there is no reason to believe that the results in the Caucasian population cannot be generalized to non-white American. The exposure in men is also fairly limited and reflects clinical practice; specifically, pure OAB without concomitant bladder outlet obstruction in adult males is not common.*

4.3. Deaths

As of 11 October 2002, death was reported in three darifenacin-treated patients due to suicide, adenocarcinoma and hepatic failure, respectively. The incidence rate for death adjusted for exposure was 2 and 3 per 1,000 person-years of exposure for both darifenacin and placebo-treated groups. None of these deaths were judged to be related to study drug by either the investigator or the sponsor. A detailed examination of each of these cases by the clinical team concurred with the sponsor's assessment.

4.4. Serious adverse events

A total of 189 patients and 40 patients in the darifenacin and placebo-treated groups, respectively, reported serious adverse events. When adjusted by number of events per 100 person-years, the totals are 18.4 for darifenacin and 16.4 for placebo. The majority of serious adverse events were clustered around the following: medical intervention for acute urinary retention, hospitalization for constipation, appendicitis, cholecystitis, intestinal obstruction and bone fracture. Table 4 lists these SAEs by treatment group

Table 4. Serious adverse events of note

	Darifenacin (N=6655, PYE*=1462)		Placebo (N=2216, PYE*=329)	
	Number	Rate (Per 100 PYE)	Number	Rate (Per 100 PYE)
Events That Are Directly Related to the Drug's Pharmacological Effects				
Constipation	5	0.34	1	0.30
Urinary retention	7	0.48	0	0
Events That May Be Indirectly Related to the Drug's Pharmacological Effects				
Acute renal failure	1	0.07	0	0
Intestinal Obstruction	2	0.14	0	0
Events of GI System				
Appendicitis	6	0.41	0	0
Cholecystitis	5	0.34	0	0
Events with Unusually High Rates				
Bone fracture	15	1.03	0	0

The clinical review team did a detailed analysis of these cases and concluded the following:

1. There was not sufficient evidence of a relationship between drug and appendicitis, or between drug and cholecystitis. This was due to the small number of cases reported during the 12-week controlled periods and due to pre-disposing background conditions in the affected patients (especially for cholecystisis).
2. Intestinal obstruction was reportedly concurrently with appendicitis and not on its own. However, intestinal obstruction is still considered a plausible result of treatment with darifenacin based upon its inducement of intestinal atony.
3. Urinary retention requiring catheterization and even resulting in one case of acute renal failure was reported and may be expected in some darifenacin-treated patients.
4. Cases of severe constipation including cases resulting in hospitalization were reported and also may be expected to occur infrequently with darifenacin treatment.
5. The reported incidence of bone fracture was unexpectedly higher in the darifenacin group compared to placebo. There was no clear rationale for this finding. Our analysis of this issue was limited by the small number of cases in controlled trials (versus open-label trials) and in many cases, a direct attribution to a fall, a motor vehicle accident or some other trauma. Additional investigation into a possible relationship would appear appropriate and should be conducted in the post-marketing period. Such a Phase 4 commitment is recommended.

4.5. Discontinuations due to adverse events

In the three OAB fixed dose Phase 3 studies (1001, 1002, and 1041), 5.6% and 12.9% patients prematurely discontinued (due to all causes) in the 7.5mg and 15mg groups respectively, compared to 8.0% in the placebo groups. The incidence of discontinuation due to adverse events was greater in the 15mg group (5.1%) than in the placebo group (2.6%). The rate in the 7.5mg group was actually lower than that in the placebo group (1.5% versus 2.6%, respectively), reflecting good tolerability in the 7.5mg group.

Constipation was the leading cause for AE-related study discontinuation (0.6% and 1.2% for 7.5mg and 15mg groups, respectively) (see Table 5).

Table 5. Study discontinuation in three OAB fixed dose phase 3 studies – a pooled analysis of Study 1001, 1002, and 1041

Adverse Events	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 PYE*=87
Discontinued (All causes)	19 (5.6%)	43 (12.9%)	31 (8.0%)
Discontinued due to AE	5 (1.5%)	17 (5.1%)	10 (2.6%)
Constipation	2 (0.6%)	4 (1.2%)	1 (0.3%)
Dry mouth	0 (0%)	3 (0.9%)	0 (0%)
Dyspepsia	0 (0%)	3 (0.9%)	0 (0%)
Cardiovascular system	1 (0.3%)	1 (0.3%)	1 (0.3%)
Nervous system	0 (0%)	2 (0.6%)	3 (0.8%)
Urogenital system	0 (%)	0 (0%)	2 (0.5%)

Source data: Table 13.1 and 19.1 of 2.7.4 Summary of Clinical Safety
PYE = person-year exposure

Reviewer's comment: The discontinuation rates due to adverse events were fairly low, especially in the 7.5mg group. There were no discontinuations due to dry mouth in the 7.5mg group and only 3 such discontinuations (0.9%) in the higher dose group. This reflects good tolerability in terms of dry mouth. The discontinuation rate due to cardiovascular adverse events was the same in the placebo and drug groups, again reflecting good tolerability in that regard.

4.6. Common adverse events

In the three pivotal Phase 3 studies combined (1001, 1002 and 1041), 54% and 66% of subjects in darifenacin 7.5mg and 15mg groups, respectively, reported one or more adverse events (AEs) during a 12-week period, compared to 49% in the placebo groups.

Table 6 shows the selected adverse events that occurred in more than 1% subjects in the darifenacin 15mg group and at a greater frequency compared with the subjects in the placebo group. The most common events were dry mouth, constipation and dyspepsia. The majority of the common adverse events appeared to be dose-dependent.

Table 6. Incidence of adverse events occurring at > 1% in darifenacin 15mg group by treatment group – a pooled analysis of three pivotal Phase 3 studies (1001, 1002 and 1041)

Adverse Event	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 PYE*=87
Dry mouth	68 (20.2%)	118 (35.3)	32 (8.2%)
Constipation	50 (14.8%)	71 (21.3%)	24 (6.2%)
Dyspepsia	9 (2.7%)	28 (8.4%)	10 (2.6%)

Urinary tract infection	16 (4.7%)	15 (4.5%)	10 (2.6%)
Abdominal pain	8 (2.4%)	13 (3.9%)	2 (0.5%)
Asthenia	5 (1.5%)	9 (2.7%)	5 (1.3%)
Dizziness	3 (0.9%)	7 (2.1%)	5 (1.3%)
Dry eyes	5 (1.5%)	7 (2.1%)	2 (0.5%)
Rhinitis	2 (0.6%)	6 (1.8%)	5 (1.3%)
Dry skin	0	6 (1.8%)	2 (0.5%)
Nausea	9 (2.7%)	5 (1.5%)	6 (1.5%)
Abnormal vision	2 (0.6%)	5 (1.5%)	1 (0.3%)
Accidental injury	4 (1.2%)	4 (1.2%)	2 (0.5%)
Arthralgia	2 (0.6%)	4 (1.2%)	3 (0.8%)

Source data: Table 45 of 2.7.4 Summary of Clinical Safety (page 84)
PYE = person-year exposure

Reviewer's comment: The common adverse events of greatest relevance were: dry mouth, constipation, dyspepsia, urinary tract infection, abdominal pain, dry eyes, abnormal vision, and accidental injury. While no direct comparison can be made, this adverse event profile is consistent with the general anticholinergic class of compounds currently marketed for OAB. There is no evidence that darifenacin is "uro-selective". Of note, there were few reports of cardiovascular adverse events such as tachycardia or palpitations. In his regard, lack of such events may be a potential benefit of darifenacin over other compounds in the class.

The clinical team conducted a more detailed assessment of the most common AEs: dry mouth, constipation and dyspepsia. Table 7 describes the severity of these events, their incidence as a cause for drop-out, and their time of onset.

Table 7. Additional analysis of dry mouth, constipation and dyspepsia

Adverse Event	Number of Subjects with the Event	% Rated as Severe	% Dropouts	% within first week
Darifenacin 7.5mg				
Dry mouth	68	1.4%	0%	60.3%
Constipation	50	4.0%	4%	38.0%
Dyspepsia	9	33.3%	0%	44.4%
Darifenacin 15mg				
Dry mouth	118	8.5%	3%	66.9%
Constipation	71	12.6%	5.6%	66.2%
Dyspepsia	28	17.8%	10.7%	50.0%

Source Data: Table 15 of 2.5 Clinical Overview and Table 13.1, 22.1, 23.2, 23.7 and 24.1 of 2.7.4 Summary of Clinical Safety

Reviewer's comment: It is clear that both the severity and incidence of dry mouth, and constipation are worse for the 15mg dosage strength compared to the 7.5mg dose. The sponsor's proposal to start all patients on 7.5mg and up-titrate as required to attain efficacy is considered appropriate.

In terms of other safety issues:

1. There appeared to be little or no effect of darifenacin on vital signs.
2. There was no evidence of an effect of darifenacin on any routine laboratory value, including liver function tests.
3. The effect of darifenacin on the QT was scrutinized thoroughly and this discussion follows in Section 5 below.

5. Effect of Darifenacin on the QT interval

Darifenacin is a new chemical entity. It has not been approved in any country. It is intended for a large and diverse patient population, including middle-aged and elderly men and women, often with co-morbid conditions. Its use for overactive bladder is expected to be widespread in the United States and it could reach millions of patients. It is metabolized by the liver, primarily via the cytochrome P450 enzymes 3A4 and 2D6. Concomitant use of potent inhibitors of CYP 3A4 (e.g. ketoconazole, ritonavir) markedly increase the plasma concentrations compared to drug alone. Approximately 8-10% percent of Americans are "poor metabolizers" for the CYP 2D6 enzyme. Such is not possible to detect without specialized genotyping methodology. Poor metabolizer status also has significant impact on metabolism of darifenacin. Finally, the drug will be indicated for symptomatic relief of OAB, not a life-threatening condition. Based on the evidence from current clinical efficacy and safety studies, darifenacin has not yet demonstrated a compelling benefit over currently available anticholinergic treatments for OAB.

In pre-clinical studies, the drug demonstrated clear and definite effects on cardiac repolarization measures, including the HERG and dofetilide-binding studies and in vivo dog studies. Our collegues in pharmacology toxicology have informed us that the pre-clinical data should be viewed as a definite "signal" of potential effect in humans.

Therefore, considering all facets of this situation, this medical team leader finds it entirely appropriate to investigate the effect of darifenacin on the QT interval in humans. It also seems appropriate to ask that the studies be designed and conducted so that a clinically meaningful effect of darifenacin on the QT interval can be ruled out (at serum concentrations that are relevant). If such is not the case, this medical team leader would be unable to conclude with assurance that the compound was safe for the intended use. In brief, the sponsor has conducted several controlled Phase 1 trials in which the effect of drug on the QT interval was assessed. These include Studies 1007, 1015, and 1035. Sponsor also collected QT information in their Phase 3 studies. Despite this data, the clincal review team has concluded that none of the studies were sufficient to exclude a clinically meaningful effect of darifenacin on the QT interval at relevant plasma concentrations. Our collegues in the Division of Cardio-Renal Drug Products concur. Herein, the results of these studies and the study design deficiencies will be presented in brief. For greater details, the reader is referred to Dr. Kim's clinical pharmacology review and the Dr. Li's primary medical officer's review.

5.1. Pooled analysis

The sponsor provided the results of a "pooled analysis" in which a total of 964 darifenacin-treated subjects and 261 placebo-treated subjects contributed digitized ECG

data from four studies: Study 137-684 (a phase 3 pivotal irritable bowel [IBS] trial), Study A1371002 (a Phase 3 pivotal OAB trial), Study A1371007 (a Phase 1 drug-drug interaction study of 15mg +/- ketoconozole) and Study A1371015 (a Phase 1 multiple-dose tolerability study of placebo, 30mg and 60mg). Table 8 summarizes the findings for the Fridericia-corrected QTc from this pooled analysis.

Table 8. Summary of QTcF statistics by age and gender – sponsor's "pooled analysis" from four studies (Studies 137-684, A1371002, A1371007 and A1371015)

Measurement	Darifenacin (3.75-60mg qd)	Placebo
Total		
Subject (N)	964	261
Baseline (ms)	395.0	395.5
Mean Change from baseline (ms)	2.2	1.9
Number and percent with QTc change ≥ 30 ms and < 60 ms	69 (7.2%)	15 (5.7%)
Number and percent with QTc change ≥ 60 ms	4 (0.4%)	1 (0.4%)
By Gender		
Male Subject (N)	224	73
Baseline (ms)	382.6	386.5
Mean Change from baseline (ms)	4.6	0.6
Number and percent with QTc change ≥ 30 ms and < 60 ms	17 (7.6%)	4 (5.5%)
Number and percent with QTc change ≥ 60 ms	0 (0%)	0 (0%)
Female Subject (N)	740	188
Baseline (ms)	398.8	399.0
Mean Change from baseline (ms)	1.4	2.4
Number and percent with QTc change ≥ 30 ms and < 60 ms	52 (7.0%)	11 (5.9%)
Number and percent with QTc change ≥ 60 ms	4 (0.5%)	1 (0.5%)
By Age		
<65 Subject (N)	833	221
Baseline (ms)	393.4	393.9
Mean Change from baseline (ms)	3.1	2.1
≥ 65 Subject (N)	131	40
Baseline (ms)	405.4	404.0
Mean Change from baseline (ms)	-0.4	0.4

Source data: Table 5-9 – Appendix F of Clinical Summary (2.7), page 1278-86

From this data, the sponsor concluded:

1. There was no evidence that darifenacin was associated with any statistically or clinically relevant increase in the QT interval.
2. The percentage of subjects with a maximum individual increase in QTcF from baseline of ≥60msec was the same for darifenacin (0.4%) and placebo (0.4%).
3. Neither females nor the elderly showed any additional risk of QT prolongation compared with the overall population;

Reviewer's comment: The pooled analysis has deficiencies. First, the protocol for Study 1002 excluded use of potent 3A4 inhibitors, thereby limiting overall exposure. [ ] *It is not clear how the sponsor selected these studies for this pooled analysis. Overall, the clinical review team does not believe that this pooled analysis adequately defines the effect of darifenacin on the QT interval.*

1.1. Studies 1007, 1035 and 1015

The sponsor conducted three controlled Phase 1 trials in which the effect of darifenacin on the QT interval was investigated as part of the trial.

Study 1007 was a drug-drug interaction study intended to investigate the effect of ketoconozole on the pharmacokinetics of darifenacin 30mg. Study 1035 was the same, except it employed darifenacin doses of 7.5mg and 15mg. These were randomized, placebo-controlled, crossover studies, designed as standard Phase 1 drug-drug interaction trials. There was no positive control and no placebo-only group in either study. ECGs were taken once at baseline and once at Hour 4 after dosing with darifenacin for six days. Patients were normal healthy volunteers. The results for Study 1007 are depicted in Table 9.

Table 9. Mean changes from baseline in QTc by treatment group – Study A1371007

Measurement	Darifenacin 30mg And Ketoconazole	Darifenacin 30mg And placebo
Fridericia's Correction		
Subject (N)	16	16
Baseline (ms)	353.6	353.6
Change from baseline (ms)		
Mean	12.1	-0.5
S.D.	14.4	11.8
Min and Max	[	]
Bazett's Correction		
Subject (N)	16	16
Baseline (ms)	354.6	364.6
Change from baseline (ms)		
Mean	6.8	-4.3
S.D.	16.7	11.6
Min and Max	[	]

Source data: Table 9.2 of Final Study Report of Study A1371007, Page 115

On 17 September 2003, the sponsor submitted a summary of QT safety results from Study 1035. Twelve male subjects (10 EM and 2 PM) for each dose group were enrolled. However, only 8 and 6 subjects for 7.5mg and 15mg dose groups, respectively, were included in the QT analysis. In summary, the results from Study 1035 were similar to those for 1007, as follows:

1. There was a mean change-from-baseline of 12 ms in QTcF in 8 subjects when they received darifenacin 7.5mg plus ketoconazole versus a mean change-from-baseline of 2 ms when they received darifenacin 7.5mg plus placebo.

2. There was a mean change-from-baseline of 10 ms in QTcF in 6 subjects when they received darifenacin 15mg plus ketoconozole versus a mean change-from-baseline of -3 ms when they received darifenacin 15mg plus placebo.

Reviewer's comments:

1. *The results of Studies 1007 and 1035 appear to demonstrate a mean difference between darifenacin + ketoconozole and darifenacin + placebo groups of approximately 10 to 12 milliseconds whether the dose of darifenacin was 7.5mg, 15mg or 30mg.*
2. *Without a placebo/placebo group, it is not possibly to determine the direct effect of darifenacin.*
3. *Without a positive control group, it is not possible to state that any of these trials were adequately sensitive to detect small changes in the QTc and further it is not possible to compare treatment groups to the active control.*
4. *These trials were also flawed in not conducting multiple ECGs at baseline and timepoint of interest and not conducting ECGs at Tmax.*
5. *The sponsor argues that the differences between groups is likely due to the effect ketoconozale on the QT. Literature is presented to support this contention. The literature presented is limited to an abstract of a small study done approximately 10 years ago. The sponsor's argument may be correct but without a concurrent ketoconozole-alone arm in Studies 1007 and 1035, it cannot be confirmed as being correct.*
6. *It is not clear why only 8 and 6 subjects were included in the analysis despite enrollment of 12 subjects at each dose.*

Study 1015 was a Phase 1 safety, tolerability and pharmacokinetics study using placebo, 30mg and 60mg of darifenacin following multiple doses. Results of the QT assessment of this study are presented in Table 10.

Table 10. Mean changes from baseline to 4 hours pose dose on Day 14 by treatment group – Study A1371015

Measurement	Darifenacin 60mg qd (n=39)	Darifenacin 30mg qd (n=9)	Placebo (n=10)
Fridericia's Correction (QTcF)			

Baseline (ms)	408.1	414.9	407.1
Change from baseline (ms) to Day 14			
Mean	-7.6	-9.4	-10.4
S.D.	15.5	14.9	15.0
Min and Max	[		]
Bazett's Correction (QTcB)			
Baseline (ms)	407.9	416.8	407.4
Change from baseline (ms) to Day 14			
Mean	-4.0	-6.7	-6.8
S.D.	19.7	16.4	19.2
Min and Max	[		]

Source data: Table 10 of Final Study Report of Study A1371015, Page 151

Reviewer's comment: While there was no significant difference between groups and acknowledging that this study was done using four times the maximum recommended dose, the clinical review team still does not find the study to be sufficient to rule out a meaningful effect on the QT. There was no positive control. ECGs were conducted once at baseline and once at Hour 4 after dosing on Day 6. And, the dose of 60 mg probably did not produce plasma concentrations of darifenacin that meet or exceed those attained when 15mg is given with ketoconozole in a cytochrome P450 2D6 poor metabolizer (a "worst-case" scenario). Real pharmacokinetic data for such a patient group is limited to perhaps 1 patient.

Therefore, in summary, despite the pooled analysis and the results of Studies 1007, 10354 and 1015, the clinical review team does not find there to be sufficient information in this application to rule out a clinically meaningful effect on the QT interval at clinically relevant plasma concentrations. Again, it should be noted that this drug's metabolism is markedly affected by inhibition of CYP450 3A4 and by genotype status for CYP450 2D6. Additional information regarding the clinical pharmacology of the compound may be found in brief in the next section of this memo as well as in greater detail in the clinical pharmacologist's review.

6. Relevant Issues from other Disciplines, Consults, or Regulatory Matters

6.1. Clinical Pharmacology and Biopharmaceutics (OCPB)

Based upon the currently available OCPB draft review (received by this team leader on September 15, 2003), the review states:

> "From the viewpoint of the Office of Clinical Pharmacology and BioPharmaceutics, the Human Pharmacokinetics and BioPharmaceutics section of NDA 21-513 is acceptable provided that a satisfactory agreement has been reached between the Agency and the sponsor regarding the language in the Package Insert."

Reviewer's comment: To my knowledge, the Clinical Pharmacology section of the proposed label was not yet revised by the review team and such will be necessary during the next cycle review.

This reviewer selected several clinically relevant points from Dr. Kim's extensive review of the Clinical Pharmacology section of this NDA, as follows:

1. Absorption of darifenacin is rapid. In the proposed extended-release (ER) formulation, the rate of absorption is limited by the rate of release from the tablet matrix. The Tmax values for this ER product occur at around 7-8 hours after dosing.
2. There is low oral bioavailability as a consequence of first-pass metabolism by the liver.
3. Ingestion of food has little effect on overall pharmacokinetics, therefore darifenacin may be taken without regard to food.
4. Darifenacin is 98% bound to plasma proteins, primarily alpha-1-acid glycoprotein.
5. The estimated half-life is around 12-18 hours. Steady state is reached around Day 6.
6. Metabolism is mediated by CYP 2D6 and CYP 3a4 enzymes. No major metabolite contributes to the overall clinical effect.
7. Darifenacin pharmacokinetics are dose-dependent. Dose-dependency appears to be related to saturation of CYP 450 3A4 metabolism in the gut wall at higher doses, combined with a reduction in the contribution of CYP 450 2D6 metabolism at steady state.
8. About 60% of a radio-labeled dose is recovered in the urine and 40% in the feces. Only approximately 3% is excreted unchanged.
9. Darifenacin exposure is lower in males than in females.
10. Darifenacin exposure is higher in elderly than in the younger population.
11. There were insufficient numbers of non-whites to assess differential effects by race.
12. In patients with poor metabolizer status for CYP 2D6, total exposure for the 7.5mg and 15mg doses is 164% and 99% higher, respectively, as compared to extensive metabolizers for 2D6. The difference between EM and PM populations appears to decrease with increasing dose. This may be due to saturation of that pathway.
13. There is no effect of renal insufficiency on pharmacokinetics of darifenacin.
14. Mild hepatic impairment did not alter darifenacin pharmacokinetics. However, steady-state exposure was increased by 168% in those with moderate liver impairment compared to normals. After adjusting for lower protein binding in the liver-impaired, that increase is even greater, approximately 300 to 370% higher than in normals. Subjects with severe hepatic impairment were not studied. The sponsor recommends that patients with moderate hepatic impairment onkly take 7.5mg and those with severe impairment should not take darifenacin at all.

    Reviewer's comment: The increase in exposure in the elderly, in women, in those with poor 2D6 metabolizer status, and especially, in the hepatically-impaired, increases this reviewer's concern regarding lack of adequate QT information.

15. Darifenacin pharmacokinetics are altered by the following concomitant drugs:

    a. With ketoconozole 400mg qd, the increase in Cmax and AUC was approximately 5x and 5x, respectively for 7.5mg, as compared to 10x and 11.6x for 15mg, respectively.

b. With erythromycin 500mg BID and with fluconozole 200 mg qd, the increases in Cmax and AUC (for 30mg) are approximately 2-fold.
c. With cimetidine 800mg BID, the increases in Cmax and AUC are only 1.42 fold and 1.34 fold, respectively.
d. With paroxetine 20mg qd, the increases in Camx and AUC are only 1.33 fold and 1.36 fold, respectively.

16. The pharmacokinetics of the following drugs are altered by darifenacin:

    a. The Cmax and AUC of desipiramine is increased by approximately 2.6 fold each.
    b. The Cmax and AUC of imipramine is increased by approximately 1.6 fold each.

    Reviewer's comment: It is not unusual to use imipramine for the treatment of incontinence in some patients who also may receive darifenacin.

17. Bioequivalence was established between the Phase 3 research formulation and the to-be-marketed formulation.

6.2. Pharmacology/Toxicology

In her supervisory pharmacology and toxicology review, Dr. Thornton concludes:

> "The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues."

Dr. Thornton also notes that appropriate labeling revisions were identified and were forwarded to sponsor. The Division Director should be aware that such revisions must be made during the next cycle review.

Dr. McLeod's primary pharmacology review is extensive, especially in regard to the cardiovascular and QT issues. Major issues that I noted include the following:

1. From the preclinical data, Dr. Mcleod expects that darifenacin will have "minor effects" on salivation and intestinal motility in the range of clinical doses.
2. Based on preclinical studies, Dr. McLeod expects the darifenacin effect on QT prolongation "to be minimal" at about 5 times the average exposure of a 15mg dose. She writes that the animal data "tends to confirm a change in QT of 3.5%, or 12.1 msec in humans; or 2.3% in dogs" at a dose of 30mg plus ketoconazole where mean total blood levels in humans were 103ng/mL.
3. Darifenacin competitively displaced 3-H-dofetilide hERG receptors with an IC_{50} value of 1.1×10^{-6} M (550 ng/mL) and an IC_{10} of about 1×10^{-7}M (50ng/mL).
4. Using whole cell patch clamp technique which examines the effect on the hERG potassium current, the parent compound exhibited an IC_{50} of 77nM (39.1 ng/mL).
5. In an in vivo dog study, at 10.7 ng/mL there was a 7% increase in the QT interval. At 43.2 ng/ml, there was a 16% increase in the QT interval. About these results, Dr. McLeod states:

"Effects on the QT interval at higher doses are consistent with changes in the potassium Ikr channels in hERG studies."

Reviewer's comment: This team leader is sufficiently convinced by the available pre-clinical data that there is a strong pre-clinical "signal" for potential QT prolongation in humans.

6.3. Biometrics

In her Biometrics review, Dr. Castillo concludes the following:

"The effectiveness of darifenacin 7.5mg and 15mg in decreasing the number of incontinent episodes per week and the effectiveness of darifenacin 15mg in decreasing the number of micturitions per day has been demonstrated. The effectiveness of darifenacin 7.5mg in decreasing the number of micturitions per day is demonstrated in one study but a second study did not reach statistical significance (p=0.066)"

Other relevant items in the Biometrics review include:

1. Dr. Castillo concurs with the sponsor's analyses of all studies.
2. Dr. Castillo concurs with the sponsor's conclusions for all studies except one, Study 1001. In this study, she notes that there was a tolterodine arm that was compared to all doses of darifenacin. These comparisons to active control followed the primary comparisons of each darifenacin dose to placebo. This is described as two "separate step-down procedures". Based upon the need to account for multiple comparisons, the sponsor intended statistical significance to be declared only at a p-value of 0.025. However, since no claims were intended for the tolterodine comparisons Dr. Castillo writes that she is:

"...inclined to view Study A1371001 as a placebo-controlled only study. Thus, the significance level for the single step-down procedure to compare all darifenacin doses to placebo should be viewed as having a significance level of 0.05. Given this view, a marginal decrease in the average number of incontinent episodes per week at Week 12 occurs in subjects taking darifenacin 15mg (-11.4 episodes) compared to subjects taking placebo (-9.0 episodes). This decrease is marginal because the p-value is close to significance level of 0.05."

6.4. Chemistry, Manufacturing and Controls (CMC)

In his final review, Dr. Fensalau concludes:

"All product quality issues that relate to the safety and efficacy of this drug have been adequately addressed to support a recommendation to approve this NDA."

The only issue of note in the review is the following:

"Several items in the 'Label and Package Insert' have been identified as having the potential for contributing to user error. These comments *have been* conveyed by the Division to the sponsor. Until responses are received, the (chemistry review team's) recommendation for the Label and Package Insert is Approvable."

In the Section designated "Basis for Approvability", Dr. Fensalau clearly states that all chemistry requirements have been met and aside from labeling, there are absolutely no unresolved issues. All manufacturing, testing and packaging sites have been inspected and are in compliance with cGMPs. A —— shelf-life was granted. The in-vitro dissolution method, specifications and acceptance criteria are acceptable. The drug substance and drug product specifications, test methods and accetpatnce criteria are acceptable.

6.5 Division of Cardio-Renal Drug Products (DCRDP)

On 16-September-2003, Dr. Stockbridge provided a written consultation to DRUDP. In this memo he describes having reviewed the following items: 1) "Key information" provided by DRUDP 2) sponsor's integrated summary of QT data from the original NDA submission (16-November-2002) and 3) the sponsor's submission dated 4-September-2003 in response to a Division Request for Information.

Reviewer's comment: Dr. Stockbridge completed his consult to DRUDP prior to the sponsor's submission of a fax document on 17-September-2003. This document contained additional summary QT information from Study 1035 which included darifenacin 7.5mg + ketoconazole and darifenacin 15mg + ketoconazole. The summary information from this study was conveyed verbally to Dr. Stockbridge by sponsor and by our review team during the teleconference held on 22-September-2003. This new information did not appear to change his opinion.

After his analysis of the information provided, Dr. Stockbridge concluded the following:

"If one could prevent drug exposure above 15mg, use in poor 2D6 metabolizers, and 3A4 inhibition, then the apparently shallow relationship to QT at these relatively high plasma levels might be relatively comforting. In practice, nose of these can be prevented. Nor can one determine post hoc what magnitude of mean QT effect has been excluded. In other words "assay validation" also serves to calibrate the observed effects against a known reference. In addition, ECGs in both studies appear to have been collected prior to attainment of peak plasm levels following a dose.

These ambiguities can be resolved only through a "thorough" QT evaluation with a positive control agent. It is recommended that such a study use as high a dose as can be tolerated during a 6-day exposure. Use of a metabolic inhibitor would necessitate an inhibitor-alone arm or crossover period. The sponsor might wish to

consider inclusion of an approved agent for overactive bladder. Prefreably of the same class as darifenacin."

6.6. Division of Scientific Investigation (DSI)

The final memo from DSI in regard to this NDA concludes that:

> "The data submitted in support of this NDA by Drs. Krajka and Rechberger appear acceptable."

Dr. Blay's memo includes the following information of note:

1. Dr. Krajka of Gdnask, Poland enrolled 35 subjects in Study 1002. Dr. Blay inspected the records for 18 of these patients. There were no significant violations
2. Dr. Blay notes that Study 1002 employed a personal electronic diary maintained by the subject themselves. Information from the diary was downloaded at the investigator's site and sent to a firm [ ] which collected the information and forwarded it to the sponsor, Pfizer. At the end of the study, Pfizer forwarded a CD to the investigator with the information from the site patients. This CD served as the source documentation for the critical study parameters. Dr. Blay concludes that, [ ] has provided substantial information to indicate that this data is original, accurate, contemporaneous and attributable."
3. Dr. Rechberger of Lublin, Poland enrolled 26 patients in Study 1002 and records for all of these were inspected. There were no signficant violations.
4. Again, a personal electronic diary was employed, but substantial evidence was provided by [ ] to justify the source documents.

6.7. Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS)

DMETS concludes that it has "no objection" to the tradename Enablex. The note, however, that DDMAC found the trade name Enablex to be [ ]

> *Reviewer's comment: The clinical review team believes that the tradename Enablex is acceptable. In our opinion, it is neither* [ ]

DMETS also provided recommendations in regard to container and carton labeling as well as two small revisions for the Description section and Dosage and Administration section of the package insert. Dr. Fensalau's final review of 25-September-2003 lists all of the DMETS comments and states, "These comments *are being* conveyed by the Division to the sponsor". I am not clear on whether the container and carton revisons were actually sent to sponsor, although in Dr. Fensalau's Executive Summary section, he states, "These comments *have been* conveyed by the Division to the sponsor". Regardless of whether these comments were conveyed to sponsor or not, this reviewer

reminds the Division Director that all container/carton labeling recommended by DMETS must be addressed by chemistry and by sponsor prior to any approval of darifenacin.

6.8. Financial Disclosure

Dr. Li's conducted a review of all financial disclosure information from required trials. In this regard, he concludes:

> "Financial disclosure was made from all required studies. The disclosure appears to be adequate and no evidence suggests that financial relationship had any impact on the study findings."

6.9. Pediatrics

The sponsor has committed to conducting studies in children after eventual approval of darifenacin in adults. Although protocols were discussed and meetings were held with The Division to determine acceptable dosing in children (among other matters), this issue is deferred until final determination that the product is safe in adults.

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
10/1/03 05:17:05 PM
MEDICAL OFFICER

Daniel A. Shames
10/1/03 07:27:13 PM
MEDICAL OFFICER

10/2/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-513	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: **darifenacin hydrobromide**	Applicant: Novartis	
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 3, 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 for approvable 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
❖ 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
❖ 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 with this approvable action. See AE letter regarding labeling
• 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
• 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 with this approvable action. See AE letter regarding labeling
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X; to assess the potential association of darifenacin with bone fracture
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A with this approvable action. See AE letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X (6/18/02)
• 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
[redacted]	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
[redacted]	
❖ Clinical review(s) *(indicate date for each review)*	X
❖ 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)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X
❖ 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
[redacted]	
❖ CMC review(s) *(indicate date for each review)*	X
❖ 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)*	N/A
❖ Facilities inspection (provide EER report)	(X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
[redacted]	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X
❖ CAC/ECAC report	X

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/s/

Jean R. King
10/2/03 10:30:22 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 2, 2003

To: Lynn McGrath, Ph.D.
Associate Director
Drug Regulatory Affairs
Company: Novartis Pharmaceuticals Corporation
Fax number: 973-781-3966

Phone number: 862-778-5139

From: Jean King
Project Manager

Division of Division of Reproductive and Urologic Drug Products
Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-513 Approvable letter

Total no. of pages including cover: 2

Comments: As per our telephone conversation today, please find the Division's Approvable letter for NDA 21-513

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Professor Tomasz Rechberger
Samodzielny Publiczny Szpital
Kliniczy NR 4
II Katedra I Klinika GinekologII
Operacy Jnej
Ul Jaczewskiego 8
Lublin, 20-954 Poland

SEP 30 2003

Dear Dr. Rechberger:

Between July 21 and 25, 2003, Mr. Kenneth Merritt and Dr. Roy Blay, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # A1371041 entitled: "A Phase 3b multicentre, double-blind, randomised, placebo-controlled, parallel group study of Darifenacin in subjects with overactive bladder (urge urinary incontinence)") of the investigational drug Enablex® (darifenacin hydrobromide) Tablets, performed for Novartis Pharmaceuticals Corporation. 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 evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Merritt and Dr. Blay 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

FEI: 3004028655
Field Classification: VAI
Headquarters Classification:
__x_ 1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

The inspection was reclassified as NAI since the first observation was addressed satisfactorily after the conclusion of the inspection, the second observation regarding contact information was either not supported by exhibits or required by regulations, and the third observation, while correct, was minor and resulted from problematic transportation issues for the elderly.

cc:
HFA-224
HFD-580/Doc.Rm. NDA# 21-513
HFD-580/Review Div.Dir./Shames
HFD-580/MO/Li
HFD-580/PM/King
HFD-46/47c/r/s/ GCP File # 010983
HFD-/47 GCP Reviewer/Blay
HFR-SE340/DIB/Lewis
HFR-SE350/BIMO Monitor/Abel
HFR-SE350/Field Investigator/Merritt
HFC-134 Kadar (for foreign only)
GCF-1 Seth Ray

r/d: (Blay):9/17/03; 9/23/03
reviewed: JPS: 9/23/03
f/t:ml:9/23/03
o:\blay\rechberger.doc

Reviewer Note to Rev. Div. M.O.
26 subjects were randomized to the study. Inclusion/exclusion criteria were met appropriately. The primary efficacy variable (average number of micturitions per week) was recalculated from CD copies of the original electronic diary records and confirmed 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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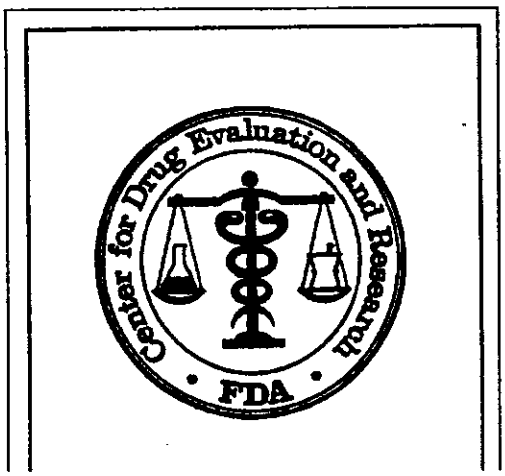
/s/

Joseph Salewski
10/7/03 03:58:01 PM

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Division of Reproductive and
Urologic Drug Products, HFD-580

Phone 301-827-2042
Fax 301-827-4267

Date: September 16, 2003

To:

Name Kenneth Kopec
Company Novartis Pharmaceuticals Corp.
City _____ State ____

Phone # 862-778-7757
FAX # 973-781-3320

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-4260 IMMEDIATELY if re-transmission is necessary.

Mr. Kopec, **NDA 21-513/N000**

Please respond to the following request for information by 23-SEP-2003. Please let me know if this deadline cannot be met. If you have any questions, just call me (301-827-2042) or the project manager Jean King (301-827-4260).

Allan Fenselau, Ph.D.
Review Chemist

NDA 21-513 **ENABLEX™ (darifenacin HBr)** **16-SEP-03**
Novartis Pharmaceuticals **Extended Release Tablets**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: Please provide the appropriate information as an amendment to the submission.

INFORMATION REQUEST

Chemist's Concerns

1. Provide a copy of the revised regulatory specification for the drug product ENABLEX. Specifically, include the changes made to the "Dissolution Requirements" statement (from the amendment dated 10-SEP-2003). Also, please revise the acceptance criterion for the Assay from '[redacted]' in accord with the conventions used in the US Pharmacopeia.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Allan Fenselau
9/16/03 11:01:20 AM
CHEMIST

David T. Lin
9/16/03 03:11:26 PM
CHEMIST
I concur.

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

Micro Efficacy Review

Not applicable to this application.

/S/

9/13/03

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

FDA PPI

Not applicable: this application does not contain a patient package insert (PPI).

/S/

9/3/03

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

Sponsor Revised PPI

Not applicable: this application does not contain a patient package insert (PPI).

9/3/03

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

Sponsor PPI

Not applicable: this application does not contain a patient package insert (PPI).

/S/

9/3/03

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

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

Application Integrity Policy (AIP)

This application is not the subject of an AIP investigation.

/S/

9/3/03

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

Post-Marketing Commitments

Not applicable to this application.

/S/

9/5/03

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

Special Programs

Not applicable to this application.

/S/

9/3/03

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

Public Communications

Not applicable for this application.

/S/
9/3/03

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

Federal Register Notices

Not applicable for this application.

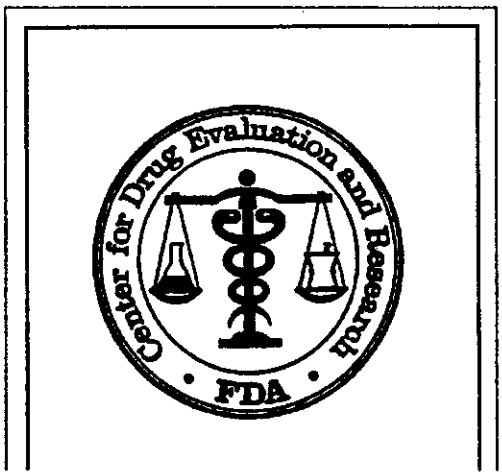
9/3/03

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

Micro Efficacy Review

Not applicable to this application.

FACSIMILE TRANSMISSION
RECORD



From: David Lin, Ph.D.

Division of Reproductive and
Urologic Drug Products, HFD-580

Phone 301-827-2003
Fax 301-827-4267

Date: September 4, 2003

To:

Name Lynne Fahey Mcgrath
Company Novartis Pharmaceticals
City _____ State ____

Phone # 862-778-5139
FAX # 973-781-3966

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2003 IMMEDIATELY if re-transmission is necessary.

Dr. Mcgrath, **NDA 21-513/N000**

Please respond to the following request for information by 10-September-03. Please let me know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call me or the project manager Jean King (301-827-4260).

David Lin, Ph.D.
Team Leader

NDA 21-513 **ENABLEX™ (darifenacin HBr)** **04-SEPT-03**
Pfizer, Inc. **Extended Release Tablets**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: Please provide the appropriate information as an amendment to the submission.

INFORMATION REQUEST

Chemist's Concerns

1. Confirm that, in accord with USP <724>, dissolution testing of the drug product proceeds to Level L3 for any product lot with results that fail to meet the conditions for Levels L1 and L2. [The STP for Dissolution Testing (D 30.71) contains no reference to the procedures to be followed in the event of failures at any test level.]

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/s/

David T. Lin
9/5/03 08:59:38 AM

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

Advisory Committee Meeting

Not applicable for this application.

/S/

9/3/03

9/2/03

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

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 21-513, Requested Tradename- Enablex
Generic: Darifenacin hydrobromide, 7.5 and 15 mg extended release tablets

Date of Application:	December 3, 2002
Date of Receipt:	December 3 , 2002
PDUFA Date:	October 3, 2003

Indication(s) requested: for the treatment of overactive bladder

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#____4346__
Clinical data? YES ___X____ NO _____ Referenced to NDA#

Date clock started after UN _____N/A_____

User Fee Goal date: ____October 3, 2003_____

Action Goal Date (optional) ____October 3, 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: 45,457

End-of-Phase 2 Meeting? Date NO

If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date 8/18/2002 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

FILING MEETING MINUTES

NDA: 21,513 **Drug:** Darifenacin

Sponsor: Pfizer

Date: January 17, 2003 **Time**: 3:00 PM – 4:00 PM

FDA/CDER/DRUDP Attendees:

Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP)
Mark Hirsch, M.D., Urology Medical Team Leader, DRUDP
Zili Li. M.D., Medical Reviewer, DRUDP
Myong-Jim Kim, Ph.D., Clinical Pharmacology Reviewer, DRUPD
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUPD
Jean King, Project Manager, DRUDP
Laurie McLeod, Ph.D., Pharmacology/Toxicology Reviewer, DRUPD
Allan Fenselau, Ph.D., Chemistry Reviewer, DRUPD
David Lin, Ph.D., Chemistry Team Leader, DRUPD

Issues Discussed:

On December 3, 2002, a new drug application (NDA) was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex (darifenacin). During this filing review meeting, the following issues were identified:

Clinical

The following are areas of concern and requests for additional clarifying information:

- The application is fileable.

- Although subsequent desk copies of Module 1 (containing volumes 1.1 and 1.2) of the NDA submission provided the appropriate listings of U.S. and non-U.S. investigators as well as the requisite FDA Certification Forms 3455, the sponsor's original submission (paper and electronic) did not include copies of the financial disclosure statement (Form FDA 3455) for 19 investigators who had made such a disclosure. We will request that the sponsor re-submit a complete Module 1 to NDA 21-513.

- We will request that the sponsor submit the names of the 25 investigators who did not respond or who were not successfully reached despite due diligence efforts.

- The non-Caucasian patient population is not well represented in the clinical studies. We will request that the sponsor provide a narrative summary of exposure, efficacy, and safety results in

the non-white population and compare that to the Caucasian population unless such information is already included in the current NDA submission.

- Data supporting the 7.5 mg dose is not derived from trials conducted at U.S. sites. We will request that the sponsor provide additional support that data derived from the non-U.S. population for the 7.5 mg dosage strength is applicable to the U.S. population.

- Statistical significance for the primary efficacy endpoint was not achieved for darifenacin 15 mg in Study A1371001, the study with the U.S. sites. This result is not consistent with results reported in the non-U.S. trials. We will request that the sponsor comment on why this difference should not affect the approval of darifenacin 15 mg for the U.S. market.

- Acute urinary retention, severe constipation, and cholecystitis have been identified as potential safety issues. We will request that the sponsor provide a narrative summary of safety experience from clinical trials for each of these adverse events and provide your conclusions regarding the causal relationship of darifenacin.

- Since this is an NME, we will request international clinical site inspections.

Clinical Pharmacology and Biopharmaceutics

The following concerns will be the subject of detailed review in the Clinical Pharmacology and Biopharmaceutics section:

- The application is fileable.

- The effects of various intrinsic and extrinsic factors on the pharmacokinetic (PK) profile of darifenacin.

- Characterization of the exposure-response relationship for both efficacy and safety.

- The dosing recommendation based on CYP2D6 genotype or with concomitant medications, particularly in the presence of CYP3A4 or CYP2D6 inhibitors or in special populations.

- The to-be-marketed and clinical trial formulations are linked via multiple-dose bioequivalence (BE) studies. The design and results of these studies will be carefully reviewed. This is especially important due to changes in the coating of the to-be-marketed tablet. The BE studies appear to be multiple-dose, not single dose. This is a review issue.

- The submission also contains the following information: gender differences, renal and hepatic dysfunction, geriatric exposure, population pharmacokinetics, and dos-proportionality studies.

Pharmacology/Toxicology

- The application is fileable.

- The sponsor did not address the possible relevance to humans of the single positive finding (e.g., hemangiosarcomas) observed in the rat two-year carcinogenicity study. This issue was identified prior to filing and a response was requested. Data showing high testosterone levels in rats but normal testosterone levels in humans taking darifenacin might provide mechanistic evidence that the hemangiosarcoma in rats were not relevant to humans. Without data to address the different responses of rats and humans and additional information relevant to exposure multiples, we must assume that the tumors are relevant to human populations taking the drug.

Chemistry

- The application is fileable.
- No review issues noted at time of filing.
- Four chemistry comments have already been sent to sponsor via IR letter.
- There are proposed manufacturing sites.
- Trade name consult and container/carton labeling will be sent to ODS/DMETS for their review.

Statistics

The Reviewer was not present; however, she conveyed the following to the Project Manager via phone the morning of this Filing Meeting:

- The application is fileable.
- No review issues noted at time of filing.

Summary of Action Items:

We will provide the above comments to the sponsor as 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. The sponsor will also be informed that if they respond to these issues during this review cycle, we may not consider your response before we take an action on their application.

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/s/

Jean R. King
9/2/03 12:55:03 PM
CSO

Jean R. King
9/2/03 12:57:46 PM
CSO

Teleconference Minutes

NDA: 21,513 **Drug:** Darifenacin (Enablex)

Sponsor: Novartis Pharmaceuticals

Date: August 19, 2003 **Time** 10:45 AM – 10:55 AM

FDA/CDER/DRUDP Attendees:
Jean King, M.S., R.D., Project Manager, DRUDP
Albert Perrine, R.N., BSN, Project Manager, DRUDP, DB2, HFD-715
Sonia Castillo, Ph.D., Biometrics Reviewer

Novartis Attendees:
Lynne Fahey McGrath, MPH, Ph.D., Regulatory Affairs
Erhard Quebe-Fehling, Ph.D., Biostatistics

Pfizer Attendees:
Katherine Prescott, Ph.D., (Biostatistics)
Moke Sharma (Project Management)

Background: This teleconference was initiated by the Agency to clarify with the Sponsor how they carried out the primary analysis for study A1371041 that used a "stratified Wilcoxon test (van-Elteren's test) with locally best weights and a normal approximation." Although the statistical analysis plan (SAP) was changed from a regular Wilcoxon test to this stratified Wilcoxon test, it is unclear in the statistical review of the original NDA submission when this change to the SAP occurred.

Issues Discussed:

1. Submit the statistical analysis plan (SAP, original and any modifications as applicable) for study A1371041 to NDA 21513, date of database lock, and date of database unblinding.

Sponsor Response: The sponsor agreed to submit the SAP with the date it was published and date data was unblinded. It is believed that the principal statistician signed the statistical analysis plan for study A1371041 off August 29, 2002. The database was locked on October 1, 2002 and unblinding of data occurred on October 2, 2002. The sponsor will verify these dates and provide a statement in writing to the NDA.

2. It is unclear in the statistical review of the original NDA submission and the protocol submissions for study A1371041 when this change to the SAP occurred. Please review the protocol amendments and provide history to FDA as to when the change in analysis occurred.

Sponsor Response: The sponsor agreed to submit a history to FDA as to when the change in analysis occurred.

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/s/

Sonia Castillo
8/21/03 02:33:06 PM

Teleconference Minutes

NDA: 21,513 **Drug:** Darifenacin (Enablex)

Sponsor: Novartis Pharmaceuticals

Date: August 13, 2003 **Time** 0900 - 0915

FDA/CDER/DRUDP Attendees:

Albert Perrine, R.N., BSN, Project Manager, DRUDP
Sonia Castillo, Ph.D., Biometrics Reviewer, DB 2, HFD-175

Novartis Attendees:
Lynne Fahey McGrath, MPH, Ph.D., Regulatory Affairs
Erhard Quebe-Fehling, Ph.D., Biostatistics

Pfizer Attendees:
Katherine Prescott, Ph.D., (Biostatistics)
Sigurdur Olafsson (Regulatory Affairs)
Moke Sharma (Project Management)

Background: This teleconference was initiated by the Agency to clarify with the Sponsor how they carried out the primary analysis for study A1371047 that used a "stratified Wilcoxon test (van-Elteren's test) with locally best weights and a normal approximation." Although the statistical analysis plan (SAP) was changed from a regular Wilcoxon test to this stratified Wilcoxon test, it is unclear in the statistical review of the original NDA submission when this change to the SAP occurred.

Issues Discussed:

1. Please provide SAS code for stratified Wilcoxon test with locally best weights.

Sponsor Response: The sponsor agreed to submit the SAS code for stratified Wilcoxon test with locally best weights.

2. Submit the statistical analysis plan (SAP, original and any modifications as applicable) for study A1371047 to NDA 21513.

Sponsor Response: The sponsor agreed to submit the SAP with the date it was published and date data was unblinded. It is believed that the principal statistician signed the statistical analysis plan for study A1371047 off November 29, 2002. The database was locked on October 1, 2002 and unblinding of data occurred on February 5, 2003. The sponsor will verify these dates and provide a statement in writing to the NDA.

3. It is unclear in the statistical review of the original NDA submission and the protocol submissions for study A1371047 when this change to the SAP occurred. Please review the protocol amendments and provide history to FDA as to when the change in analysis occurred.

Sponsor Response: The sponsor agreed to submit a history to FDA as to when the change in analysis occurred.

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/s/

Sonia Castillo
8/21/03 02:31:59 PM

6 Pages Redacted of
Deliberative Process
§ 552(b)(5)

7/11/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-513

INFORMATION REQUEST LETTER

Novartis Pharmaceutical Corporation
Attention: Mathias Hukkelhoven, Ph.D.
Sr. Vice President, Global Head
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Hukkelhoven:

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 hydrobromide) 7.5 mg and 15 mg dosages.

We are reviewing the statistical section of your submission and the following comments and information requests refer to Study A 1371047. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide the database in SAS transport file format. The data formats and elements need to be consistent with the Agency's Electronic Submission Guidance Document and with those previously submitted for the pivotal trials of this NDA.

2. Present the change in number of incontinence episodes per week from baseline at Week 2, Week 6 and Week 12 by treatment groups, stratified by the decision to tritrate upward at Week 2 (i.e., subjects who took 7.5 mg for the entire study vs. subjects who started at 7.5 mg and then titrated upward to 15 mg at Week 2). The mean and standard deviation, and median numbers of incontinence episodes at baseline need to be presented for each group or strata. Please employ the following two approaches to handle any post baseline missing data and present them separately:

(a.) At-Visit Approach: include only subjects who had completed the particular visit and had a valid (non-missing) assessment of the number of incontinence episodes for that visit. Therefore, the number of subjects included in the analysis for each visit could be different.

(b.) LOCF Approach: The number of subjects included in the analysis for each visit should be the same.

3. Conduct a similar analysis to the one requested under Item #2 for the micturition frequency endpoint.

4. It appears that many of the investigators in Study A1371047 also participated in Study 1371001. Verify that center or investigator identification numbers used in the SAS database or e-submission for both studies are the same so that the number could be used to identify those investigators who participated in both studies. If not, give a listing of center numbers for the same investigator for both studies. In addition, please verify that none of subjects in Study A1371001 also participated in Study 1371047 and vice versa. If some subjects did, provide a mechanism of linking those subjects from both studies.

If you have any questions, please call Jean King, R.D., Regulatory Project Manager, at 301-827-4260.

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
7/11/03 04:04:01 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-513

Novartis Pharmaceuticals Corporation
Attention: Mathias Hukkelhoven, Ph.D.
Sr. Vice President, Global Head
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Hukkelhoven:

We acknowledge receipt on April 28, 2003, of your April 23, 2003 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: UK-88,525 (darifenacin) at 7.5 mg and 15 mg dosages.

NDA Number: 21-513

Name of New Applicant: Novartis Pharmaceuticals Corporation

Name of Previous Applicant: Pfizer Pharmaceuticals, Inc.

Under 21 CFR 314.72, labeling (draft or final) to show the changes in name and address of the manufacturer, packer, or distributor of the drug is required to complete the change of ownership procedure.

Additionally, all changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. Refer to the *Guidance for Industry: changes to an Approved NDA or ANDA* for information on reporting requirements.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Address all communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

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

cc: Pfizer Global Research & Development
Attention: Sigurdur O. Olafsson, M.Sc.
Associate Director II
50 Pequot Avenue
New London, CT 06320

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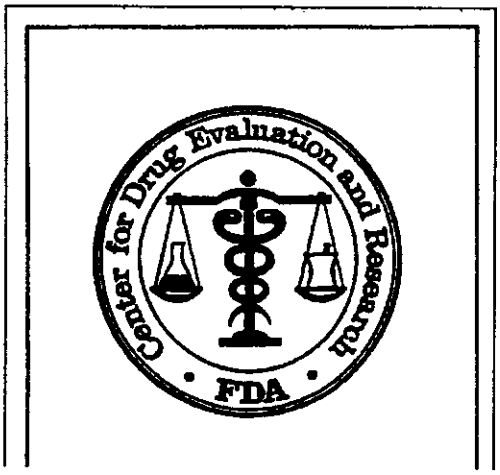
/s/

Margaret Kober
5/27/03 04:44:03 PM
Chief, Project Management Staff

FACSIMILE TRANSMISSION RECORD



From: Allan Fenselau, Ph.D.

Division of Reproductive and Urologic Drug Products, HFD-580

Phone 301-827-4260
Fax 301-827-4267

Date: May 5, 2003

To:

Name Sigurdur Olafsson
Company Pfizer, Inc
City _____ State ____

Phone # 860-732-4889
FAX # 860-732-0870

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-4260 IMMEDIATELY if re-transmission is necessary.

Mr. Olafsson,

NDA 21-513/N000

Please respond to the following request for information by 15-MAY-03. Please let me know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call me or the project manager Jean King (301-827-4260).

Allan Fenselau, Ph.D.
Review Chemist

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: Please provide the appropriate information as an amendment to the submission.

INFORMATION REQUEST

Chemist's Concerns

1. Provide a representation of the molecular structure of darifenacin hydrobromide that displays the stereochemistry at the C-3 chiral center more clearly than the one shown on p. 13 in Section 3.2.S.3 "Characterisation."

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/s/

Allan Fenselau
5/5/03 02:01:28 PM
CHEMIST

David T. Lin
5/5/03 04:53:05 PM
CHEMIST
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

1/30/03

NDA 21-513

INFORMATION REQUEST LETTER

Pfizer, Inc.
Attention: Sigurdur O. Olafsson
50 Pequot Avenue
New London, CT 06320

Dear Mr. Olafsson:

Please refer to your new drug application (NDA) dated December 3, 2002 and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex (darifenacin HBr) Extended Release Tablets, 7.5 and 15 mg.

We are reviewing various sections of your submission and have the following comments and information requests. Please provide a written response by February 21, 2003 in order to permit continuity in the review process for your NDA. In addition to submitting an official amendment to the NDA, we would much appreciate receiving your response as a faxed copy or a hardcopy by overnight delivery.

1. [ ]

2. [ ]

3. Provide details on the preparation of the Reference Standard [ ] used in the preparation of the [ ] (in STP [ ]
Provide details on its structure elucidation.

4. Provide details on the source of material described as [ ] (in STP Nos. [ ]) and on the preparation of the [ ] that contains this material.

5. Provide details on the preparation of the enantiomer of darifenacin hydrobromide, UK-88,258-04, batch 8461/012/1. Indicate if [ ] analysis was performed on this substance. If so, summarize the differences in data from the analyses of UK-88,525-04 and [ ]

6. Provide quantitative data on the content of darifenacin HBr [UK-88,525-04] and its degradants following treatment with [ ]

   Provide representative chromatograms of the mixtures obtained from each of these treatments. For comparative purposes, provide the chromatogram of UK-88,525-04 after treatment with [ ]

7. Provide copies of the [ ] used in the [ ] testing for each of the three batches of darifenacin hydrobromide employed in the submitted stability studies: Batch Nos. 99135003/M4, 99135005/M3, and 99135007/M5.

If you have any questions, call either Allan Fenselau, Review Chemist, or Jean King, Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

/S/

David Lin, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic
Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Allan Fenselau
1/30/03 12:41:33 PM

Filing Meeting Minutes

NDA: 21,513 **Drug:** Darifenacin

Sponsor: Pfizer

Date: January 17, 2003 **Time**: 3:00 PM – 4:00 PM

FDA/CDER/DRUDP Attendees:

Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP)
Mark Hirsch, M.D., Urology Medical Team Leader, DRUDP
Zili Li. M.D., Medical Reviewer, DRUDP
Myong-Jim Kim, Ph.D., Clinical Pharmacology Reviewer, DRUPD
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUPD
Jean King, Project Manager, DRUDP
Laurie McLeod, Ph.D., Pharmacology/Toxicology Reviewer, DRUPD
Allan Fenselau, Ph.D., Chemistry Reviewer, DRUPD
David Lin, Ph.D., Chemistry Team Leader, DRUPD

Issues Discussed:

On December 3, 2002, a new drug application (NDA) was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enablex (darifenacin). During this filing review meeting, the following issues were identified:

Clinical

The following are areas of concern and requests for additional clarifying information:

- The application is fileable.

- Although subsequent desk copies of Module 1 (containing volumes 1.1 and 1.2) of the NDA submission provided the appropriate listings of U.S. and non-U.S. investigators as well as the requisite FDA Certification Forms 3455, the sponsor's original submission (paper and electronic) did not include copies of the financial disclosure statement (Form FDA 3455) for 19 investigators who had made such a disclosure. We will request that the sponsor re-submit a complete Module 1 to NDA 21-513.

- We will request that the sponsor submit the names of the 25 investigators who did not respond or who were not successfully reached despite due diligence efforts.

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- The application is fileable.

- The effects of various intrinsic and extrinsic factors on the pharmacokinetic (PK) profile of darifenacin.

- Characterization of the exposure-response relationship for both efficacy and safety.

- The dosing recommendation based on CYP2D6 genotype or with concomitant medications, particularly in the presence of CYP3A4 or CYP2D6 inhibitors or in special populations.

- The to-be-marketed and clinical trial formulations are linked via multiple-dose bioequivalence (BE) studies. The design and results of these studies will be carefully reviewed. This is especially important due [ ] of the to-be-marketed tablet. The BE studies appear to be multiple-dose, not single dose. This is a review issue.

- The submission also contains the following information: gender differences, renal and hepatic dysfunction, geriatric exposure, population pharmacokinetics, and dos-proportionality studies.

Pharmacology/Toxicology

- The application is fileable.

- The sponsor did not address the possible relevance to humans of the single positive finding (e.g., hemangiosarcomas) observed in the rat two-year carcinogenicity study. This issue was identified prior to filing and a response was requested. Data showing high testosterone levels in rats but normal testosterone levels in humans taking darifenacin might provide mechanistic evidence that the hemangiosarcoma in rats were not relevant to humans. Without data to address the different responses of rats and humans and additional information relevant to exposure multiples, we must assume that the tumors are relevant to human populations taking the drug.

Chemistry

- The application is fileable.

- No review issues noted at time of filing.

- Four chemistry comments have already been sent to sponsor via IR letter.

- There are proposed manufacturing sites.

- Trade name consult and container/carton labeling will be sent to ODS/DMETS for their review.

Statistics

The Reviewer was not present; however, she conveyed the following to the Project Manager via phone the morning of this Filing Meeting:

- The application is fileable.

- No review issues noted at time of filing.

Summary of Action Items:

We will provide the above comments to the sponsor as 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. The sponsor

will also be informed that if they respond to these issues during this review cycle, we may not consider your response before we take an action on their application.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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/s/

Mark S. Hirsch
8/5/03 05:29:12 PM
I concur.

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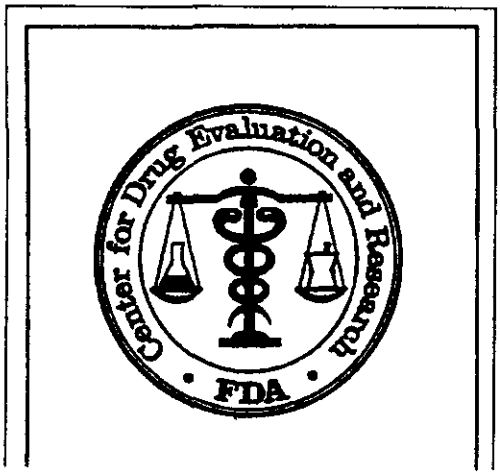
RECORD



From: Allan Fenselau, Ph.D.

Division of Reproductive and
Urologic Drug Products, HFD-580

Phone 301-827-4260
Fax 301-827-4267

Date: January 9, 2003

To:

Name Sigurdur Olafsson
Company Pfizer, Inc
City _____ State ____

Phone # 860-732-4889
FAX # 860-732-0870

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-4260 IMMEDIATELY if re-transmission is necessary.

Mr. Olafsson,

NDA 21-513/N000

Please respond to the following request for information by 17-JAN-03. Please let me know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call me or the project manager Jean King (301-827-4260).

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-513 Applicant: Pfizer, Inc. 09-JAN-03
Drug Name: ENABLEX™

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission.

Chemist's Concerns

1. Provide detailed information on all manufacturing/testing facilities (including contract facilities), site address (including full street address), site CFN (or CIN), and contact persons (including the phone/fax numbers or e-mail address). Also, please indicate site readiness for inspection.

2. Specify the site for stability testing of drug substance.

3. Confirm that the sites employed in obtaining the drug product stability data reported in this submission [Sec. 3.2.P.3, p. 2] will not be used as alternative testing sites for the drug product, if approved.

4. Clarify the need to include in this NDA submission, if it will not be used for manufacturing, packaging, and performing release and stability testing of the drug product for the US market (as indicated in Sec. 3.2.P.3, p. 1). Unless data generated at this site have been submitted to support the NDA, reference to the site should be deleted from the submission.

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/s/

Allan Fenselau
1/9/03 03:06:18 PM
CHEMIST

David T. Lin
1/9/03 03:56:34 PM
CHEMIST
I concur.

Meeting Minutes

Date: November 8, 2002 **Time**: 2:00 – 3:30 PM **Location**: PKLN; Con Rm Chesapeake

IND 45,457 **Drug:** Darifenacin UK-88,525

Indication: Overactive bladder

Sponsor: Pfizer Global Research & Development

Type of Meeting: Pre-NDA - Chemistry

Meeting Chair: David Lin, Ph.D. –Chemistry Team Leader, Division of New Drug Chemistry (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, NP - Project Manager, DRUDP (HFD-580)

FDA Attendees:
David Lin, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Sarah Pope, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)
Ronald J. Orleans, M.D., Medical Officer, DRUDP (HFD-580)
Margaret Kober, R.Ph. - Chief, Project Management Staff, DRUDP (HFD-580)
Karen Anderson, NP – Project Manager, DRUDP (HFD-580)
George Lyght, R.Ph. – Project Manager, DRUDP (HFD-580)

External Attendees:
John Berridge, Ph.D. - Pharmaceutical Sciences, UK
Ron Ogilvie, Ph.D. - Regulatory CMC, UK
Pete Dunn, Ph.D. - Chemical R and D, UK
Rob Burrows, Ph.D. - Pharmaceutical R and D, UK
Simon Bale, Ph.D. - Analytical R and D, UK
Sigurdur O. Olafsson, M.S.- Associate Director US Regulatory Strategy, Policy & Registration

Meeting Objective: To discuss the chemistry, manufacturing and controls section of the NDA submission.

Background: The darifenacin pre-NDA meeting held June 18, 2002 with DRUDP did not include a discussion of the Chemistry, Manufacturing and Controls data. This is the Chemistry portion of the pre-NDA meeting.

Discussion / Agreements Reached:

Drug Substance:
1. DRUDP will need literature references for the two proposed starting materials [ ] if available.
   - Both substances are organic. References will be provided.

- Starting materials are acceptable as long as the control strategy is acceptable upon review and supporting literature references are provided for [ ]

2. Are there data available to demonstrate equivalency between the drug substances obtained from [ ] the manufacturing process?
   - Yes, the purity profiles are similar. One has an additional impurity in commercial route but this is explained in the summary.
   - This is satisfactory provided all impurities had been qualified appropriately.
   - Discussed [ ] darifenacin – [ ]

3. What is the time duration of the stability testing? Will there be any more discussion in the package? Data will be provided and explained.

4. Are chemical names or code names used for the starting materials?
   - Yes – both are used - Given on page 5.

5. Noted that a few of the batches of drug substance did not meet the proposed specification.
   - Last 12 batches of commercial produced product have met quality control specifications and are inside the range.

Drug Product:

1. Because the 30mg dosage strength is not proposed for commercialization, a commitment should be provided to perform stability testing on both the 7.5 mg and 15 mg dosage strengths.
   - Market packaging has not been decided but once decided the stability information will be provided.

2. Proposed manufacturing sites for both drug substance and drug product should provide statements of readiness for evaluation of cGMP compliance by the FDA field inspectors.
   - Product for the US market will be manufactured in Brooklyn, NY [ ]

3. A methods validation package should be provided.

4. Having the 30 mg dose in the stability program is acceptable but this does not indicate that it will be possible to market this strength without clinical concurrence.
   - Agreed – this is not Pfizer's intention.

5. An Environmental Assessment or Environmental Exclusion will be provided in Module 1. No calculations to support the categorical exclusion is needed.

6. The zero time point data for accelerated stability studies should be the actual release data for drug substance and drug product.
   - Stability batches were tested at release and retested at the initial checkpoint. Will be in the table.

7. Data will be provided regarding [ ] values for stability.

8. Data will be provided that confirms that the [ ] tablets does not effect other properties of the drug product.

- The data is available to support that this is a cosmetic issue and there is no subsequent effect on the tablets.

9. Particle size data should be provided, indicating that it has no significant effect of in vitro dissolution, homogencity, and processing properties of the drug product.

10. The acceptance criteria for the 15 mg and 7.5 mg dosage strengths are the same.

11. How many tablets of each dosage strength were tested for the development of the dissolution acceptance criteria?
    - Routinely 6 tablets were used, but for biobatches testing was done with 12 tablets.

12. Batch manufacturing: sites are proposed for the manufacture, packaging, labeling, release and stability testing of the drug product. Some additional stability testing may be performed at an alternate Pfizer site (Groton). Re: discrepancy between the numbers on pages 31 and 33 - Page 31, Paragraph 3 refers to batches, 3 strengths, at 3 sites at scales of Kg (of proposed commercial scale). Page 33 lists the typical commercial batch scale (batch size) as kg.
    - The is European facility nomenclature. The European site will not be used for US product. The proposed commercial batch size is kg.

13. Clarification of the scale of the batches placed on stability Batch @ and batches @ of commercial batch size.

Action Items:

- **Sponsor agrees to submit updated stability data close to expected 4-month safety report date.**
- **To include label mock-ups in NDA submission.**
- **Sponsor will submit the NDA electronically with the exception of a written copy of Module 1.**

Attachment to minutes – condensed transparency slide presentation by Pfizer:

Redacted 8

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

Drafted:
K. Anderson 11.27.02

Revised:
D. Lin
S. Pope 12.02.02
M. Kober 11.27.02

Final:

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/s/

David T. Lin
12/4/02 11:17:30 AM
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 45,457

9/23/02

Pfizer Global Research & Development
Attention: Sigurdur Olafsson, M.S.
Associate Director, Strategy, Policy, and Registration
50 Pequot Avenue
New London, CT 06320

Dear Mr. Olafsson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for darifenacin.

We refer to your telephone conversation with Jennifer Mercier, Regulatory Health Project Manager for this Division. In that conversation it was brought to our attention the meeting minutes for the June 18, 2002 meeting were incorrect. Specifically, Page 6, the answer to question 6, line 7: "The safety data should be presented separately for 7.5 mg, for 15 mg and 15 mg plus higher doses". We have re-reviewed this information and agree with your statement that the safety datasets were requested as follows:

1. 7.5 mg alone
2. 15 mg alone
3. 7.5 mg + 15 mg combined, and
4. 7.5 mg + 15 mg + all other doses.

Please consider this an addendum to the June 18, 2002 meeting minutes.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

[S]

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

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/s/

Daniel A. Shames
9/23/02 06:24:11 PM

Teleconference Meeting Minutes

Date: September 17, 2002 **Time:** 1:00 – 1:30 PM

Location: Parklawn; 17B-43

IND: 45,457 **Indication:** Treatment of overactive bladder (OAB)

Drug Name: darifenacin

Sponsor: Pfizer Pharmaceuticals Group

Meeting Type: Pharmacology Guidance Meeting

Meeting Chair: Alex Jordan, Ph.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Alex Jordan, Ph.D. – Pharmacology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Laurie McLeod-**Flynn**, Ph.D. – Pharmacologist, DRUDP (HFD-580)
Jennifer Mercier – Regulatory Project Manager, DRUDP (HFD-580)

Sponsor Attendees:
Sigurdur Olafsson, M.S. – Regulatory Affairs, US
Ben Kramer, M.D. – Pfizer Pharmaceutical Group, Medical, US

Purpose of the Meeting: To discuss the pharmacology comments raised at the PreNDA meeting on June 18, 2002.

Discussion/Decisions Made:
General Comments:

1. PreNDA Meeting Comment:

   The issue of a positive carcinogenicity findings for which there are potential mechanisms described in the scientific literature still remains; the Division has concerns for the risk through these mechanisms to both adults and pediatric population.

   For Consideration:
   Pfizer seeks clarification concerning the question raised by the FDA reviewer. Could Dr. McLeod please respond to the following questions:
   1) What was the carcinogenicity finding of concern to the FDA?
   2) What are the mechanisms Dr. McLeod is referring to?

3) Why are these mechanisms considered to be a risk for adult and pediatric populations?

Questions and answers:

1. What is the carcinogenicity finding of concern?

Answer: Karl Lin's statistical review, showing an increase in hemangiosarcomas in male rats, was sent to the sponsor.

2. What are the mechanisms Dr. McLeod is referring to?

Answer: Angiosarcoma in rats has been demonstrated in some instances to be associated with androgenic/anabolic steroids.

3. Why are these mechanisms considered to be a risk for adult and pediatric populations?

Answer: All increases in neoplastic responses are considered to be a risk to all treated populations until a reasonable scientific explanation to the contrary has been demonstrated. In this case, a reasonable explanation may *include* data showing that male rats respond to an increase in androgens at the doses studied in the carcinogenicity assay, and that similar exposures and/or androgenic responses are not observed in adult and/or pediatric populations.

2. Pre-NDA Meeting Comment
   The controlled release formulations result in higher exposure levels than were originally used to calculate animal to human exposure levels in toxicology studies. There is concern that some effects in animal studies, particularly carcinogenicity and developmental effects, occur at smaller multiples of the intended clinical exposures than were originally calculated.

   For Consideration:
   Pfizer wishes to reassure the reviewer that all safety multiples of exposure in the toxicology species are compared with exposures from humans with the controlled release formulation. These multiples will be presented in the non-clinical section of the CTD format.

   Answer:
   This proposal is acceptable to the Division.

Action Items:

- Fax meeting minutes within 30 days.

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/s/

Jennifer L. Mercier
10/2/02 03:09:37 PM
CSO

Alexander W. Jordan
10/3/02 02:06:49 PM
PHARMACOLOGIST

Meeting Minutes

Date: June 18, 2002 **Time:** 3:00 – 4:30 PM

Location: Parklawn; Conference Room "Chesapeake"

IND: 45,457 **Indication:** Treatment of overactive bladder (OAB)

Drug Name: darifenacin

Sponsor: Pfizer Pharmaceuticals Group

Meeting Type: Pre-NDA Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Daniel Shames, M.D. – Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Mark Hirsch, M.D. – Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Zili Li, M.D. – Medical Officer, DRUDP (HFD-580)
Laurie McLeod, Ph.D. – Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader Clinical Pharmacology and Biopharmaceutic Reviewer, Office of Clinical Pharmacology and Biopharmaceutic (OCPB) @ DRUDP (HFD-580)
Myong Jin Kim, Pharm.D. - Clinical Pharmacology and Biopharmaceutic Reviewer, OCPB @ DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Margaret Kober – Chief, Project Management Staff, DRUDP (HFD-580)
Jennifer Mercier – Regulatory Project Manager, DRUDP (HFD-580)

Sponsor Attendees:
Sigurdur Olafsson, M.S. – Regulatory Affairs, US
John Goka, M.D. – Clinical Development, UK
Ian Mills, M.D. – Clinical Development, UK
Sef Kurstjens, M.D. – Clinical Development, US
Suhail Nurbhai, M.D. – Clinical Development, US
Mike Smith, Ph.D. – Biostatistics and Reporting, UK
Ashley Milton, Ph.D. – Clinical Sciences, UK
Seong-Won Han, M.D. – Clinical and Regulatory Submissions, UK
John Picciano, M.S. – Pfizer Pharmaceutical Group, Regulatory Affairs, US
Ben Kramer, M.D. – Pfizer Pharmaceutical Group, Medical, US

Background:
Darifenacin is an anticholinergic, selective muscarinic M_3 receptor antagonist currently being studied under ~ INDs. On June 6, 1994, IND 45,457 was submitted to evaluate darifenacin for the indication [ ] The IND was opened with Protocol 101: a Phase 2 cognitive function, urodynamics, and UUI study. On December 14, 2000 in N-077, the sponsor requested that the proposed indication for IND 45,457 be changed to "overactive bladder" (OAB). [ ]

Purpose of the Meeting: To discuss the meeting package and the planned NDA submission for this drug product.

Discussion/Decisions Made:
General Comments:

Pharmacology:

- The issue of a positive carcinogenicity finding for which there are potential mechanisms described in the scientific literature still remains; the Division has concerns for the risk through these mechanisms to both adult and pediatric populations.
- The controlled release formulations result in higher exposure levels than were originally used to calculate animal to human exposure levels in toxicology studies. There is concern that some effects in animal studies, particularly carcinogenicity and developmental effects, occur at smaller multiples of the intended clinical exposures than were originally calculated.

Clinical Pharmacology and Biopharmaceutics:
The sponsor should submit the following information with the original NDA:

- Development of in vitro extended release test method, in vitro release and dissolution profile (eg. Effect of pH, Media, Methods etc)
- Solubility/Permeability data
- Exposure-Response data to address dose selection
- Individual and Mean data for in vitro and PK studies
- Since various formulations were used during Phase I and II studies, please identify formulations, Lot number for each of relevant clinical pharmacology studies
- Darifenacin is a CYP2D6 substrate. The sponsor has conducted CYP2D6 genotyping in all clinical studies. The sponsor is requested to submit CYP2D6 genotype/PK/PD assessment to address exposure response in terms of safety and efficacy; these data could be submitted to the Clinical Pharmacology section in ASCII or SAS format.
- QT information has been collected over the exposures that range over x24 the proposed therapeutic range; the information submitted should include the measurements at times where maximum concentrations are anticipated.

Clinical

- Darifenacin 7.5 mg CR was only evaluated in one Phase 3 Study, 1002, in a total of 107 patients. The Clinical reviewer believes this in an inadequate number of patients and an inadequate number of trials to approve darifenacin 7.5 mg CR.
- There was a marked difference in primary efficacy endpoint results for darifenacin 15 mg between Study 1001, conducted in the USA and Canada (i.e. -2.4 incontinence episodes per week) and Study 1002, conducted in Europe (i.e. -4.3 incontinence episodes per week).
- It appears from pages 259-264 that sponsor wishes to pool analysis of data into a meta-analysis to demonstrate efficacy. The sponsor was reminded that the EOP2 meeting minutes dated June 1, 1999 state "pooled analysis of data solely in order to achieve statistical significance is usually not accepted and results of pooled analyses are not included in the labeling". The sponsor clarified that they did not intend to pool analyses of data into a meta-analysis to demonstrate efficacy.
- Sponsor did not provide the number of patients exposed for 6 months and 1 year to the doses and formulation of darifenacin requested for approval. On pg. 67, sponsor stated that in all Phase 2/3 studies for any dose or formulation of darifenacin, 472 subjects had been exposed for at least 180 days and 257 subjects for at least 351 days. The sponsor clarified that they submitted in Serial No. 127 on June 13, 2002 regarding darifenacin controlled release 7.5 or 15 mg od that 260 patients have been exposed for 6 months and 122 patients have been exposed for 12 months. The Division felt these were small numbers, however may be sufficient if the number of patients exposed to doses of darifenacin higher than 15 mg can be included.
- It appears to the reviewer that a specific QT study has not been conducted. Sponsor clarified that they do not intend to conduct QT study, however with the NDA they will be submitting ECG data from approximately 900 patients. The Division clarified that adequate QT data to rule out an effect of drug will be necessary for approval; ECG performed at T_{max}, placebo controls, and ECG data following exposure to significantly higher darifenacin dosages than 15 mg are some fundamental requirements.
- Only one Phase 3 protocol was submitted for DRUDP review prior to initiation.
- Phase 3 studies 1011 and 1013 used the 30 mg dose in dose-titration designs. Since the sponsor seeks approval of the 7.5 mg and 15 mg dosage strengths, studies 1011 and 1013 cannot provide "pivotal" evidence of safety or efficacy.
- There is preliminary evidence that starting at a lower dose and "up-titrating" may lessen adverse events.
- Preliminary evidence with the 30 mg dose make its safety profile concerning, especially in light of severe AEs and discontinuations secondary to AEs.
- The Adverse Event (AE) profile presented in N-125 demonstrated significantly higher adverse event report rates for darifenacin than reported with the tolterodine 2 mg bid comparator, for example:
    - For A1371011 (pg. 51), constipation rate reported for darifenacin was 25% versus 5.3% for tolterodine
    - For A1371011 (pg. 51), dry mouth reported for darifenacin was 60.9% versus 37.9% for tolterodine

- The Adverse Event (AE) profile presented in N-125 demonstrated significantly higher adverse event report rates for darifenacin than reported in the tolterodine extended release and oxybutynin extended release labeling regarding their Phase 3 trials.

Questions posed in the meeting packages:

The eight questions (in **bold** font) with Clinical responses (in *italic* font) are as follows:

1) **Does the Division agree that this is a reviewable NDA with regard to determining the efficacy of darifenacin for the treatment of OAB at the proposed doses of 7.5 and 15 mg once daily?**

Answer:

- No, the NDA may be fileable however the Division is not able to agree that the NDA will be fileable.
- Since darifenacin is a new molecular entity, the Division expects two Phase 3 fixed dose 12 week treatment duration clinical trials to be conducted with both trials evaluating the formulation of darifenacin proposed for approval and each dose proposed for approval (i.e. 7.5 and 15 mg controlled release once daily). In each of these trials, the Division anticipates that each dose of darifenacin proposed for approval would demonstrate efficacy for absolute change from baseline to Week 12 in number of incontinent episodes per week compared to placebo and for absolute change from baseline to Week 12 in the number of micturitions per day; the sponsor clarified that results of Study 1041 should be available early 2003 and asked if it could be submitted as a complete final study report at the time of the NDA submission without integrating the Study 1041 safety data; the Division prefers that the results of Study 1041 be submitted at the time of the NDA submission, even if the safety results are not integrated.
- The sponsor commented that DRUDP had not previously required efficacy for two endpoints and that the study may have been designed differently had such been the case. DRUDP acknowledges the sponsor's comment and stated that efficacy in one versus two endpoints will be a review issue.
- The Division requested that the sponsor submit pediatric clinical development plan and any pediatric clinical trial waivers and/ or deferral requests as soon as possible; the Division advised that requests for defferal would appear most appropriate at this time. Defferal request must contain at least broad outlines of study plans and dates. The sponsor clarified that they intend to make this submission in July 2002.
- Sponsor confirmed that proposed labeling has not been submitted.

2) **Does the Division agree that this is a reviewable NDA with regard to safety and tolerability of darifenacin for the treatment of OAB at the proposed doses of 7.5 and 15 mg once daily?**

Answer:

- We are not able to agree since it appears that the number of patients exposed for 6 months and 1 year to the doses and formulation of darifenacin requested for approval are low. We agree that you have treated at least 1500 individuals with the investigational drug, including short-term exposure, as specified by ICH Guidelines. ICH Guidelines recommend that long term safety data come from studies with exposure at dosage levels intended for clinical use.

3) **Does the Division agree that the dose related adverse events associated with darifenacin are well characterized and will not require any special labeling (e.g. contraindications, warnings) in the presence of CYP3A4 or DYP2D6 inhibitors at the doses intended for marketing, e.g. 7.5 and 15 mg?**

Answer:

- It is premature for the Division to enter into any agreements with the sponsor regarding labeling at this time.

4) **Does the Division concur with our efficacy presentations and our general approach to the Statistical Analysis of darifenacin efficacy data?**

Answer:

- It is premature for the Division to enter into any agreements at this time since protocols for the Phase 3 Studies 1002, 1011, 1013 and Statistical Analysis Plans for the Phase 3 Studies 1001, 1002, 1011, 1013, and 1014 have not been reviewed.
- In Study 1001 it is concerning regarding darifenacin 15 mg controlled release tablets. Although a comprehensive review of the data is beyond the scope of the PreNDA Meeting, the Division shared the following with sponsor:
  - The primary efficacy variable, **number of incontinence episodes per week**, the "median change from baseline to Week 12 for darifenacin 15 mg od minus median change from baseline for placebo" using the last observation carried forward (LOCF) and full analysis set (FAS) was -2.4 incontinence episodes per week and was not statistically significant ($p=0.049$; to be statistically significant by the Wilcoxon test, p had to be <0.025)
  - The secondary efficacy variable, **number of micturitions per day**, the "median change from baseline to Week 12 for darifenacin 15 mg od minus median change from baseline for placebo" using the last observation carried forward (LOCF) and full analysis set (FAS) was -0.5 micturitions per day and was **not** statistically significant ($p=0.076$; to be statistically significant by the Wilcoxon test, p had to be <0.025)

5) **Does the Division agree that our presentation of efficacy data in the CTD Summary of Clinical Efficacy meets the requirements of and contains all necessary components normally seen in an ISE and therefore do not require a separate ISE?**

Answer:

- Clinical would prefer a separate ISE. Sponsor clarified that they intend to submit in the CTD all the information and in as much detail as normally in the ISE. Sponsor stated they would provide a map to direct the reviewer to where the information in the ISE would be located in the CTD. Sponsor confirmed that the CTD would include analyses of response in subsets of the overall population (ex. demographics of age, gender, or race). Clinical agreed that they are willing to review the CTD without the ISE if the CTD contained all the information and in as much detail as normally in the ISS. Sponsor is prepared for additional requests for information during the NDA review process.

6) **Does the Division concur with our proposals for the darifenacin safety data presentations?**

Answer:

- No. On its face, the safety presentations are confusing since multiple types of darifenacin formulations and multiple doses of darifenacin appear to be lumped together for several of the data sets. The Division requests that the safety data obtained with the formulation of darifenacin intended for marketing at the doses proposed for approval be presented as a separate data set. Sponsor clarified on pg. 266 that the requested data would be available by dose in the "All DB PC 12 week Phase 2 studies" and "Fixed dose Phase 3 studies" data sets. The safety data should be presented separately for 7.5 mg, for 15 mg, and for 15 mg plus higher doses.

7) **Does the Division agree that our presentation of safety data in the CTD Summary of Clinical Efficacy meets the requirements of and contains all necessary components normally seen in an ISS and therefore do not require a separate ISS?**

Answer:

- Clinical would prefer a separate ISS. Clinical agreed that they are willing to review the CTD without the ISS if the CTD contained all the information and in as much detail as normally in the ISS. Sponsor is prepared for additional requests for information during the NDA review process.

8) **There were few non-white subjects in the darifenacin program. Is it acceptable to remove the presentation of adverse event data by race?**

Answer:

- No. Adverse event data pertaining to common adverse events, deaths, serious adverse events and adverse drop-outs should be presented by age, gender, and race. The sponsor should be aware that in a final rule published February 11, 1998 and effective August 10, 1998, FDA amended 21 CFR 314.50 (d)(5)(v) and 314.50 (d)(5)(vi)(a) to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. The final rule also notes that FDA may refuse to file an application if there is "inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets."

Additional issues:

1) The sponsor requested feedback regarding their tradename. On November 7, 2001 in N-105, sponsor requested the tradename Enablex. The Office of Post Marketing Drug Risk Assessment (OPDRA or HFD-400) has been asked to evaluate the tradename. The sponsor stated that their proposed labeling has not been submitted yet, however they did submit one page of additional information in December, 2001. Sponsor was informed that a response from OPDRA has not been received as of yet. The sponsor should be aware that the tradename must be reevaluated after the NDA is submitted.
2) The sponsor inquired if it was still acceptable to provide narratives for patients who died, had treatment-related serious adverse events, and those who were discontinued from therapy due to safety-related events, as they had proposed in Serial No. 066 on October 4, 2000. The Division confirmed that no change had occurred since we agreed with this proposal in a regulatory letter dated November 6, 2000.
3) The sponsor inquired if the darifenacin NDA is anticipated to go to an Advisory Committee. Division clarified that it is not anticipated at this time to present the darifenacin NDA to an Advisory Committee.
4) The Division requested that the sponsor submit, preferably to the IND prior to submitting the NDA, a tabular listing by study for Studies 1001, 1002, 1011, and 1013 to include the site number, the principal investigator, site address and phone number, and the number of patients screened, enrolled, and discontinued at the site. This information will be used to determine DSI inspection sites.

Action Items:

- Fax meeting minutes within 30 days.

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/s/

Mark S. Hirsch
7/19/02 05:00:43 PM

DEPARTMENT 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

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. 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 can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Pfizer Global Research and Development
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

2. TELEPHONE NUMBER *(Include Area Code)*

(860) 732-4889

3. PRODUCT NAME

ENABLEX™ Darifenacin Hydrobromide

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021513

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).

6. USER FEE I.D NUMBER

4346

7. IS THIS 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)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	John E. Wolleben, Ph.D. Senior Vice President, Worldwide Regulatory Affairs	11-7-02

FORM FDA 3397 (3/01)

"ENABLEX™ (DARIFENACIN HYDROBROMIDE)"
NDA 21-513

FINANCIAL DISCLOSURE COVER NOTE

There are five covered studies for this NDA. The covered studies were not funded via variable compensation and none of the investigators in the studies hold any form of propriety interest in **ENABLEX™**.

Information regarding Pfizer's efforts to eliminate bias in these studies is described in the Common Technical Document, Module 1, Section 1.3.5.

Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity as provided by the investigators, as defined in 21 CFR 54.2. Disclosure: Financial Interests and Arrangements of Clinical Investigators.

With a total of 1319 investigators listed in the five studies, 19 of the listed investigators had financial information to disclose. Nine of these investigators have equity in Pfizer Inc, eight of the investigators received significant payments of other sorts and two of the investigators have both equity in Pfizer Inc and received significant payments of other sorts. This information is listed in the 3455 forms in this item.

It is important to note that the investigator list for the studies determined by FDA Form 1572s is not necessarily the same as that for financial disclosure. The FDA criteria for the two lists are not equivalent. Personnel involved with the studies but not necessarily with the data are listed on FDA Form 1572. There is a complete investigator population list for the covered studies attached to this cover note.

Pfizer Inc is submitting financial disclosure information on the following five covered studies:

> Protocol A1371001 entitled "A Phase III multicenter, double-blind, randomized, placebo controlled parallel group study of the efficacy and safety of controlled release darifenacin versus tolterodine in the treatment of subjects with overactive bladder"
>
> Protocol A1371002 entitled "A Phase III multicentre, double blind, randomised, placebo controlled, dose response study of darifenacin in patients with overactive bladder

Protocol A1371011 entitled "A Phase III multicentre, double blind, randomised, placebo controlled, parallel group study of darifenacin versus tolterodine in patients with overactive bladder [ ]

Protocol A1371013 entitled "A Phase III multicentre, double blind, randomised, placebo controlled, parallel group study of darifenacin in patients with overactive bladder [ ]

Protocol A1371041 entitled "A Phase 3b multicentre, double blind, randomised, placebo controlled, parallel group study of Darifenacin in subjects with overactive bladder [ ]

Each of the individual investigators listed was sent the Financial Disclosure Form directly or via the principal investigator for their site. For the investigators for which we provided due diligence, we contacted the site by telephone and/or sent 2 separate follow-up letters to those individuals who did not return the Financial Disclosure Form. All investigators contacted were reminded to disclose financial information for Warner-Lambert Company and its affiliates including Parke-Davis and Agouron, as they are now wholly owned by Pfizer.

Certification

Per Form 3454, certification is provided for 1300 of the 1319 investigators in the five covered studies indicating

- Certified investigators (1275 of the 1319 investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2)

or

- Due diligence in collecting the information on Equity. (A total of 25 of the 1319 investigators did not respond or were not reached by our due diligence effort.)

Please note that all investigators are assessed for Significant Payments of Other Sorts, Variable Compensation, & Propriety Interest.

Disclosure

In the five covered studies, nineteen investigators had financial information to disclose as defined in 21 CFR 54.2. A completed Form 3455 is attached for each of the investigators. All Independent Grants associated with our investigators are paid directly to the Institution rather than to the individual investigator.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02
NDA Number : 21-513

FORM FDA 3455 (3/99)

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY THE APPLICANT

Name of Investigator

The following information concerning [ ] who participated as a clinical investigator in the submitted study

Name of Clinical Study

Darifenacin [ ]

is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the Applicable Check box

(1) any financial arrangements entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

(2) any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

(3) any proprietary interest in the product tested in the covered study held by the clinical investigator;

(4) any significant equity interest as defined in the 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME -JOHN J. REGAN
FIRM/ORGANIZATION PFIZER INC
SIGNATURE John J. Regan

TITLE SR. DIRECTOR - MEDICAL FINANCE
DATE OCTOBER 24, 2002

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02
NDA Number 21-513

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

FORM FDA 3454 (3/99)

TO BE COMPLETED BY THE APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Applicable check box is marked

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as define in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whethe the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests, I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Investigators (See attached.)

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the liste clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in th product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Investigators (See attached)

NAME JOHN J. REGAN

TITLE SR. DIRECTOR - MEDICAL FINANCE

FIRM/ORGANIZATION PFIZER INC

SIGNATURE John J. Regan

DATE OCTOBER 24, 2002

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

8/21/01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,457

Pfizer Inc.
Attention: Sigurdur Olafsson, M.Sc.
Associate Director, Regulatory Strategy and Registration US
212 East 42nd Street
New York, NY 10017-5755
USA

Dear Mr. Olafsson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for darifenacin.

We also refer to your amendment dated June 6, 2001 (serial number 088), containing a meeting request to discuss [ ] as well as draft Protocol A1371029, Protocol Synopsis [ ] and draft summary of Study A137102.

We have completed the review of your submission and have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However, response to them is requested.

Comments pertaining to DRAFT Protocol A1371029 :

1. Please provide a copy of the Pfizer sample informed consent form.

2. Please, add height and weight to screening visit on Flow Chart (page 24 of 33).

3. You stated (on page 19 of 33) "if a urinary tract infection is indicated, then a mid-stream urine sample for microscopy will be taken." Please, prespecify the urine stick test results that will result in mid-stream urine sample for microscopy being taken.

4. We recommend eliminating lab safety blood draws at Visit 5 and Visit 6.

5. We recommend that you incorporate into screening and treatment procedures and into inclusion and exclusion (I/E) criteria that prior to randomization the patients are required to demonstrate, in a voiding diary completed during the three week screening period, an average of at least eight micturitions per day and urgency on at least seven occasions per week on average.

6. The protocol exclusions should exclude local pathological factors explaining OAB symptoms.

7. We recommend obtaining urine sample for culture and sensitivity at screening.

8. If the urinary flow rate is less than 15 and the volume voided was less than 175 mL, we recommend repeating the test with a voided volume greater than 175 mL.

9. We recommend that you reword Subject Inclusion Criteria 3.3.2 to as follows:

   Females must have a negative pregnancy test. Females must be on adequate contraception (double barrier method or oral contraceptive) or subject and parent or legal guardian must sign a statement of abstinence for the duration of the study.

10. We recommend listing Exclusion 3.4.11 under the Inclusions. This criteria is listed on page 44 of Protocol 137-1029 ("HbcAg and HbcAb results must be negative; anti-hepatitis C virus serology , as determined by a multi-antigen EIA, must also be negative."

11. The sampling should be adequate to characterize the complete PK profile in this age group. Descriptive analysis should included reporting of AUC, Cmax, and Cmin for drug and metabolite.

12. No claims should be anticipated regarding the salivary pharmacodynamic data.

13. You are again encouraged to enroll on a subset of patients with spina bifida or other neurologic component in the study (see meeting minutes dated November 10, 1999). You should perform a perform a subset analysis on this population.

14. [ ]

Comments pertaining only to DRAFT Protocol Synopsis . [ ]

[ ]

[ ]

IND 45,457

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

/S/

{See appended electronic signature page}

Daniel Shames, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
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/

Daniel A. Shames
8/21/01 11:56:01 AM

Meeting Minutes

Date: July 11, 2001 **Time:** 1:00-2:30 PM, EST **Location:** PKLN; Conf Room C

IND 45,457 **Drug:** darifenacin **Indication:** overactive bladder

Sponsor: Pfizer Global Research and Development

Type of Meeting: guidance

Meeting Chair: Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Susan Allen, M.D., M.P.H. – Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Brenda Gierhart, M.D.- Medical Officer, DRUDP (HFD-580)
Venkat Jarugula, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jeanine Best, R.N., M.S.N. – Project Manager, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

External Constituents:
Susan DeCorte, R.Ph., RAC – Regulatory Strategy and Registration US
John Goka, M.D. – Clinical Development UK, Global Team Leader
Sef Jurstjens, M.D. – Clinical Development US, Global Therapeutic Leader
Ashley Milton, Ph.D. – Clinical Sciences Team Leader UK
Sigurdur Olafsson, M.Sc. – Associate Director, Regulatory Strategy and Registration US
Joe Gavetas – Regulatory Affairs EU
Suhail Nurbhai – US Team Leader/Clinical Development

Meeting Objective: To discuss proposed pediatric plan.

Background:

Redacted 3

page(s) of trade secret

and/or confidential

commercial information

~~(b4)~~

(b5)

Drafted: Farinas/July 23, 2001
Revised: Rumble 7.23/ Best 7.23/Gierhart 7.23/Hirsch 7.25/Benson 7.23/Jarugula 7.25.01/Allen 8.7.01
Final: Farinas/August 8, 2001

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

/s/

Susan Allen
8/8/01 11:41:12 AM