

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-995

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-995	
		NAME OF APPLICANT / NDA HOLDER MERCK & CO., INC.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) JANUVIA™			
ACTIVE INGREDIENT(S) Sitagliptin phosphate		STRENGTH(S) 25, 50, and 100mg	
DOSAGE FORM Tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,303,661		b. Issue Date of Patent October 16, 2001	c. Expiration Date of Patent April 24, 2017
d. Name of Patent Owner PROSIDION LIMITED		Address (of Patent Owner) Watlington Road	
		City/State Oxford, United Kingdom	
		ZIP Code OX4 6LT	FAX Number (if available) 44-1865-782601
		Telephone Number 44-1865-782600	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) OSI PHARMACEUTICALS, INC.		Address (of agent or representative named in 1.e.) 58 South Service Road, Suite 110	
		City/State Melville, New York	
		ZIP Code 11747	FAX Number (if available) 631-752-3880
		Telephone Number 631-962-2000	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling)
	JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated to improve glycemic control in combination with metformin or a PPAR-Gamma agonist when diet and exercise plus the single agent do not provide adequate glycemic control.

4. Method of Use (continued)	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling) JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated to improve glycemic control in combination with metformin or a PPAR-Gamma agonist when diet and exercise plus the single agent do not provide adequate glycemic control
4. Method of Use (continued)	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling) JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated to improve glycemic control in combination with metformin or a PPAR-Gamma agonist when diet and exercise plus the single agent do not provide adequate glycemic control
4. Method of Use (continued)	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling) JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated to improve glycemic control in combination with metformin or a PPAR-Gamma agonist when diet and exercise plus the single agent do not provide adequate glycemic control.
4. Method of Use (continued)	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling) JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. JANUVIA is also indicated to improve glycemic control in combination with metformin or a PPAR-Gamma agonist when diet and exercise plus the single agent do not provide adequate glycemic control

5. No Relevant Patents

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

December 5, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA, 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Merck & Co., Inc.

Address

P.O. Box 2000, RY60-30

City/State

Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-4568

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

phil_durette@merck.com

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA #: 21-995 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 16, 2006 PDUFA Goal Date: October 16, 2006

HFD-510 Trade and generic names/dosage form: Januvia (sitagliptin phosphate) Tablets

Applicant: Merck & Co., Inc. Therapeutic Class: antidiabetic agent

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next section.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) *previously approved* (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indication #1: Monotherapy

Indication #2: Combination therapy with metformin when diet and exercise plus the single agent do not provide adequate glycemic control

Indication #3: Combination therapy with a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist (e.g., thiazolidinediones) when diet and exercise plus the single agent do not provide adequate glycemic control

Responses below apply to all three indications.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 10 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 (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 11 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): December 31, 2010

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 (fill in applicable criteria below):

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.

NDA 21-995

Page 3

to DFS.

This page was completed by:

{See appended electronic signature page}

**Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager**

cc: NDA 21-995
HFD-960/ Rosemary Addy or Grace Carmouze

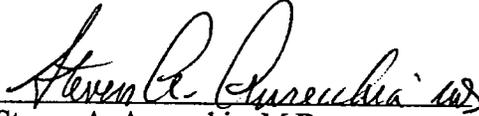
**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG
DEVELOPMENT, HFD-960, 301-594-7337.
(revised 6-23-2005)**

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/s/

Lina Aljuburi
10/17/2006 04:28:11 PM

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



Steven A. Aurecchia, M.D.

Director
Regulatory Affairs

11/21/05
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-995

Merck & Co.
Attention: Patricia Tway
BLA-20 P.O. Box 4
West Point, PA 19486

Dear Dr. Tway:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sitagliptin phosphate tablets.

We refer to the meeting between representatives of your firm and the FDA on June 29, 2006. The purpose of the meeting was to discuss the questions and comments provided in the IR letter dated May 18, 2006.

The official minutes of the above meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

ADRA Rev #1 of Action Package for NDA 21-995

Reviewer: Lee Ripper, HFD-102

Date received: 9/25/06

Date of review: 9/26/06; 10/16/06

Date original NDA received: 12/16/05

UF goal date: 10/16/06

Proposed Indication: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.

Action type: AP

RPM: Lina AlJuburi

Drug Classification: 1S

505(b)(1) application

Patent Info on form FDA 3542a: AC

Debarment Certification: AC

Financial Disclosure: Addressed in MOR #1, p. 28.

Safety Update: Dated 5/4/06, MOR #1, p. 181

Risk Management Plan: PPI and pregnancy registry; *OSE rev 9/14/06*

Clinical Inspection Summary: 9/5/06, data appear AC

DMETS Review of Proprietary Name: UN 11/30/05 and 8/2/06. No review of carton and container labels. 9/27: RPM reports DMETS has the labels UR. *Rev 10/5/06. DD memo finds proprietary name AC.*

DSRCS Review of PPI: 8/25/06

DDMAC Review: 9/13/06

SEALD Review: 8/23/06; 10/11/06

EA: Merck requested a categorical exemption

EER: One inspection pending - finished dosage manufacturer/release tester, MSD in Pavia Italy. RPM was told on 9/25 that the inspection has been completed; probably AC, but decision not official yet. *EER AC 10/12/06*

PSC/WU Mtg: 9/26/06

CMC section to Chi-Wan Chen, CMC review is pending; when completed will check to see if CWC needs a separate review package. *CMC rev 10/16/06*

P/T section to Ken Hastings, 9/27/06; *rev 10/16/06*

1. No DMETS review of carton and container labels; most recent version of labels are not in pkg. I have asked the RPM to provide a copy of most recent version if final version or, if not final version, final version when available.
2. *Final labeling received from Merck on 10/16/06*

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/s/

Leah Ripper
10/16/2006 06:15:56 PM
CSO

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Wednesday, October 11, 2006 9:34 AM
To: 'Aurecchia, Steven A.'
Subject: NDA 21-995 Januvia dissolution method

Attachments: Picture (Metafile)

Steve,

Your request for disintegration in lieu of dissolution for sitagliptin phosphate is unacceptable. Disintegration does not necessarily correlate with solubilization of the drug substance. Dissolution testing, on the other hand, incorporates both disintegration and the solubilization of the drug substance into the media in its specification. ICH 6A guidance (decision tree #7) stipulates that when a relationship has not been determined between dissolution and disintegration, disintegration is not acceptable instead of dissolution. For your product, there was no relationship between dissolution and disintegration. Therefore, the dissolution test is requested.

Please refer to the following dissolution method and acceptance criterion:

Apparatus	
In vitro dissolution medium	
Volume of dissolution medium	
Medium temperature	
Stirring speed	
Acceptance criterion	

We request that you submit an amendment to NDA 21-995 to reflect this information.

Feel free to contact me if you have questions.

Thanks,
Lina

Lina Aljuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)

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/s/

Lina Aljuburi
10/11/2006 09:43:26 AM
CSO



MEMORANDUM

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

DATE: September 14, 2006

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

FROM: Office of Surveillance and Epidemiology (OSE) Risk Management Team

DRUG: Januvia (sitagliptin phosphate) Tablets

NDA#: 21-995

SPONSOR: Merck & Co.

SUBJECT: Review of Proposed Risk Management Plan (RMP) submitted
December 16, 2005

PID #: D060096

INTRODUCTION/BACKGROUND

This consult follows a request by the Division of Metabolic and Endocrine Products (DMEP), for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Sponsor's proposed Risk Management Plan (RMP) for Januvia (sitagliptin phosphate) Tablets.

Sitagliptin is a new molecular entity that belongs to a new class of therapeutic agents recognized as dipeptidyl peptidase IV (DPP4) inhibitors. The DPP4 inhibitors exert glycemic control in patients with type 2 diabetes by preventing the rapid degradation of incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The proposed indication for Januvia at 100 mg once daily is as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus and as combination therapy in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

The Sponsor's summary of safety data in the Risk Management Plan submission did not identify any safety signals in any of the studies or potential risks that would warrant risk management measures beyond routine labeling and pharmacovigilance. They did mention that there is one important potential risk identified by the FDA, necrotic skin lesions in the monkey and there is missing information in children, i.e., patients <18 years of age and in pregnant women.

Ilan Irony, M.D., the medical officer assigned to the clinical review of this NDA, indicated in his review¹ that common adverse events (at least 3% of subjects in the group) and present with higher incidence in sitagliptin-treated subjects than in control subjects include diarrhea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, arthralgia and headache. The frequency of hypoglycemic symptoms or events was similar in sitagliptin-treated subjects as in control-treated subjects and much lower than those treated with glipizide. He also noted laboratory findings of interest include a dose-related decrease in serum levels of alkaline phosphatase, small and transient mean increases in serum uric acid and creatinine, white blood cell counts and absolute neutrophil counts, and small decreases in hemoglobin. He agrees with the risk management plan proposed by the Sponsor.

REVIEW OF SPONSOR'S RMP

The Sponsor does not believe that a Risk Minimization Action Plan (RiskMAP) is warranted for this product. They are proposing the following Pharmacovigilance/Surveillance and Post-marketing Activities:

- Labeling – professional labeling and the patient package insert will be utilized to convey to prescribers, other healthcare professionals, and patients about the risks associated with Januvia. A separate Patient Package Insert (PPI) consult was performed by the OSE Division of Surveillance, Research and Communication Support (DSRCS)².
- Routine Pharmacovigilance Practices - reporting of adverse event information (including AE's of special interest to the Sponsor, hypoglycemia, selected gastrointestinal and laboratory events) will be accomplished in accordance with the relevant legal requirements and appropriate international declarations and protocols.
- Necrotic skin lesions in monkeys – based on the Agency's concern regarding animal data indicating that the administration of DPP-IV inhibitors to monkeys results in dose-dependent and duration-dependent increases in necrotic skin lesions, the Sponsor is undertaking an oral toxicity study in monkeys over a range of doses for up to 3 months duration, the design of which has been reviewed and agreed upon by the U.S. FDA.
- Pregnancy Registry - In order to develop a better assessment of the safety profile of Januvia in pregnant women, the Sponsor proposes the establishment of a pregnancy

¹ Ilan Irony, MD, Medical Officer. Clinical Review of Januvia (sitagliptin phosphate), NDA 21-995; in DFS, dated August 31, 2006.

² Sharon Mills, Patient Product Information Specialist, DSRCS Review of Patient Labeling for Januvia, in DFS, dated August 25, 2006.

registry for more intensified follow-up of pregnancy exposures. The pregnancy registry will be an enhanced surveillance program of women exposed to Januvia at any time from the date of the last menstrual period through the duration of the pregnancy.

CONCLUSION

The Sponsor's proposed RMP does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance. The Sponsor has proposed other measures including a plan to undertake an oral toxicity study in monkeys to assess the risk of necrotic skin lesions over a range of doses and a pregnancy registry to determine if there is any risk to the pregnant woman.

The Division of Surveillance, Research and Communication Support (DSRCS) completed a separate Patient Package Insert (PPI) consult and the Division of Medication Error and Technical Support (DMETS) conducted a separate review of the proprietary name³.

OSE concludes (after consulting with the MO in DMEP) that the Sponsor's proposal for routine risk management measures and planned pharmacovigilance activities is sufficient at this time. If the sponsor or the review division identifies a safety concern in the future and determines that a RiskMAP is warranted or should the review division wish OSE to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

³ Linda Wisniewski, R.N., DMETS Proprietary Name Review of Januvia, August 2, 2006.

OSE Risk Management Team

Mary Dempsey, Project Management Officer

Claudia Karwoski, PharmD, Scientific Coordinator for Risk Management (Lead author)

Joyce Weaver, PharmD, Senior Risk Management Analyst

Mary Willy, PhD, Senior Risk Management Epidemiologist

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/s/

Mary Dempsey
9/14/2006 08:38:52 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
9/14/2006 08:42:24 AM
DRUG SAFETY OFFICE REVIEWER

Steven A. Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

August 24, 2006

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Response to FDA Request for Information

Reference is made to the New Drug Application cited above, submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. Reference is also made to the telephone conversation between Dr. Todd Bourcier (FDA) and Dr. Steven Aurecchia (MRL) on August 14, 2006, in which Dr. Bourcier requested MRL's pre-clinical study reports for the MK-0431/metformin combination toxicity studies in the dog. Further reference is made to the e-mail communications on August 14, 2006 and August 18, 2006, from Dr. Aurecchia to Dr. Bourcier, that contained .pdf copies of these reports.

With this response, MRL is providing the official submission of the pre-clinical reports e-mailed on August 14, 2006 and August 18, 2006 entitled, *MK-0431 and Metformin: Exploratory Single Dose Oral Toxicokinetic Study in Dogs* [Ref. 4.2.3.2: TT051150], *Metformin: Exploratory 5-Week Oral Tolerability Study in Female Dogs* [Ref.4.2.3.2: TT066018], *MK-0431 + Metformin: Fourteen-Week Oral Toxicity Study in Dogs* [Ref.4.2.3.2: TT066000] and *MK-0431 + Metformin: Sixteen-Week Oral Toxicity Study in Female Dogs* [Ref.4.2.3.2: TT066017], to the pending New Drug Application for JANUVIA™.

Information in [Sec.2.6.6], [Sec.2.6.7] and [Sec.2.4] has been updated to include these 4 pre-clinical dog reports.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator (cover letter)
Division of Metabolism & Endocrinology Products

Todd M. Bourcier, Pharmacologist (cover letter)
Division of Metabolism & Endocrinology Products

Steven A. Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099
Tel: 267 305 6669
Fax: 267 305 6406
steven_aurecchia@merck.com

August 15, 2006

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism
& Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Response to FDA Request for Information

Reference is made to the New Drug Application cited above for JANUVIA™, submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., as an electronic archive on December 16, 2005. Reference is also made to the July 31, 2006 teleconference between representatives from FDA and MRL to discuss the sitagliptin population pharmacokinetic study report, *entitled, MRL Technical Report: Population Pharmacokinetic Analysis of Oral MK-0431*. Further reference is made to the e-mail communication from Dr. Lina Aljuburi (FDA) to Dr. Steve Aurecchia (MRL) in which Dr. Aljuburi requested written responses to the questions listed in [Sec 1.11.4] regarding the population pharmacokinetic report (in addition to the last question regarding disintegration).

With this submission MRL is providing a response to the Agency's questions in [Sec.1.11.4]. Data sets in support of Response #2 are provided in [Sec.5.3.5.3]. We hope that the responses provided in this submission have adequately addressed the Agency's questions.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certifications are included as paper for archival purposes.

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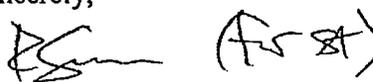
Mary H. Parks, M.D., Director
NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Page 2

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products.

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Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, to Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Manager (*cover letter*)
Division of Metabolism and Endocrinology Product, Room 3101

Steven A Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P O Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
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steven_aurecchia@merck.com

August 14, 2006

Mary Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Response to FDA Request for Information

Reference is made to the New Drug Application cited above for JANUVIA™, submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., as an electronic archive on December 16, 2005. Reference is also made to the telephone conversation on August 10, 2006 between Dr. Lina Aljuburi (FDA) and Dr. Steven Aurecchia (MRL), in which Dr. Aljuburi requested a listing of the 23 countries in which the trademark JANUVIA has been registered, as cited in the response letter submitted by MRL to the above-referenced NDA on January 26, 2006.

To date, the trademark JANUVIA has been registered in 63 countries, as listed in the table below. Please note that our Community Trade Mark (CTM) registration covers all of the EU countries.

JANUVIA registered trademarks	
Country	Registration Number
Albania	10217
Armenia	10055
Australia	1050829
Austria	225956
Azerbaijan	20060154
Belize	317705
Benelux	773438
Bermuda	41890
Brunei Darussalam	37003
Burundi	4368BUR
Cambodia	KH2182105
Colombia	308487
Costa Rica	157622
CTM	4375952
Czech Republic	276921
Denmark	VR200501849
Dominican Republic	150026
Estonia	42510
Finland	234577

JANUVIA registered trademarks (continued)	
Country	Registration Number
Germany	30522676
Guatemala	138993
Haiti	320Reg147
Honduras	95308
Hong Kong	300405512
Iceland	4872005
Iran	131440
Ireland	232089
Jamaica	46668
Japan	04917528
Jordan	79691
Laos	12221
Lebanon	102362
Lesotho	LSM0500089
Macao	N16790
Malawi	1622005
Malta	43453
Mexico	883390
Mongolia	5285
Morocco	97699
Netherlands Antilles	11303
New Zealand	728186
Nicaragua	84119
Norway	230758
Panama	142042
Romania	68386
Russian Federation	306683
Rwanda	5548IRK
Saudi Arabia	83032
Seychelles	7156
Singapore	T0506222Z
Slovenia	200570562
Spain	2650107
Sweden	376044
Switzerland	534167
Taiwan	1179359
Thailand	KOR233288
Turkey	2005014655
Turkmenistan	9023
Uganda	27607
United Arab Emirates	56506
United Kingdom	2389570
Uzbekistan	MGU14071
Yemen, Republic of	26983
Zimbabwe	4062005

With this submission, MRL is providing a response to the Agency's request. We hope that the information provided in this submission has adequately addressed the Agency's questions.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

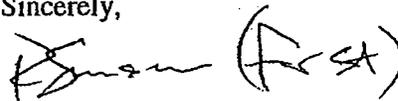
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A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, to Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,

Handwritten signature of Steven A. Aurecchia, M.D., with the initials "SA" in parentheses to the right.

Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

Enclosure: CD

Desk Copy: Dr. Lina AlJuburi, Regulatory Health Project Manager (*cover letter w/attachment*)
Division of Metabolism and Endocrinology Products, Room 3101

DFS Aug 9, 2006

Executive CAC

Date of Meeting: August 8, 2006

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Jim Farrelly, Ph.D., DAVP, Alternate Member
William Taylor, Ph.D., DSPTP, Alternate Member
Karen Davis-Bruno, Ph.D. DMEP, Team Leader
Todd Bourcier, Ph.D., DMEP, Presenting Reviewer

NDA# 21,995

Drug Name: Januvia (Sitagliptin phosphate)

Sponsor: Merck

Background:

Januvia is a dipeptidyl peptidase-4 (DPP4) inhibitor being developed by Merck for the treatment of Type 2 diabetes.

Rat Carcinogenicity Study: Sprague Dawley rats were administered daily gavage doses of placebo (2 control groups) or sitagliptin phosphate at 50, 150, and 500mg/kg for 106 weeks. Selection of the high dose was based on MTD and provides ~60-fold multiple of maximum recommended clinical exposure (100mg q.d., 10 μ M*h/ml).

Mouse Carcinogenicity Study: CD-1 mice were administered daily gavage doses of placebo (2 control groups) or sitagliptin phosphate at 50, 125, 250, and 500mg/kg for 106 weeks. Selection of the high dose was based on MTD and provides ~70-fold multiple of maximum recommended clinical exposure (100mg q.d., 10 μ M*h/ml).

Executive CAC Recommendations and Conclusions:

Rat Carcinogenicity Study:

The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the doses of 50, 150, and 500mg/kg.

The Committee concurred that the study was positive for combined liver adenomas and carcinomas in males and females and for liver carcinomas in females at the 500mg/kg dose.

Mouse Carcinogenicity Study:

The Committee agreed that the study was adequate, based on MTD (renal toxicity).

The Committee concurred that there were no drug-related neoplasms.

Abigail Jacobs, Ph.D.

Acting Chair, Executive CAC

cc:\

DMEP/Division File,

Karen Davis-Bruno/Team leader, DMEP

Todd Bourcier/Reviewer, DMEP

Lina Aljuburi/CSO/PM, DMEP

/ASeifried, OND IO

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

/s/

Abby Jacobs

8/9/2006 12:09:26 PM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(WO: 22, Mailstop 4447)

DATE RECEIVED: March 31, 2006 DATE OF DOCUMENT: January 26, 2006	DESIRED COMPLETION DATE: May 1, 2006 PDUFA DATE: October 16, 2006	OSE REVIEW #: 05-0162-1
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TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Linda Kim-Jung, PharmD., Team Leader
Denise Toyer, Pharm D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Januvia
(Sitagliptin Phosphate Tablets)
100 mg

NDA#: 21-995

NDA SPONSOR: Merck & Co., Inc.

RECOMMENDATIONS:

DMETS continues to recommend against the use of the proprietary name, Januvia. Merck & Co., Inc has not provided persuasive evidence, at this time, to diminish our concerns with potential confusion between Januvia and Tarceva.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 5, 2006

NDA#: 21-995

NAME OF DRUG: Januvia
(Sitagliptin Phosphate Tablets)
100 mg

NDA HOLDER: Merck & Co., Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for a re-assessment of the proprietary name, "Januvia". The name Januvia was previously reviewed by DMETS in ODS consult 05-0162-1 dated, November 30, 2005 and was found unacceptable due to its similarity in orthographic appearance and overlapping product characteristics with Tarceva. The sponsor then submitted a rebuttal to DMETS consult on January 26, 2006. This review will evaluate the concerns noted in the January 26th letter.

PRODUCT INFORMATION

Januvia (sitagliptin phosphate) is an orally-active, potent, and highly selective inhibitor of dipeptidyl peptidase 4 (DPP-4) enzyme. The DPP-4 inhibitors are a class of agents that act as incretin enhancers, which improve glycemic control in patients with type 2 diabetes. Januvia is prescribed as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus or in combination with metformin or a PPAR_γ agonist when diet and exercise, plus single agent do not provide adequate glycemic control. The recommended dose of Januvia is 100 mg once daily. Januvia is supplied in 25 mg, 50 mg, and 100 mg tablets in bottles containing 30, 90, 500, and 1000 tablets, and in unit dose blister packages of 100 tablets.

II. RISK ASSESSMENT:

The sponsor has requested a re-consideration of the proprietary name Januvia for Sitagliptin Phosphate. This rebuttal included a letter dated January 26, 2006. The sponsor's comments are listed first and are followed by the DMETS response.

- A. When developing a global trademark Merck performs an exhaustive review of the proposed trademarks to insure the selection of a worldwide trademark that is appropriate for the product and avoids conflict and confusion with existing trademarks and nonproprietary names. Such a review was performed on JANUVIA and no prior confusingly similar trademarks or generic names were disclosed. Not only is a search made of the Federal Register, but State registration searches are made as well as extensive searches for "common law" uses (marks which are used but were never registered through the United States Patent and Trademark Office [USPTO] or State Registers) and domain names. TARCEVA™ was not identified as a potential for confusion by sight or sound within any of these searches. An application to register the trademark JANUVIA was filed in the USPTO on April 7, 2005. No prior trademarks were cited by the Examining Attorney during the examination of the application to register JANUVIA, nor were any oppositions filed by other companies or interested parties after the mark was published for opposition on November 15, 2005. Additionally, the trademark JANUVIA has now been registered in 23 countries.

DMETS Response:

DMETS acknowledges the sponsor's remarks with respect to a legal search. However, the Patent and Trademark Office does not compare names from a safety perspective concerning how the drug is going to be spoken or scripted on a prescription or inpatient order. Nor do they examine how the product profile of the medication, in conjunction with the name, may lead to medication errors when used within the medication use system. When comparing these names in writing, DMETS identified Tarceva as a potential source of confusion.

We acknowledge that Januvia is registered in 23 other countries. However, what is unclear is if Tarceva is registered in the same countries as Januvia and whether or not there have been reported cases of confusion in the countries in which they both co-exist.

B.

Analytic Focus: The [redacted] has organized the data gathered from the pharmacists and carried out the analysis with the aim of discovering potential medication error dangers associated with suggested brand names. Also the potential concerns of the FDA and [redacted] are addressed. These concerns are as follows:

1. **Look-Alike Issues:** The likelihood for the new brand name being misread as another drug product in a written document, such as prescriptions or hospital orders.
2. **Sound-Alike Issues:** The likelihood for the new brand name being misheard as another drug product during an oral exchange, such as in doctor's offices, phoned prescriptions to pharmacies, phoned hospital orders, hospital physician rounds, or hospital hallway consultations.
3. **USAN/INN Issues:** The degree to which the new brand name contains letter strings (prefix, suffix, or infix) that have been reserved for generic names. This is primarily a USAN/INN concern. (Note: analysis of this item and items 4, 7, 8, 9, 10, 11, and 14 below, can only be carried out when information is available from the manufacturer).
4. **Therapeutic Indications:** The likelihood that the new brand name will suggest a therapeutic indication for which clinical data has not been supplied or approved.
5. **Prefix and Suffix Issues:** The likelihood that a prefix or suffix could be misunderstood or that its omission would cause a dosing error or dispensing error by health professionals.
6. **Use of Acronyms and Abbreviations as Part of the Name.** In addition to the FDA/EMEA-related issues, the [redacted] factors in the following error causing variables, which will greatly influence the potential for look alike and sound alike names to result in errors.
7. **Availability of the Same Dosage Form** (e.g., both are tablets).
8. **Availability of the Same Strength or Concentration** (e.g., both 40 mg dosage forms).
9. **Same or Similar Dosing Direction** (e.g., both taken once daily).
10. **Dose Overlapping** (e.g., both doses are between 5 to 20 mg once daily).
11. **Same or Similar Clinical Indication(s).**
12. **Popularity of Established Product with a Similar Name.** Health professionals "see" what they know [confirmation bias]. If a similar product is widely prescribed, it offers a higher chance of being mistaken for the intended product.
13. **Similar Brand Names Already Marketed by This Firm.** Glaxo SmithKline's Zantac injection and Zofran injection sit next to each other on the shelf increasing the possibility of pharmacists selecting the wrong drug since the containers have the same corporate dress. This problem is unavoidable for companies with large product lines, but the problem

DMETS Response:

DMETS acknowledges the analytic focus of the study that was conducted by [redacted]. However, without the full analysis for evaluation, DMETS cannot comment on the conclusion of the [redacted] Analysis. Additionally, we have learned through our post-marketing experiences that many of the factors to which the [redacted] analysis focuses on are not necessarily distinguishing features (e.g., similar dosage forms, dosing directions). We have seen errors that have occurred even when these product characteristics did not overlap.

- C. DMETS speculates that "Tarceva and Januvia may look similar when written. The beginning letters (T and J) may look similar when scripted and the remaining letters (-arceva vs. -anuvia) could look similar when scripted as well." (emphasis added). Merck respectfully submits that this conjecture on the part of DMETS does not meet "the objective facts of record" standard that the FDA is required to meet in rejecting a trademark pursuant to 108 Congressional Record 21066 (September 27, 1962). Further, this review of the objective facts of record must find the proposed trademark to be demonstrably false or demonstrably misleading, another standard which is not met by speculation.

DMETS Response:

In 1962 there were not as many drugs on the market as seen today. Additionally, over the last ten years, we have learned a great deal from post-marketing reporting concerning medication errors. Thus, the reasons for rejection must not be held to a standard that was created 44 years ago. New information on issues relating to the safe use of proprietary names must be considered in order to avert today's medication errors.

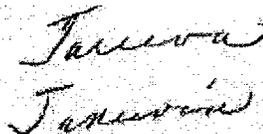
- D. Merck submits that the true source of potential confusion is poor handwriting on the part of the physician and/or poor dispensing practices by the pharmacist. Scripting can therefore only be a valuable tool when the writing can be read. There is no foolproof test for illegible penmanship and Merck has no control over illegible writing. Poorly handwritten scripts should not be filled until further clarified.

DMETS Response:

DMETS acknowledges that poor handwriting may contribute to the error and that in the perfect world all scripts would be verified prior to dispensing. However, post-marketing evidence has shown that if the names look similar when scripted, errors have occurred even if the penmanship is not necessarily poor. DMETS emphasizes "when scripted" as the names may not contain many overlapping letters in the same sequence, but when written the names can possess similar orthographic characteristics. An example is the confusion that occurred between Amaryl and Reminyl. In this case the similar orthographic appearances contributed to numerous errors involving this pair (see below) despite the lack of numerous overlapping letters. Consequently, the name Reminyl was changed to Razadyne.

Tarce	Am
Janu	Remin

Both Tarceva and Januvia may look similar when written. When scripted, a capital 'T' may look similar to a capital 'J' if the non-traditional scripting of each name is used, as seen below. Additionally, the letters 'ar' may look similar to the letters 'an'. It is not uncommon for people to script words using both block printed and cursive letters. In this case, the 'n' will have one hump and may appear as an 'r'. Additionally, the last few letters 'va vs. via' may also look similar if the letters are scripted close together and not clearly differentiated. The rest of the letters may also look similar due to the lack of differentiating upstrokes and downstrokes.



- E. DMETS further states that "... both products share an overlapping strength of 100 mg with a dosing frequency of once daily and [REDACTED]". The latter is in part incorrect: the maximum recommended dose of JANUVIA is 100 mg once daily with or without food. Both products do share this overlapping 100 mg strength; however, the 100 mg TARCEVA™ dose pertains only to its pancreatic cancer indication and the TARCEVA™ dosing recommendation in pancreatic cancer is 100 mg taken at least one hour before or two hours after the ingestion of food in combination with gemcitabine. Additionally, each product has distinct tablet characteristics. TARCEVA™ (erlotinib) 100 mg tablets are white, round, have a biconvex face and straight sides, are film-coated, and are printed in gray with "T" and "100" on one side. JANUVIA 100 mg tablets are beige, round, and film-coated with "277" on one side. These distinct images minimize the potential for confusion and dispensing error. Merck also submits that the U.S. Patient Package Insert (PPI) developed for JANUVIA and submitted with the NDA provides clear and concise information to patients on the approved indications for JANUVIA, and mitigates the risk of unintended patient use.

DMETS Response:

1. DMETS first evaluated the proprietary name Januvia in ODS Consult 05-0162. At that time, the product dosing and strength information was provided by the project manager and obtained from the end of phase 2 meeting minutes dated June 9, 2004. As seen below, the dose for monotherapy is [REDACTED] with or without food...in combination with metformin is 100 mg once daily. Therefore, the dose of [REDACTED] obtained from the information available at the time the consult was requested.

IND 65,495 for L-000224715 (MK-0431) Tablets was submitted on August 9, 2002. MK-0431 is a Dipeptidyl-peptidase IV (DPP-IV) inhibitor under investigation as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. [REDACTED] is also under investigation to improve glycemic control in combination with metformin when diet, exercise, plus the single agent do not provide adequate glycemic control. The proposed dose of MK-0431 in combination with metformin is 100 mg once daily.

2. The sponsor acknowledges that there is an overlapping strength of 100 mg between Tarceva and Januvia. However, the sponsor notes that this overlap only occurs for the Tarceva indication of pancreatic cancer. If the "indication of use" is included on a prescription, this would be helpful in deciphering the drug name. However, practitioners do not commonly include this information on prescriptions filled in the retail or inpatient setting. Thus, this overlap in strength may be a problem.

Additionally, the sponsor states that Januvia can be taken once daily with or without food. It is also noted that Tarceva should be taken without food. However, since either product can be taken without food, this information would not be a differentiating characteristic between the two names. Therefore, the indication of use and whether the products or drugs are taken with or without food cannot be relied upon as a distinguishing characteristic between Tarceva and Januvia.

3. The sponsor states that the tablet's physical characteristics may help to differentiate Januvia from Tarceva. If the name of the product was misinterpreted at the beginning of the prescription fill process, the image or the physical characteristics of the tablet would not be much of an asset in prompting the practitioner that they have made an error. The perception that the order reads as Tarceva would lead the dispenser to select the product Tarceva. The tablet characteristics would not be a distinguishing characteristic in this scenario. With regards to patients, drug identifiers such as different tablet appearance, only help if the patient has prior knowledge of what the tablets look like and/or have received the medication before.

4. The sponsor states that the Patient Package Insert (PPI) will help to identify approved indications for Januvia. However, this assumes that all patients will be reading the PPI fully, and understanding it completely. If the patient does not read the PPI or receives Tarceva in lieu of Junivia, then the availability of the Tarceva PPI is of no benefit.
- F. Furthermore, the likelihood of a clinically meaningful clinical or laboratory adverse event occurring as a consequence of inadvertent dispensing of JANUVIA is quite low. JANUVIA was well-tolerated in placebo-controlled clinical trials as both monotherapy and combination therapy with metformin or pioglitazone. These studies included patients treated with JANUVIA 200 mg daily (two times the recommended daily dose of 100 mg). The overall incidence of side effects and of discontinuation of therapy due to clinical adverse experiences was similar to that reported with placebo. Importantly, the rates of hypoglycemia reported with JANUVIA were also similar to rates in patients receiving placebo. Likewise, in normal subjects in Phase I studies, JANUVIA did not produce hypoglycemia, consistent with the physiology of the incretin axis and the mechanism of action of JANUVA. In clinical studies of JANUVIA in diabetics, adverse experiences reported in $\geq 3\%$ of patients and more commonly than in patients given placebo, irrespective of causality attribution, included upper respiratory tract infection, nasopharyngitis, headache, diarrhea, and arthralgia. Across clinical studies, small mean increases in white blood cell count and uric acid and a small mean decrease in alkaline phosphatase were observed. These changes in laboratory parameters are not considered clinically relevant. There were no clinical meaningful changes in vital signs or in ECG parameters (including QTc interval) with JANUVA treatment.

DMETS response:

Although 'clinically meaningful clinical or laboratory adverse event occurring as a consequence of inadvertent dispensing of Januvia is quite low', this does not change the fact that a medication error has already occurred and the error has reached the patient. Despite the lack of significant adverse events occurring as a consequence of inadvertent administration of Januvia, this error would result in the patient not receiving treatment for their disease. Conversely, approved labeling for Tarceva states that 'there have been reports of serious events, including fatalities, in patients receiving Tarceva...' DMETS considers the potential for confusion and the resultant adverse event as potentially clinically significant if a patient receives Tarceva instead of Junivia.

In summary, the data submitted by Merck & Co., Inc. has not provided persuasive evidence to diminish our concerns with potential orthographic confusion between Januvia and Tarceva. As concluded in our previous review, DMETS does not recommend the use of the proprietary name Januvia.

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

/s/

Denise Toyer
8/2/2006 12:56:30 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/2/2006 03:00:21 PM
DRUG SAFETY OFFICE REVIEWER

Steven A Aurecchia, MD
Director
Worldwide Regulatory Affairs

Merck & Co., Inc
P O Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

August 2, 2006



Mary H. Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Amendment to a Pending Application

Reference is made to the New Drug Application cited above, submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. As indicated on the attached Form FDA 356h, this amendment provides for the submission of the pre-clinical reports, entitled, *L-000224715: Exploratory Single Dose Oral Toxicokinetic Study in Monkeys* [Ref. 4.2.3.2: TT051151], *L-000000826: Twelve-Week Oral Toxicity Study in Monkeys* [Ref. 4.2.3.2: TT061025], and *L-000233357: Fourteen-Week Oral Toxicity Study in Monkeys, Drug Week 9 - Status Update* [Ref. 4.2.3.2: TT061056], to the pending New Drug Application for JANUVIA™.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

Mary H. Parks, M.D., Acting Director
NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Page 2

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

Enclosure: CD

Desk Copy: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Steven A. Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
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Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

July 20, 2006



Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Response to FDA Request for Information

Reference is made to the New Drug Application cited above for JANUVIA™, submitted as an electronic archive on December 16, 2005. Reference is also made to the May 18, 2006 letter from the FDA to Merck, which included a list of 15 questions regarding the Chemistry, Manufacturing, and Controls section of the New Drug Application referenced above. Reference is also made to the Response to FDA Request for Information on June 13, 2006, which included responses to questions 1, 2, 3, 6, 7, 10 and 11. Reference is also made to the Response to FDA Request for Information on June 22, 2006, which included responses to questions 8 and 9.

With this submission, Merck is providing a final response to the questions from the FDA. This submission includes a response to questions 4, 5, 12, 13, 14, and 15 in [Sec. 1.11.1].

We hope that responses provided in this submission have adequately addressed the Agency's comments. To the extent possible, please notify Merck of any issues that the Agency feels have not been adequately addressed. Once the Agency has communicated to Merck that the 15 questions have been addressed successfully, we will update the information in Module 3 and submit this to the Agency.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, to Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

Enclosure: CD

DHL #1

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Manager (*cover letter*)
Division of Metabolism and Endocrinology Products, Room 3101
DHL#1

Amy Bertha, Regulatory Health Project Manager (*cover letter*)
Division of Metabolism and Endocrinology Products, Room 2623
DHL#1

Chi Wan Chen, Ph.D., Deputy Directory, Office of New Drug Quality
Assessment, Division of Metabolism and Endocrinology Products, Room 2626
(*cover letter*)
DHL#1



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-995

Merck & Co.
Attention: Patricia Tway
BLA-20 P.O. Box 4
West Point, PA 19486

Dear Dr. Tway:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sitagliptin phosphate tablets.

We refer to the meeting between representatives of your firm and the FDA on June 14, 2006. The purpose of the meeting was to discuss the questions and comments in the IR letter dated May 18, 2006.

The official minutes of the above meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1647.

Sincerely,

(See appended electronic signature page)

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 14, 2006
TIME: 3:00 pm- 4:00 pm
LOCATION: Food and Drug Administration, White Oak Room 1421
APPLICATION: NDA 21-995
DRUG NAME: Sitagliptin phosphate tablets
TYPE OF MEETING: Type C
MEETING CHAIR: Chi-wan Chen
MEETING RECORDER: Amy Bertha

JUL 14 2006

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Chi-wan Chen, Deputy Director
Christine Moore, Branch Chief, Manufacturing Science Branch
Stephen Moore, Pharm. Assessment Lead, Division of Pre-Marketing Assessment I
Vibhakar Shah, Chemist, Regulatory Science and Policy
Amy Bertha, Regulatory Health Project Manager

OFFICE OF TESING AND RESEARCH

Jack Spencer, Chemist

EXTERNAL CONSTITUENT ATTENDEES:

Paula Fricchione, Senior Regulatory Scientist
Patricia Tway, Vice President Regulatory and Analytical Science
Gert Thurau, Manager

BACKGROUND:

The NDA for sitagliptin phosphate tablets was accepted into the CMC pilot program on September 1, 2005, and was submitted to the FDA on December 16, 2005. The purpose of this meeting was to discuss the questions and discussion points outlined in the IR letter dated May 18, 2006.

THE MEETING:

Questions 8, 9, 11e of the May 18, 2006 IR letter were clarified and discussed. It was agreed by both parties that these minutes would not capture the details of the discussion. No further requests or recommendations were made outside of what was stated in the May 18, 2006 IR letter.

ACTION ITEMS:

Merck will send their official response to the IR letter in the form of an NDA amendment.

Minutes Preparer: *Bertha*

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: *Chi-wan Chen*

Chi-wan Chen
Deputy Director
Office of New Drug Quality Assessment

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this page is the manifestation of the electronic signature.**

/s/

Amy Bertha

7/18/2006 12:07:31 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-995

Merck & Co.
Attention: Patricia Tway
BLA-20 P.O. Box 4
West Point, PA 19486

Dear Dr. Tway:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sitagliptin phosphate tablets.

We refer to the teleconference between representatives of your firm and the FDA on May 30, 2006. The purpose of the teleconference was to discuss the questions and comments provided in the IR letter dated May 18, 2006.

The official minutes of the above teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1647.

Sincerely,

(See appended electronic signature page)

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

TELECONFERENCE DATE: May 30, 2006
TIME: 1:00 pm- 2:00 pm
APPLICATION: NDA 21-995
DRUG NAME: Sitagliptin phosphate tablets
TYPE OF MEETING: Type C
TELECONFERENCE CHAIR: Chi-wan Chen
TELECONFERENCE RECORDER: Amy Bertha

JUL 14 2006

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Chi-wan Chen, Deputy Director
Christine Moore, Branch Chief, Manufacturing Science Branch
Stephen Moore, Pharm. Assessment Lead, Division of Pre-Marketing Assessment I
Vibhakar Shah, Chemist, Regulatory Science and Policy
Amy Bertha, Regulatory Health Project Manager

OFFICE OF NEW DRUGS

Ilan Ivony, Clinical Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Paula Fricchione, Senior Regulatory Scientist
Patricia Tway, Vice President Regulatory and Analytical Science
John Curran, Director, RAS-CMC

BACKGROUND:

The NDA for sitagliptin phosphate tablets was accepted into the CMC pilot program on September 1, 2005, and was submitted to the FDA on December 16, 2005. The purpose of this meeting was to discuss the questions and comments provided in the IR letter dated May 18, 2006.

THE TELECONFERENCE:

Questions 5, 6 and 13 of the May 18, 2006 IR letter were clarified and discussed. It was agreed by both parties that these minutes would not capture the details of the discussion. No further requests or recommendations were made outside of what was stated in the May 18, 2006 IR letter.

ACTION ITEMS:

Merck will send their official response to the IR letter in the form of an NDA amendment.

Minutes Preparer: 
Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: 
Chi-wan Chen
Deputy Director
Office of New Drug Quality Assessment

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

/s/

Amy Bertha

7/18/2006 11:53:35 AM

Steven A. Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

July 7, 2006



Mary H. Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Amendment to a Pending Application

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. As indicated on the attached Form FDA 356h, this amendment provides for the submission of the pre-clinical report entitled, *MK-0431, Fourteen-Week Oral Toxicity Study in Monkeys*, [Ref. 4.2.3.2: TT061005], to the pending New Drug Application for JANUVIA™.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing 1 Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on 1 CD and is not more than 100MB/GB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

Mary H. Parks, M.D., Acting Director
NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Page 2

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

DHL #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products
DHL #1

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Steven A. Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

June 23, 2006



Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Response to FDA Request for Information

Reference is made to the New Drug Application cited above for JANUVIA™, submitted as an electronic archive on December 16, 2005. Reference is also made to the May 18, 2006 letter from the FDA to Merck which included a list of 15 questions regarding the Chemistry, Manufacturing, and Controls section of the New Drug Application referenced above. Reference is also made to the Response to FDA Request for Information on June 13, 2006 which included responses to questions 1, 2, 3, 6, 7, 10 and 11.

With this submission Merck is providing a second partial response to the questions from the FDA. This submission includes a response to questions 8 and 9.

We hope that responses provided in this submission have adequately addressed the Agency's comments. To the extent possible, please notify Merck of any issues that the Agency feels have not been adequately addressed. Responses to the remaining questions will follow. Once the 15 questions have been addressed successfully, the information in Module 3 will be updated.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, to Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

Enclosure: CD

DHL #1

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Manager (*cover letter*)
Division of Metabolism and Endocrinology Product, Room 3101
DHL#1

Amy Bertha, Regulatory Health Project Manager (*cover letter*)
Division of Metabolism and Endocrinology Product, Room 2623
DHL#1

Chi Wan Chen, Ph.D., Deputy Directory, Office of New Drug Quality
Assessment Division of Metabolism and Endocrinology Product, Room 2626
(*cover letter*)
DHL#1

Steven A Aurecchia, M.D
Director
Worldwide Regulatory Affairs

Merck & Co., Inc
P O Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

June 21, 2006



Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

**GENERAL CORRESPONDENCE
Update to SUR**

Reference is made to the New Drug Application cited above, submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. Reference is also made to the safety information included in the May 4, 2006 Safety Update Report [Sec.2.7.4].

With this submission, MRL is providing information for patient AN50727 who participated in Protocol 035 entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Glimepiride Alone or in Combination With Metformin".

Data for this patient was inadvertently omitted from Table 2.7.4:46, entitled, "Listing of Patients Who Died in the MK-0431 Phase II and Phase III Studies Reported During The Period of 19-Oct-2005 to 03-Mar-2006," of the May 4, 2006 submission. The information for this patient was reported to Merck on 14-Feb-2006 but was not in the database at the time the SUR and Sec. 2.7.4 were prepared. With this submission, MRL is providing the information for this patient.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director, Regulatory Affairs

DHL #1

Enclosure: CD

Desk Copy: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products
DHL #2

Steven A. Aurecchia, M.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steven_aurecchia@merck.com

June 13, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995 Januvia™ (Sitagliptin Phosphate) Tablets
Response to FDA Request For Information**

Reference is made to the New Drug Application cited above for Januvia™ submitted as an electronic archive on December 16, 2005. Reference is also made to the May 18, 2006 letter from the FDA to Merck which included a list of 15 questions regarding the Chemistry, Manufacturing, and Controls section of the New Drug Application referenced above.

With this submission Merck is providing a partial response to the questions from the FDA. This submission includes a response to questions 1, 2, 3, 6, 7, 10, and 11.

We hope that responses provided in this submission have adequately addressed the Agency's comments. To the extent possible, please notify Merck of any issues that the Agency feels have not been adequately addressed prior to the face to face meeting currently being scheduled by Amy Bertha. This will help ensure the meeting is productive. Responses to the remaining questions will follow. Once the 15 questions have been addressed successfully, the information in Module 3 will be updated.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

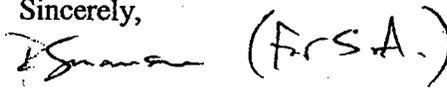
All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, to Robert E. Silverman (267-305-6712).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

Enclosure: CD

DHL #

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Manager (*cover letter*)
Amy Bertha, Regulatory Health Project Manager (*cover letter*)
Chi-wan Chen, Ph.D., Deputy Directory, Office of New Drug Quality Assessment
(*cover letter*)

filepath

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-995

Supplement # N/A

Efficacy Supplement Type SE- N/A

Trade Name: Januvia Tablets
Established Name: sitagliptin phosphate
Strengths: 25 mg, 50 mg, 100 mg

Applicant: Merck & Co., Inc.
Agent for Applicant: Steven Aurecchia, M.D.

Date of Application: December 16, 2005
Date of Receipt: December 16, 2005
Date clock started after UN: N/A
Date of Filing Meeting: February 6, 2006
Filing Date: February 14, 2006
Action Goal Date (optional): TBD

User Fee Goal Date: October 16, 2006

Indication(s) requested: as an adjunct to diet and exercise to improve glycemic control as monotherapy and in combination therapy with metformin or a PPAR- γ agonist (e.g. thiazolidinedione) when diet and exercise plus the single agent do not provide adequate glycemic control.

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.) 1
Other (orphan, OTC, etc.)

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 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

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

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

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:

- Patent information submitted on form FDA 3542a? YES NO
- 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"

- 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
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 65,495 and 70,934
- End-of-Phase 2 Meeting(s)? Date(s) June 9, 2004 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) July 26, 2005 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
- Has DOTCDP been notified of the OTC switch application? 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 NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 06, 2006

BACKGROUND:

NDA 21-995 for sitagliptin phosphate tablets was submitted for review on December 16, 2005. Sitagliptin phosphate is a dipeptidyl-peptidase IV (DP-IV) inhibitor for the use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy and in combination with metformin or a PPAR- γ agonist (e.g. thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

Phase 3 Clinical Program

Monotherapy

Protocol Number 021, *A Multicenter Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of MK-0431 Monotherapy in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*: There were three arms in this study: placebo, 100 mg once daily and 200 mg once daily. A total of 741 patients were randomized. The study duration was 104 weeks (24-weeks placebo controlled followed by 80-weeks single-blind.)

Protocol Number 023, *A Multicenter, Randomized, Double-Blind Study of MK-0431 in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*: There were three arms in this study: placebo, 100 mg once daily and 200 mg once daily. A total of 521 patients were randomized. The study duration was 18-weeks placebo controlled (Phase A), followed by 36-week active controlled, double-blind (Phase B).

Combination with Metformin

Protocol Number 020, *A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who have Inadequate Glycemic Control on Metformin Therapy*: There were two arms in this study: placebo and 100 mg once daily. A total of 701 patients were randomized. The study duration was 104-weeks (24-weeks placebo controlled followed by 80-weeks active-controlled.)

Combination with PPAR

Protocol Number 019, *A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Pioglitazone Therapy*: There were two treatment arms: placebo and 100 mg once daily. A total of 353 patients were randomized. The study duration was 24-weeks.

This new molecular entity is under standard review with a user fee goal date of October 16, 2006.

ATTENDEES: Mary Parks, Karen Mahoney, Ilan Irony, Todd Bourcier, Jeri ElHage, Jim Wei, Hae-Young Ahn, Chi-wan Chen, Amy Bertha, Christine Moore, Vibhakar Shah, Lina AlJuburi

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
Regulatory Project Management:
Other Consults:

Reviewer

Ilan Irony
Mary Parks
Lee-Ping Pian
Todd Bourcier
N/A
Stephen Moore, Christine Moore, Vibhakar Shah
N/A
Jim Wei
N/A
N/A
Andrea Slavin
Lina AlJuburi
Office of Drug Safety

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed? YES X NO
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- 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 X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

- Biopharm. inspection needed? YES NO X

PHARMACOLOGY N/A FILE X REFUSE TO FILE

- GLP inspection needed? YES NO X

CHEMISTRY FILE X REFUSE TO FILE

- Establishment(s) ready for inspection? YES X NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X 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.
- X Filing issues to be communicated by Day 74. List (optional): Study report from 3-month monkey oral toxicity

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. 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.
3. X Convey document filing issues/no filing issues to applicant by Day 74.

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

If "No," skip to question 3.

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

(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

(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, YES NO
ORP?

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

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").
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
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
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
10. Are there certifications for each of the patents listed for the listed drug(s)? YES 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):

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

Patent number(s):

- 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):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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 NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES 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 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):

- 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/

Lina Aljuburi
5/17/2006 02:27:49 PM
CSO

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steve_aurecchia@merck.com

May 10, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. Reference is also made to e-mail communications between Dr. Steven Aurecchia of MRL and Dr. Ilan Irony of FDA on April 17, 2006 and April 26, 2006.

As stated in the April 17th communication, there is an error in Tables 2.5:18 and 2.7.4:13 of the eCTD. Specifically, "Urinary Tract Infection" meets the pre-defined criteria for inclusion in these Tables and was inadvertently omitted. This term has been captured in the Januvia Safety Update Report (SUR). We will update Table 5 in our draft Januvia USPC under separate cover.

The April 26th communication was in response to a clarification requested by Dr. Irony regarding the temperature range for the MK-0431 100 mg group in the Pooled Phase III Population. Below is the range of body temperatures for the MK-0431 100 mg group, including and excluding (AN33165) in study P020V1 who had a baseline temperature recorded in the database as 36.1 deg. C and subsequent value of 96.2 deg C. This value was incorrectly recorded as Celsius instead of Fahrenheit and resulted in the upper value for the change from baseline for temperature being recorded as 60.1 deg C (i.e., baseline 36.1 - subsequent value 96.2).

**Summary Statistics for Change From Baseline for Body Temperature (deg. C) at Week 18/24
Pooled Phase III Population (P019, P020, P021, P023)
MK-0431 100 mg Exposed**

	Baseline		Week 18/24		Change From Baseline	
	Mean	Range	Mean	Range	Mean	Range
MK-0431 100 mg (including AN 33165)	36.5	34.4 to 37.7	36.5	34.1 to 96.2	0.06	-2.8 to 60.1
MK-0431 100 mg (excluding AN 33165)	36.5	34.4 to 37.7	36.5	34.1 to 38.6	-0.01	-2.8 to 1.9

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

DHL #1
Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steve_aurecchia@merck.com

May 4, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

Safety Update Report

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. Reference is also made to a February 23, 2006 telephone conversation between Dr. Lina AlJuburi and Dr. Steven Aurecchia, during which Dr. AlJuburi agreed to a brief delay in the receipt of the 120-day Safety Update Report, allowing for the inclusion of one-year sitagliptin clinical safety data from protocols 020 and 021.

With this submission we are providing an update to the safety information included in the December 16, 2005 original application [Sec. 2.7.4]. SAS transport files are included in support of this update, providing incremental data on the new safety information collected for protocols 010, 014, 020 and 021 since the frozen files for the original application. The electronic Case Report Forms (eCRFs) provided to support this updated safety information reflect data from inception, not just the incremental data because the eCRFs were not provided with the initial submission for the long term safety, although some of the eCRFs were included in the Clinical Study Reports (CSRs) for protocols 010, 014, 020, and 021.

Also included in this submission are the one-year clinical safety data memos for protocols 020 and 021. The SAS files included in this submission include data from the inception of the studies through one year of exposure, and could contain duplicate information to that included in the original application and the overall safety update included in this submission. Likewise, the eCRFs included in this submission could potentially overlap with those provided in the phase a Clinical Study Reports provided in the original application as the data provided is from the study start and the overall safety update included in this submission as the data is provided from the study start.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (267-305-6669) or, in my absence, Robert E. Silverman, M.D., Ph.D. (267-305-6710).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

DHL #1
Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Q:\Campbell\Januvia NDA 21-995\SUR.doc

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Tuesday, April 25, 2006 3:59 PM
To: 'Aurecchia, Steven A.'
CC: El Hage, Jeri D; Bourcier, Todd
Subject: RE: NDA 21-995 - Januvia (sitagliptin phosphate)

Hi, Steve

We prefer to review the study report for both compounds before discussing the similarity of the findings to other DPP-4 inhibitors. Any mechanistic data you have pertinent to lesion development would also be useful.

Therefore, your request for a teleconference is denied.

Feel free to contact me if you have additional questions.

Best wishes,
Lina

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)

-----Original Message-----

From: Aurecchia, Steven A. [mailto:steven_aurecchia@merck.com]
Sent: Tuesday, April 25, 2006 2:56 PM
To: Aljuburi, Lina
Subject: FW: NDA 21-995 - Januvia (sitagliptin phosphate)

> -----Original Message-----

> **From:** Aurecchia, Steven A.
> **Sent:** Tuesday, April 25, 2006 2:53 PM
> **To:** 'Jeri.Elhage@fda.hhs.gov'; 'Bourcier, Todd'
> **Cc:** 'lina.aljuburi@fda.hhs.gov'; 'Irony, Ilan'
> **Subject:** NDA 21-995 - Januvia (sitagliptin phosphate)

> Jeri, Todd -

> Good afternoon! Hope all is well.

> I want to update you on our MK-0431 monkey study (and an ongoing companion study with L-826) and ask if you would be available early next week for an informal teleconference with myself and Bob Silverman (MRL Regulatory) and George Lankas and Joe DeGeorge (MRL Safety Assessment) to discuss the questions below. We'll of course accommodate whatever your schedule(s) may require.

> As requested by the Division, MRL initiated a 14-week oral toxicity study in monkeys (TT#06-1005) in January 2006. Doses of MK-0431 (sitagliptin) for this study are 0, 10, 30, and 100 mg/kg/day. The doses were based on a single dose toxicokinetic study and are anticipated to give safety margins of approximately 5, 10, and 15-fold the AUC values relative to the 100 mg/day human therapeutic dose. The study has been completed. There were no signs of skin lesions in any of the treated monkeys on this study.
> The animals were carefully examined daily for evidence of skin lesions or changes in the hair coat.

>
> The above findings are in distinct contrast to those evident in a recently
> initiated 14-week oral toxicity study with _____, a
> _____ In
> this study doses of 0, 50, 150, and 450 mg/kg/day are being administered.
> This study is currently in Drug Week 7. Findings to date include distinct
> changes in the skin of animals in all drug-treated groups. These changes
> include red discoloration of the skin and swelling on the face, limbs,
> abdomen, and inguinal region, including the scrotum. These findings first
> appeared in the mid and high dose groups in Drug Week 3 and in the low
> dose group in Drug Week 5. Following the initial observations in the
> affected animals, the signs appear to have partially or completely
> reversed in most of the affected monkeys. In addition to the drug-induced
> skin findings, there have 3 animals (2 mid dose and 1 high dose)
> sacrificed due to morbidity. Postmortem changes found to date include
> paleness of the kidneys and tubular necrosis/degeneration.

>
> In your letter of November 1, 2005 and subsequent communications with MRL,
> you indicated that the dermal toxicity observed in the monkey was
> considered a _____

> _____ Are the findings described above with L-000000826
> consistent with the Division's observations thus far with DPP-4 inhibitors
> as a class? Additionally, subject to your review of the final reports for
> these two studies, are the contrasting findings with MK-431 sufficient to
> support a waiver of the anticipated class labeling with respect to
> sitagliptin phosphate (Januvia)?

>
> Thanks in advance,
> Steve

>
> Steven Aurecchia, MD
> Director, Regulatory Affairs
> Merck Research Laboratories
> P.O. Box 1000
> North Wales, PA 19454-1099
> tel: 267-305-6669
> fax: 267-305-6406
> e-mail: steven_aurecchia@merck.com
> admin. assistant: Ms. Sharon Stukowski
>
>

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (One Merck Drive, Whitehouse Station, New Jersey, USA 08889), and/or its affiliates (which may be known outside the United States as Merck Frosst, Merck Sharp & Dohme or MSD and in Japan, as Banyu) that may be confidential, proprietary copyrighted and/or legally privileged. It is intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

"EMF <fda.hhs.gov>" made the following annotations.

This message was sent by Merck across the Internet in encrypted format and was successfully decrypted, unless otherwise noted. Merck & Co., Inc.
=====

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 1000, UG2CD-48
North Wales PA 19454-1099
Tel 267 305 6669
Fax 267 305 6406
steve_aurecchia@merck.com

April 25, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Amundale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 16, 2005. Reference is also made to an e-mail request from Dr. Todd Bourcier of FDA to Dr. Steven Aurecchia dated March 6, 2006, in which Dr. Bourcier requested Historical Control Tables for both the rats and rabbits for external, coronal, visceral, skeletal and ossification findings.

With this submission, we are supplying the above-referenced information [Sec. 1.11.2].

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

DHL #1
Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,934

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA, 19486

Dear Dr. Aurecchia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0431A (sitagliptin phosphate plus metformin hydrochloride fixed dose combination) Tablet.

We also refer to the meeting between representatives of your firm and the FDA on March 6, 2006. The purpose of the meeting was to discuss the content of the proposed NDA for MK-0431A.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of PreNDA minutes from meeting held on March 6, 2006

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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April 5, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005. Reference is also made to telephone conversation on February 23, 2006 between Ms. Andrea Slavin from the Division of Scientific Investigations and Dr. Steven Aurecchia of MRL during which Ms. Slavin requested that unblinded HgbA1c values be provided to [REDACTED] investigational site for FDA audit purposes.

A sealed envelope containing the Phase A unblinded HbA1c results for patients randomized into the MK-0431 Phase III clinical studies has been sent to this investigational site with the following instructions:

This envelope is not to be opened by site personnel, as the protocols specify that Phase B of these studies will be conducted in a double-blind manner. These unblinded patient records are intended for presentation, in a sealed manner, to the FDA inspector upon request during his/her visit to the site.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1
Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Ms. Andrea Slavin, Consumer Safety Officer
CDER/OMP/DSI/GCPBI
Metro Park North 1 - RM1430
7520 Standish Place
Rockville, MD 20855

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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March 22, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a division of Merck & Co., Inc. as an electronic archive on December 16, 2005. Reference is also made to the telephone conversation between Dr. Ilan Irony of FDA and Dr. Steven Aurecchia on February 2, 2006. In this conversation Dr. Irony requested SAS datasets with patient line listings for the controlled portion of each pivotal Phase III clinical study displaying HgbA1c values over time prior to initiation of rescue therapy.

With this submission we are providing the above-referenced review aids.

We hope this response adequately addresses the Agency's comments and requests.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

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A list of reviewers from the Division of Metabolism and Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina Al-Juburi, Regulatory Project Manager, Division of Metabolism and Endocrinology Products.

We consider the filing of this submission to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, to Robert Silverman, M.D., PhD. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

Enclosure: CD

UPS # 1

Desk Copies: Dr. Lina AlJuburi, Regulatory Project Manager
Division of Metabolism and Endocrinology Products

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Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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March 13, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005 and to e-mail communications on March 1, 2006 between Dr. Todd Bourcier of FDA and Dr. Steven Aurecchia of MRL in which Dr. Bourcier requested that physical signs be submitted for the skin and fur of the dogs in the chronic (27-and 53-week) oral toxicity studies with sitagliptin.

With this submission, we are providing tables listing all signs related to the skin, pelage, and skin structures for the individual animals in these studies [Sec. 1.11.2 - TT#02-079-0 Sign Charts, Sec. 1.11.2 - TT#02-071-0 Sign Charts].

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs



UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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Email: steven_aurecchia@merck.com

March 3, 2006



Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005 and to a February 23, 2006 telephone conversation between Ms. Andrea Slavin of FDA and Dr. Steven Aurecchia of MRL, during which information was requested relevant to a planned audit of [REDACTED] as well as a planned sponsor audit. Reference is also made to a February 27, 2006 telephone conversation between Ms. Slavin and Dr. Aurecchia during which this information request was discussed and clarified.

With this submission, we are providing the following in response to Ms. Slavin's information request:

1) Three FDA 1572 forms for [REDACTED] for clinical study protocols 020, 021, and 023. The unblinded HgA_{1c} data for this site has been requested from our central laboratory and will be submitted separately.

2) With regard to clinical monitoring, this was performed in a blinded manner by individual investigators and MRL personnel for studies 020 and 021. For study 023, monitoring was performed in a blinded manner by individual investigators and both MRL and CRO personnel [REDACTED]. The study sites for which [REDACTED] had responsibility are listed below, with those sites listed with strikethrough not having screened any patients:

Site No.	Institution	PI Name
023-0001	International Clinical Research Network, Inc	Geroges Argoud

023-0004	Sioux Valley Clinic—Clinical Research Center	Verdayne Brandenburg
023-0005	Springfield Family Medicine	Donald Brideau, Jr
023-0007	Tucson Clinical Research, LLC	Howard Brown
023-0008	Professional Network Research	Dennis Buth
023-0009	Southern Clinical Research and Management, Inc.	Albert Carr
023-0011	The Endocrine Clinic	A. Jay Cohen
023-0014	Theodore G. Dunean MD and Associates	Theodore Dunean
023-0015	Deerbrook Medical Associates	Ira Fenton
023-0022	Professional Clinical Research, Inc at Great Lakes Family Care	William George
023-0021	Endocrine Research Associates	Raymond Grenfell Jr.
023-0024	South Arlington Primary Care Associates	Bruce Henry
023-0031	Diabetes Care and Information Center of New York	Daniel Lorber
023-0034	Atlanta Pharmaceutical Research Center, Inc.	Alan Miller
023-0032	Earle A. Chiles Research Institute	Frank McBarron
023-0039	Wells Institute for Health Awareness	Naynesh Patel
023-0041	St. Lukes Roosevelt Hospital Division of Endocrinology, Diabetes and Nutrition	Francis Pi-Sunyer
023-0043	Mercury Street Medical Group	John Pullman
023-0044	Clinical Research of South Florida	Jeffrey Rosen
023-0046	CSRA Partners in Health	Diane Smith
023-0047	Coastal Carolina Research Center	Cynthia Strout

023-0048	Genesis Research International	Raul Tamayo
023-0049	Endocrinology and Diabetes Consultants, PC	Paul Tung
023-0050	Clinical Trials Research Services, LLC	X. Helen Wang
023-0053	Clinical Research Limited	Frederick Whittier

3) The MRL clinical, clinical pharmacology and statistical personnel involved in the core clinical trials for the JANUVIA NDA are located at our Rahway facilities at 126 East Lincoln Avenue, Rahway, New Jersey. Study documentation, however, is archived primarily at our [REDACTED]. For purposes of scheduling and coordinating a sponsor site inspection in Blue Bell, please advise the FDA Philadelphia District Office to contact Ms. Mary Ann Tupy-Visich, Associate Director, Clinical Quality Assurance, directly at 484-344-2800.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

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A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 4

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D.
(484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Ms. Andrea Slavin, Consumer Safety Officer (2 copies)
CDER/OMP/DSI/GCPBI
Metro Park North 1 - RM1430
7520 Standish Place
Rockville, MD 20855

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Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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March 1, 2006



Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Amendment to a Pending Application**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005. As indicated on the attached Form FDA 356h, this amendment provides for changes in the Labeling of the pending New Drug Application for JANUVIA™. This submission contains draft physician sample packaging components in addition to those provided in the December 16, 2005 submission.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D.
(484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-995

2/27/06

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA, 19486

Dear Dr. Aurecchia:

Please refer to your December 16, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Januvia (sitagliptin phosphate) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 14, 2006, in accordance with 21 CFR 314.101(a).

As a reminder, we request the final study report for the 3-month oral toxicity study in monkeys to assess the potential for necrotic skin lesion toxicity associated with the administration of dipeptidyl peptidase-4 (DPP-4) inhibitors be submitted as an amendment to your NDA as soon as possible but no later than July 16, 2006, 3-months before the user fee goal date.

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.

We do not expect a response to this letter.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Project Management Staff
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/

Lina Aljuburi
2/27/2006 06:20:43 PM
Lina AlJuburi for Kati Johnson

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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February 17, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005 and to telephone and e-mail communications between Dr. Xiaoxiong Wei of FDA and Dr. Steven Aurecchia of MRL on February 6th, 7th, 8th, and 10th, 2006 regarding Dr. Wei's request for SAS data files for the population PK report [Sec. 5.3.3.5: R1]. Reference is also made to the February 13, 2006 teleconference between Dr. Wei and Dr. Lina AlJuburi of FDA and Dr. Aurecchia and Dr. Arthur Bergman of MRL, during which this request was clarified as to specific dataset and file format.

With this submission MRL provides the NONMEM control file for the final model in text format (named as dv900r2.ctl) and the final data file (named as final7d_PO20200.nmdat).

We hope this response adequately addresses the Agency's comments and requests.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

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Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

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February 16, 2006

Mary Parks, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Response to FDA Request for Information**

Reference is made to the New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005 and to the telephone call from Dr. Ilan Irony of FDA to Dr. Steven Aurecchia of MRL on February 2, 2006 in which Dr. Irony requested the unblinded treatment assignments for patients in Tables 2.5:19 and 2.7.4:44 of the NDA. These treatment assignments are provided in Table 1 below, which reflects all known deaths in the sitagliptin Clinical Development Program as of 18-Oct-2005, the cut-off date for all reports of serious adverse events included in the original NDA submission.

Table 1

Allocation Number / Protocol	Therapy
3882 / P010-20	MK-0431 100 mg q.d.
33240 / P020	MK-0431 100 mg q.d.
40030 / P028	MK-0431 50 mg q.d.
42185 / P024	Glipizide 5 mg q.d.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 2

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

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**45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

**NDA #21-995
Original Submission
Januvia (sitagliptin phosphate)
Merck Research Laboratories
Date Received: 16 Dec 2005**

NDA #: 21-995
Submission date: 16 December 2005
Drug: Januvia (sitagliptin phosphate; MK-0431)
Dosage form: Tablets 25, 50, 100mg
Indication: Type 2 Diabetes
IND#: 65,495

A complete Pharm/Tox development program, including pharmacology and pharmacokinetic studies, single and repeat dose toxicity, carcinogenicity, reprotoxicity and genotoxicity studies, has been carried out with sitagliptin. Study species included mice, rats, rabbits, and dogs. Phase 3 clinical trials evaluated doses of 100 and 200mg QD as monotherapy (18 and 24 months) and in combination with metformin or pioglitazone. The recommended human dose is 100 mg/day which produces a C_{max} of 950nM (trough, 100nM) and AUC_{0-24h} of 8.5 µg*h/mL. The 50mg and 25mg doses are recommended for patients with moderate and severe renal insufficiency, respectively. The NDA was submitted in electronic format and is well organized.

The 3 month monkey study required for all DPP4 inhibitors is ongoing.

It is suggested that the draft label conform to the Final Rule formatting for new drug labels.

Pharmacology/Toxicology supports the filing of NDA 21-995.

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		eCTD format Summary report Tabulated Summaries Study reports
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		eCTD format
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		eCTD
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission, communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotoxicity, reprotoxicity, chronic toxicity of adequate duration, carcinogenicity)	X		All necessary studies have been submitted. <ul style="list-style-type: none"> • In vivo metabolites, humans/tox species • 6 month rat, 12 month dog toxicology • Genotoxicity • 2 yr Carcinogenicity • Reprotoxicity: Segments I, II, III 3 month monkey study is ongoing.
Have electronic files of the carcinogenicity studies been submitted for statistical review?	X		

5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		<p>Yes, but conforms to the old template. It would be in Merck's interest to submit labeling in the new template now rather than later.</p> <p>Dose multiples provided for carci/mutagenesis and reprotox sections. Other Animal Tox not reported.</p> <p>Monkey Tox results not ready yet; no class effect statement provided.</p>
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file: N/A			

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

/s/

Todd Bourcier
2/8/2006 05:35:10 PM
PHARMACOLOGIST

Jeri El Hage
2/10/2006 10:43:16 AM
PHARMACOLOGIST

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

January 30, 2006

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Mary Parks, M.D., Acting Director
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Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



Dear Dr. Parks:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
Request for Type C Meeting

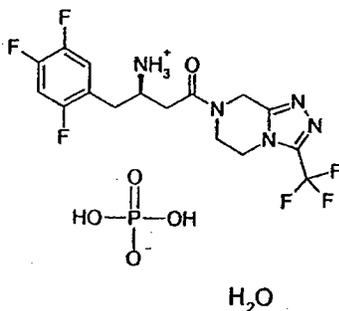
Reference is made to the subject New Drug Application (NDA) submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005. Reference is also made to IND 65,495 and to the November 1, 2005 meeting between CDER and MRL to discuss the quality by design aspects in the drug development of sitagliptin phosphate as it relates to the CMC pilot program. Further reference is made to the notification from Amy Bertha, Regulatory Project Manager, that a meeting has been scheduled for March 13, 2006, 2:00-3:30 PM to continue these discussions. Final reference is made to the Guidance for Industry: "Formal Meetings with Sponsors and Applicants for PDUFA Products," issued in February, 2000.

Per the Guidance document, the required information for this meeting follows:

Product name and NDA number: JANUVIA™ (sitagliptin phosphate; MK-0431), NDA 21-995.

Chemical name and structure:

7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate:



Proposed indication(s): As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus and to improve glycemic control in patients with type 2

diabetes mellitus in combination with metformin or a PPAR γ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

Type of meeting: Type C

Purpose and objective of the meeting: Discuss issues related to the CMC pilot program.

Proposed agenda, including estimated time and designated speaker(s): To Be Determined.

Draft list of questions: Not Applicable

Preliminary list of attendees representing MRL: To Be Determined

Agency staff requested by Merck to participate in the meeting: To Be Determined.

Approximate date on which the Background Package will be sent to the review division: Not Applicable.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Mary Parks, M.D., Acting Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 3

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Ms. Amy Bertha, Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/ CDER/ FDA

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Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

January 26, 2006

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Mary Parks, M.D., Acting Director
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5901-B Ammendale Road
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Dear Dr. Parks:

**NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets
General Correspondence**

Reference is made to the subject New Drug Application cited above submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on December 16, 2005 and to IND submission #233 (June 23, 2005) in which the proposed JANUVIA trademark was submitted for FDA review. Final reference is made to FDA correspondence dated December 20, 2005 in which the Division cites the Division of Medication Errors and Technical Support (DMETS) opinion that the trademark JANUVIA is unacceptable.

Merck recognizes the DMETS concern that the trademark it adopts should not be "misleading", as defined in 21 CFR 201.10(c)(5), by reason of "a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or established name of a different drug." However, Merck believes its use of the JANUVIA trademark is not likely to cause errors due to confusion with TARCEVA™.

When developing a global trademark Merck performs an exhaustive review of the proposed trademarks to insure the selection of a worldwide trademark that is appropriate for the product and avoids conflict and confusion with existing trademarks and nonproprietary names. Such a review was performed on JANUVIA and no prior confusingly similar trademarks or generic names were disclosed. Not only is a search made of the Federal Register, but State registration searches are made as well as extensive searches for "common law" uses (marks which are used but were never registered through the United States Patent and Trademark Office [USPTO] or State Registers) and domain names. TARCEVA™ was not identified as a potential for confusion by sight or sound within any of these searches. An application to register the trademark JANUVIA was filed in the USPTO on April 7, 2005. No prior trademarks were cited by the Examining Attorney during the examination of the application to register JANUVIA, nor were any oppositions filed by other companies or interested parties after the mark was published for opposition on November 15, 2005. Additionally, the trademark JANUVIA has now been registered in 23 countries.

Merck also submitted the mark for evaluation by _____, which conducted an in-depth Error Potential Analysis (EPA). The EPA process can be summarized as follows:

Methods and Material: The _____ recruited pharmacists to provide various inputs that became the primary data sources for an in-depth Error Potential Analysis. The pharmacists have sensitivity for the potential of proposed brand names to be confused with existing drug names.

Simulating activities that routinely occur in the prescribing, dispensing and administration chain generated the data for analysis. The inputs for the analysis were scripted prescriptions written by five different

physicians. This is an important component of the analytic process focused on "look alike" issues. The evaluators also assessed the potential of "sound alike" problems based on how they perceive the names will be pronounced.

Analytic Focus: The [redacted] has organized the data gathered from the pharmacists and carried out the analysis with the aim of discovering potential medication error dangers associated with suggested brand names. Also the potential concerns of the FDA and [redacted] are addressed. These concerns are as follows:

1. **Look-Alike Issues:** The likelihood for the new brand name being misread as another drug product in a written document, such as prescriptions or hospital orders.
2. **Sound-Alike Issues:** The likelihood for the new brand name being misheard as another drug product during an oral exchange, such as in doctor's offices, phoned prescriptions to pharmacies, phoned hospital orders, hospital physician rounds, or hospital hallway consultations.
3. **USAN/INN Issues:** The degree to which the new brand name contains letter strings (prefix, suffix, or infix) that have been reserved for generic names. This is primarily a USAN/INN concern. (Note: analysis of this item and items 4, 7, 8, 9, 10, 11, and 14 below, can only be carried out when information is available from the manufacturer).
4. **Therapeutic Indications:** The likelihood that the new brand name will suggest a therapeutic indication for which clinical data has not been supplied or approved.
5. **Prefix and Suffix Issues:** The likelihood that a prefix or suffix could be misunderstood or that its omission would cause a dosing error or dispensing error by health professionals.
6. **Use of Acronyms and Abbreviations as Part of the Name.** In addition to the FDA/[redacted]-related issues, the [redacted] factors in the following error causing variables, which will greatly influence the potential for look alike and sound alike names to result in errors.
7. **Availability of the Same Dosage Form** (e.g., both are tablets).
8. **Availability of the Same Strength or Concentration** (e.g., both 40 mg dosage forms).
9. **Same or Similar Dosing Direction** (e.g., both taken once daily).
10. **Dose Overlapping** (e.g., both doses are between 5 to 20 mg once daily).
11. **Same or Similar Clinical Indication(s).**
12. **Popularity of Established Product with a Similar Name.** Health professionals "see" what they know [confirmation bias]. If a similar product is widely prescribed, it offers a higher chance of being mistaken for the intended product.
13. **Similar Brand Names Already Marketed by This Firm.** Glaxo SmithKline's Zantac injection and Zofran injection sit next to each other on the shelf increasing the possibility of pharmacists selecting the wrong drug since the containers have the same corporate dress. This problem is unavoidable for companies with large product lines, but the problem

worsens depending on the degree of similarity and whether there are other similarities such as strength.

After the above analysis was completed, — concluded that JANUVIA may be considered for this product. In fact, — concluded that “The similarity between Januvia and Tarceva should NOT prove to be a safety issue.”

DMETS speculates that “Tarceva and Januvia may look similar when written. The beginning letters (T and J) may look similar when scripted and the remaining letters (-arceva vs. -anuvia) could look similar when scripted as well.” (emphasis added). Merck respectfully submits that this conjecture on the part of DMETS does not meet “the objective facts of record” standard that the FDA is required to meet in rejecting a trademark pursuant to 108 Congressional Record 21066 (September 27, 1962). Further, this review of the objective facts of record must find the proposed trademark to be demonstrably false or demonstrably misleading, another standard which is not met by speculation.

Merck submits that the true source of potential confusion is poor handwriting on the part of the physician and/or poor dispensing practices by the pharmacist. Scripting can therefore only be a valuable tool when the writing can be read. There is no foolproof test for illegible penmanship and Merck has no control over illegible writing. Poorly handwritten scripts should not be filled until further clarified.

DMETS further states that “... both products share an overlapping strength of 100 mg with a dosing frequency of once daily ~~_____~~ The latter is in part incorrect: the maximum recommended dose of JANUVIA is 100 mg once daily with or without food. Both products do share this overlapping 100 mg strength; however, the 100 mg TARCEVA™ dose pertains only to its pancreatic cancer indication and the TARCEVA™ dosing recommendation in pancreatic cancer is 100 mg taken at least one hour before or two hours after the ingestion of food in combination with gemcitabine. Additionally, each product has distinct tablet characteristics. TARCEVA™ (erlotinib) 100 mg tablets are white, round, have a biconvex face and straight sides, are film-coated, and are printed in gray with “T” and “100” on one side. JANUVIA 100 mg tablets are beige, round, and film-coated with “277” on one side. These distinct images minimize the potential for confusion and dispensing error. Merck also submits that the U.S. Patient Package Insert (PPI) developed for JANUVIA and submitted with the NDA provides clear and concise information to patients on the approved indications for JANUVIA, and mitigates the risk of unintended patient use.

Furthermore, the likelihood of a clinically meaningful clinical or laboratory adverse event occurring as a consequence of inadvertent dispensing of JANUVIA is quite low. JANUVIA was well-tolerated in placebo-controlled clinical trials as both monotherapy and combination therapy with metformin or pioglitazone. These studies included patients treated with JANUVIA 200 mg daily (two times the recommended daily dose of 100 mg). The overall incidence of side effects and of discontinuation of therapy due to clinical adverse experiences was similar to that reported with placebo. Importantly, the rates of hypoglycemia reported with JANUVIA were also similar to rates in patients receiving placebo. Likewise, in normal subjects in Phase I studies, JANUVIA did not produce hypoglycemia, consistent with the physiology of the incretin axis, and the mechanism of action of JANUVA. In clinical studies of JANUVIA in diabetics, adverse experiences reported in $\geq 3\%$ of patients and more commonly than in patients given placebo, irrespective of causality attribution, included upper respiratory tract infection, nasopharyngitis, headache, diarrhea, and arthralgia. Across clinical studies, small mean increases in white blood cell count and uric acid and a small mean decrease in alkaline phosphatase were observed. These changes in laboratory parameters are not considered clinically relevant. There were no clinical meaningful changes in vital signs or in ECG parameters (including QTc interval) with JANUVA treatment.

In summary, MRL respectfully maintains that its use of the JANUVIA trademark is not likely to cause errors due to confusion with TARCEVA™.

This application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document - Annex - Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolism & Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Lina AlJuburi, Regulatory Health Project Manager, Division of Metabolism & Endocrinology Products.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

UPS #1

Enclosure: CD

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products



NDA 21-995

NDA ACKNOWLEDGMENT

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA, 19486

1/12/06

Dear Dr. Aurecchia:

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: Januvia (sitagliptin phosphate) Tablets
Review Priority Classification: Standard
Date of Application: December 16, 2006
Date of Receipt: December 16, 2006
Our Reference Number: NDA 21-995

We acknowledge your request for a priority review designation. We have reviewed your request and concluded that this application does not qualify for priority review status. We refer to the CDER MaPP for Priority Review Policy (MaPP 6020.3, <http://www.fda.gov/cder/mapp.htm>) which, in addition to outlining the following criteria for an application to qualify for priority review, states that the drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease:

1. Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;
2. Elimination or substantial reduction of a treatment-limiting drug reaction;
3. Documented enhancement of patients compliance; or
4. Evidence of safety and effectiveness of a new subpopulation.

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 February 14, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 16, 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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. An assessment of your request will be made during the review of the application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
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/

Lina Aljuburi
1/12/2006 11:50:41 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,495

12/20/05

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Aurecchia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sitagliptin phosphate (MK-0431) tablets.

We also refer to your amendment dated June 23, 2005 (serial # 233), containing a request for a review of the JANUVIA trade name.

The Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety (ODS) has reviewed the proposed proprietary name, JANUVIA, and found it unacceptable. The following is excerpted from their review:

In reviewing the proprietary name, Januvia, the primary concerns were related to look-alike confusion with Tarceva. Tarceva and Januvia may look similar when written. Tarceva (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The recommended daily dose is [redacted] taken at least one hour before or two hours after the ingestion of food. Tarceva is available as 25 mg, 50 mg and 100 mg tablets. The beginning letters (T and J) may look similar when scripted and the remaining letters (-arceva vs. -anuvia) could look similar when scripted as well. Additionally, both products share an overlapping strength of 100 mg with a dosing frequency of once daily and daily recommended dosage of [redacted]. Thus, a prescription for Tarceva 200 mg daily could be misinterpreted as Januvia 200 mg daily and vice versa. If Tarceva is inadvertently dispensed instead of Januvia, the patient may experience rash, diarrhea, anorexia and fatigue. Moreover, Tarceva is cleared predominately by the liver, thus patients with hepatic impairment may experience hepatotoxicity (increases in liver transaminases). If Januvia is inadvertently dispensed instead of Tarceva patients may experience serious adverse events associated with hypoglycemia (confusion, abnormal behavior, visual disturbances, heart palpitations, anxiety, sweating, tremor, hunger, seizures and loss of consciousness). The strong look-alike similarities with overlapping strength (100 mg), [redacted] and route of administration compounds the likelihood for confusion between the two drugs which may result in medication errors.

As you prepare to respond to these comments, if you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-796-1168.

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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this page is the manifestation of the electronic signature.**

/s/

David Orloff

12/20/2005 05:29:30 PM

Steven A. Aurecchia, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 4662
215 652 5000
Fax 484 344 2516
Email: steven_aurecchia@merck.com

December 16, 2005

David Orloff, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-12666



Dear Dr. Orloff:

NDA 21-995: JANUVIA™ (Sitagliptin Phosphate) Tablets

ORIGINAL NEW DRUG APPLICATION

User Fee ID No. PD3006260

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., submits a New Drug Application (NDA) for JANUVIA™ (sitagliptin phosphate) Tablets.

JANUVIA™ (sitagliptin phosphate; MK-0431) is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme. DPP-4 inhibitors are a class of agents that act as incretin enhancers, which improve glycemic control in patients with type 2 diabetes mellitus (T2DM) by enhancing an endogenous system involved in the physiologic regulation of glucose homeostasis.

MRL and FDA personnel have met on two occasions to discuss the development program for JANUVIA™. An End-of-Phase II meeting was held on June 9, 2004 to discuss various issues pertaining to the JANUVIA™ program, particularly Phase III study designs, endpoints, and the clinical safety program. A Pre-NDA meeting was also held on July 26, 2005 between MRL and FDA representatives to discuss the format and content of the forthcoming NDA. The understandings and agreements reached at these meetings, which are summarized in Section 2.5.1 of this application, have been incorporated into the program.

Data from the clinical studies included in this application, which included over 2300 patients at study centers in the United States and throughout the world, support the clinical safety and antihyperglycemic efficacy of JANUVIA™ in patients ages 18 and older with T2DM. Specifically, MRL proposes in this NDA that JANUVIA™ be indicated as an adjunct to diet and exercise to improve glycemic control as monotherapy and in combination therapy with metformin or a PPAR-γ agonist (e.g. thiazolidinedione) when diet and exercise plus the single agent do not provide adequate glycemic control. As discussed at the above-referenced meetings, MRL believes that until a safety database in adults has been developed that is adequate to

support pediatric trials, studies in children should not be undertaken. MRL therefore requests herewith a deferral of the pediatric data requirement for these indications.

Sitagliptin differs in both chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists, alpha-glucosidase inhibitors, and amylin analogues. JANUVIA™ represents the first member of a novel class of oral antihyperglycemic agents. In clinical studies, JANUVIA™ has been well tolerated, with an overall incidence of hypoglycemia similar to placebo; it has provided substantial glucose-lowering efficacy; and treatment with JANUVIA™ has significantly improved pancreatic beta-cell function, as assessed by several markers. As such, MRL would welcome a priority (1P) review designation.

Per the Agency's Information Request dated November 1, 2005; the telephone conversation between Dr. Steven Aurecchia of MRL and Dr. Jeri El-Hage of FDA on November 2, 2005; and the e-mail communication from Dr. Lina Aljuburi of FDA to Dr. Steven Aurecchia dated November 17, 2005, a 14-week oral toxicity study in monkeys is being undertaken with sitagliptin (MK-0431) to assess the potential for dermal toxicity. These data will be submitted to this NDA as soon as available. This submission may also include an amendment to the proposed USPC.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic Format – Content of Labeling*, the proposed labeling is provided in SPL format. The SPL-formatted content of labeling was prepared in accordance with the *SPL Implementation Guide for FDA Content of Labeling Submissions, Version 2a/Revision 1, October, 2005*.

The Microsoft WORD version of the proposed labeling text is supplied as PROPOSED.DOC within Section 1.14.1.3 Draft labeling text on the CD provided.

This original application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing two DVDs which contain the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on two DVDs and is not more than 6.5 GB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Metabolic and Endocrinology Products who should be provided access to this electronic submission on their desktops may be obtained from

David Orloff, M.D., Director
NDA 21-995: JAUNVIA™ (Sitagliptin Phosphate) Tablets
Page 3

Dr. Lina AlJuburi, Regulatory Project Manager, Division of Metabolic and Endocrinology Products.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorization in the Food and Drug Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), a check (Check No. C08674118), in the amount of \$767,400.00, was sent to the Mellon Client Services Center, Pittsburgh, PA on November 28, 2005. The User Fee I.D. number is PD3006260.

We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Steven A. Aurecchia, M.D. (484-344-4662) or, in my absence, Robert E. Silverman, M.D., Ph.D. (484-344-2944).

Sincerely,



Steven A. Aurecchia, M.D.
Director,
Regulatory Affairs

Enclosure: 2 DVDs

Desk Copies: Dr. Lina AlJuburi, Regulatory Health Project Coordinator
Division of Metabolism & Endocrinology Products

Patent Information (2 copies)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Amendale Road
Beltsville, MD 20705-1266

Maryann Holovac (cover letter and patent)
Orange Book Staff
Office of Generic Drugs
HFD-610, Room 134
7500 Standish Place
Rockville, MD 20855-2773

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>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>MERCK AND CO INC Michelle Kloss, Ph.D. DIVISION OF MERCK AND CO INC SUMNEYTOWN PIKE BLA 20 P O BOX 4 WEST POINT PA 19486-0004 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>21995</p>
<p>2. TELEPHONE NUMBER</p> <p>484-344-2905</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>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:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>JANUVIA (sitagliptin phosphate)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006260</p>
---	---

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

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

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>Michelle W. Kloss</i></p>	<p>TITLE</p> <p><i>Executive Director, Regulatory Affairs</i></p>	<p>DATE</p> <p><i>November 28, 2005</i></p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$767,400.00

Form FDA 3397 (12/03)

(F1BE PRMT CLOSE G) (Print Cover sheet)

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
White Oak Building 22; Mail Stop 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 29, 2005
IND# 65,495
NAME OF DRUG: **Januvia™** (Sitagliptin phosphate tablets)
100 mg
IND HOLDER: Merck Research Laboratories

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510) for an assessment of the proprietary name Januvia in regard to potential name confusion with other proprietary and/or established drug names. Container labels, carton and insert labeling were not provided for review and comment at this time.

PRODUCT INFORMATION

Januvia is a dipeptidyl-peptidase IV (DP-IV) inhibitor under investigation to be used as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. The proposed starting dose for monotherapy is 200 mg once daily with or without food. It is also under investigation to improve glycemic control in combination with metformin when diet, exercise, plus the single agent do not provide adequate glycemic control. The proposed dose of Januvia in combination with metformin is 100 mg daily.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Januvia to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1>

A. EXPERT PANEL DISCUSSION (EPD)

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

1. DDMAC finds the proprietary name, Januvia™, acceptable from a promotional perspective.
2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Januvia. These products with the available dosage forms and usual dosage are listed in Table 1 (see below).

Product Name	Established name, Dosage Form(s), Strength(s)	Usual adult dose*	Other**
Januvia	Sitagliptin phosphate Tablet: 100 mg per information submitted to date	_____ (monotherapy) 100 mg once daily (combination therapy with metformin HCl) Januvia is given without regard to food	N/A
Enjuvia	Estrogens, Conjugated Synthetic B Tablets: 0.3 mg, 0.45 mg, 0.625 mg, 1.25 mg	Adults: Tablets are taken orally, once daily. Patients should start with the lowest approved dose of 0.3 mg daily. Subsequent dosage adjustment may be made based upon the individual patient response.	SA
Jantoven	Warfarin sodium Tablets: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg	Adults: Initially, 5 mg PO once daily, with dosage adjustments made according to INR results. The maintenance dosage of warfarin should be based on INR and is usually 2 mg -10 mg PO once daily.	LA
Tarceva	Erlotinib Tablets: 25 mg, 100 mg, 150 mg	Adults: The recommended daily dose is 150 mg taken at least one before or two hours after ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

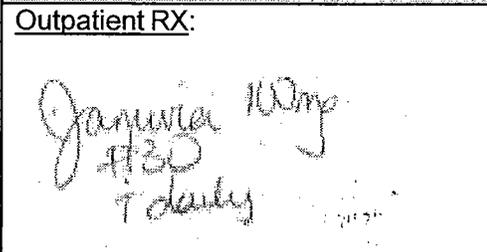
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists that operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Januvia were captured by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Januvia with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Januvia (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	"Januvia 100 mg 1 tablet daily, dispense #30"
<u>Inpatient RX:</u> 	

2. Results:

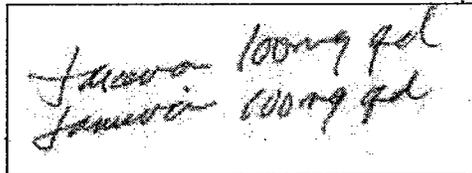
None of the interpretations of the proposed name overlap, sound similar or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Januvia, the primary concerns raised were related to look-alike and/or sound-alike confusion with Enjuvia, Jantoven and Tarceva.

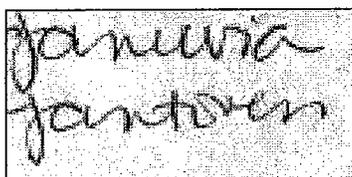
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name Januvia could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the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

1. Tarceva and Januvia may look similar when written. Tarceva (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The recommended daily dose is 200 mg taken at least one hour before or two hours after the ingestion of food. Tarceva is available as 25 mg, 50 mg and 100 mg tablets. The beginning letters (T and J) may look similar when scripted and the remaining letters (-arceva vs. -anuvia) could look similar when scripted as well (see below). Additionally, both products share an overlapping strength of 100 mg, dosing frequency of once daily and daily recommended dosage. Thus, a prescription for Tarceva 200 mg daily could be misinterpreted as Januvia 200 mg daily and vice versa. If Tarceva is inadvertently dispensed instead of Januvia, the patient may experience rash, diarrhea, anorexia and fatigue. Moreover, Tarceva is cleared predominately by the liver, thus patients with hepatic impairment may experience hepatotoxicity (increases in liver transaminases). If Januvia is inadvertently dispensed instead of Tarceva, patients may experience serious adverse events associated with hypoglycemia (confusion, abnormal behavior, visual disturbances, heart palpitations, anxiety, sweating, tremor, hunger, seizures and loss of consciousness). The strong look-alike similarities with overlapping strength (100 mg), and route of administration compounds the likelihood for confusion between the two drugs which may result in medication errors.



2. Enjuvia was identified to have a sound-alike similarity with Januvia. Enjuvia is a synthetic conjugated estrogen, B indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause. It is available as 0.3 mg, 0.45 mg, 0.625 mg, and 1.25 mg tablets. The phonetic similarity of this name pair is attributed to the fact that both names end with the same suffix ("-uvia"). Additionally, both names have four syllables which contribute to the rhyming characteristics between the name pair. However, the beginning portions of the names are phonetically different (ENH- vs. JAN-) which will help differentiate the two names. Both drugs share an overlapping dosing schedule (once daily). However, they do not share similar strengths (0.3 mg, 0.45 mg, 0.625 mg, and 1.25 mg vs. 100 mg) which may help to differentiate between a prescription called in for Enjuvia and Januvia. The phonetic differences along with the differences in strengths (multiple strengths of Enjuvia and the single strength of Januvia) minimize the potential for errors to occur between the two products.
3. Januvia and Jantoven were identified as having look-alike potential when scripted. Jantoven (Warfarin Sodium Tablets, USP) is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism; for the

prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; and to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction. Jantoven is available as 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg tablets. Januvia and Jantoven have similar look-alike characteristics where each name shares an identical prefix ("Jan-") and have similar looking suffixes ("-ven" vs. "-via") when scripted. However, Jantoven has an upstroke at the beginning of the second syllable with the letter "t", which may help to distinguish the names when scripted. Both products have an overlapping dosing frequency of once daily. However, Jantoven is also available in multiple strengths (1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg) whereas Januvia is only available in one strength (100 mg). Due to the multiple strengths of Jantoven, strength will be indicated on an order and the specific dosing for Januvia (100 mg) on a prescription will help to differentiate the two names. Despite some orthographic similarities between the two names, the differences in the strengths will help minimize potential confusion between Jantoven and Januvia.

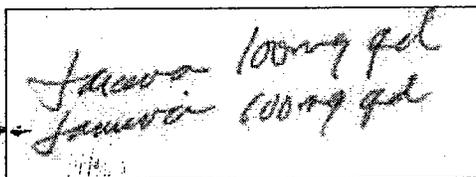


III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name, Januvia. In reviewing the proprietary name, Januvia, the primary concerns were related to look-alike confusion with Tarceva.

Tarceva and Januvia may look similar when written. Tarceva (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The recommended daily dose is 200 mg taken at least one hour before or two hours after the ingestion of food. Tarceva is available as 25 mg, 50 mg and 100 mg tablets. The beginning letters (T and J) may look similar when scripted and the remaining letters (-arceva vs. -anuvia) could look similar when scripted as well (see below). Additionally, both products share an overlapping strength of 100 mg, dosing

Thus, a prescription for Tarceva 200 mg daily could be misinterpreted as Januvia 200 mg daily and vice versa. If Tarceva is inadvertently dispensed instead of Januvia, the patient may experience rash, diarrhea, anorexia and fatigue. Moreover, Tarceva is cleared predominately by the liver, thus patients with hepatic impairment may experience hepatotoxicity (increases in liver transaminases). If Januvia is inadvertently dispensed instead of Tarceva, patients may experience serious adverse events associated with hypoglycemia (confusion, abnormal behavior, visual disturbances, heart palpitations, anxiety, sweating, tremor, hunger, seizures and loss of consciousness). The strong look-alike similarities with overlapping strength (100 mg), dosing frequency and route of administration compounds the likelihood for confusion between the two drugs which may result in medication errors.



IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name, Januvia.
- B. Container labels, carton and insert labeling were not submitted for review and comment at this time. Please forward the container labels, carton and insert labeling to DMETS when they become available.
- C. DDMAC finds the proprietary name, Januvia™, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Tselaine Jones Smith, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Y. Kim-Jung, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results (Januvia)

Inpatient	Outpatient	Voice
Genuvia	Januvia	Jamivia
Ginuvia	Januvia	Jamivia
Genevia	Januria	Jamivier
Genovia	Januvia	Jamivia (Jamivier?)
Genuvia	Januvia	Januvia
Genuvia	Januvia	Januvia
Genuvia	Januvia	Januira
Genuvia	Januria	Januvia
Januvia	Lanuvia	Janrvia
Genovia	Januvia	Jamivia
Genuvia	Lanuvia	Januvia
Genuvia	Januvia	Januvia
Chinovea	Januvia	Jamivia
Genuvia	Januvia	Januria (or Januvia? or Jamivia?)
		Januria
		Janrvia ? Jamivia? Januvia? Januria

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

/s/

Tselaine Jones-Smith
11/30/2005 11:24:20 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
11/30/2005 11:44:00 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/30/2005 02:04:39 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/30/2005 03:18:41 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,495

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BL A-20
West Point, PA 19486

Dear Dr. Aurecchia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0431 (L-000224715) Tablets.

We also refer to the PreNDA meeting between representatives of your firm and the FDA on July 26, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from PreNDA meeting held on July 26, 2005

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 26, 2005
TIME: 2:00 to 3:00 pm
LOCATION: Parklawn Building, *Potomac Room*
APPLICATION: IND 65,495
DRUG NAME: Sitagliptin Phosphate Tablets (MK-0431)
TYPE OF MEETING: Type B; PreNDA

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolic & Endocrine Drug Products:

David Orloff, M.D.	Director
Dragos Roman, M.D.	Medical Officer
Jeri El Hage, Ph.D.	Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics:

Sang Chung, Ph.D. Clinical Pharmacology and Biopharmaceutics Reviewer

Office of Biometrics:

J. Todd Sahlroot, Ph.D.	Biometrics Team Leader
Joy Mele, Ph.D.	Biometrics Reviewer

Office of Information Management

Zei-Pao Huang Regulatory Information Specialist

EXTERNAL CONSTITUENT ATTENDEES:

Merck & Co., Inc.:

Robert Silverman, M.D., Ph.D.	Senior Director, Regulatory Affairs
Steven Aurecchia, M.D.	Director, Regulatory Affairs
Peter Stein, M.D.	Director, Clinical Research
Debora Williams-Herman	Director, Clinical Research
Daniel Bloomfield, M.D.	Director, Clinical Research
Keith Kaufman, M.D.	Executive Director, Clinical Research
Gary Herman, M.D.	Director, Clinical Pharmacology
John Wagner, M.D., Ph.D.	Senior Director, Clinical Pharmacology
Arthur Bergman, Ph.D.	Research Fellow, Clinical Drug Metabolism
Matilde Sanchez, Ph.D.	Associate Director, Clinical Biostatistics
Mei Wu, M.S.	Senior Biometrician, Biostatistics
Jana Laidlaw, M.S.	Senior Regulatory Coordinator, Regulatory Coordination

BACKGROUND:

IND 65,495 for sitagliptin phosphate tablets was submitted on August 9, 2002. Sitagliptin phosphate is a dipeptidyl-peptidase IV (DP-IV) inhibitor under investigation as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy and in combination with metformin or a PPAR- γ agonist (e.g. thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control.

Phase 3 Clinical Program

Monotherapy

Protocol Number 021, *A Multicenter Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of MK-0431 Monotherapy in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*: There were three arms in this study: placebo, 100 mg once daily and 200 mg once daily. A total of 741 patients were randomized. The study duration was 104 weeks (24-weeks placebo controlled followed by 80-weeks single-blind.)

Protocol Number 023, *A Multicenter, Randomized, Double-Blind Study of MK-0431 in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*: There were three arms in this study: placebo, 100 mg once daily and 200 mg once daily. A total of 521 patients were randomized. The study duration was 18-weeks placebo controlled (Phase A), followed by 36-week active controlled, double-blind (Phase B).

Combination with Metformin

Protocol Number 020, *A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who have Inadequate Glycemic Control on Metformin Therapy*: There were two arms in this study: placebo and 100 mg once daily. A total of 701 patients were randomized. The study duration was 104-weeks (24-weeks placebo controlled followed by 80-weeks active-controlled.)

Combination with PPAR

Protocol Number 019, *A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Pioglitazone Therapy*: There were two treatment arms: placebo and 100 mg once daily. A total of 353 patients were randomized. The study duration was 24-weeks.

The sponsor requested this Type B PreNDA meeting on May 19, 2005, and the background package was submitted on June 27, 2005.

MEETING OBJECTIVES:

To discuss the available data and plans to address any potential issues to support an NDA

DISCUSSION POINTS:

The sponsor requested responses to the following questions. The questions are repeated below and the responses are bolded.

1. MRL believes that the chemistry, manufacturing and control (CMC) data together with the nonclinical, clinical pharmacology, and clinical studies listed and described in tabular form in Section 3 are sufficient to support an NDA filing and registration of MK-0431 for the indications and dosage/administration proposed in the MK-0431 prototype labeling provided in this background package. Does the Agency concur?

Since CMC information was not included in the background package, the Division cannot comment at this time. The nonclinical, clinical pharmacology, and clinical studies listed in your background package appear to be sufficient for NDA filing with a request for additional information. The Division refers to the minutes from the End-of-Phase 2 meeting held on June 9, 2004. At that meeting the following statement was made,

“Since MK-0431 has a chiral center, chiral inversion needs to be studied. The sponsor is asked to submit preclinical findings if the results have not been submitted to the Agency. A stereospecific human pharmacokinetic study might be needed depending on the preclinical findings.

The issue of chiral inversion of MK-0431 to S form was not addressed in the background package. In a telephone conversation between Fred Alavi, of the Division, and the sponsor, the Division was informed that the potential chiral inversion after a 200 mg dose in humans was less than 0.06% in blood and specific non-clinical studies were deemed unnecessary.

Note that NDA filing determination will be made after the application is submitted.

2. Preliminary results of a thorough QT study (Protocol 032) are described in Section 4, Attachment 1. This study utilized two doses of MK-0431 (100- and 800-mg), placebo and a positive control (moxifloxacin); the high dose of MK-0431 that was used provided exposures which are approximately 8-fold higher than the anticipated clinical dose of 100-mg. This section also summarizes preliminary ECG data with QTc assessments from diabetic patients in MK-0431 Protocol #005 and describes the comprehensive QTc analysis of ECG data across the Phase I to Phase III MK-0431 clinical program that will be provided with the NDA filing. MRL believes that this ECG database is sufficient to support the filing and registration of the 100 mg and 200 mg clinical doses of MK-0431. Does the Agency concur?

Yes, the Division concurs.

3. Section 4 provides an overview of the clinical data and key analyses to be provided with the NDA in support of the efficacy and safety of MK-0431. The referenced statistical data analysis plan (DAP) for the pooled analyses for efficacy and safety and sample tables are included in Section 7.d.
 - a. Does the Agency concur with the proposed efficacy analyses of the pooled study results for the Phase III monotherapy studies (Protocols #021 and #023) with respect to time-points, glycemic efficacy-related endpoints, and subgroups?

Pooling is acceptable for subgroup analyses but not for dose response assessments. Statistically significant dose response is not required for approvability. Dose response is best evaluated by looking at the individual studies which will provide unbiased estimates of treatment effects at each dose.

- b. Does the Agency concur with the proposed durability analysis of the MK-0431 treatment effect on HbA_{1c} from the MK-0431 Phase II extension study data (Protocols #010 and #014)?

The primary analysis is the change of HbA_{1c} from baseline between treatment groups. The proposed durability analysis (HbA_{1c} change from baseline at one-year) is considered a descriptive analysis.

- c. Does the Agency concur with the patient populations and subgroups proposed for the MK-0431 integrated analysis of safety?

The proposed patient populations are acceptable.

- d. Does the Agency concur with the format of the sample tables provided?

Section 10.1 of the study report should contain a patient disposition table showing the number (%) of patients on study at screening and Weeks -2, 0, 6, 12, 18 and 24. Include a table of reasons for discontinuation – it is not clear to the Division if that information is included in Figure 10-1. The appendix should show a summary table showing the reason for dropout by discontinuation week.

- e. Does the Agency have any further comments on the DAP for the integrated analyses for efficacy and safety?

Add to the safety summary an analysis of adverse events that can be theoretically anticipated on the basis of the mechanism of action of DPP-IV inhibition.

4. A prototype CSR for the MK-0431 NDA is provided in Section 5. Does the Agency concur with the format of this prototype CSR?

In section 10.5, please include a link to a table in the appendix showing a breakdown of the race category OTHER. Also refer to the response to question 3d.

5. Section 6 summarizes MRL's plans for submission of the MK-0431 eCTD. Does the Agency concur with these plans?

The sponsor's proposal in section 6 appears to be acceptable for an eCTD submission. If this is the sponsor's first time submitting an eCTD to the Agency, please contact Kenneth Edmunds, in the Office of Information Management, at (301) 827-7706. A template may be required.

6. Note: there is no Question 6 in the meeting package.

7. Consistent with the Agency's prior concurrence conveyed at MRL's End of Phase 2 meeting with FDA on June 9, 2004, MRL currently has no clinical studies ongoing in the pediatric population and believes that with the exception of short-term studies, e.g., pharmacokinetic (PK) studies, pediatric trials should not be undertaken until an appropriate safety database has been developed in adults. MRL therefore plans to include a request for a deferral of the requirement for pediatric studies in the NDA submission. Does the Agency continue to concur?

The Division agrees that pediatric studies should not be initiated until the safety profile of MK-0431 is characterized in adults. Therefore, the sponsor's request for a deferral of pediatric studies will be granted.

Additional Comments

- A. The sponsor has not conducted a drug-drug interaction study of MK-0431 with pioglitazone. A drug-drug interaction study was done with rosiglitazone. The sponsor will submit their rationale for the assumption that the two drugs (rosiglitazone and pioglitazone) are interchangeable for the purpose of drug interaction with MK-0431. The Division agrees to review the available information without requiring a pioglitazone pharmacokinetic study at this time. Additional comment is deferred until the data and rationale have been submitted and reviewed.
- B. The Division recommends that the sponsor evaluates the drug interaction potential on renal secretion because:
- about 80% of MK-0431 was excreted into urine,
 - MK-0431 exposure was significantly increased in renal impairment patients, and
 - there was significant net renal secretion.
- The sponsor agrees to evaluate the interaction potential using an *in vitro* study.
- C. The information for the column headings in the SAS datasets should be labeled in an easy-to-understand, user-friendly way that will allow for an easy transition to the clinical information described in the NDA. The Division suggests adding a folder that describes such data in detail or clarifies what the data actually represents (often times descriptions require more than one word or sentence in order to be clear.) Please refer to the guidance document entitled, *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs*, which can be found at <http://www.fda.gov/cder/guidance/2353fnl.pdf>.
- D. The sponsor agrees to specify which version of Meddra will be used in the NDA safety data presentation and will clarify how the specific adverse events are counted in various system groups (e.g. once, more than once, etc).
- E. The Division requests inclusion of the following when presenting the laboratory data: mean values at various time points (and changes from baseline for each specific time point); out of range values; extreme out of range values (e.g. $\geq 2X$ ULN and/or $\geq 3X$ ULN, etc. for LFTs) with the specific numerical values and explanations, if appropriate)). Similar analyses should be included for ECGs and vital signs.

COMMENTS FROM THE OFFICE OF DRUG SAFETY (ODS) *not discussed at the meeting:*

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- If the NDA includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

RiskMAPs

2.5.5 Overview of Safety with appropriate cross references to section
2.7.4 Summary of Clinical Safety
and any other relevant sections of the Common Technical Document for the NDA/BLA application.

Pharmacovigilance plans

2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4
Other Clinical Study Reports or other sections as appropriate
(e.g., module 4 if the study is a nonclinical study).

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA.

ACTION ITEMS:

The sponsor plans to submit the NDA for sitagliptin phosphate (MK-0431) in December 2005.

Meeting Recorder: Lina AlJuburi
Chair Concurrence: David Orloff

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/s/

Lina Aljuburi
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,495

Merck Research Laboratories
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Aurecchia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for L-000224715 Tablets.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on June 9, 2004. The purpose of the meeting was to discuss issues pertaining to the L-000224715 (MK-0431) development program.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from the End-of-Phase 2 meeting held on June 9, 2004

Executive CAC

Date of Meeting: May 27, 2003

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Abby Jacobs, Ph.D., HFD-540, Alternate Member
David Jacobson-Kram, Ph.D., HFD-024, Alternate Member
John Leighton, Ph.D., HFD-150, Alternate Member
Jeri El Hage, Ph.D., Team Leader
Fred Alavi, Ph.D., Presenting Reviewer

Author of Draft: Fred Alavi

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application'.

IND # 65,495
Drug Name: L-000224715
Sponsor: Merck

Background:

On April 21, 03, the sponsor submitted the results of a 14-week dose ranging study in rats (0, 500, 1000, 1500, and 2000 mg/kg/day, oral gavage) and a 5-week toxicokinetic study in mice (0, 250, 500, 1000 and 2000 mg/kg/day, oral gavage) to support dose selections for the respective 2-year carcinogenicity studies. Dose selection in rats was based on MTD. In mice, dose selection was based on 25-fold AUC exposure relative to maximum recommended human therapeutic dose.

In the rat dose-ranging study, food intake was restricted by approximately 25% (female:16 g of food/day, males:22 g/day). Although, the food restriction was not mentioned in the 2-year rat bioassay protocol, use of dietary restriction in the rat protocol was confirmed by the sponsor.

_____ will be suspended in 0.5 % methylcellulose in acidified deionized water and given by oral gavage (5 ml/kg, rats, 10 ml/kg, in mice). Both control groups will receive the vehicle by oral gavage. Rats will be housed individually and mice will be housed in pairs. All the animals will be implanted with a microchip for identification. At the end of the studies, all animals will be necropsied and histopathology evaluation of all animals will be conducted.

Rat Carcinogenicity Study Protocol and Dose Selection:

- Food restricted male and female rats: 0, 0, 50, 150 and 500 mg/kg/day by oral gavage

Mouse Carcinogenicity Study Protocol and Dose Selection:

- Male mice: 0, 0, 100, 250, 500 and 1000 mg/kg/day
- Female mice: 0, 0, 50, 150, 450 and 750 mg/kg/day

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee noted that the use of dietary restriction should be clearly identified as such in the protocol.
- The Committee concurred with the proposed doses of 0, 0, 50, 150, 500 mg/kg/day in dietary restricted rats based on the dental effects.

Mouse:

- The Committee could not give concurrence due to insufficient information. Five-week toxicokinetic study evaluation is too short to establish tolerated doses for chronic study. In addition, there were no toxicological data and the cause of deaths in mice was not identified. The Committee notes that while there isn't a basis for concurrence, the sponsor can proceed without eCAC concurrence. Should the sponsor decide to proceed without eCAC concurrence, the sponsor takes a chance that the eCAC may decide when evaluating the results of the study that the dose selection was not acceptable.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\

/Division File, HFD 510

/JEIHage, Team leader, HFD-510

/FAlavi, HFD-510

/JWebber, CSO/PM, HFD-510

/ASeifried, HFD-024

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/s/

Joe Contrera
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