CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-925

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA 21-925 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: June 29, 2005 Action Date: April 29, 2006

Division of Metabolism & Endocrinology Products (DMEP)

Trade and generic names/dosage form: ~~[redacted]~~ (pioglitazone HCl + glimepiride fixed-dose combination tablets) 30 mg/2 mg; 30 mg/4 mg; ~~[redacted]~~

Applicant: Takeda Global Research & Development Center Therapeutic Class: 4

Indication previously approved: 1

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

Number of indications for this application: 1

Indication #1: For use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

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

☐ Yes: Please proceed to Section A.

No: Please check all that apply: ____Partial Waiver __✓__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:
☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval

- ☐ **Formulation needed**
- ☐ **Other:**_____

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason for deferral: PPSR rescinded for pioglitazone on 11/18/02

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by: Jena Weber, RHPM

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-925
HFD-960/ Grace Carmouze

(revised 12-22-03)

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/s/

Jena Weber
10/14/2005 02:13:13 PM

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REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

Reference is made to Takeda Global Research and Development Center, Inc. (TGRD) PreNDA Briefing Document, 22 December 2004, requesting deferral of the requirement to conduct studies evaluating AD-4833SU in the pediatric population for the treatment of type 2 diabetes. The request is predicated on the need to characterize AD-4833SU more fully in the adult population prior to conducting studies in pediatric subjects. As part of the Agency's written responses to TGRD's PreNDA meeting questions on 03 February 2005, the Agency agreed to grant a deferral.

EXCLUSIVITY SUMMARY

NDA # 21-924 SUPPL # HFD # 510

Trade Name DUETACT

Generic Name pioglitazone HCl + glimepiride fixed-dose tablets, 30 mg/2 mg; 30 mg/4 mg.

Applicant Name Takeda Global Research & Development Center, Inc.

Approval Date, If Known July 28, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

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 ☐ 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.

3 BE studies and a food-effect study submitted.

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 ☒

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 ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No; note that pediatric exclusivity for the pioglitazone ingredient was rescinded 11/18/02.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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# 20-496 Amaryl (glimepiride)

NDA# 21-073 Actos (pioglitazone)

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

BE

(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:

Study 01-04-TL-OPISU-001
Study 01-04-TL-OPISU-002
tudy 01-04-TL-OPISU-003
Study 01-04-TL-OPISU-004

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 ☒

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

Study 01-04-TL-OPISU-001
Study 01-04-TL-OPISU-002
Study 01-04-TL-OPISU-003
Study 01-04-TL-OPISU-004

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"):

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 # 69.686	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 69,686	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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

Name of person completing form: Jena Weber
Project Manager
Title: 7/31/06
Date:

Name of Office/Division Director signing form:
Title:

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/s/

Jena Weber

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

ACTING DIVISION DIRECTOR MEMO

NDA #:	21-925
Drug product:	Duetact® (pioglitazone hydrochloride and glimepiride fixed-dose combination tablets)
Applicant:	Takeda
Date of Submission:	June 28, 2005
Date of Submission of Major Amendment:	May 20, 2006
PDUFA Due Dates:	extended PDUFA due date – July 29, 2006
Reviewers:	Robert Misbin, MD (clinical) Jayabharathi Vaidyanathan, PhD (biopharm) William M. Adams (chemistry)

BACKGROUND

This NDA is for a fixed-dose combination (FDC) of pioglitazone hydrochloride and glimepiride for the treatment of type 2 diabetes mellitus in patients who are already treated with both drugs co-administered or have inadequate glycemic control while receiving treatment with sulfonylurea (SU) monotherapy. The proposed dosage strengths are (pio/glimepiride): 30 mg/2 mg, 30 mg/4 mg, [redacted]

The concomitant administration of these two drugs was approved as part of the original NDA for pioglitazone (NDA 21-073) in 1999. Two studies were conducted and reviewed in NDA 21-073 in support of this indication. Study AD-4833/PNFP-010 was a 16-week, randomized, placebo-controlled study of patients not acheiving adequate glycemic control on a stable SU dose who were randomized to receive either pbo, pio 15 mg, or pio 30 mg added on to their SU dosing regimen. Study AD-4833/PNFP-341 was also conducted in type 2 diabetics not adequately controlled with a stable SU dosing regimen. This was a 24-week study which randomized patients to either pio 30 mg [redacted] In both studies, reduction in HbA1c from baseline was the primary efficacy parameter.

The applicant stated that dose-selection for the FDC tablets was based on information regarding the most frequently prescribed doses of pioglitazone and glimepiride when co-administered as separate tablets. Their market analysis suggests that the majority of patients (~80%) are prescribed a combination of 30 or 45 mg of pioglitazone with either 2 or 4 mg of glimepiride. During a preIND meeting with the agency in May 2004, it was agreed that only one bioequivalence study comparing each of the FDC dosage strengths to its individual components co-administered and one food-effect study using the [redacted] would be required for marketing approval. Provided the applicant could demonstrate adequate bridging between the FDC tablets and the separately administered pioglitazone and glimepiride, no new clinical efficacy or safety studies were required for this NDA.

CLINICAL PHARMACOLOGY STUDIES AND CMC DATA

In her original review of this NDA, Dr. Vaidyanathan concluded that the 30 mg/2 mg and 30 mg/4 mg FDC tablets were bioequivalent to Actos and Amaryl commercial tablets given concomitantly.

As stated earlier, the 30 mg/4 mg and 30 mg/2 mg FDC tablets are bioequivalent to their individual components administered separately. In this setting, the expiry would be based on the stability data as reviewed by CMC. Dissolution profiles for bottles with dessicant would support an expiry not to exceed 18 months.

CLINICAL EFFICACY AND SAFETY DATA

Dr. Misbin summarized the clinical efficacy and safety data from Study AD-4833/PNFP-341, previously reviewed under the original Actos NDA. Results from Study AD-4833/PNFP-010 were not summarized in his review; however, that study evaluated the 15 and 30 mg doses of Actos in combination with SU therapy. As the proposed dosage strengths are only 30 mg/2 mg, 30 mg/4 mg, and ne more relevant efficacy and safety data are from Study AD-4833/PNFP-010 which employed the 30 doses of pioglitazone.

As noted in his review, the mean percent reduction from baseline in HbA1c after 24 weeks add-on therapy to a stable dose of SU was 1.55% for the pio 30 mg vs 1.67% for pio 45 mg.

Findings of bladder cancer from nonclinical studies pre-approval are described in the Actos label. Pioglitazone and several other PPAR dual agonists have tested positive for induction of tumors of the epithelium in the urogenital system. The applicant has argued that pioglitazone is highly selective for the gamma receptor and the animal findings are of unknown clinical significance. Several attempts at negotiating the nonclinical findings are summarized in Dr. Misbin's review. However, lingering concerns regarding this finding resulted in the agency rescinding a pediatric written request in 2003.

A post-approval clinical study evaluating hepatic safety revealed an imbalance in bladder cancer with 3 cases in the pioglitazone group versus none in the placebo group. Two of the cases were diagnosed during the trial but within one year of study randomization and 1 case was a recurrence. These results were submitted to the agency in 2003 and the findings discussed at a CAC meeting. The clinical relevance of these findings was disputed by the applicant, possibly due to the relation between duration of exposure to drug and diagnosis of bladder cancer. No changes to the label were made regarding clinical bladder cancer cases.

In reviewing this FDC application, the results of a more recently completed long-term, placebo-controlled study of pioglitazone was evaluated for bladder cancer findings. The cardiovascular outcomes trial, PROactive, randomized 5238 patients with Type 2 diabetes to pioglitazone (n=2605) or placebo (n=2633) in addition to current anti-diabetic therapies. In this study with an average duration of observation of 34.5 months, an imbalance in bladder cancer cases was again observed with 14 cases reported in pioglitazone-treated patients versus 5 in placebo-treated patients. Dr. Misbin reported that cases diagnosed after one year of study exposure included 6 patients treated with pioglitazone versus 2 on placebo. This finding again raises concern that the non-clinical findings have some clinical relevance. Although the duration of exposure to pioglitazone is likely too short to establish a carcinogenic effect of the drug, it may be suggest a tumor-promoting effect in an at-risk population. Regardless, the accumulating findings of imbalance in bladder cancer from clinical trials support a change in labeling. I concur with Dr. Misbin that a descriptive summary of the clinical trial findings should be included in the Actos label and any label for a combination drug product that contains pioglitazone. Consequently, Takeda should incorporate changes to their Duetact label to reflect the findings from PROactive and the hepatic safety study.

CONCLUSIONS AND RECOMMENDATIONS

In this application for a fixed-dose combination of pioglitazone and glimepiride, Takeda has provided sufficient data to support approval of the FDC 30 mg/ 2 mg and 30 mg/ 4 mg dosage strengths from its previously conducted clinical study and the BE study allowing bridging between the FDC tablets and the two products co-administered.

The dissolution data support an expiry date of 18 months. Additional BE studies will be necessary to extend the expiry beyond 18 months.

Since two different actions are recommended for this NDA (approval of 30 mg/2 mg and 30 mg/4 mg and , this application will be administratively split. Labeling negotiations will proceed with the two dosage strengths. Pending agreement on labeling for these two dosage strengths, Duetact may be approved.

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/s/

Mary Parks
7/28/2006 03:25:46 PM
MEDICAL OFFICER

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Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

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

TAKEDA GLOBAL REASEARCH AND DEVELOPMENT CENTER INC
Mary Jo Pritza
475 Half Day Road
Lincolnshire IL 60069
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21925

2. TELEPHONE NUMBER
847-383-3739

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] 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:

3. PRODUCT NAME
(pioglitazone HCl and glimepiride)

6. USER FEE I.D. NUMBER
PD3006104

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

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

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

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	RA MANAGER	6/6/05

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$336,000.00

Form FDA 3397 (12/03)

Close Print Cover sheet

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW of FA

NDA 21-925 DUETACT™ (pioglitazone HCl + glimepiride) tablets,
30 mg/2 mg and 30 mg/4 mg.

Sponsor: Takeda Global Research & Development Center, Inc.

NDA Submission Date: June 28, 2005 **Receipt Date:** June 29, 2005
Approval Date: July 28, 2006 **FA Date:** August 4, 2006

Material Reviewed:

PPI, PI, carton and container labels submitted on August 4, 2006.

Background and Summary Description: DUETACT is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin, or whose diabetes is not adequately controlled with metformin alone.

Review:
Carton and Container Labels:

30 mg/2 mg, 30-count bottle
30 mg/2 mg, 90-count bottle
30 mg/2 mg 30-count SAMPLE

30 mg/4 mg, 30-count bottle
30 mg/4 mg, 90-count bottle
30 mg/4 mg, 30-count SAMPLE

Labeling is acceptable as submitted on July 28, 2006. Blister containers will not be distributed at this time; therefore, blister panel labeling has not been provided.

Patient Package Insert: Labeling is acceptable. Final PPI is identical to that submitted on July 28, 2006. Identifier D-4833S-PPI-v01, July 2006.

Package Insert: Labeling acceptable. Final PI is identical to that submitted on July 28, 2006. Identifier AS-4833S-01; 05-112; July 2006.

Conclusion: Issue Acknowledge and Retain letter.

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/s/

Jena Weber
8/21/2006 10:10:37 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-925

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Dr. Pritza:

We acknowledge receipt of your August 4, 2006, submission containing final printed labeling in response to our July 28, 2006, letter approving your new drug application (NDA) for DUETACT (pioglitazone HCl + glimepiride) tablets, 30 mg/2 mg and 30 mg/4 mg..

We have reviewed the labeling that you submitted in accordance with our July 28, 2006, letter, and we find it acceptable.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Eric Colman

8/18/2006 10:05:18 AM

Eric Colman for Mary Parks

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Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

NDA Number: 21-925 Duetact (pioglitazone HCl + glimepiride) fixed-dose combination tablets, 30 mg/2 mg; 30 mg/4 mg. This NDA

Sponsor: Takeda Global Research & Development Center, Inc.

NDA Submission Date: June 28, 2005 **Receipt Date:** June 29, 2005

Major Amendment received on April 20, 2006. **Approval Date:** July 28, 2006

Material Reviewed:

Final PI, PPI, and carton/container labels submitted on July 28, 2006.

Background and Summary Description: Duetact is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea, or whose diabetes is not adequately controlled with a sulfonylurea alone.

Review:
Carton and Container Labels:

30 mg/2 mg, bottles of 30	30 mg/4 mg, bottles of 30
30 mg/2 mg, bottles of 90	30 mg/4 mg, bottles of 90

Labeling is acceptable; post approval changes to be implemented as per DMETS review dated July 11, 2006.

Patient Package Insert: **Revisions made to according to recommendations specified in DSRCS reviews dated December 27, 2005, and April 11, and June 29, 2006. No other changes noted.**

Package Insert: **Draft labeling acceptable as submitted to the Division on July 28, 2006. No additional changes noted. Identifier AD-4833S-01 July 2006**

Conclusion: Issue approval (AP) letter; request FPL for PI and PPI.

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/s/

Jena Weber
8/1/2006 07:46:55 AM
CSO

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-925		Supplement Number	
Drug:DUETACT		Applicant: Takeda	
RPM: Jena Weber		DMEP	Phone: 301-796-1306

Application Type: ( ) 505(b)(1) **(X)** 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: Amaryl (NDA 20-496) **Note: NDA 21-925:** [redacted] Duetact (pioglitazone HCl + glimepiride) fixed-dose combination tablets, 30 mg/2 mg; 30 mg/4 mg. - **AP**

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	NA
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Dates	**July 29, 2006**
❖ 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 #PD3006104
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ 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)	NN
• OC clearance for approval	7/28/06
❖ 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 (11 patents)
• 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.	21 CFR 314.50(i)(1)(*i*)(A) **(X)** 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).	
• [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)).*	( ) N/A (no paragraph IV certification) **(X)** 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).* (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).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	**(X)** Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

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).*	**(X)** 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 **(X)** 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.)	7/28/06
• 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)*	✔es

General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) 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)	7/28/06
• Most recent applicant-proposed labeling	7/28/06
• Original applicant-proposed labeling	5/31/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DSRCS: 6/30/4/11/06; 12/27/06. DDMAC:7/12/06; 12/30/05 DMETS: 7/17/4/26/3/6/06/8/10/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NN
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	7/28/06;5/31/05
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	None
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	2/3/05
• Pre-Approval Safety Conference (indicate date; approvals only)	NN
• Other	Pre-IND 5/25/04
❖ Advisory Committee Meeting	
• Date of Meeting	NN
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DD: 7/28/06
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	7/20/06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NN
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	NN
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NN
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	10/14/06
❖ Demographic Worksheet *(NME approvals only)*	NN
❖ Statistical review(s) *(indicate date for each review)*	NN
❖ Biopharmaceutical review(s) *(indicate date for each review)*	4/7/&7/11/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NN
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NN
• Bioequivalence studies	2/28/06 AC
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	3/20/7/12& 7/21/06
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Granted, see review #1
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NN
❖ Facilities inspection (provide EER report)	Date completed: 2/28/06 ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X)** Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NN (cross reference)
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NN
❖ CAC/ECAC report	NN

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/s/

Jena Weber
7/31/2006 02:29:18 PM

Weber, Jena M

From: Weber, Jena M
Sent: Monday, July 31, 2006 1:50 PM
To: CDER-APPROVALS
Cc: Colangelo, Kim M
Subject: NDA 21-925

From the Division of Metabolism & Endocrinology Products:

NDA 21-925
Duetact (pioglitazone HCl + glimepiride) fixed-dose combination tablets
30 mg/2 mg, 30 mg/4 mg
Takeda Global Research & Development Center
Approved: 7/28/06
This NDA provides for the use of Duetact (pioglitazone HCl + glimepiride) fixed-dose combination tablets, 30 mg/2 mg, and 30 mg/4 mg, as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes, who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone.

Please note that NDA 21-925 was [redacted]

NDA 21-925: for Duetact (pioglitazone HCl + glimepiride) fixed-dose combination tablets, 30 mg/2 mg; 30 mg/4 mg. - **AP**

Special thanks to Kim Colangelo for all her help in bringing this 505(b)(2) submission to a timely completion.

Jena Weber

Project Manager
Division of Metabolism & Endocrinology Products
New e-mail address: Jena.Weber@fda.hhs.gov

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MEMORANDUM

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

DATE: July 18, 2006

TO: Gail Stone

FROM: Jena Weber

SUBJECT: [redacted] **of NDA 21-925**
Duetact (pioglitazone HCl + glimepiride) tablets, 30 mg/2 mg; 30 mg/4 mg; [redacted]

On April 20, 2006, TGRD submitted a major amendment extending the UFGD for this NDA to **July 29, 2006.** This submission provided [redacted] revised chemistry, manufacturing and control (CMC) documents.

[redacted] However, sufficient information/data has been provided to approve the [redacted] strengths (30 mg/2 mg & 30 mg/4 mg).

The Division made the decision to [redacted] NDA with the [redacted] doses remaining with the [redacted] application (NDA 21-925), and th [redacted] Appropriate action letters will issue to each NDA.

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/s/

Jena Weber
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DDMAC

FROM: Jena Weber, PM
Division of Metabolism & Endocrinology Products, HFD-510

DATE: 6/7/06		NDA 21-925	TYPE OF DOCUMENT: PPI , PI, carton & container labels	DATE OF DOCUMENT:5/25/06
NAME OF DRUG: DUETACT(pioglitazone + glimepiride) fixed-dose tablets	PRIORITY CONSIDERATION: NO		CLASSIFICATION OF DRUG: Anti diabetic	DESIRED COMPLETION DATE: 7/01/06

NAME OF FIRM: Takeda Global Research Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Comments: Reference May 25, 2006, submission. Please review and comment prn on all proposed LBL. Each section (PI, PPI, carton & container) is available via EDR. **User Fee Goal Date: 7/29/06.**

SIGNATURE OF REQUESTER: Jena Weber, PM 301-796-1306.	METHOD OF DELIVERY: DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kanika Vij
7/12/2006 09:15:13 AM

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****PRE-DECISIONAL AGENCY INFORMATION*****

Date: **July 12, 2006**

To: **Jenna Weber, PM**
Division of Metabolic and Endocrine Products

From: Kanika Vij, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

Subject: **Drug: Duetact (pioglitazone + glimepiride)**
NDA: 21-925

DDMAC has reviewed the proposed product labeling (PI), patient package insert (PPI), as well as the carton and container labeling for Duetact (pioglitazone + glimepiride) and we offer the following comments.

If you have any questions or concerns regarding my comments, please contact me.

Proposed Product Labeling

1. We have reviewed the proposed product labeling and do not have any comments on this at this time.

Patient Package Insert

Who should not take DUETACT?

" • ***have a condition called diabetic ketoacidosis***." *(original emphasis)*

Carton and Container Labeling

3. We have reviewed the carton and container labels and do not have any comments on these at this time.

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Thank you. If you have any questions, please contact Kanika Vij at 301.796.0580 or Kanika.Vij@fda.hhs.gov

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/s/

Kanika Vij

7/12/2006 09:07:53 AM

DDMAC REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT: Reply to DMETS review, and updated LBL.	DATE OF DOCUMENT
7/3/06		21-925		7/23/06

NAME OF DRUG: DUETACT™ AD-4833SU (pioglitazone + glimepiride fixed-dose combination tablet).	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
	S	Anti-diabetic	**7/15/06**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Takeda response to DMETS (letter dated 5/30/06, from DMEP). Please review prn; submission available via EDR.

PDUFA DATE: 7/29/06

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber

7/3/2006 06:09:06 AM

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MEMORANDUM

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

DATE: June 29, 2006

TO: Mary Parks, MD, Acting Director
Division of Metabolic and Endocrine Products

VIA: Jena Weber, Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products

FROM: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review #3 of Patient Labeling for DUETACT (pioglitazone hydrochloride and glimepiride) tablets, NDA 21-925.

On December 27, 2005 DSRCS provided recommendations and comments on the patient labeling (Patient Package Insert or PPI) submitted with the New Drug Application for pioglitazone hydrochloride and glimepiride, NDA 21-925 with the proposed brand name of [redacted] A second review dated April 11, 2006 was in response to the sponsor submission of a revised PPI with the brand name of DUETACT on March 24, 2006. Additional Recommendations were provided in a memorandum at that time. The sponsor has submitted revised labeling with a PPI dated May 25, 2006 and corresponding revised PI dated May 17, 2006. We reviewed the patient labeling and have the following comments and recommendations:

1. The sponsor has adequately addressed the changes requested in the April 11 DSRCS review.

2. In the Warnings section of the PI, for glimepiride, there is a bolded SPECIAL WARNING OF INCREASED RISK OF CARDIOVASCULAR MORTALITY related to the administration of oral hypoglycemic drugs. In the original PPI reviewed by DSRCS, the first bullet point under the section header "**What are the side effects of** [redacted] states:

   - **increased chance of death from heart or blood vessel problems** when used

instead of treatment with diet alone or diet and insulin to control your high blood sugar levels from diabetes.

This statement has been deleted by the sponsor in the March 23, 2006 and May 25, 2006 versions of the PPI from the section "**What are the possible serious side effects of DUETACT**." Patient information should always be consistent with the prescribing information, thus DSRCS recommends adding back the deleted statement.

3. In the May 25, 2006 PPI under the section "**What are the possible serious side effects of DUETACT**," the sponsor has modified the following bullet point:

From:

•

To:

•

Patient information should always be consistent with the prescribing information. DSRCS recommends that the language for this bullet point be made consistent with the language in the approved PPI for dated August 8, 2005 (NDA 21-842) so that the important message regarding possible serious liver problems remains in the PPI and is appropriately conveyed to patients. For consistency, all ACTOS (pioglitazone) containing products should contain the same statement in their PPIs.

Please call us if you have any questions.

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/s/

Sharon Mills
6/30/2006 01:27:43 PM
CSO

Toni Piazza Hepp
7/3/2006 08:33:22 AM
DRUG SAFETY OFFICE REVIEWER

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Surveillance, Research, and Communication Support (DSRCS), HFD-410

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT: New LBL to include tradename, "DUETACT."	DATE OF DOCUMENT
6/7/06		21-925		5/25/06

NAME OF DRUG: DUETACT™ AD-4833SU (pioglitazone + glimepiride fixed-dose combination tablet).	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: Anti-diabetic	DESIRED COMPLETION DATE: **7/1/06**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Takeda's response to our letters dated 12/28/05 and 4/13/06 (comments per DSRCS). Please review prn; submission dated 5/25/06 available via EDR.

PDUFA DATE: 7/29/06

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Jena Weber

6/7/2006 02:01:55 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-925 **DISCIPLINE REVIEW LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Dr. Pritza:

Please refer to your June 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duetact™ (pioglitazone HCl and glimepiride tablets), [redacted] 30 mg/4 mg, and 30 mg/2 mg.

In review of the container labels, carton, and package insert labeling, The Division of Medication Errors and Technical Support (DMETS) has identified the following areas of possible improvement, which may minimize potential user error. These revisions are based on revised draft labeling submitted on **March 24, 2006,** that responded to our communication to you dated **March 8, 2006.** We note that you have modified the labels and labeling according to some of DMETS' recommendations and have provided the following responses to the remainder of our recommendations.

GENERAL COMMENTS

From Takeda:

In an effort to find a suitable trademark, TGRD utilized a marketing research firm to evaluate a number of proposed candidates for the fixed-dose combination. The outcome of the firm's primary research findings and secondary research analysis concludes that Duetact appears worthy of consideration as a trademark. Of note, a conclusion from their primary research finding is that of the 170 respondents, none misinterpreted Duetact for an existing product name in a simulated verbal and written order evaluation. Eleven of the 170 healthcare professionals sampled did note an associative similarity of Duetact with the marketed product Duet Vitamins; however [redacted] cites the following:

- Although DUETACT and Duet® both begin with the 'DUET,' prefix they are visually and phonetically differentiated. DUETACT is a much longer word than Duet® (seven letters vs. four) and is three syllables in length (vs. two). In addition, Duet® Vitamins are also marketed with brand modifier suffixes which further distinguish the names from each other (Duet® DHA;Duet® Chewable).

- Although Duet® Vitamins are administered orally the product is intended for a very specific patient audience. Duet® is indicated as a nutritional supplement in pregnancy, prenatal and postnatal periods. Duet® Vitamins are also available in multiple oral formulations (tablets; chewable tablets; tablets dispensed with soft gel tablets).

- There are differences in the product's dosage strengths. DUETACT, which is a fixed-dose combination tablet, would be written for in combination dosage strengths (e.g. 30 mg/2 mg, etc) while Duets tablets contain varying doses of multiple vitamins/minerals. Also, TGRD believes that italicizing the first half of the trademark may promote correct pronunciation thereby enhancing physician awareness and potentially less product confusion.

DMETS Response:

DMETS addressed the potential for look-alike and sound-alike confusion between Duetact and Duet in our previous review. In agreement with the sponsor's comments above and the [redacted] independent market research analysis, our previous conclusion stated "DMETS believes the differing lengths of the names and presentation of strength will decrease the likelihood for confusion between Duet and Duetact." However, the conclusion was made by evaluating the name "Duetact" as a whole, not with the name separated into two portions.

With respect to italicizing the first half of the tradename, we remain concerned. By italicizing a portion of the name, this places emphasis on certain parts of the name, thus separating the name into two portions, "Duet" and "Act". This separation creates added potential for confusion by emphasizing "Duet", which is an already marketed drug product. Furthermore, by separating and emphasizing "Act", this may imply the "Actos" component of this combination product. Emphasizing only one component of a combination product is misleading. Italicizing the first half of the name on the carton and container labeling to promote proper pronunciation is unlikely a reliable method to promote public awareness of the pronunciation of the name. Achieving this goal is more likely through detailing, marketing, and advertising. DMETS believes the current presentation of the proprietary name, utilizing two different fonts, creates a greater potential for confusion and error. Please revise the presentation of the proprietary name, so that only one font is used throughout the entire proprietary name.

From Takeda:

TGRD will ensure that the professional sample for DUETACT will include a child resistant closure, as we have with ACTOS and ACTOPLUS MET, which are both available as 30-day samples. FDA acknowledged receipt and approval of final-printed labeling submitted by TGRD on August 22, 2005, and approved August 29, 2005, which included 30-day professional samples of ACTOPLUS MET. Also 30-day physician samples for ACTOS have been available since product approval in July 1999.

DMETS Comment:

DMETS acknowledges the sponsor's comments and has no further comments.

From Takeda:

Included in this submission are revised container labels for the 30 mg/2 mg strength in order to differentiate between the 30 mg/4 mg and 30 mg/2 mg strengths. TGRD believes this change will address DMETS concern.

DMETS Comment:

DMETS acknowledges that the sponsor's revisions to the coloring of the 30 mg/2 mg strength labels and labeling and believes the changes provide a greater differentiation between the strengths. Although improved, the labels maintain similar shades of purple which may cause confusion and selection error between the 30 mg/2 mg and 30 mg/4 mg strength. DMETS believes utilizing distinctively different color schemes for each of the three strengths will provide a greater differentiation between the strengths, thus reducing the risk for error. Please revise the purple accordingly.

SAMPLE BLISTER LABELING

From Takeda:

TGRD has taken DMETS comments into consideration and would like to maintain use of the plus sign (+) to remain consistent with the presentation of the established name for our other approved fixed dose combination product ACTOPLUS MET. We believe the use of the plus sign helps to define the fixed-dose presentation of the product.

DMETS Comment:

DMETS acknowledges the sponsors choice to maintain the use of the plus sign (+) to remain consistent with the presentation of the established name for their other approved fixed dose combination products. However, the plus sign (+) is not a recognized symbol for combination products. Furthermore, a plus sign (+) is not used in the USP monograph titles of any combination drug name. DMETS believes the word "and" will more accurately reflect Duetact is a combination product and is more consistent with other combination products currently marketed in the U.S.

Additionally, the plus sign (+) is not used consistently throughout the labeling of this product line or within the sponsors other approved fixed dose combination products (i.e. Actoplus Met). Currently the word "and" appears on the container labels and the plus sign (+) appears on the carton labeling and the sample blister labeling (see figure below). Please revise all labels and labeling by removing the plus sign (+) and replacing with the word "and".

From Takeda:

TGRD would like to clarify the manufacturing and configuration of the blister card. The blister card will contain 7-tablets. The Physician Sample will be produced in a

Included in our submission dated February 7, 2006, was a three dimensional mockup for the Agency's consideration. Finally, due to this packaging configuration, and its inherent design features TGRD believes the packaging will provide the patient all relevant information regarding the product.

DMETS Response:

DMETS acknowledges the sponsors intention; however, we recommend, at a minimum, that the proprietary name, established name, product strength, lot number, and expiration date be included on the panel which contains the tablets. The current presentation of the three dimensional mock-up only provides this information on the front and back of the cover flap.

Should the top flap of the booklet be separated, from the tablets, the established name, product strength, lot number, and expiration date will no longer be included with the tablets. Additionally, scissors are commonly used to cut out tablets from blister cards so that they can be easily carried in a patient's purse, wallet, clothing pocket, or used in an inpatient unit-dose setting. Thus, the requirement for the name to be included on each individual blister or at a minimum, repeated on the back panel. Additional comments regarding the blister package labeling are provided in the labeling comments of this review.

LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Also, DMETS reviewed the revised container labels, carton and insert labeling of Duetact from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

The established name and expression of strength should be revised on all labels and labeling for all strengths to read:

pioglitazone HCl and glimepiride XX mg/X mg
or
pioglitazone HCl XX mg
glimepiride X mg

Currently, and as discussed in the Sample Blister Labeling section, the presentation of the established name and expression of strength varies between the container labels and carton labeling.

B. SAMPLE BLISTER LABELING

1. See General Comments.

2. The strength should always be accompanied by the proprietary and established names. Currently the strength is presented separately in different locations on the sample blister card.

INDEPENDENT NAME ANALYSIS

From Takeda:

The sponsor submitted an independent market research analysis, conducted by [redacted] for the proposed name Duetact, dated November 2005. [redacted] conducted a name validation study known as the [redacted] to evaluate the potential for error between Duetact and currently marketed brand and generic drug products.

reported that 170 healthcare professionals including 120 pharmacists (60 retail-based and 60 hospital based) and 50 physicians (25 primary care physicians, 25 endocrinologists) participated in the primary research intended to identify potential drug similarity conflicts specific to simulated verbal and written prescription interpretation. The study consisted of an online survey with three portions; a simulated prescription evaluation, unaided assessment of the potential tradename, and an aided overall assessment of the potential tradename. A summary of the analysis as well as study findings are discussed below. concluded that Duetact is an acceptable trademark for the combination product pioglitazone and glimepiride.

A. Simulated Prescription Evaluation

An online survey of 170 healthcare professionals including 120 pharmacists (60 retail-based and 60 hospital-based) and 50 physicians (25 primary care physicians, 25 endocrinologists) was conducted in the form of two separate studies, approximate half reviewed a simulated verbal order and the remaining half of the participants reviewed a written prescription. Not one of the participants misinterpreted Duetact for an existing product name. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Duetact.

DMETS Response:

DMETS acknowledges the results and has no additional comments at this time.

B. Unaided (Pre-Profile) Candidate Associations

All participants were also asked to rate (unaided) the ability of the proposed proprietary name to be communicated clearly when spoken as well as when written and to identify (unaided) potential associations, which could include existing trade and/or established names. One hundred fifty four of the 170 participants (91%) did not associate the name Duetact with an existing product name. The product names cited as potential similarities include Cymbalta (one mention), Duet (eleven mentions), Duac (three mentions), and dutasteride (one mention). concluded that none of the product names cited represents a significant 'risk of confusion/potential for misprescription' concern based on additional analysis.

The evaluation identified the names Cymbalta and dutasteride to have potential look-alike and/or sound alike confusion with Duetact that were not discussed by the Expert Panel.

DMETS Response:

DMETS previously reviewed the names Duet and Duac.

After reviewing the product profiles of the additional names identified by [redacted], DMETS has determined that the potential for name confusion between Duetact and Cymbalta or dutasteride is minimal due to visual and phonetic differences.

C. Aided (Post-Profile) Candidate Associations

All participants were also asked to provide an overall assessment (aided by product description/context) of the proposed proprietary name as a pharmaceutical trade name, potentially including a determination that the name is unsuitable due to the risk of misprescription with currently marketing drug names. One hundred forty four of the 170 participants (85%) did not associate the name Duetact with an existing product name. The product names cited as potential similarities include Actos (eight mentions), Caduet (one mention), Duac (one mention), Duet (eight mentions), duloxetine (one mention), and DuoNeb (seven mentions) [redacted] concluded that none of the product names cited represents a significant 'risk of confusion/potential for misprescription' concern based on additional analysis.

The [redacted] evaluation identified the names Actos, Caduet, Duloxetine and Duoneb to have potential look-alike and/or sound alike confusion with Duetact that were not discussed by the Expert Panel.

DMETS Response:

After reviewing the product profiles of the names identified by [redacted] DMETS has determined that the potential for name confusion between Duetact and Actos, Caduet, duloxetine, or Duoneb is minimal due to visual and phonetic differences, in addition to differing product characteristics.

D. Results

Two of the names [redacted] analyzed for potential confusion with Duetact (Duet and Duac) were previously evaluated. [redacted] also analyzed the proprietary names Cymbalta, dutasteride, Actos, Caduet, duloxetine, and DuoNeb [redacted] did not find the reviewed names to be of concern for look-alike or sound-alike confusion with the proposed trade name, Duetact. [redacted] concluded that Duetact is an acceptable proprietary name for the combination product pioglitazone and glimepiride tablets.

DMETS Response:

DMETS concurs with [redacted] that the names Duet, Duac, Cymbalta, dutasteride, Actos, Caduet, duloxetine, and DuoNeb do not pose a safety risk for the prescribing and dispensing of Duetact.

However, the written and verbal samples used in the [redacted] studies were not provided; therefore, we are unable to provide a thorough assessment of the analysis.

In summary, DMETS recommends implementation of the label and labeling revisions outlined above.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so.

If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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/

Mary Parks

5/30/2006 08:42:52 AM

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MEMORANDUM	Division of Medication Errors and Technical Support Office of Drug Safety HFD-420; WO22, Rm. 4447 Center for Drug Evaluation and Research

To: Mary Parks, MD
Acting Director, Division of Metabolism and Endocrinology Products, HFD-510

From: Tina M. Tezky, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Through: Alina R. Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: April 10, 2006

Re: ODS Consult#04-0273-3; Duetact (Pioglitazone HCl and Glimeperide) Tablets; NDA 21-925

This memorandum is in response to the April 7, 2006 request from your Division for a review of Takeda's March 24, 2006 response to our comments regarding the labels and labeling for the proprietary name, Duetact. The proposed proprietary name was previously found acceptable by the Division of Medication Errors and Technical Support (DMETS) on March 6, 2006 (ODS consult 04-0273-1). The sponsor has modified the labels and labeling according to some of DMETS' recommendations and has provided the following responses to the remainder of our recommendations. DMETS initial comments appear in bold. The sponsor's comments appear italicized. DMETS response follows.

Additionally, the sponsor has submitted an independent market research analysis conducted in November 2005 by [redacted]. Our review and comment of this study follows the written responses to Takeda's March 24, 2006 letter.

I. RESPONSES TO TAKEDA'S MARCH 24, 2006 LETTER

GENERAL COMMENTS

3. The word "duet" in the Duetact appears italicized. Emphasis on the portion of the proprietary name will increase the potential for confusion with the currently marketed product Duet. Please revise the font of "duet" so it is consistent with the remainder of the proprietary name in accordance with 21 CFR 201.10(g)(2).

In an effort to find a suitable trademark, TGRD utilized a marketing research firm to evaluate a number of proposed candidates for the fixed-dose combination. The outcome of the firm's primary research findings and secondary research analysis concludes that Duetact appears worthy of consideration as a trademark. Appended to this document is a summary of [redacted] findings for the Agency's review and consideration ***(Appendix A).*** *Of note, a conclusion from their primary*

research finding is that of the 170 respondents, none misinterpreted Duetact for an existing product name in a simulated verbal and written order evaluation. Eleven of the 170 healthcare professionals sampled did note an associative similarity of Duetact with the marketed product Duet Vitamins; however [redacted] cites the following:

- *Although DUETACT and Duet® both begin with the 'DUET' prefix they are visually and phonetically differentiated. DUETACT is a much longer word than Duet® (seven letters vs. four) and is three syllables in length (vs. two). In addition, Duet® Vitamins are also marketed with brand modifier suffixes which further distinguish the names from each other (Duet® DHA; Duet® Chewable).*
- *Although Duet® Vitamins are administered orally the product is intended for a very specific patient audience. Duet® is indicated as a nutritional supplement in pregnancy, prenatal and postnatal periods. Duet® Vitamins are also available in multiple oral formulations (tablets; chewable tablets; tablets dispensed with soft gel tablets).*
- *There are differences in the product's dosage strengths. DUETACT, which is a fixed-dose combination tablet, would be written for in combination dosage strengths (e.g. 30 mg/2 mg, etc) while Duets tablets contain varying doses of multiple vitamins/minerals.*

Similarly, TGRD believes that italicizing the first half of the trademark may promote correct pronunciation thereby enhancing physician awareness and potentially less product confusion.

DMETS Response:

DMETS addressed the potential for look-alike and sound-alike confusion between Duetact and Duet in our previous review (ODS consult 04-0273-1, Section II.D.1). In agreement with the sponsor's comments above and the [redacted] independent market research analysis (see comments, page 7), our previous conclusion stated "DMETS believes the differing lengths of the names and presentation of strength will decrease the likelihood for confusion between Duet and Duetact." However, the conclusion was made by evaluating the name "Duetact" as a whole, not with the name separated into two portions.

With respect to italicizing the first half of the tradename, we remain concerned. By italicizing a portion of the name, this places emphasis on certain parts of the name, thus separating the name into two portions, "Duet" and "Act". This separation creates added potential for confusion by emphasizing "Duet", which is an already marketed drug product. Furthermore, by separating and emphasizing "Act", this may imply the "Actos" component of this combination product. Emphasizing only one component of a combination product is misleading. Italicizing the first half of the name on the carton and container labeling to promote proper pronunciation is unlikely a reliable method to promote public awareness of the pronunciation of the name. Achieving this goal is more likely through detailing, marketing, and advertising. DMETS believes the current presentation of the proprietary name, utilizing two different fonts, creates a greater potential for confusion and error. Please revise the presentation of the proprietary name, so that only one font is used throughout the entire proprietary name.

4. We note that you propose a professional sample size of 30 tablets. DMETS believes this number is inappropriate for a physician sample. Thirty tablets represent a unit-of-use package size appropriate for a one-month supply of medication. If allowed, this package size must have child resistant closures to be in compliance with the Poison Prevention Act.

TGRD will ensure that the professional sample for DUETACT will include a child resistant closure, as we have with ACTOS and ACTOPLUS MET, which are both available as 30-day samples. FDA acknowledged receipt and approval of final-printed labeling submitted by TGRD on August 22, 2005, and approved August 29, 2005, which included 30-day professional samples of ACTOPLUS MET. Also 30-day physician samples for ACTOS have been available since product approval in July 1999.

DMETS Response:

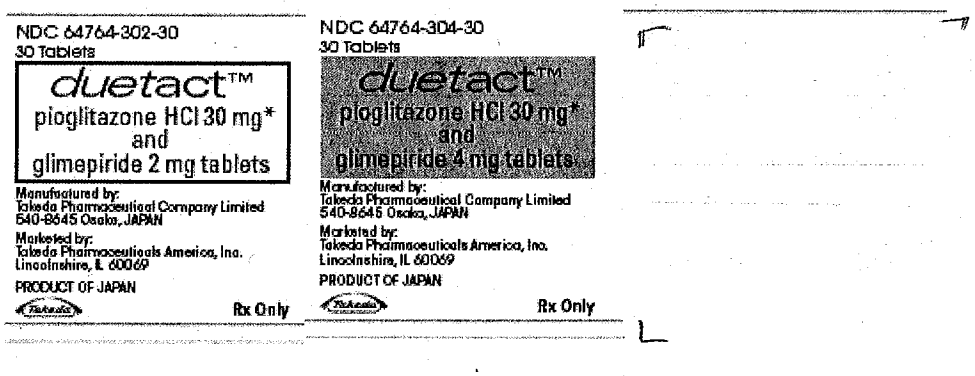
DMETS acknowledges the sponsor's comments and has no further comments.

5. The background colors utilized for the container labels of the 30 mg/2 mg and 30 mg/4 mg strengths are purple and light purple, respectively. Although the shades are different, the same color family for both strengths makes it difficult to differentiate between the strengths. We recommend making the packaging more distinct between the two strengths in order to minimize confusion and selection errors between the two product strengths.

Included in this submission ***(Appendix B)*** *are revised container labels for the 30 mg/2 mg strength in order to differentiate between the 30 mg/4 mg and 30 mg/2 mg strengths. TGRD believes this change will address DMETS concern.*

DMETS Response:

DMETS acknowledges that the sponsor's revisions to the coloring of the 30 mg/2 mg strength labels and labeling (see figure below) and believes the changes provide a greater differentiation between the strengths. Although improved, the labels maintain similar shades of purple which may cause confusion and selection error between the 30 mg/2 mg and 30 mg/4 mg strength. DMETS believes utilizing distinctively different color schemes for each of the three strengths will provide a greater differentiation between the strengths, thus reducing the risk for error. Please revise the purple accordingly.



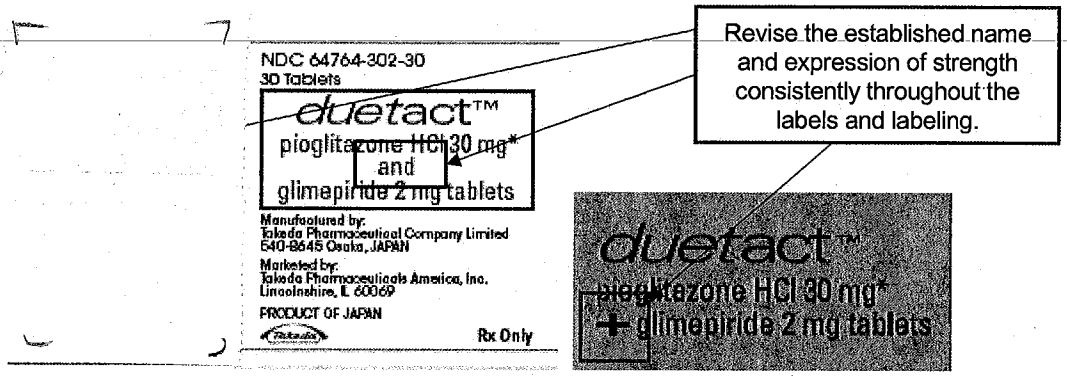
C. SAMPLE BLISTER LABELING

2. The established name is presented with the active ingredients joined by a plus sign *(+)*. For consistency throughout the labeling, please remove the plus sign and replace with the word "and".

TGRD has taken DMETS comments into consideration and would like to maintain use of the plus sign (+) to remain consistent with the presentation of the established name for our other approved fixed dose combination product ACTOPLUS MET. We believe the use of the plus sign helps to define the fixed-dose presentation of the product.

DMETS Response:

DMETS acknowledges the sponsors choice to maintain the use of the plus sign (+) to remain consistent with the presentation of the established name for their other approved fixed dose combination products. However, the plus sign (+) is not a recognized symbol for combination products. Furthermore, a plus sign (+) is not used in the USP monograph titles of any combination drug name. DMETS believes the word "and" will more accurately reflect Duetact is a combination product and is more consistent with other combination products currently marketed in the U.S. Additionally, the plus sign (+) is not used consistently throughout the labeling of this product line or within the sponsors other approved fixed dose combination products (i.e. Actoplus Met). Currently the word "and" appears on the container labels and the plus sign (+) appears on the carton labeling and the sample blister labeling (see figure below). Please revise all labels and labeling by removing the plus sign (+) and replacing with the word "and".



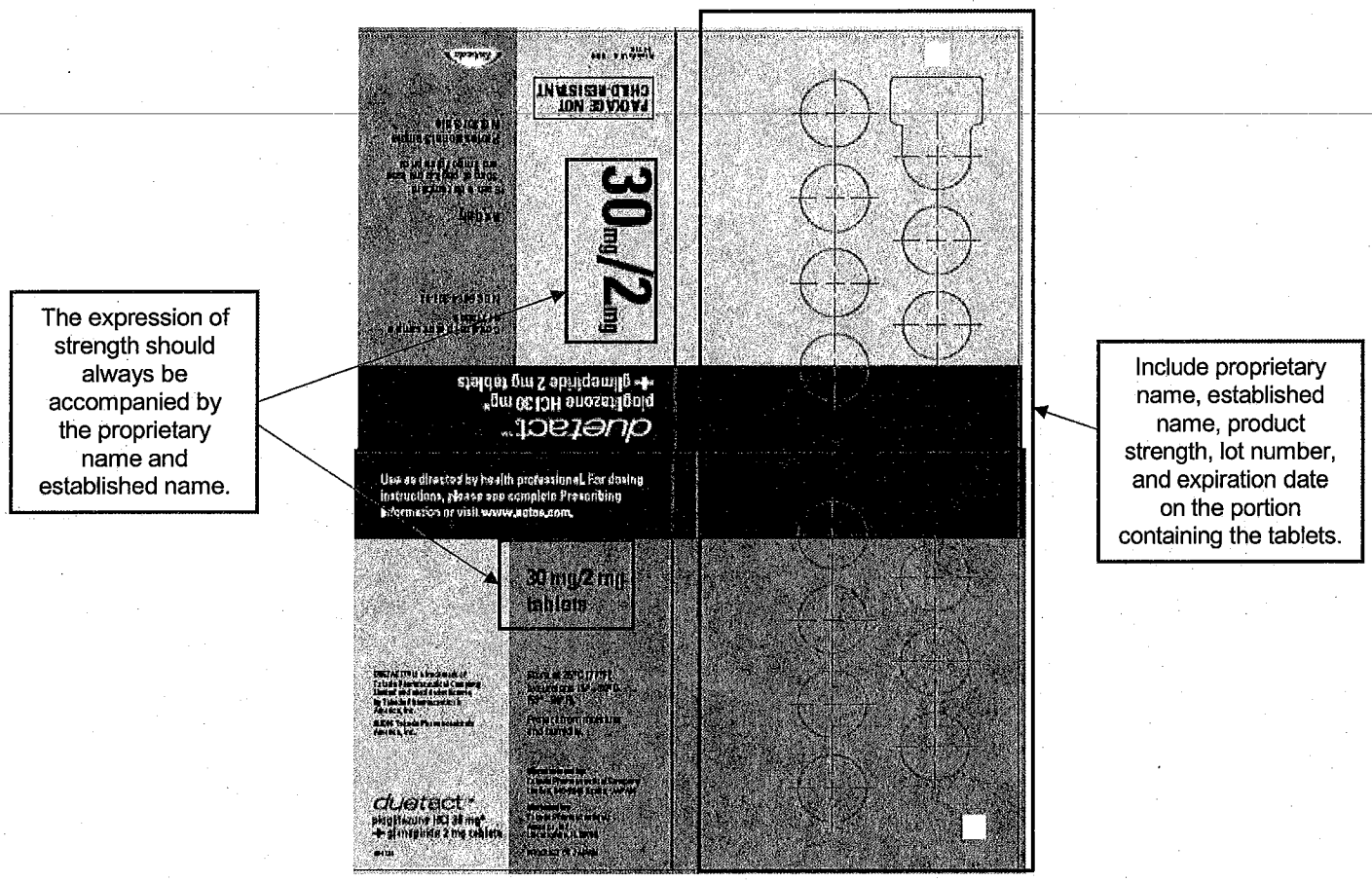
3. Each individual blister should contain the proprietary name, established name, product strength, lot number, and expiration date in case the blister is separated from the sample blister carton or cut into single tablets.

TGRD would like to take this opportunity to clarify the manufacturing and configuration of the blister card. The blister card will contain 7-tablets. The Physician Sample will be produced in

Included in our submission dated February 7, 2006, was a three dimensional mock-up for the Agency's consideration. Finally, due to this packaging configuration, and its inherent design features , TGRD believes the packaging will provide the patient all relevant information regarding the product.

DMETS Response:

DMETS acknowledges the sponsors intention; however, we recommend, at a minimum, that the proprietary name, established name, product strength, lot number, and expiration date be included on the panel which contains the tablets. The current presentation of the three dimensional mock-up only provides this information on the front and back of the cover flap. Should the top flap of the booklet be separated, from the tablets, the established name, product strength, lot number, and expiration date will no longer be included with the tablets (see figure below). Additionally, scissors are commonly used to cut out tablets from blister cards so that they can be easily carried in a patient's purse, wallet, clothing pocket, or used in an inpatient unit-dose setting. Thus, the requirement for the name to be included on each individual blister or at a minimum, repeated on the back panel. Additional comments regarding the blister package labeling are provided in the labeling comments on page 6 of this review.



II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Additionally, DMETS reviewed the revised container labels, carton and insert labeling of Duetact from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

The established name and expression of strength should be revised on all labels and labeling for all strengths to read:

pioglitazone HCl and glimepiride XX mg/X mg
or
pioglitazone HCl XX mg
glimepiride X mg

Currently, and as discussed in the Sample Blister Labeling section above, the presentation of the established name and expression of strength varies between the container labels and carton labeling.

B. SAMPLE BLISTER LABELING

1. See General Comments.

2. The strength should always be accompanied by the proprietary and established names. Currently the strength is presented separately in different locations on the sample blister card (see figure, page 5).

III. INDEPENDENT NAME ANALYSIS

The sponsor submitted an independent market research analysis, conducted by [redacted], for the proposed name Duetact, dated November 2005. [redacted] conducted a name validation study known as the [redacted] to evaluate the potential for error between Duetact and currently marketed brand and generic drug products. [redacted] reported that 170 healthcare professionals including 120 pharmacists (60 retail-based and 60 hospital-based) and 50 physicians (25 primary care physicians, 25 endocrinologists) participated in the primary research intended to identify potential drug similarity conflicts specific to simulated verbal and written prescription interpretation. The study consisted of an online survey with three portions; a simulated prescription evaluation, unaided assessment of the potential tradename, and an aided overall assessment of the potential tradename. A summary of the analysis as well as study findings are discussed below. [redacted] concluded that Duetact is an acceptable trademark for the combination product pioglitazone and glimepiride.

A. Simulated Prescription Evaluation

An online survey of 170 healthcare professionals including 120 pharmacists (60 retail-based and 60 hospital-based) and 50 physicians (25 primary care physicians, 25 endocrinologists) was

conducted in the form of two separate studies, approximate half reviewed a simulated verbal order and the remaining half of the participants reviewed a written prescription. Not one of the participants misinterpreted Duetact for an existing product name. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Duetact.

DMETS Response:

DMETS acknowledges the results and has no additional comments at this time.

B. Unaided (Pre-Profile) Candidate Associations

All participants were also asked to rate (unaided) the ability of the proposed proprietary name to be communicated clearly when spoken as well as when written and to identify (unaided) potential associations, which could include existing trade and/or established names. One hundred fifty four of the 170 participants (91%) did not associate the name Duetact with an existing product name. The product names cited as potential similarities include Cymbalta (one mention), Duet (eleven mentions), Duac (three mentions), and dutasteride (one mention). [redacted] concluded that none of the product names cited represent a significant 'risk of confusion/potential for misprescription' concern based on additional analysis.

The [redacted] evaluation identified the names Cymbalta and dutasteride to have potential look-alike and/or sound alike confusion with Duetact that were not discussed by the Expert Panel.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by rxmark

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Duetact	Pioglitazone/Glimepiride Tablets [redacted] 30 mg/4 mg, 30 mg/2 mg	One tablet once daily	
Cymbalta Rx	Duloxetine Capsules 20 mg, 30 mg, 60 mg	40 mg – 60 mg daily, in single or divided doses.	LA/SA
Avodart Rx	**Dutasteride** Capsules 0.5 mg	0.5 mg once daily.	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

DMETS Response:

DMETS previously reviewed the names Duet and Duac (ODS Consult 04-0273-1). After reviewing the product profiles of the additional names identified by [redacted], DMETS has determined that the potential for name confusion between Duetact and Cymbalta or dutasteride is minimal due to visual and phonetic differences.

C. Aided (Post-Profile) Candidate Associations

All participants were also asked to provide an overall assessment (aided by product description/ context) of the proposed proprietary name as a pharmaceutical trade name, potentially including a determination that the name is unsuitable due to the risk of misprescription with currently marketing drug names. One hundred forty four of the 170 participants (85%) did not associate the name Duetact with an existing product name. The product names cited as potential similarities include Actos (eight mentions), Caduet (one mention), Duac (one mention), Duet (eight mentions), duloxetine (one mention), and DuoNeb (seven mentions). [redacted] concluded that none of the

product names cited represent a significant 'risk of confusion/potential for misprescription' concern based on additional analysis.

The [redacted] evaluation identified the names Actos, Caduet, Duloxetine and Duoneb to have potential look-alike and/or sound alike confusion with Duetact that were not discussed by the Expert Panel.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by rxmark

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Duetact	Pioglitazone/Glimepiride Tablets [redacted]0 mg/4 mg, 30 mg/2 mg	One tablet once daily	
Actos Rx	Pioglitazone Tablets 15 mg, 30 mg, 45 mg	15 mg – 45 mg once daily.	LA/SA
Caduet Rx	Amlodipine/Atorvastatin Tablets 2.5 mg/10 mg, 2.5 mg/20 mg, 2.5 mg/40 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	One tablet daily.	LA/SA
Cymbalta Rx	**Duloxetine** Capsules 20 mg, 30 mg, 60 mg	40 mg – 60 mg daily, in single or divided doses.	LA/SA
DuoNeb Rx	Albuterol Sulfate/Ipratropium Bromide Solution for Inhalation 3 mg (0.1%)/0.5 mg (0.017%) per 3 mL	One 3 mL vial 4 times per day via nebulization.	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

DMETS Response:

After reviewing the product profiles of the names identified by [redacted] DMETS has determined that the potential for name confusion between Duetact and Actos, Caduet, duloxetine, or Duoneb is minimal due to visual and phonetic differences, in addition to differing product characteristics.

D. Results

Two of the names [redacted] analyzed for potential confusion with Duetact (Duet and Duac) were previously evaluated in our previous review (ODS consult 04-0273-1). [redacted] also analyzed the proprietary names Cymbalta, dutasteride, Actos, Caduet, duloxetine, and DuoNeb. [redacted] did not find the reviewed names to be of concern for look-alike or sound-alike confusion with the proposed trade name, Duetact. [redacted] concluded that Duetact is an acceptable proprietary name for the combination product pioglitazone and glimepiride tablets.

DMETS Response:

DMETS concurs with [redacted] that the names Duet, Duac, Cymbalta, dutasteride, Actos, Caduet, duloxetine, and DuoNeb do not pose a safety risk for the prescribing and dispensing of Duetact. However, the written and verbal samples used in the [redacted] studies were not provided; therefore, we are unable to provide a thorough assessment of the analysis.

In summary, DMETS recommends implementation of the label and labeling revisions outlined above. If you have any questions or need clarification, please contact Diane Smith at 301-796-3242.

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/s/

Tina Tezky
4/26/2006 03:44:05 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
4/27/2006 09:56:21 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/27/2006 11:32:32 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/27/2006 06:27:40 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-925

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Dr. Pritza:

Please refer to your June 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duetact (pioglitazone HCl + glimepiride) fixed-dose combination tablets, 30 mg/2 mg; 30 mg/4 mg.

On April 21, 2006, we received your April 20, 2006, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **July 29, 2006.**

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber

4/24/2006 12:38:29 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-925 **DISCIPLINE REVIEW LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Dr. Pritza:

Please refer to your June 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duetact™ (pioglitazone HCl and glimepiride tablets), [redacted], 30 mg/4 mg, and 30 mg/2 mg.

The Division of Surveillance, Research, and Communication Support (DSRCS) has completed their review of the proposed patient labeling for Duetact™. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information.

These revisions are based on revised draft labeling submitted on March 24, 2006. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

1. Remove [redacted] under the heading, "What are the possible serious side effects of DUETACT?" Start the list of side effects immediately after the heading.

2. Revise the last sentence under "General information about DUETACT" to "You can also get this "prescribing information" by visiting www.actos.com or calling 1-877-825-3327." The phone number [redacted] may be difficult for some patients to understand and use.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug 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 subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Eric Colman

4/13/2006 09:17:47 AM

Eric Colman for Mary Parks

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MEMORANDUM

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

DATE: April 11, 2006

TO: Mary Parks, MD, Acting Director
Division of Metabolic and Endocrine Drug Products

VIA: Jena Weber, Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products

FROM: Catherine Miller, MT(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza Hepp, PharmD, Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review #2 of Patient Labeling for DUETACT (pioglitazone hydrochloride and glimepiride) tablets, NDA 21-925

On December 27, 2005, DSRCS provided recommendations and comments on the patient labeling (PPI) submitted with the New Drug Application for pioglitazone hydrochloride and glimepiride tablets, NDA 21-925 with the proposed brand name of [redacted] The sponsor submitted a revised PPI with the brand name of DUETACT on March 24, 2006. We reviewed the revised PPI and have the following recommendations.

1. Remove "[redacted]" under the heading, "What are the possible serious side effects of DUETACT?" Start the list of side effects immediately after the heading.

2. Revise the last sentence under "General information about DUETACT" to "You can also get this "prescribing information" by visiting www.actos.com or calling 1-877-825-3327." The phone number "[redacted]" may be difficult for some patients to understand and use.

Our review is based on draft labeling submitted on June 28, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

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/s/

Catherine Miller
4/11/2006 11:47:26 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/12/2006 09:06:22 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT: Reply to DMETS review.	DATE OF DOCUMENT
4/7/06		21-925		3/24/06

NAME OF DRUG: DUETACT™ AD-4833SU (pioglitazone + glimepiride fixed-dose combination tablet).	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
	S	Anti-diabetic	**4/18/06**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Takeda's response to our letter dated 3/8/06 (comments per DMETS review). Please review prn; submission available via EDR.

PDUFA DATE: 4/29/06

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber
4/7/2006 01:21:58 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
rector, Division of Surveillance, Research, and Communication Support (DSRCS), HFD-410

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT: Takeda's reply to DSRCS review.	DATE OF DOCUMENT
4/7/06		21-925		3/24/06

NAME OF DRUG: DUETACT™ AD-4833SU (pioglitazone + glimepiride fixed-dose combination tablet).	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: Anti-diabetic	DESIRED COMPLETION DATE: **4/18/06**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Takeda's response to our letter dated 12/28/05 (comments per DSRCS). Please review prn; submission available via EDR.

PDUFA DATE: 4/29/06

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/
Jena Weber
4/7/2006 01:48:51 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-925 **DISCIPLINE REVIEW LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Pritza:

Please refer to your June 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duetact (pioglitazone HCl and glimepiride) tablets, [redacted] 30 mg/4 mg, and 30 mg/2 mg.

In the review of the container labels, carton, and package insert labeling, The Division of Medication Errors and Technical Support (DMETS), has identified the following areas of possible improvement, which may minimize potential user error. Please address these in writing to your NDA file.

GENERAL COMMENTS

1. DMETS has no objections to the use of the proprietary name, Duetact.

2. DDMAC finds the proprietary name, Duetact, acceptable from a promotional perspective.

3. The word "duet" in Duetact appears italicized. Emphasis on this portion of the proprietary name will increase the potential for confusion with the currently marketed U.S. product Duet. Please revise the font of "duet" so it is consistent with the remainder of the proprietary name in accordance with 21 CFR 201.10(g)(2).

4. We note that you propose a professional sample size of 30 tablets. DMETS believes this number is inappropriate for a physician sample. Thirty tablets represent a unit-of-use package size appropriate for a one month supply of medication. If allowed, this package size must have child resistant closures to be in compliance with the Poison Prevention Act.

5. The background colors utilized for the container labels of the 30 mg/2 mg and 30 mg/4 mg strengths are purple and light purple, respectively. Although the shades are different, the same color family for both strengths makes it difficult to differentiate between the strengths. We recommend making the packaging more distinct between the two strengths in order to minimize confusion and selection errors between the two product strengths.

B. CONTAINER LABELS (30 COUNT and 90 COUNT BOTTLES)

1. See General Comments A.3 and A.5.

2. Please ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 tablets, 90 tablets) to be in accordance with the Poison Prevention Act.

C. SAMPLE BLISTER LABELING

1. See General Comment A.3.

2. The established name is presented with the active ingredients joined by a plus sign (+). For consistency throughout the labeling, please remove the plus sign and replace it with the word "and".

3. Each individual blister should contain the proprietary name, established name, product strength, lot number, and expiration date in case the blister is separated from the sample blister carton or cut into single tablets.

D. SAMPLE CARTON LABELING

1. See General Comment A.3.

2. See Sample Blister Labeling Comment C.2.

E. PACKAGE INSERT LABELING

No comments at this time.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug 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 subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks

3/8/2006 01:15:56 PM

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MEMORANDUM

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

DATE: February 28, 2006

TO: Mary H. Parks, M.D.
Director
Division of Metabolic and Endocrine Products, DMEP

FROM: Michael F. Skelly, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-925 [redacted]
(pioglitazone HCl + glimepiride tablets, AD-4833SU),
Sponsored by Takeda

At the request of DMEP, the Division of Scientific Investigations audited the clinical and analytical portions of the following bioequivalence study, performed at [redacted] in [redacted], and [redacted] in [redacted], respectively.

Study 01-04-TL-OPISU-002: "An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 4 mg when Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

Following the inspection at [redacted] Form 483 was issued. Following the inspection at [redacted], there were no objectionable observations and no Form 483 was issued. The objectionable observation at [redacted] and our evaluation are as follows:

[redacted]

1. **The investigation was not conducted in accordance with the investigational plan, in that 6 of the 38 subjects did not have two negative serum hCG tests of which the first hCG test was conducted at least 7 days prior to the first dose, and the second before dosing. The first serum hCG tests for six subjects (1003/[redacted] 1007/[redacted] 1021/[redacted] 1033/[redacted] 1035/[redacted] and 1037/[redacted] were done only 2 or 3 days prior to the first dose.**

One negative hCG test either 2 or 3 days prior to dosing, and another negative hCG test 1 day prior to dosing, provide adequate assurance that the 6 subjects were not pregnant. An earlier first hCG test would not have given better assurance that subjects were not pregnant at the time of dosing. This technical protocol violation did not compromise subject protection.

Additional Comment:

Subject #055 (acquisition number 1003), a 27-year-old female, had no glimepiride in her plasma for any sample in Period I, although there were expected concentrations of pioglitazone. [redacted] repeated the glimepiride assays to confirm the results. Our audits found no explanation for this aberrant outcome in the clinical, dosing, or analytical records. During the other replicate Period with the same two approved (reference) tablets, the expected concentrations of both drugs were present.

Conclusions:

DSI recommends that the clinical and analytical data from study 01-04-TL-OPISU-002 are acceptable for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly, Ph.D.
Pharmacologist

Final Classification:

VAI - [redacted]
NAI - [redacted]

Recommendation: The data from study 01-04-TL-OPISU-002 are acceptable for review.

cc:
HFA-224
HFD-45/RF
HFD-48/Himaya
HFD-48/CF
DMEP (formerly HFD-510)/Weber
HFR- [redacted]
HFR-
Drafted: MFS 2/28/06
Edits: JAO/MFS 2/28/06
DSI: [redacted]; O:\BE\EIRCover\21925tak.piogli.doc
FACTS: 701252

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/s/

Amalia Himaya
2/28/2006 03:06:48 PM
CSO

Paper copy signed by Dr. Viswanathan on 2/28/06 and available upon request.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM: Jena Weber, PM
Division of Metabolism & Endocrinology Products

DATE: 2/22/06		NDA 21-925	TYPE OF DOCUMENT: Tradename Review Request	DATE OF DOCUMENT:2/7/06 (BB & BL)
NAME OF DRUG: [redacted] Tablets (pioglitazone HCl + glimepiride) fixed-dose combination.	PRIORITY CONSIDERATION: NO		CLASSIFICATION OF DRUG: Anti-diabetic	DESIRED COMPLETION DATE: **4/1/06**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Tradename review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

Comments: Please review and comment on proposed tradename. Note that a previous request was sent to you on 12/22/05. Company now requests that the tradename "DUETACT" be considered. Both documents are available via EDR.
User Fee Goal Date: 4/29/06

SIGNATURE OF REQUESTER: Jena Weber, PM 301-796-1306.	METHOD OF DELIVERY: DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber

2/22/2006 07:55:49 AM

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FDA/CDER/OMP/DDMAC

Internal Consult

*** Pre-decisional Agency Information ***

To: Jena Weber, Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Debi Tran, Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: December 30, 2005

Re: Consult request for product labeling

[redacted]™ **(pioglitazone hydrochloride and glimepiride) Tablets**

NDA 21-925

Thank you for consulting DDMAC on the proposed package insert, patient package insert, carton and container labeling. The following comments are based on the version dated June 28, 2005, found in the electronic document room. If you have any questions, please contact me at 301-796-0633.

PACKAGE INSERT

We note that the [redacted] draft package insert is a combination of the approved package inserts for pioglitazone hydrochloride and glimepiride; however, we have the following concerns addressed below:

DESCRIPTION

Lines 8-12:

> "The concomitant use of pioglitazone and a sulfonylurea, the class of drugs that includes glimepiride, has been previously approved based on clinical trials in

patients with type 2 diabetes inadequately controlled on a sulfonylurea. Additional efficacy and safety information about pioglitazone and glimepiride monotherapies may be found in the prescribing information for each individual drug."

Lines 14-18:

"Pioglitazone hydrochloride is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance. Pioglitazone is used in the management of type 2 diabetes. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels."

Lines 20-22:

"Pioglitazone (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride *belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, biguanides, or the α-glucosidase inhibitors.*" (emphasis added)

Lines 34-36:

"Glimepiride 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl] sulfonyl]-3-(*trans*-4-methylcyclohexyl)-urea is an oral blood glucose-lowering drug of the sulfonylurea class and *is used in the management of type 2 diabetes.*" (emphasis added)

Pursuant to the regulations governing the specific requirements on content and format of labeling for human prescription drugs [21 CFR 201.57(a)], we recommend deletion of these statements from the Description section because the information does not pertain to the chemical or physical properties of the drug.

CLINICAL PHARMACOLOGY

Mechanism of Action

Lines 68-69:

"Pioglitazone is a *potent* and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ)." (emphasis added)

We recommend deletion of the word "potent" because it is promotional in tone.

Lines 71-72:

> "Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and *lipid metabolism.*" (emphasis added)

Lines 74-75:

> "In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and *hypertriglyceridemia* characteristic of insulin-resistant states such as type 2 diabetes." (emphasis added)

The referenced statements imply that [redacted] may have a positive effect on "[redacted] and "[redacted] and can be included in promotion to suggest off-label uses for the drug.

Special Populations

Renal Insufficiency

Lines 196-197:

> "Glimepiride was found to be *well tolerated* in all 3 groups." (emphasis added)

Pharmacokinetic study results showed that glimepiride serum levels decreased as renal function decreased. Hence, the word "well tolerated" minimizes risks that can result from administration of the drug to patients with renal impairment. [redacted]

Lines 205-206:

> "All patients with a CLcr less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily."

The statement infers that all patients with renal impairment can expect to achieve glycemic control with the lowest dose of glimepiride and further implies that these patients are exposed to less adverse events because of the lower dose. Are these implications supported by substantial evidence?

Elderly

[redacted]

Pharmacodynamics and Clinical Effects

Lines 396-400:

> "Patients with lipid abnormalities were included in placebo-controlled monotherapy clinical studies with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL cholesterol and total cholesterol compared to the placebo group. A similar pattern of results was seen in 16-week and 24-week combination therapy studies of pioglitazone with a sulfonylurea."

The paragraph suggests that [redacted] has demonstrated efficacy in the treatment of lipid abnormalities. The proposed indication is for adjunctive therapy to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone. Does the paragraph promote an off-label use for [redacted]?

Clinical Studies

Lines 455-457:

> "Based on these reductions in A1C and FPG (Table 2), the addition of pioglitazone to sulfonylurea resulted in *significant* improvements in glycemic control irrespective of the sulfonylurea dosage." (emphasis added)

ADVERSE REACTIONS

Lines 919-923:

> "In *rare* cases, there may be an elevation of liver enzyme levels. In *isolated* instances, impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including glimepiride." (emphasis added)

PATIENT PACKAGE INSERT

Comments for the draft patient package insert will be provided under separate cover as part of the Office of Drug Safety's Division of Surveillance, Research, and Communication Support review.

CARTON AND CONTAINER LABELING

We have reviewed the draft carton and container labeling for [redacted] and have no comments at this time.

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/s/

Debi Tran

12/30/2005 12:03:52 PM

DDMAC REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-925 **DISCIPLINE REVIEW LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Dr. Pritza:

Please refer to your June 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (pioglitazone HCl and glimepiride tablets) [redacted], 30 mg/4 mg, and 30 mg/2 mg.

The Division of Surveillance, Research, and Communication Support (DSRCS) has completed their review of the proposed patient labeling for [redacted] We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information.

These revisions are based on draft labeling submitted on June 28, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Patient Information

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Version: AD-4833S-PPI-01

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug 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 subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Eric Colman

12/28/2005 11:08:32 AM

Eric Colman for David Orloff

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MEMORANDUM

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

Comments to DA Meeting - DFS on 12/22/05

DATE: December 27, 2005

TO: David Orloff, MD, Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Jena Weber, Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Catherine Miller, MT (ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza Hepp, PharmD, Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for [redacted] (pioglitazone/hydrochloride and glimepiride) tablets, NDA 21-925

The attached patient labeling (PPI) represents our revisions to the draft patient labeling submitted with the New Drug Application for [redacted] (pioglitazonehydrochloride and glimepiride) tablets, NDA 21-925. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although this format is not required for voluntary PPIs. 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 on June 28, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

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

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Catherine Miller
12/27/2005 02:26:16 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
12/27/2005 03:54:16 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM: DEMP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/22/05	69,686	21-925	Tradename Proposal	12/7/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AD-4833SU (pioglitazone + glimepiride fixed-dose combination tablet).	S	Anti-diabetic	3/15/06

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Review and comment on proposed tradenames:
First choice: Duetact Second choice: [redacted] Third choice: [redacted]

PDUFA DATE: 4/29/06
ATTACHMENTS: Package Insert, Patient Information Leaflet, Container and Carton Labels – available via EDR

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Jena Weber

12/23/2005 11:39:05 AM

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MEMORANDUM

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

DATE: December 14, 2005

TO: Director, Investigations Branch

Dallas District Office
4040 N. Central Expressway, Suite 900
Dallas, TX 75204

Detroit District Office
300 River Place, Suite 5900
Detroit, MI 48207

FROM: C.T. Viswanathan, Ph.D. Dec 19, 05
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2006, **High Priority CDER User Fee NDA,** Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

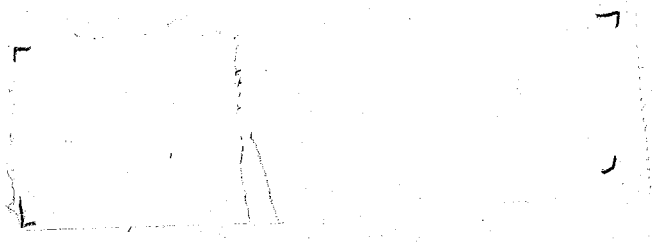
RE: NDA 21-925
DRUG: [redacted] (pioglitazone HCl + glimepiride) Tablets (AD-4833SU)
SPONSOR: Takeda

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence study.

Because of review division deadlines, the inspections should be completed by March 1, 2006.

Study 01-04-TL-OPISU-002: An Open-Label, Randomized, 4-Period, Crossover, Replicate Study to Determine the Bioequivalency of Pioglitazone 30 mg and Glimepiride 4 mg when Administered as Separate Commercial Tablets and as a Fixed-Dose Combination Tablet

Clinical Site:



Clinical Investigator: [redacted]

Please check the batch numbers of both the test and the reference drug formulations used in the studies with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, pharmacokinetic blood sample collection and processing, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site:

Instrumentation: [redacted]

Method [redacted] for pioglitazone
Method [redacted] for glimepiride

[redacted] assayed samples from Study 01-04-TL-OPISU-002 for pioglitazone and glimepiride concentrations, and reported the results in document 0221-04167.

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files

of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigators, background material will be forwarded directly. A member of the Bioequivalence Team from DSI will participate in the inspection of the analytical portion at ~~[redacted]~~.

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301) 594-2043

cc:
HFD-45/RF
HFD-48/Skelly(3)/Himaya/CF
DMEP/HFD-510/Weber (NDA 21-842)
HFR-CE750/Bellamy (Please FAX to 313-226-3717)
HFR-SW1540/Joel Martinez (Please FAX to 210-541-0394)
Draft: MFS 12/14/05
Edit:
DSI ~~[redacted]~~ O:\BE\assigns\bio21925.doc
FACTS 701252

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-925

Name of Drug: [redacted] (pioglitazone HCl/glimepiride fixed-dose combination tablets)

Sponsor: Takeda Global Research & Development Center

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Electronic

Submission Date: June 28, 2005 **Receipt Date:** June 29, 2005

Filing Date: August 28, 2005 **User-fee Goal Date: April 29, 2006**

Proposed Indication: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	•		Vol. 1
2. Form FDA 356h (original signature)	•		Vol. 1
Establishment information (facilities ready for inspection?)		•	N/A
b. Reference to DMF(s) & Other Applications	•		Electronic
3. User Fee FDA Form 3397	•		Vol. 1
4. Patent information & certification	•		Vol. 1
5. Debarment certification (Note: Must have a definitive statement)	•		Vol. 1

6. Field Copy Certification		•	ACK - NN
7. Financial Disclosure	•		Vol. 1
8. Comprehensive Index	•		Vol. 1
9. Pagination	•		Where applicable
10. Summary Volume	•		Electronic
11. Review Volumes	•		Electronic
12. Labeling (PI, container, & carton labels)	•		Electronic
a. unannotated PI	•		Electronic
b. annotated PI	•		Electronic
c. immediate container	•		Electronic
d. carton	•		Electronic
e. patient package insert (PPI)			Electronic
f. foreign labeling (English translation)		•	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	•		Electronic
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	•		Electronic

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	•		Electronic
2. Foreign Marketing History		•	N/A
3. Summary of Each Technical Section	•		Electronic, where applicable
a. Chemistry, Manufacturing, & Controls (CMC)	•		Electronic
b. Nonclinical Pharmacology/Toxicology		•	NN Cross-reference where applicable
c. Human Pharmacokinetic & Bioavailability	•		Electronic
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis		•	Electronic, cross reference where applicable
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	•		Electronic
5. Summary of Safety	•		Electronic, cross reference & BE data
6. Summary of Efficacy	•		Electronic, cross reference & BE data

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	•		Electronic

2. Controlled Clinical Studies		•	Electronic, cross reference
a. Table of all studies	•		Electronic
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	•		Electronic, cross reference & BE data
c. Optional overall summary & evaluation of data from controlled clinical studies		•	Electronic, cross reference & BE data
3. Integrated Summary of Efficacy (ISE)	•		Electronic, cross reference
4. Integrated Summary of Safety (ISS)	•		Electronic, cross reference
5. Drug Abuse & Overdosage Information			Electronic, labeling
6. Integrated Summary of Benefits & Risks of the Drug	•		Electronic, cross reference & BE data
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	•		Electronic (not for ped population), labeling

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		•	Deferral Requested (rescinded for pioglitazone in adults).
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		•	
a. Proposed unannotated labeling in	•		

MS WORD			Electronic
b. Stability data in SAS data set format (only if paper submission)		•	•
c. Efficacy data in SAS data set format (only if paper submission)		•	•
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		•	•
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		•	•
3. Exclusivity Statement (optional)		•	•

Y=Yes (Present), N=No (Absent)

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/s/

Jena Weber

10/12/2005 02:25:57 PM

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-925 Supplement # Efficacy Supplement Type SE-

Trade Name: [redacted]
Established Name: pioglitazone HCl/glimepiride fixed-dose combination tablets
Strengths: 30 mg/2 mg; 30 mg/4 mg[redacted]

Applicant: Takeda Global Research & Development
Agent for Applicant: same

Date of Application: 6/28/05
Date of Receipt: 6/29/05
Date clock started after UN: NA
Date of Filing Meeting: 8/22/05
Filing Date: 8/28/05
Action Goal Date (optional): User Fee Goal Date: **4/29/06**

Indication(s) requested: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification (1,2,3 etc.): 4
Other (orphan, OTC, etc.): No

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity 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 yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒

  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☒ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Is the submission complete as required under 21 CFR 314.50? YES ☒ NO ☐

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.

  Which parts of the application were submitted in electronic format? All

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Was the patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Was exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  ~~**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**~~

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Were financial disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- Are the 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.

- Are the trade, established, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
  Is the established name correct in COMIS IND(s) file(s): YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- List referenced IND numbers: 69,686

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 2/3/05 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO ☒

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☒ NO ☐
- ~~If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for~~ scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☒
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/12/05

NDA #: 21-925

DRUG NAMES: [redacted]

APPLICANT: Takeda Global Research & Development Center

BACKGROUND: 3 BE & BA studies submitted to this NDA. Clinical information/data cross-references NDA 21-073 (pioglitazone) and 20-496 (glimepiride). This NDA provides for a fixed-dose combination tablet (convenience package).

ATTENDEES: Orloff, Misbin, Vaidyanathan, Adams, Weber

ASSIGNED REVIEWERS (including those not present at filing meeting): Orloff, Misbin, El-Hage, Moore, Adams, Ahn, Vaidyanathan, Johnson, Weber.

Discipline	**Reviewer**
Medical:	Orloff
Secondary Medical:	Misbin
Statistical:	NN
Pharmacology:	El-Hage
Statistical Pharmacology:	NN
Chemistry:	Adams
Environmental Assessment (if needed):	Adams
Biopharmaceutical:	Vaidyanathan
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	Vishwanathan
Regulatory Project Management:	Weber
Other Consults:	DSRCS, DDMAC, DMETS

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	X	FILE	☐	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐
• Biopharm. inspection needed?					YES ☒	NO ☐
PHARMACOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐
• GLP inspection needed?					YES ☐	NO ☒
CHEMISTRY			FILE	☒	REFUSE TO FILE	☐
• Establishment(s) ready for inspection?					YES ☒	NO ☐
• Microbiology					YES ☐	NO ☒

ELECTRONIC SUBMISSION: Yes
Any comments: No

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g, orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

NAME JMWeber
Regulatory Project Manager, HFD-DMEP

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES X NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

   NDA 21-073 (pioglitazone HCl) and
   NDA 20-496 (glimepiride).

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO X

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO X

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO X

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. 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").

This NDA provides for a fixed-dose combination tablet (convenience package).

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO X

8. 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)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO X

9. 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 (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO X

10. Are there certifications for each of the patents listed for the listed drug(s)? YES X NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number: 4,379,785 (glimepiride).

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 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. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(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): The patent on the listed drug is 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 as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

X * Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s): 4,687,777 (drug, drug product)
6,150,383 (MOU) 6,211,205 (MOU)
6,329,404 (MOU) 6,303,640 (MOU)

***Due to corporate reorganization, the entity holding NDA 21-073 for Actos (pioglitaone HCl) has changed over time fromTakeda America Research & Development Center, Inc., to Takeda Pharmaceuticals America, Inc., to Takeda Pharmaceuticals North America, Inc. The NDA approval letter for Actos was issued to Takeda America Research & Development Center, Inc.**

The ownership of the NDA was transferred to Takeda Pharmaceuticals America, Inc. The name of the company changed from Takeda Pharmaceuticals America, Inc. to Takeda Pharmaceuticals North America, Inc. Takeda Global Research & Development Center, Inc (TGRD) is acting on behalf of TPNA with regard to NDA 21-925. TPNA has no objections to the immediate approval of NDA 21-925 for [redacted]

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES X NO ☐

  Published literature and cross-reference to NDA's cited.

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES ☐ NO X

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A ☐ YES X NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
  N/A ☐ YES X NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): Not seeking exclusivity.

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?
YES ☒ NO ☐

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

/s/

Jena Weber

10/13/2005 02:59:26 PM

CSO

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: September 1, 2005

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

DFS 9/1/05

THROUGH: David Orloff, M.D.
Division Director, HFD-510

FROM: Jena Weber, Regulatory Project Manager, HFD-510

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-925
_____ (pioglitazone HCl + glimepiride) Tablets

Study/Site Identification:

The following studies/sites are pivotal to approval and have been identified for inspection:

Study #	**Clinical Site**	**Analytical Site**
Protocol 01-04-TL-OPISU-002		

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **March 15, 2006**. We intend to issue an action letter on this application by **April 29, 2006.**

Should you require any additional information, please contact Ms. Jena Weber at 301-827-6422.

Hae-Young Ahn, Ph.D. Biopharm Team Leader Jaya Vaidyanathan, Ph.D. Biopharm Reviewer

Weber, Jena M

From: mjpritza@tgrd.com
Wednesday, August 31, 2005 11:51 AM
weberj@cder.fda.gov
Subject: NDA 21-925

Hi Jena- More complete information for each contact. Let me know if you need additional information. Mary Jo

These are the contacts:

###

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Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-925

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Pritza:

Please refer to your June 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (pioglitazone HCl and glimepiride) tablets, 30 mg/2 mg, 30 mg/4 mg, [redacted]

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 28, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Please provide dissolution profiles for glimepiride in pH 6.8 phosphate buffer containing 0.05%, 0.1%, and 0.2% SDS using USP apparatus 2 at 75 rpm.

2. In addition, please submit bioanalytical reports No. 0221-04165, 0221-04167 and 0224-04168-2.

3. The starting dose of Actos is 15 mg in patients whose hyperglycemia is inadequately controlled on sulfonylureas. It would be advantageous to propose a formulation of [redacted] containing 15 mg of pioglitazone.

[redacted]

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
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/

Jena Weber

8/26/2005 10:01:10 AM

Appears This Way
On Original

Weber, Jena M

From: Adams, Shawnte L
Sent: Friday, August 26, 2005 9:53 AM
To: Adams, William M; Moore, Stephen K; Weber, Jena M
Subject: FW: NDA 21925 Third Request

This is the third request for the intermediate manufacturers to be cancelled from this EER. Unless there is some extenuating circumstance that these sites absolutely need a GMP inspection please cancel the request for the intermediate manufacturers due to the reasoning below. Otherwise provide the reasoning that they should be inspected.

Thank you,

Shawnte L. Adams
Project Specialist
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

-----Original Message-----
From: Adams, Shawnte L
Sent: Tuesday, August 23, 2005 1:16 PM
To: Adams, William M
Subject: FW: NDA 21925

Please provide a status of the cancellation of the intermediate manufacturers in this application?

Thank you,

Shawnte L. Adams
Project Specialist
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

-----Original Message-----
From: Adams, Shawnte L
Sent: Friday, August 19, 2005 1:43 PM
To: Adams, William M
Subject: NDA 21925

Please provide contact information for all foreign facilities listed in NDA 21925. Also please note that in regards to intermediate manufacturers the following applies:

Resources do not permit pre-approval inspections of every facility with any connection to the product. We must apply risk-management principles in order to use inspectional resources to the greatest advantage as follows:

INTERMEDIATE MANUFACTURERS

CGMP as provided in the ICH Q7A applies to both APIs and some intermediates, but judgment must be used to decided if a pre-approval inspection is needed. Generally, we do not inspect those facilities which manufacture intermediates, including final intermediates. If the intermediate is made in the same facility as the final API, the pection of the API facility usually covers all final steps in producing the API. An Establishment Evaluation ntermediate manufacturers should only be requested if the review finds a specific problem that can best be resolved by an inspection. In these cases, the specific reason for requesting an inspection should be described in the comments field in EES and discussed with the inspection team. Such requests should usually be limited to the final intermediate manufacturing facility.

STARTING MATERIALS, EXCIPIENTS, CONTAINER-CLOSURES, ETC.

Neither 21 CFR 211 nor Q7A applies to manufacturing starting materials, excipients, containers, or closures, and we do not routinely inspect these facilities because of resource restraints and risk-management principles. We have authority to make inspections if needed, but we seldom have reason to exercise that authority. Establishment Evaluations or PAIs should not be requested for these facilities except to audit questionable data submitted in an application or to evaluate questionable manufacturing or testing practices. In these cases, the specific justification for requesting an inspection should be entered into the comments field of EES.

TESTING FACILITIES FOR INTERMEDIATES, EXCIPIENTS, AND CONTAINER-CLOSURES

Each testing facility for release and stability testing of both the drug product and final API should be entered into EES for compliance evaluation. No Establishment Evaluation is necessary for laboratory facilities testing starting materials, intermediates, or other components, containers or closures, or for laboratories which may have done one test on a development batch, but is not expected to perform any tests on the API or drug product after approval. Any exceptions should be discussed with Compliance before requested in EES.

ıy facility that is listed as an intermediate manufacturer should be cancelled in EES.

Thank you,

Shawnte L. Adams
Project Specialist
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-8909 (Fax)

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM: Jena Weber, PM
Division of Metabolic and Endocrine Drug Products, HFD-510

DATE: 7/5/05	IND 69,686	NDA 21-925	TYPE OF DOCUMENT: Tradename Review Request	DATE OF DOCUMENT:6/28/05

NAME OF DRUG: [redacted] Tablets (pioglitazone HCl + glimepiride) fixed-dose combination.	PRIORITY CONSIDERATION: NO	CLASSIFICATION OF DRUG: Anti-diabetic	DESIRED COMPLETION DATE: **12/31/05**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Tradename review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

Comments: Please review and comment on proposed tradename. Note that a previous request was sent to you on 10/5/04, under IND 69,686. We have not received comments from this initial consult. Document is available via EDR.
User Fee Goal Date: 4/29/06

SIGNATURE OF REQUESTER: Jena Weber, PM 301-827-6422	METHOD OF DELIVERY: DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

pending DFS sign-off 7/7/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DDMAC; attention: Shannon Benedetto

FROM: Jena Weber, PM
Division of Metabolic and Endocrine Drug Products, HFD-510

DATE: 7/5/05		NDA 21-925	TYPE OF DOCUMENT: PPI , PI, carton & container labels	DATE OF DOCUMENT:6/28/05
NAME OF DRUG: [redacted] (pioglitazone + glimepiride) fixed-dose tablets	PRIORITY CONSIDERATION: NO		CLASSIFICATION OF DRUG: Anti-diabetic	DESIRED COMPLETION DATE: **12/31/05**

NAME OF FIRM: Takeda Global Research Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ✔ LABELING
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW

OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Comments: Original NDA Submission. Please review and comment prn on all proposed LBL. Each section (PI, PPI, carton & container) is available via EDR. **User Fee Goal Date: 4/29/06.**

SIGNATURE OF REQUESTER: Jena Weber, PM 301-827-6422	METHOD OF DELIVERY: DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Shannon Benedetto

7/25/05 10:23:49 AM

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Weber, Jena M

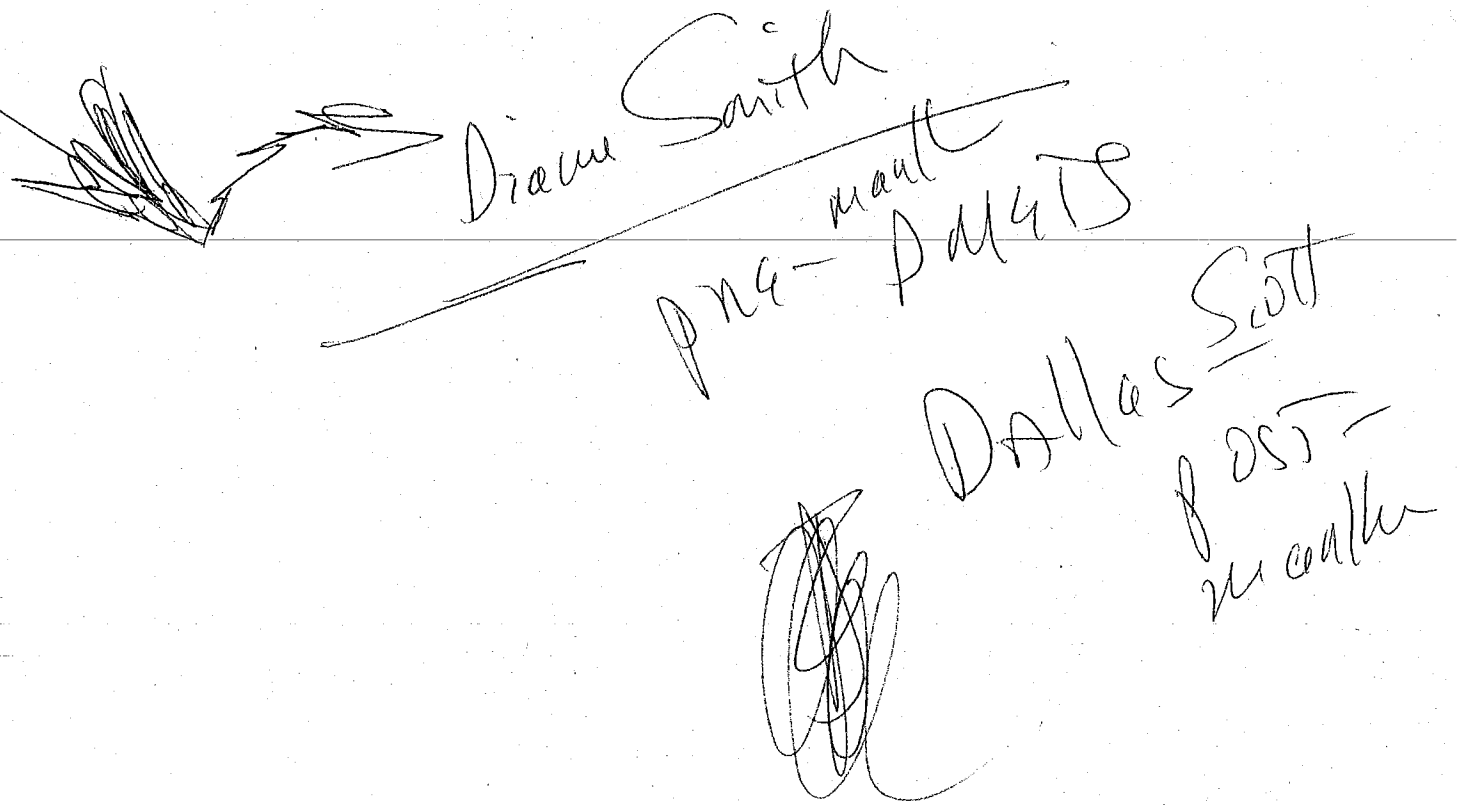
From: CDERDocAdmin
Sent: Thursday, July 07, 2005 9:15 AM
To: weberj@cder.fda.gov
Subject: New DFS Email - weberj - Forms

A document C:\ \TradenameConsult.doc has been returned to you for revision by Laura Pincock Please check your DFS Inbox

---

Document Type: Forms
Form Group: CONSULT
Form Name: Request for Trade Name (proprietary name) Review
Submission Description: Tradename Review Request

Author(s)/Discipline(s)
---
1. Jena Weber, CSO



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Surveillance, Research and Communication Support, HFD-410

FROM: Jena Weber, PM
Division of Metabolic and Endocrine Drug Products, HFD-510

DATE: 7/5/05		NDA 21-925	TYPE OF DOCUMENT: PPI	DATE OF DOCUMENT:6/28/05

NAME OF DRUG: [redacted] (pioglitazone + glimepiride) fixed-dose tablets	PRIORITY CONSIDERATION: NO	CLASSIFICATION OF DRUG: Anti-diabetic	DESIRED COMPLETION DATE: **12/31/05**

NAME OF FIRM: Takeda Global Research & Development Center, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ✔ LABELING
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Comments: Original NDA Submission. Please review and comment prn proposed Patient Information Sheet. This is available via EDR. **User Fee Goal Date: 4/29/06.**

SIGNATURE OF REQUESTER: Jena Weber, PM 301-827-6422	METHOD OF DELIVERY: DFS
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/s/

Jeanine Best

7/5/05 09:07:52 AM

Weber, Jena M

From: El Hage, Jeri D
Sent: Monday, July 04, 2005 11:55 AM
To: Vora, Bharati*; Galliers, Enid M; Weber, Jena M
Subject: RE: NEW 505(b)(2) NDA 21-925 [redacted] (pio + glimepiride) tablets [redacted] strengths, fixed dose combination to tx type 2 d.m. has arrived from Takeda

~~You can assign this NDA to me, but I doubt any pharm tox review will be needed.~~

Jeri

Jeri El-Hage, Ph.D.
Supervisory Pharmacologist
Division of Metabolic and Endocrine Drug Products
CDER, FDA
301-827-6369
jeri.elhage@fda.hhs.gov

-----Original Message-----
From: Vora, Bharati*
Sent: Thursday, June 30, 2005 4:26 PM
To: Galliers, Enid M; Weber, Jena M; Orloff, David G; Ahn, Hae Young; Sahlroot, Jon T; El Hage, Jeri D; Moore, Stephen K; CDER-DRTL-FDR
Cc: Johnson, Kati; Colangelo, Kim M; Peat, Raquel
Subject: RE: NEW 505(b)(2) NDA 21-925 [redacted] (pio + glimepiride) tablets [redacted] strengths, fixed dose combination to tx type 2 d.m. has arrived from Takeda

Hi Enid,

Requested pool and comis is update.
Thanks
Bharati

-----Original Message-----
From: Galliers, Enid M
Sent: Thursday, June 30, 2005 4:20 PM
To: Weber, Jena M; Orloff, David G; Ahn, Hae Young; Sahlroot, Jon T; El Hage, Jeri D; Moore, Stephen K; CDER-DRTL-FDR
Cc: Johnson, Kati; Colangelo, Kim M; Peat, Raquel
Subject: NEW 505(b)(2) NDA 21-925 [redacted] (pio + glimepiride) tablets [redacted] strengths, fixed dose combination to tx type 2 d.m. has arrived from Takeda

The stamp date is 29-JUNE-2005. Filing date = 28-AUG-2005.
Only the administrative stuff is in paper, but the NDA is entirely electronic and it is still being processed in the EDR.
Please email reviewer assignments to Jena after she sends you the link to the EDR.

FDR:

PM = WEBER
THER CODE = 3031400
CHEM TYPE = 4
PRIORITY = S
PT. 3 = N

DRUG NAME = [redacted] **TABLETS**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-925

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, PharmD, MPH
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Pritza:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: [redacted] (pioglitazone HCL/glimepiride fixed-dose combination tablets), 30 mg/2 mg, 30 mg/4 mg, [redacted]

Review Priority Classification: Standard

Date of Application: June 28, 2005

Date of Receipt: June 30, 2005

Our Reference Number: NDA 21-925

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **April 29, 2006.**

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 reference the deferral granted on February 3, 2005, for the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber

7/1/05 03:26:53 PM

55 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process