

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-044

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

Application Information

NDA # NDA # 22-044	BLA STN# NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: Janumet Established Name: sitagliptin/metformin HCl Dosage Form: Tablet		Applicant: Merck & Co., Inc.
RPM: Lina AlJuburi, Pharm.D, M.S.		Division: 510 Phone # 301-796-1168
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 20-357 Glucophage (metformin HCl) Tablets</p> <p>Provide a brief explanation of how this product is different from the listed drug. Fixed-dose combination of sitagliptin and metformin HCl</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: March 5, 2007</p>
❖ User Fee Goal Date		March 31, 2007
❖ Action Goal Date (if different)		March 30, 2007
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<p>X Included</p>
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<p>X No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p>
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<p>X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<p>21 CFR 314.50(i)(1)(i)(A) X Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>Division Director and Team Leader: March 30, 2007</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
Labeling	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>March 30, 2007</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>May 31, 2006</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>NDA 21-995 Januvia (sitagliptin) NDA 20-357 Glucophage (metformin)</p>
Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>March 30, 2007</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>May 31, 2006</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>NDA 21-995 Januvia (sitagliptin)</p>
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>N/A</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	<p>N/A</p>
Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>February 5, 2007</p>

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	X DMETS March 15 and 29, 2007 X DSRCS March 20 and 28, 2007 X DDMAC March 9, 2007 X SEALD March 30, 2007 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs <i>no labeling meetings held with the sponsor. All labeling discussions conducted via email.</i>
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Administrative Documents

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	December 18, 2006
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	None needed None needed
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	March 8, 2007
<ul style="list-style-type: none"> • Incoming submission documenting commitment 	March 21, 2007
Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	June 7 and July 17, 2006 March 8 and 16, 2007
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	Not NME, none needed
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg March 6, 2006
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg December 15, 2004
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	None
❖ Advisory Committee Meeting	X No AC meeting
<ul style="list-style-type: none"> • Date of Meeting 	
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information

❖ CMC/Product review(s) (<i>indicate date for each review</i>)	February 28 and March 4, 2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> • X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	February 28, 2007
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	

<ul style="list-style-type: none"> • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	X Not a parenteral product
Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: January 24, 2007 X Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	March 1, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	None
❖ Nonclinical inspection review Summary (DSI)	X None requested

Clinical Information

❖ Clinical review(s) (<i>indicate date for each review</i>)	March 8, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	X Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	RMP review by OSE February 20, 2007
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	X Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> • Clinical Studies 	None
<ul style="list-style-type: none"> • Bioequivalence Studies 	March 19, 2007
<ul style="list-style-type: none"> • Clin Pharm Studies 	None
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 5, 2007 (labeling only)
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 22, 2007

Appendix A to Action Package Checklist

NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

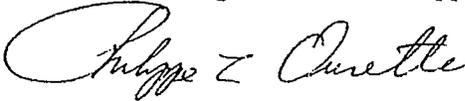
JANUMET™ (Sitagliptin phosphate/metformin hydrochloride) Tablets
NDA No. 22-044

Patent Certification under 21 U.S.C. 505(b)(2)(A) (Item 14)

The NDA Applicant certifies that, in the opinion of the NDA Applicant and to the best of the NDA Applicant's knowledge, no patent information has been filed for a patent claiming the drug or a use of the drug for which investigations were conducted by or for someone other than NDA Applicant, for which NDA Applicant does not have a right of reference, and for which information is required to be filed under section 505(b)(1) or 505(c).

Authorized Signature of NDA Applicant:

Date Signed:



May 10, 2006

Philippe L. Durette

NDA Applicant's Attorney
Merck & Co., Inc.
P.O. Box 2000, RY 60-30
Rahway, NJ 07065-0907
Telephone Number: (732)-594-4568
FAX Number: (732)-594-4720
E-Mail Address: phil_durette@merck.com

Appears This Way
On Original

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 22-044	
		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) JANUMET™			
ACTIVE INGREDIENT(S) Sitagliptin phosphate/Metformin hydrochloride		STRENGTH(S) Sitagliptin phosphate/metformin hydrochloride 50mg/500mg and 50mg/1000mg	
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 only 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.			
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) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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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? Yes 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? Yes 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.)
JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin

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? Yes 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? Yes 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.)
JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin

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? Yes 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? Yes 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.)
JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin

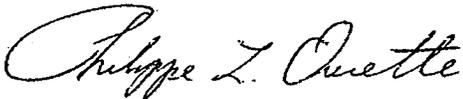
4. Method of Use (continued)

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? 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? Yes 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.)

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. <input type="checkbox"/> 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. <i>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</i>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	May 10, 2006
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.	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> 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

Appears This Way
On Original

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 22-044	
		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) JANUMET™			
ACTIVE INGREDIENT(S) Sitagliptin Phosphate/Metformin hydrochloride		STRENGTH(S) Sitagliptin phosphate/metformin hydrochloride 50mg/500mg and 50mg/1000mg	
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 6,699,871		b. Issue Date of Patent March 2, 2004	c. Expiration Date of Patent July 26, 2022 (with PTA)
d. Name of Patent Owner MERCK & CO., INC.		Address (of Patent Owner) P.O. BOX 2000, RY 60-30	
		City/State RAHWAY, NEW JERSEY	
		ZIP Code 07065-0907	FAX Number (if available) 732-594-4720
		Telephone Number 732-594-4568	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)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	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? **See Attachment 1** 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) 21	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
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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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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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) 22	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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.
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) 23	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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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) 24	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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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 type="checkbox"/> Yes <input type="checkbox"/> 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? <input 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.)

5. No Relevant Patents

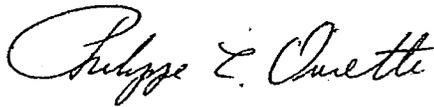
For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement 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

May 10, 2006

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

FORM FDA 3542a
JANUMET™ (Sitagliptin phosphate/metformin hydrochloride) Tablets
NDA No. 22-044
US Patent No. 6,699,871

ATTACHMENT 1

Items 2.2 and 2.3:

The claims of Patent No. 6,699,871 are not limited to any particular polymorphic form of the drug substance. The patent claims encompass all polymorphic forms of the drug substance described in the NDA for which approval is being sought to the extent that they exist. Because the patent is submitted for listing on that basis, no testing of other polymorphic forms of the drug substance is required, and Questions 2.2 and 2.3 are accordingly left blank.

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On Original

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		NDA NUMBER 22-044	
For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		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) JANUMET™			
ACTIVE INGREDIENT(S) Sitagliptin Phosphate/Metformin hydrochloride		STRENGTH(S) Sitagliptin phosphate/metformin hydrochloride 50mg/500mg and 50mg/1000mg	
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 6,890,898	b. Issue Date of Patent May 10, 2005	c. Expiration Date of Patent February 2, 2019	
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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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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) 2	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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin
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) 35	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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

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) 38	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) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

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) 42	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) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

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) 44	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.) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

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) 45	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) JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

5. No Relevant Patents

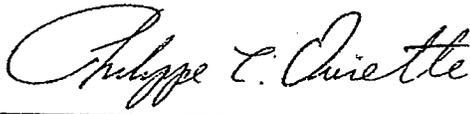
For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement 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

May 10, 2006

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)

NDA #: 22-044 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: May 31, 2006 PDUFA Goal Date: March 31, 2007

HF-510 Trade and generic names/dosage form: Janumet (sitagliptin/metformin HCl fixed-dose combination) 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): 2

Indication #1: treatment of patients with type 2 diabetes mellitus who have not achieved a adequate glycemic control with either agent alone

Indication #2: treatment of patients who are already being treated with the combination of sitagliptin and metformin

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.

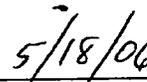
Sitagliptin Phosphate/Metformin Hydrochloride Fixed-Dose Combination Tablet
Debarment Certification

1

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 Aurecchia, M.D.
Director
Regulatory Affairs



Date

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On Original



DIVISION DIRECTOR'S MEMO

NDA 22-044

Sponsor Merck and Co.

Drug Product Janumet® (sitagliptin/metformin fixed-dose combination) tablets

Date of Submission May 31, 2006

Indication Treatment of type 2 diabetes mellitus; use in patients who are inadequately responding to the individual components or who are already being treated with both sitagliptin and metformin

Primary medical reviewer Ilan Irony, M.D.

BACKGROUND

Januvia® (sitagliptin phosphate), hereafter referred to as sitagliptin, was approved in 2006 for the treatment of type 2 diabetes mellitus as monotherapy or as combined therapy with metformin or a PPAR gamma agonist when the single agent does not provide adequate glycemic control. This NDA is for a fixed-dose combination (FDC) drug product containing sitagliptin and metformin in the dosage-strength tablets (sita/met) of 50 mg/500 mg and 50 mg/1000 mg. The proposed indication is similar to that approved under NDA 21-995 for sitagliptin. As per submitted labeling the proposed language is as follows:

Janumet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

The combined use of sitagliptin and monotherapy was evaluated in Study P020, which was reviewed under NDA 21-995. This was a 24-week randomized, double-blind, placebo-controlled study in patients who had been on a stable dose of metformin (at least 1500 mg daily) and who had HbA1c values between 7 and 10%. Patients were randomized to receive sitagliptin 100 mg daily or placebo. At the end of the 24-week double-blind treatment period, placebo-treated patients were switched to glipizide while sitagliptin-treated patients remained on therapy. This second treatment period was 80 weeks in duration. Sitagliptin 100 mg daily added onto metformin in Type 2 diabetics who have not achieved adequate glycemic control resulted in greater HbA1c reduction than placebo. The LSM difference from placebo was -0.65 (p<0.001).

As the safety and effectiveness of sitagliptin plus metformin for the proposed indication has already been established to be sufficient for approval under NDA 21-995, the approval of Janumet can be based primarily on a study establishing bioequivalence between the FDC tablet and the individual components co-administered. In this NDA, Merck has provided such evidence in Study P048, an open-label,

randomized, 2-period crossover study that compares the 50/500mg and 50/1000 mg FDC tablets to their respective individual components, co-administered. In addition, a pharmacodynamic study (P050) was conducted to explore the effects of coadministered sitagliptin and metformin versus individual administration on active and total GLP-1 and GIP concentration. No clinical studies using the actual to-be-marketed FDC tablets were conducted; however, other clinical data were submitted in support of the combined use of these two drugs. These additional data are not essential to the approval of this application included but they have been described in detail in the primary medical officer's review for completeness.

For purposes of this memo, I will only discuss the findings from the pivotal BE study and any data proposed for labeling. Please see the reviews of Drs. Vaidyanathan and Irony for a comprehensive summary of the Janumet clinical development program.

STUDY P048

This was an open-label, randomized, 2-part, 2-period crossover study designed to demonstrate the bioequivalence of the Final Market Image (FMI) of sitagliptin/metformin 50/500 mg and 50/1000 mg FDC tablets and the concomitant administration of the 50 mg doses of sitagliptin and 500- or 1000 mg doses of metformin as individual tablets in healthy adult volunteers. Part I specifically studied the FDC 50/500 mg tablet versus single doses of sitagliptin 50 mg and metformin 500 mg while Part II specifically studied the FDC 50/1000 mg tablet versus single doses of sitagliptin 50 mg and metformin 1000 mg.

All test products were administered as single doses and the primary endpoint was the area under the plasma concentration versus time curve ($AUC_{0-\infty}$) for sitagliptin and metformin. The hypothesis was that the geometric mean ratio (GMR) for the ($AUC_{0-\infty}$) of sitagliptin and metformin after administration of the FDC tablet and co-administration of the individual tablets would fall within the confidence limits of 0.80 to 1.25 and bioequivalence would therefore be established.

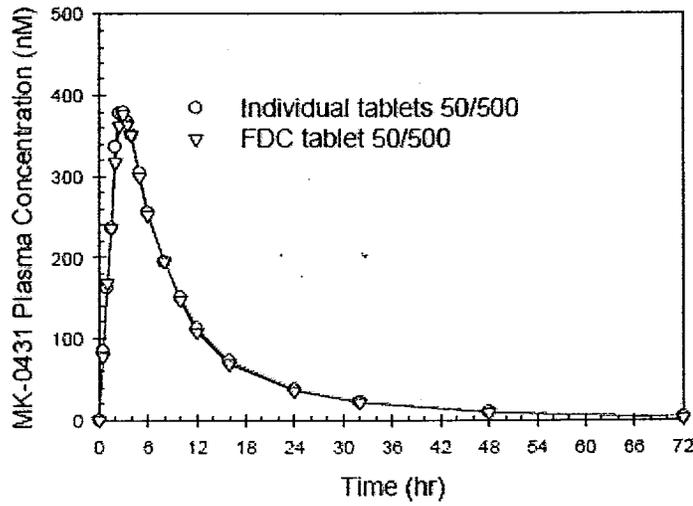
The study enrolled 24 adult males and females in both Parts 1 and 2. All patients enrolled completed the study. Blood samples were collected at Baseline and up to 72 hrs post-dose for pK analysis. There was a 7-day washout period between each period.

The FMI for the FDC 50/500 mg and 50/1000 mg tablets was bioequivalent to the concomitant administration of sitagliptin and metformin at their respective doses. The following figures from the Clinical Study Report for P048 illustrate a finding of superimposable pK curves.

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Figure 11-1

Mean Plasma Concentration-Time Profiles of Sitagliptin After Administration of a Single Dose of the FMI Sitagliptin/Metformin 50/500 mg/mg FDC Tablet and a Concomitant Administration of a 50-mg Dose of Sitagliptin and a 500-mg Dose of Metformin in Healthy Adult Subjects (n=24)

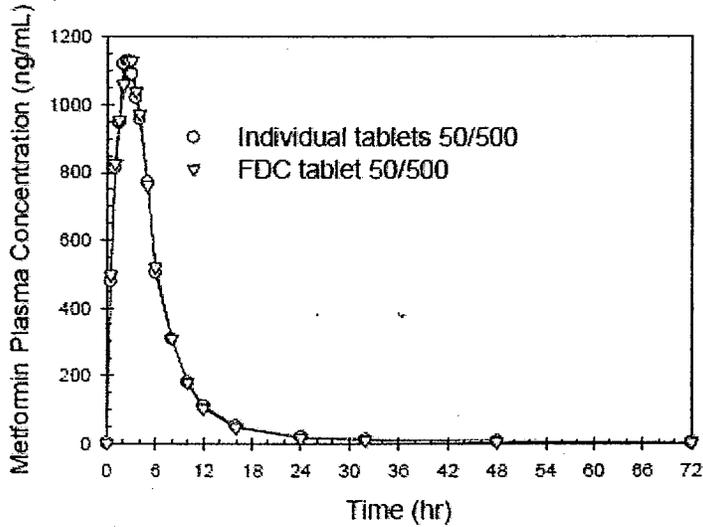


Data Source: [16.4.4]

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Figure 11-2

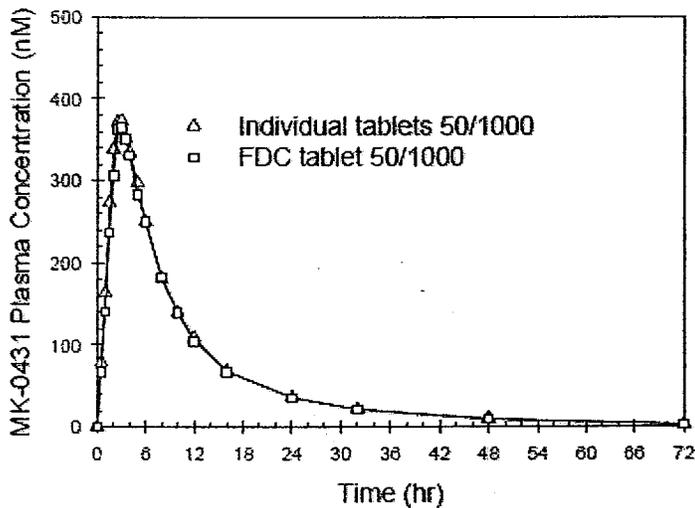
Mean Metformin Plasma Concentration-Time Profiles After Administration of a Single Dose of the FMI Sitagliptin/Metformin 50/500-mg/mg FDC Tablet and Concomitant Administration of a 50-mg Dose of Sitagliptin and a 500-mg Dose of Metformin in Healthy Adult Subjects (n=24)



Data Source: [36.4.4]

Figure 11-3

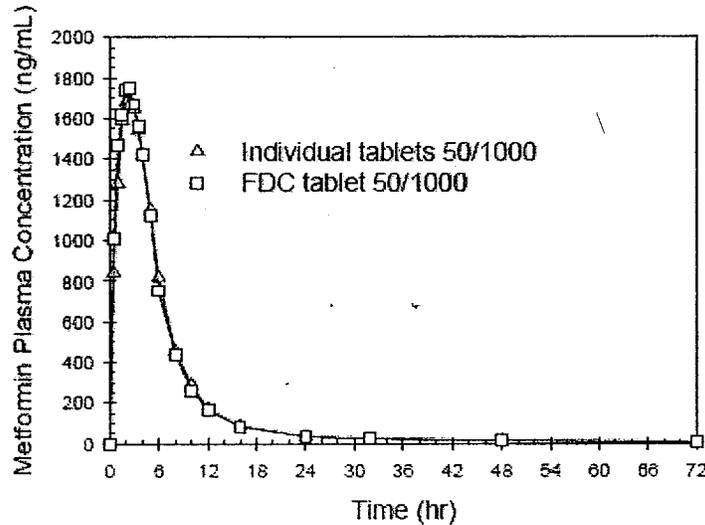
Mean Plasma Concentration-Time Profiles of Sitagliptin After Administration of a Single Dose of the FMI Sitagliptin/Metformin 50/1000 mg/mg FDC Tablet and Concomitant Administration of a 50-mg Dose of Sitagliptin and a 1000-mg Dose of Metformin in Healthy Adult Subjects (N=24)



Data Source: [16.4.4]

Figure 11-4

Mean Plasma Concentration-Time Profiles of Metformin After Administration of a Single Dose of the FMI Sitagliptin/metformin 50/1000 mg/mg FDC Tablet and Concomitant Administration of a 50-mg Dose of Sitagliptin and a 1000-mg Dose of Metformin in Healthy Adult Subjects (N=24)



Data Source: [16.4.4]

The following table summarizes the GMR (90% CI) of the $AUC_{0-\infty}$ for sitagliptin and metformin pharmacokinetics obtained in Parts I and II of this study.

	Part I (FDC 50/500 mg vs coadministered sitagliptin 50 mg and metformin 500 mg)	Part II (FDC 50/1000 mg vs coadministered sitagliptin 50 mg and metformin 1000 mg)
Sitagliptin	0.98 (0.96, 1.00)	0.97 (0.95, 0.99)
Metformin	1.00 (0.95, 1.04)	1.00 (0.94, 1.07)

Based on these findings, I concur with Dr. Vaidyanathan that bioequivalence between the FMI tablets (50/500 and 50/1000 mg) has been established with the individual components co-administered and therefore support bridging of clinical efficacy and safety data in NDA 21-995 to this NDA.

ADDITIONAL STUDIES

Study P015

This was a Phase 2, 4-week study in 28 patients originally designed as a 2-period crossover study in patients with T2DM treated with stable doses of metformin (≥ 1500 mg daily) who were randomized to first receive placebo or sitagliptin 50 mg bid then in the second period to have the treatments reversed. Due to carry-over effect, the applicant only considered the first treatment period valid hence the trial then became a 4-week, randomized, placebo-controlled study evaluating 24-hr weighted mean glucose values as an endpoint. This study was submitted and reviewed under NDA 21-995 but never included in

labeling. Similarly, the results of this study should not be included into Janumet's labeling as they provide no additional information to what is observed in the Phase 3 study, P020.

Study P036 and P024

These studies have been described in Dr. Irony's review. Study P036 was conducted to support the use of the sitagliptin and metformin in treatment-naïve patients with T2DM and is currently under review as Supplement 003 to NDA 21-995. Study P024 is a non-inferiority study comparing addition of sitagliptin 100 mg daily or glipizide to metformin. Neither of these studies is discussed in the proposed label for Janumet. For this NDA, Dr. Irony has reviewed these studies to obtain additional safety information on the use of sitagliptin and metformin.

SAFETY

New safety data are available from the 24-week Study P036 and the 52-week Study P024. Including exposures from studies reviewed under NDA 21-995, there have been 1,569 patients who have received sitagliptin and metformin in combination. The mean duration of exposure has been 254.8 days; 579 patients have received the two drugs together for more than a year. Review of the new studies have not identified any additional safety concerns for the co-administration of sitagliptin and metformin.

CMC

Approval is recommended. An expiration dating period of _____ for the proposed storage conditions is acceptable as per CMC review.

PHARMACOLOGY/TOXICOLOGY

No specific nonclinical studies were conducted with the FDC tablets. Studies with the co-administered drugs evaluating metformin doses that better approximated clinical exposures did not identify toxicities that precludes approval. Deaths in a dog study were attributed to use of high doses of metformin that exceeded recommended clinical dosing.

DMETS

Dr. Irony has presented the basis for accepting the proposed tradename, Janumet®. I concur with his conclusions.

CONCLUSIONS/RECOMMENDATIONS

Bioequivalence has been established between the FDC tablets containing sitagliptin and metformin and the two drugs co-administered to allow bridging of clinical efficacy and safety data from NDA 21-995. Updated safety data for the co-administration of sitagliptin and metformin have not identified any new safety concerns.

Pending labeling negotiations, this application can be approved for the treatment of type 2 diabetes mellitus in patients who have inadequate glycemic control with the individual components or who are already receiving treatment with sitagliptin and metformin. Jindo4me*6

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

/s/

Mary Parks
3/30/2007 01:57:57 PM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 70,934

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 Pre-Investigational New Drug Application (PIND) file for MK-0431A.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2004. The purpose of the meeting was to discuss your Phase 3 program for MK-0431A, the fixed dose combination of MK-0431/metformin hydrochloride.

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 meeting minutes from EOP2 meeting held on December 15, 2004

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 15, 2004
TIME: 3:00 to 4:00 pm
LOCATION: Parklawn Conference Center, Potomac Room
APPLICATION: PIND 70,934
DRUG NAME: MK-0431A (MK-0431/metformin hydrochloride)
TYPE OF MEETING: Type B; End-of-Phase 2/Pre-Phase 3

MEETING CHAIR: David Orloff, M.D.

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

FDA ATTENDEES: (Title and Office/Division)

David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Dragos Roman, M.D.	Clinical Reviewer
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Jim Wei, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
J. Todd Sahlroot, Ph.D.	Statistics Team Leader
Joy Mele	Statistics Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager, DMEDP

EXTERNAL CONSTITUENT ATTENDEES:

Merck Research Laboratories

Robert Silverman, M.D., Ph.D.	Senior Director, Regulatory Affairs
Steven Aurecchia, M.D.	Director, Regulatory Affairs
Keith Kaufman, M.D.	Executive Director, Clinical Research, Metabolism
Peter Stein, M.D.	Director, Clinical Research, Metabolism
Debora Williams-Herman, M. D.	Director, Clinical Research, Metabolism
Gary Herman, M.D. Director	Clinical Pharmacology
Arthur Bergman, Ph.D.	Research Fellow, Clinical Drug Metabolism
Soumojeet Ghosh, Ph.D.	Director, Biopharmaceutics and Product Enhancement
Matilde Sanchez, Ph.D.	Associate Director, Clinical Biostatistics
Brian M. Mayhew	Global Regulatory Policy

BACKGROUND:

MK-0431A is a fixed dose combination of MK-0431 and metformin. MK-0431 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 being studied under IND 65,495. MK-0431 is currently in Phase 3 of its clinical development program.

The proposed indication for MK-0431A is as adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. A second indication is to improve glycemic

control in patients with type 2 diabetes mellitus when diet, exercise, plus treatment with either metformin or MK-0431 alone does not provide adequate glycemic control. According to the sponsor, there is a potential clinical advantage with a fixed dose combination formulation because MK-0431 and metformin have complementary mechanisms and targets of action.

MK-0431A is a tablet to be taken twice daily, prior to the morning and evening meals. The sponsor recommended doses are 50 mg MK-0431/500 mg metformin and 50 mg MK-0431/1000 mg metformin, with a maximum total daily dose of 100 mg MK-0431/2000 mg metformin.

Proposed Phase 3 Clinical Program

Protocol Number 036 is a study of MK-0431 and metformin co-administration in initial therapy use, entitled *A Multicenter, Double-Blind, Randomized, Placebo- and Active-Controlled Factorial Study of MK-0431 and Metformin Co-administration in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*. There are six arms in this study: placebo, MK-0431 100 mg once daily; MK-0431/metformin 50/500 mg twice daily, MK-0431/metformin 50/1000 mg twice daily, metformin 500 mg twice daily, and metformin 1000 mg twice daily. A total of 720 subjects will be enrolled, 240 of which will be exposed to the combination of MK-0431 and metformin. Phase A is 24-weeks placebo-controlled and Phase B is 30-weeks active controlled.

Protocol Number 020 is a metformin add-on study, entitled *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 are two arms in this study: placebo and 100 mg once daily. A total of 525 patients are to be enrolled for 104 weeks (24-weeks placebo controlled followed by 80-weeks single-blind.) This study will be included in the initial NDA submission for MK-0431.

Protocol Number 024 is a metformin add-on study, entitled *A Multicenter, Randomized, Double-Blind, Active-Comparator (Glipizide) Controlled, Parallel Arm, Fixed Dose, Study of Type 2 Diabetic Patients Inadequately Controlled on Metformin*. There are two arms in this study: metformin \geq 1500 mg/day plus MK-0431 100 mg once daily and metformin \geq 1500 mg/day plus Glipizide (titrated doses from 5 to 20 mg once daily). A total of 1300 subjects will be enrolled, 650 of which will be exposed to the combination of MK-0431 and metformin. The study duration is 52-weeks.

The firm requested this Type B End-of-Phase 2/Pre-Phase 3 meeting on October 5, 2004, and the background package was submitted on November 16, 2004.

MEETING OBJECTIVES:

To discuss the Phase 3 program for MK-0431A, a fixed dose combination of MK-0431/metformin hydrochloride

DISCUSSION POINTS:

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

1. MRL has reviewed the available pre-clinical data for metformin and will submit a complete pre-clinical safety assessment package for MK-0431 with the initial MK-0431 NDA filing. We conclude that no additional pre-clinical studies with MK-0431 and metformin in combination are warranted to support the proposed MK-0431/metformin fixed dose combination (MK-0431A) program and MK-0431A NDA filing. Does the Agency concur?

Yes, the Division agrees that no toxicology studies with the drug combination are needed.

2. With respect to the proposed MK-0431/metformin coadministration factorial study (PN036):
 - a. Does the Agency have specific comments on the clinical or statistical design aspects of the proposed study protocol?

The Division recommends that the regimen in the MK-0431 monotherapy arm be changed from 100 mg once daily to 50 mg twice daily. Please note that the Division has not reviewed any specific data to concur that the 50 mg twice daily and the 100 mg once daily regimens are equally effective.

The sponsor explained that 100 mg once daily has been selected because the 50 mg twice daily and 100 mg once daily MK-0431 dosing regimens had similar efficacy and safety in the Phase 2 studies. The Division agrees that the selection of the 100 mg dose in Protocol Number 036 is acceptable, with the understanding that the study will include a "dummy" design feature.

The primary and secondary hypotheses are all stated in terms of combining the data for both combination products and combining the data for the metformin arms. This approach will provide a global test of the efficacy of the combination (assuming no interaction) but is inadequate for establishing the efficacy of each combination product. The efficacy of each combination product should be established as described in the last paragraph on page 82 of the protocol which states that "the comparisons of the individual doses of the MK-0431/metformin combination versus corresponding doses of metformin alone and versus MK-0431 will also be assessed"; the latter should be considered the primary analyses.

Tests for interaction are underpowered tests so an alpha level of 0.10, as suggested on page 83 of the protocol, is too small for rejecting the null hypothesis

of no interaction. The Division would recommend using a level of 0.20.

An acceptable alpha level was further discussed. Since there is no set rule for what alpha level is acceptable for interactions, a p-value greater than 0.10 with data that suggests the presence of an interaction may be sufficient statistical evidence of an interaction.

- b. MRL maintains that the design, objectives, hypotheses and proposed statistical analysis plan would support a labeling presentation of study endpoints in a manner similar to that in the sample table below. Does the Agency concur?

Total Daily Dose	N	ΔHbA_{1c}	ΔFPG	$\Delta 2$ hr PP glucose
Pooled data (all MK-0431A doses)*	216			
Pooled data (all Metformin doses)*	216			
MK-0431 100 mg q.d.*	108		Appears This Way On Original	
Placebo	108			
MK-0431 / Metformin 50/ 500 b.i.d	108			
MK-0431 / Metformin 50/ 1000 b.i.d	108			
Metformin 500 mg b.i.d.	108			
Metformin 1000 mg b.i.d.	108			

*MK-0431/metformin provided significantly greater reductions compared to metformin and compared to MK-0431 for all glycemc endpoints

The sample table is acceptable in that it is in general consistent with that of other labels for antidiabetic fixed dose combinations (refer to the labels for Glucovance and Metaglip). However, the final format will depend on the data presented in the NDA submission.

No, the Division does not agree with presenting the pooled data. The pooled data does not provide information that further elucidates the treatment effects beyond the individual treatment group results.

The sponsor can conduct a pooled analysis (global test); however the comparisons of each combination to its components are the primary analyses that need to be done for drug approval.

3. MRL maintains that, when completed, the proposed MK-0431A clinical and clinical pharmacology development program, in conjunction with efficacy and safety data from ongoing studies in the MK-0431 core program [i.e., the Add-on to Metformin Study (PN020) and the Active-Comparator Study with Metformin plus MK-0431 versus Metformin plus Glipizide (PN024)], will be sufficient to support the following:

Does the Agency concur?

- a. An MK-0431A NDA filing for treatment of hyperglycemia in patients with type 2 diabetes mellitus.

The proposed data appears adequate for the NDA submission. However, the Division makes the decision for filing after the NDA is submitted and takes many aspects of the application into consideration.

In principle, the demonstration of bioequivalence between combination tablets and individual tablets should be established based on both AUC and C_{max} , especially when the combination tablets are not used in pivotal Phase 3 clinical trials. The sponsor has proposed the AUC to be used as the primary endpoint and the C_{max} as the secondary endpoint. After the C_{max} values are reviewed, the Agency will decide whether or not the two products (i.e., combination products vs. individual tablets) are bioequivalent.

- b. _____ indications as proposed in the prototype labeling.

If found safe and effective, the fixed-dose combination of MK-0431/metformin can be approved as _____ indications. The decision for approval for _____ will particularly depend on the safety profile of the fixed dose combination.

- c. Dosage and administration labeling as proposed in the prototype labeling.

The dosage and administration of the proposed MK-0431/ metformin fixed dose combination (one tablet twice daily of either 50 mg MK-0431/500 mg metformin or 50 mg MK-0431/1000 mg metformin) is acceptable based on the data presented to date. The actual label will reflect the data presented in the NDA.

Note: The sponsor will conduct combination drug studies under IND 65,495 MK-0431 tablets and will use a currently marketed metformin product until the MK-0431A tablet is formulated.

Meeting Recorder: Lina AlJuburi

Chair Concurrence: David Orloff

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/s/

Lina Aljuburi
1/12/05 05:16:04 PM

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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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 6, 2006
TIME: 1:00 to 2:00 pm
LOCATION: White Oak Campus
APPLICATION: IND 70,934
DRUG NAME: MK-0431A (sitagliptin phosphate plus metformin hydrochloride fixed dose combination) Tablet
TYPE OF MEETING: Type B; PreNDA
MEETING CHAIR: Mary Parks, M.D.

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

FDA ATTENDEES: (Title and Office/Division)

Robert Meyer, M.D.	Director, Office of Drug Evaluation II
Curtis Rosebraugh, M.D.	Deputy Director, Office of Drug Evaluation II
Mary Parks, M.D.	Acting Director, Division of Metabolism and Endocrinology Products (DMEP)
Karen Mahoney, M.D.	Acting Diabetes Team Leader
Ilan Irony, M.D.	Clinical Reviewer
Suong Tran, Ph.D.	Product Assessment Lead, Office of New Drug Quality Assessment
Hae-Young Ahn, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Jim Wei, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
J. Todd Sahlroot, Ph.D.	Biometrics Team Leader
Lee-Ping Pian, Ph.D.	Biometrics Reviewer
Joslyn Swann, Pharm.D.	Safety Evaluator, Office of Drug Safety
Cherye Milburn	Regulatory Project Manager, Office of Drug Safety
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Merck & Co., Inc.

Robert Silverman, M.D., Ph.D.	Senior Director, Regulatory Affairs
Steven Aurecchia, M.D.	Director, Regulatory Affairs
Debora Williams-Herman, M.D.	Director, Clinical Research
Peter Stein, M.D.	Senior Director, Clinical Research
Keith Kaufman, M.D.	Executive Director, Clinical Research
Elizabeth M. Migoya, Pharm.D	Associate Director, Clinical Pharmacology
John Wagner, M.D., Ph.D.	Executive Director, Clinical Pharmacology
George Lankas, Ph.D.	Executive Director, Safety Assessment
Mark Alasandro, Ph.D.	Director, Pharmaceutical Development
Lawrence Rosen, Ph.D.	Sr. Research Fellow, Pharmaceutical Development
Mr. Kyle Fliszar	Research Chemist, Pharmaceutical Development
Soumojeet Ghosh, Ph.D.	Director, Biopharmaceutics and Product Enhancement
Jared Lunceford, Ph.D.	Senior Biometrician, Biostatistics

BACKGROUND:

MK-0431A is a fixed dose combination of MK-0431 and metformin. 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 being studied under IND 65,495 and reviewed by the Agency under NDA 21-995. The proposed indication for MK-0431A is for treatment of hyperglycemia in patients with type 2 diabetes mellitus when diet and exercise, plus treatment with metformin, do not provide adequate glycemic control; or as a substitute for patients who are adequately controlled on combination therapy with sitagliptin phosphate plus metformin. According to the sponsor, there is a potential clinical advantage with a fixed dose combination formulation because MK-0431 and metformin have complementary mechanisms and targets of action.

MK-0431A is a tablet to be taken twice daily, prior to the morning and evening meals. The Sponsor recommended doses are 50 mg MK-0431/500 mg metformin and 50 mg MK-0431/1000 mg metformin, with a maximum total daily dose of 100 mg MK-0431/2000 mg metformin.

Phase 3 Clinical Program

Protocol Number 036 is a study of MK-0431 and metformin co-administration in initial therapy use, entitled *A Multicenter, Double-Blind, Randomized, Placebo- and Active-Controlled Factorial Study of MK-0431 and Metformin Co-administration in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*. There are six arms in this study: placebo, MK-0431 100 mg once daily, MK-0431/metformin 50/500 mg twice daily, MK-0431/metformin 50/1000 mg twice daily, metformin 500 mg twice daily, and metformin 1000 mg twice daily. A total of 720 subjects will be enrolled, 240 of which will be exposed to the combination of MK-0431 and metformin. Phase A is 24-weeks placebo-controlled and Phase B is 30-weeks active controlled.

Protocol Number 020 is a metformin add-on study, entitled *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 are two arms in this study: placebo and 100 mg once daily. A total of 525 patients are to be enrolled for 104 weeks (24-weeks placebo controlled followed by 80-weeks single-blind.) This study will be included in the initial NDA submission for MK-0431.

Protocol Number 024 is a metformin add-on study, entitled *A Multicenter, Randomized, Double-Blind, Active-Comparator (Glipizide) Controlled, Parallel Arm, Fixed Dose, Study of Type 2 Diabetic Patients Inadequately Controlled on Metformin*. There are two arms in this study: metformin \geq 1500 mg/day plus MK-0431 100 mg once daily and metformin \geq 1500 mg/day plus Glipizide (titrated doses from 5 to 20 mg once daily). A total of 1300 subjects will be enrolled, 650 of which will be exposed to the combination of MK-0431 and metformin. The study duration is 52-weeks.

The Sponsor requested this PreNDA meeting and submitted the briefing document on January 10, 2006.

2. Results from a formulation comparison study (PN038) using probe fixed-dose combination (FDC) tablet formulations containing sitagliptin phosphate (MK-0431) and metformin hydrochloride are presented in Section 4 and show that the FDC tablet formulation met bioequivalence criteria when compared to co-administration of corresponding doses of the individual tablets. The proposed MK-0431A market formulation differs only with respect to the amount and type of _____, differences which are not expected to alter the bioavailability of either MK-0431 or metformin. MRL maintains that data from PN038, in conjunction with the biopharmaceutical properties of MK-0431 and metformin (both are highly soluble and readily absorbed), are sufficient to demonstrate bioequivalence for the proposed commercial FDC tablet compared to coadministration of single-entity tablets of sitagliptin phosphate and metformin. Does the Agency concur?

No, the Agency does not concur. The change of _____ which indicates that it is a Level 3 change in excipients. Therefore, an *in vivo* bioequivalence study is required. The biowaiver based on BCS classification does not apply to this fixed dose combination drug product. This is considered a filing issue.

3. MRL maintains that, when completed, the proposed MK-0431A clinical pharmacology and clinical development program, as described in Section 5, will be sufficient to support the following:
 - a. An MK-0431A NDA filing for treatment of hyperglycemia in patients with type 2 diabetes mellitus when diet, exercise, plus treatment with metformin alone do not provide adequate glycemic control; or as a substitute for patients who are adequately controlled on combination therapy with sitagliptin phosphate (MK-0431) plus metformin. Does the Agency concur?

The proposed indication for MK-0431A as second-line treatment is acceptable assuming sitagliptin phosphate alone is approved.

The Agency concurs that the clinical development program may support the proposed second line indication. Data from the Factorial Study Protocol number 036, entitled *A Multicenter, Double-Blind, Randomized, Placebo- and Active-Controlled Factorial Study of MK-0431 and Metformin Co-administration in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control*, will need to be submitted and reviewed for safety. Efficacy data from that study will be essential to support the efficacy of MK-0431A as _____ if the Sponsor decides to seek such indication.

The Sponsor will need to make certain that the safety database has a sufficient number of subjects conducive to analyses among important demographic subsets (e.g. age, race) and important baseline characteristics (e.g. hemoglobin A1c, concomitant illnesses). Detailed narratives for adverse events (AEs) leading to discontinuation and serious adverse events (SAEs) need to be submitted at the time of submission, and updated as necessary in the 4-month safety update. The Sponsor should avoid using non-specific reasons for study discontinuations (e.g. withdrawal of consent, patient decision). For those study subjects listed as discontinuing treatment for these reasons, the Sponsor must provide documentation that there were no adverse events or any loss of efficacy preceding the discontinuation.

- b. Dosage and administration as proposed in the prototype labeling. Does the Agency concur?

Determination of dosage and administration is a review issue.

Fixed-dose combination (FDC) tablets should include the full dosing range of each component of the combination drug. The Division notes that this FDC tablet does not include the 850 mg dose of metformin. The Sponsor will provide a rationale for marketing a FDC tablet that does not contain metformin 850 mg.

Additional Comments from the Division:

- A. If the Sponsor plans to reference any part of a previously approved metformin application (such as preclinical data), 505(b)(2) status, patent certifications and exclusivity obligations will apply to the MK-0431A application.
- B. It is the Division's understanding that a drug-drug interaction study between sitagliptin phosphate and metformin has been conducted. The Sponsor will submit the final study report to the Agency for review.

Additional comments from the Office of Drug Safety (ODS) not discussed at the meeting:

- C. 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).
- D. 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/6357fn1.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fn1.htm>

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

- E. If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- F. The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Minutes prepared by: Lina AlJuburi
Chair concurrence: Mary Parks

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/s/

Lina Aljuburi
4/4/2006 01:31:37 PM

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. Merck Research Laboratories Division of Merck & Co., Inc. UG2CD-48 PO Box 1000 North Wales PA 19454-1099 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>22044</p>
<p>2. TELEPHONE NUMBER</p> <p>267-305-6694</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>JANUMET (Sitagliptin Phosphate/Metformin Hydrochloride Fixed-Dose Combination)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006494</p>
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7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A 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 738(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>Executive Director Regulatory Affairs</p>	<p>DATE</p> <p>May 5, 2006</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$767,400.00

Form FDA 3397 (12/03)

(BE PRMT CLOSE G) (Print Cover sheet)



NDA 22-044

NDA ACKNOWLEDGMENT

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
UG2CD-48, P.O. Box 1000
North Wales, PA 19454-1099

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:	Janumet (sitagliptin phosphate/metformin hydrochloride fixed-dose combination) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	May 31, 2006
Date of Receipt:	May 31, 2006
Our Reference Number:	NDA 22-044

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 July 30, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 31, 2007.

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.

NDA 22-044

Page 2

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

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Lina Aljuburi
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-044

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
P.O. Box 1000
North Wales, PA 19454-1099

Dear Dr. Aurecchia:

Please refer to your May 31, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Janumet (sitagliptin phosphate/metformin hydrochloride fixed-dose combination) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on July 30, 2006, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

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

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/s/

Lina Aljuburi
7/17/2006 04:55:50 PM
Lina AlJuburi for Kati Johnson

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DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: December 1, 2006

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

FROM: Lina AlJuburi, Regulatory Project Manager, HFD-510

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-044
Janumet (sitagliptin phosphate/metformin HCl FDC) Tablet

Study/Site Identification:

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

Study #	Clinical Site (name, address, phone, fax, contact person, if available)
048	Maria J. Gutierrez, Comprehensive Phase One, 108 NE 1st Street, Ft. Lauderdale, FL 33301

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **March 16, 2007**. We intend to issue an action letter on this application by **March 30, 2007**.

Should you require any additional information, please contact Lina AlJuburi at 301-796-1168.

Concurrence:

Jim Wei, Ph. D. Biopharm Team Leader
Jaya Vaidyanathan, Ph.D. Biopharm Reviewer

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/s/

Julie Marchick
12/1/2006 04:03:59 PM
On behalf of Lina AlJuburi.

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MEMORANDUM

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

DATE: December 11, 2006

TO: Director, Investigations Branch

Florida District Office
555 Winderly Place
Ste 200
Maitland, FL 32751

Kansas City District Office
11630 West 80th Street
Lenexa, KS 66214-3338

Baltimore District Office
6000 Metro Drive
Suite 101
Baltimore, MD 21215

FROM: C.T. Viswanathan, Ph.D. CTV
Associate Director (Bioequivalence)
Division of Scientific Investigations

SUBJECT: FY 2007, **High Priority CDER User Fee NDA**, Pre-Approval
Data Validation Inspection, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 22-044
DRUG: JANUMET™ (Sitagliptin Phosphate/Metformin)
Tablets, 50 mg/500 mg, 50 mg/1000 mg
SPONSOR: Merck & Co., Inc.

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study in your respective district. **Due to the user fee deadline, this inspection should be completed by February 9, 2007.**

Study Number: 048

Study Title: "An Open-Label, Randomized, Two-Part, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the of MK-0431/Metformin 50/500 mg and 50/1000 mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50-mg Doses of MK-0431 and 500- or 1000-mg Doses of Metformin as Individual Tablets to Healthy Adult Subjects"

Clinical Site: Comprehensive Phase One
A Division of Comprehensive NeuroScience,
Inc.
3400 Enterprise Way
Miramar, FL 33025

Clinical Investigator: Maria J. Gutierrez, M.D.
TEL: (954) 266-1000
FAX: (954) 266-1011

This was an open-label, randomized, two-part, two-period crossover, bioequivalence study designed to compare a single dose of Merck's FMI sitagliptin¹/metformin (50/500 or 50/1000 mg/mg) FDC tablet (test drug) and concomitant administration of a single dose of Merck's sitagliptin (50 mg) and Apotex's metformin (500 mg in Part I or 1000 mg [2 x 500 mg] in Part II) as individual tablets under fasting conditions in healthy male and female adults. Please note that the study consisted of two parts (Parts I and II) and each part consisting of a two-period, crossover design. Each subject was to have participated in only one part of the study, either Part I or Part II.

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

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the

¹ Sitagliptin = MK-0431

Page 4 - BIMO Assignment, NDA 22-044, JANUMET™ (Sitagliptin Phosphate/Metformin) Tablets, 50 mg/500 mg, 50 mg/1000 mg

stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. **A DSI scientist with specialized knowledge will participate in the inspections at _____ and _____ to provide scientific and technical expertise.**

Headquarters Contact Person: John A. Kadavil, Ph.D.
(301) 594-1048

cc:

DSI/RF

DSI GLPBB/Kadavil(2)/Himaya/CF

HFR-SE250/Sinninger/DIB (Please fax, 407-475-4768)

HFR-SE250/Torres/BIMO (Please fax, 407-475-4768)

HFR-SW350/Thompson/DIB (Please fax, 913-752-2413)

HFR-SW350/Wimberly/BIMO (Please fax, 913-752-2413)

HFR-CE250/Wagner/DIB (Please fax, 410-962-2219)

HFR-CE250/Salisbury/BIMO (Please fax, 410-779-5705)

OND ODEII DMEP/AlJuburi/NDA 22-044

Draft: JAK 12/7/06

Edit: MKY 12/8/06

DSI: 5742; O:\BE\assigns\bio22044.doc

FACTS: 803330C Comprehensive

FEI: _____

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-044 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Janumet
Established Name: sitagliptin phosphate/metformin hydrochloride fixed-dose combination
Strengths: 50/500 mg/mg and 50/1000 mg

Applicant: Merck & Co, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: May 31, 2006
Date of Receipt: May 31, 2006
Date clock started after UN: May 31, 2006
Date of Filing Meeting: July 17, 2006
Filing Date: July 30, 2006
Action Goal Date (optional): TBD User Fee Goal Date: March 31, 2007

Indication(s) requested: Treatment of patients with type 2 diabetes mellitus who do not achieve adequate glycemic control with either agent alone or for patients already being treated with the combination of sitagliptin and metformin.

Type of Original NDA: (b)(1) (b)(2) X
AND (if applicable)
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 or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.) N/A

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

User Fee Status: Paid X 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 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 any approved (b)(1) or (b)(2) application? YES X NO

If yes, explain: Sitagliptin alone was approved on October 16, 2006 – the sponsor is also Merck (ref NDA 21-995).

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO X

- 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 X
If yes, explain:

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

- Does the submission contain an accurate comprehensive index? YES X NO
If no, explain:

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

- Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES X
This application is: All electronic X Combined paper + eNDA
This application is in: NDA format CTD format X
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES X NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES X

If an eCTD NDA, 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 X NO
- Exclusivity requested? YES, 2 Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 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) YES NO X
- PDUFA and Action Goal dates correct in tracking system? YES X 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: 70,934 (FDC) and 65,495 (sitagliptin phosphate alone)
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) December 15, 2004 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 6, 2006 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? N/A YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? To be submitted at a later date. YES NO X
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES X NO
- Risk Management Plan consulted to OSE/IO? N/A YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 17, 2006

NDA #: 22-044

DRUG NAMES: Janumet (sitagliptin phosphate/metformin hydrochloride fixed-dose combination) Tablet

APPLICANT: Merck & Co., Inc.

BACKGROUND: Janumet is a fixed dose combination of sitagliptin phosphate and metformin. Sitagliptin phosphate is a dipeptidyl peptidase IV (DPP-IV) inhibitor approved 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., thiazolidinediones) when diet and exercise plus the single agent do not provide adequate glycemic control. The proposed indication for Janumet is for treatment of hyperglycemia in patients with type 2 diabetes mellitus when diet and exercise, plus treatment with metformin, do not provide adequate glycemic control; or as a substitute for patients who are adequately controlled on combination therapy with sitagliptin phosphate plus metformin. According to the sponsor, there is a potential clinical advantage with a fixed dose combination formulation because sitagliptin phosphate and metformin have complementary mechanisms and targets of action.

Janumet is a tablet to be taken twice daily, prior to the morning and evening meals. The Sponsor's application includes doses of 50 mg sitagliptin/500 mg metformin and 50 mg sitagliptin/1000 mg metformin, with a maximum total daily dose of 100 mg sitagliptin/2000 mg metformin.

ATTENDEES: Mary Parks, Ilan Irony, Suong Tran, Hae-Young Ahn, Jim Wei, Lee-Ping Pian, Todd Sahlroot, Todd Bourcier, Lina AlJuburi

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

Discipline/Organization

Reviewer

Medical:

Ilan Irony

Secondary Medical:

Mary Parks

Statistical:

Lee-Ping Pian

Pharmacology:

Todd Bourcier

Statistical Pharmacology:

Chemistry:

Xavier Ysern

Environmental Assessment (if needed):

N/A

Biopharmaceutical:

Jim Wei

Microbiology, sterility:

N/A

Microbiology, clinical (for antimicrobial products only):

N/A

DSI:

TBD

OPS:

Regulatory Project Management:

Lina AlJuburi

Other Consults:

DMETS, DDMAC, OSE IO

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

CLINICAL FILE X REFUSE TO FILE

• Clinical site audit(s) needed? YES NO
If no, explain:

• 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. study site audits(s) needed? YES X NO

PHARMACOLOGY/TOX N/A FILE X REFUSE TO FILE

• GLP audit needed? YES NO X

CHEMISTRY FILE X REFUSE TO FILE

• Establishment(s) ready for inspection? YES X NO

• Sterile product? YES NO X

If yes, was microbiology consulted for validation of sterilization?
YES NO

ELECTRONIC SUBMISSION:

Any comments: All electronic in the edr.

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.

X No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

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

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
OND-ODE-II-DMEP

Concurrence by: Kim Colangelo
Associate Director of Regulatory Affairs
OND-IO

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Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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**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): **metformin hydrochloride (NDA 20-357)**

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval 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," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s): metformin hydrochloride

6. (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," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s): extended release metformin HCl was not listed as a referenced product – but this FDC contains immediate release – not extended release metformin HCl

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application is a fixed-dose combination of two approved drugs sitagliptin phosphate (data owned by sponsor) and metformin hydrochloride (data referenced by sponsor).

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

10. Is the application for a duplicate of a listed drug whose only difference is that 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)? YES NO

(See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. 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.)

Not applicable (e.g., solely based on published literature. See question # 7)

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)]. OND will contact you to verify that this documentation was received.

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):

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):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) metformin HCl and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug All for the metformin related info

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Lina Aljuburi
12/18/2006 05:24:04 PM
CSO

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Aljuburi, Lina

From: Aljuburi, Lina
nt: Thursday, March 08, 2007 6:09 PM
Subject: 'Aurecchia, Steven A.'
NDA 22-044 Janumet Pediatric Deferral - RESPONSE REQUESTED

Hi Steve,

In regard to the pediatric deferral, please see below:

1. Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive.

Protocol Submission: by March 31, 2008
Study Start: by June 30, 2008
Final Report Submission: by December 31, 2010

I have inserted the dates used for NDA 21-995 Januvia. Are you planning to keep those same dates for NDA 22-044 Janumet or would you like to propose different dates? If the same dates are to be used, please submit an amendment to your pending NDA 22-044 committing to this pediatric postmarketing commitment. If you would like to propose a different timeline for Janumet, please send me an email first so we can agree before you send in the formal submission.

Feel free to contact me if you have any 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)*

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MEMORANDUM

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

DATE: March 14, 2007

FROM: Sriram Subramaniam, Ph.D.
Jagan Mohan R. Parepally, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-044, JANUMET™
(Sitagliptin Phosphate/Metformin HCl) 50 mg/500 mg,
50mg/1000 mg Tablets, Sponsored by Merck & Co., Inc.

TO: Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Drug Products
(DMEP)

At the request of DMEP, the Division of Scientific Investigations (DSI) conducted audits of the clinical and analytical portions of the following bioequivalence study:

Study: 048-00 MK-0431A: "An Open-Label, Randomized, Two-Part, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the of MK-0431/Metformin 50/500 mg and 50/1000 mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50-mg Doses of MK-0431 and 500- or 1000-mg Doses of Metformin as Individual Tablets to Healthy Adult Subjects"

The clinical portion of the study was conducted at Comprehensive Phase One, Miramar, FL, and the analytical portions were performed at _____
(for Sitagliptin), and _____ (for Metformin).

Following the inspection at Comprehensive Phase One (3/5-9/07) and _____ (2/20-22/07), Form 483s were issued. No Form 483 was issued at the conclusion of the inspection at _____ (2/26-3/2/07). DSI's evaluation of the inspectional findings follows:

Clinical Site: Comprehensive Phase One, Miramar, FL

1. Failure to maintain accurate case report forms (CRF).

There were errors in data transcription from the source documents to CRFs. The errors are listed in Table 1. However, these errors are not likely to affect the safety evaluation and study outcome. Nonetheless, the clinic should take corrective measures to assure accurate reporting of data.

2. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

a) **Contrary to protocol, post-study visit body weights were not documented for 20 out of 38 subjects reviewed.**

The subjects are listed in Table 2. The OCP reviewer should determine if the finding affects the safety evaluation.

b) **Duties and responsibilities for Protocol 048-00 were delegated to 101 employees but training records did not document protocol training for all these employees.**

The inspection found that approximately 40 of 101 employees received some sort of training specific to this protocol. Nonetheless, only a limited number of employees were directly involved in the conduct of Study 048-00. Review of qualifications of selected clinical staff who participated in the study indicated that they were qualified and experienced. The clinic stated that they will take corrective measures to assure that all study personnel are trained on their specific duties.

c) **Some study subjects were recruited by phone calls without an approved phone script.**

Potential subjects were informed of the study by phone. The clinic did not have standardized phone script for recruiting potential subjects. Nonetheless, all subjects reviewed and signed IRB-approved informed study consents prior to participating in the study. The clinic stated that they would develop an SOP for recruiting subjects by phone.

Analytical Site (for Sitagliptin): _____

NO significant observations.

Analytical Site (for Metformin): _____

3. The data in the analytical report (Project JSP) is not complete in that the analyte and internal standard (IS) responses for failed study samples were excluded in the run summary reports included with the analytical report.

The samples with unacceptable IS response, above detection range response, and poor chromatography were excluded from the run summary reports. Nonetheless, PPD objectively and consistently rejected data from study samples with an assignable cause for failure. In future, PPD stated that run summary reports in the analytical reports will include all study samples analyzed.

Conclusion:

The data from Study 048-00 are acceptable for Agency review.

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

Jagan Mohan R. Parepally, Ph.D.

Sriram Subramaniam, Ph.D.

Final Classifications:

VAI: Comprehensive Phase One, Miramar, FL

NAI: _____

VAI: _____

cc:

HFD-45/RF

HFD-48/Himaya/Parepally/Subramaniam(2)/CF

OND/AlJuburi/NDA 22-044

HFD-870/Vaidyanathan/Wei

HFR-SE2590/Barreto-Pettit

HFR-CE2545/Seeman

HFR-SW350/Kuchenthal

Draft: JP, SS 3/13/07

Edit: MKY 3/15/07

DSI:5742;O:\BE\eircover\22044mer.jan.doc

FACTS ID 803330 and _____

TABLE 1

Subject	Discrepancy in CRF	Comment
1022/0016	Period 2, 72 hr sample was collected 1.25 hrs later than what was reported in CRF.	Collected at 0945 instead of 0830 on 12/16/05.
1027/0019	Period 2, 72 hr sample was collected 3.83 hrs later than what was reported in CRF.	Collected at 1226 instead of 0836 on 12/16/05.
1042/0025	Post study vital signs and ECG data for Subject 1053/0032 reported in the CRF	Vital signs and ECG for Subject 1042/0025 were normal.
1053/0032	Post study vital signs and ECG data for Subject 1042/0025 reported in the CRF	Vital signs and ECG for Subject 1053/0032 were normal.
1055/0033	Post study ECG tracing indicated "abnormal ECG, cannot rule out anterior infarct". The CFR reported the ECG as normal, instead of reporting it as tracing not in normal limits but determined as NCS by PI, as required by the sponsor's data entry instructions.	The ECG was verified by the PI during the study and ruled as not clinically significant.
1049/0029	Visit 1 urinalysis reported as normal although the result showed occult blood. Test repeated, but the repeat result was not reported in CRF.	The repeat urinalysis was normal.
1068/0038	Repeat hematology test on 12/5/05 not reported in CRF.	Repeat result was normal.
1036/0022	Post-study body weight was reported as missing in CRF although weight was recorded.	The subject's weight was within normal limits.

TABLE 2: Subjects with no post study body weights

Subject
1001/0001
1002/0002
1004/0003
1006/0004
1007/0005
1008/0006
1009/0007
1010/0008
1015/0010
1017/0011
1018/0012
1019/0013
1020/0014
1021/0015
1022/0016
1025/0018
1027/0019
1029/0020
1033/0021
1037/0023

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/s/

Amalia Himaya

3/19/2007 12:52:55 PM

CSO

Paper copy signed by Dr. Viswanathan on 3/16/07.

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Aljuburi, Lina

From: Aljuburi, Lina
Sent: Friday, March 16, 2007 3:37 PM
To: 'Aurecchia, Steven A.'
Subject: NDA 22-044 Janumet comments

Steve,

Re: NDA 22-044 Janumet (sitagliptin/metformin HCl) Tablet

Please see attached document containing general comments in addition to remarks on the carton and container labels:



Janumet_Comment
sToMerck_03.16....

Feel free to contact me if you have any 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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Comments regarding NDA 22-044 Janumet (sitagliptin/metformin HCl) Tablets

1. GENERAL COMMENTS

- a. Because of the experiences we have learned from post-marketing errors with drug products having similar propriety prefixes and identical established names, it will be imperative to educate healthcare providers and patients about the differences between Januvia and Janumet. Selection errors may also occur because these products will be stored in close proximity on pharmacy shelves and the product poses similar labels because they are from the same manufacturer. When placing this product into a busy clinic, pharmacy, or inpatient unit the wrong product will likely be dispensed especially if healthcare providers are unaware of the introduction of this new product. Thus, it is important to distinguish the Januvia labels and labeling from Janumet in addition to educating health care providers and patients about its existence and product differences. Distinct labeling and education prior to launch, during launch and during postmarketing are critical in order to minimize confusion between Januvia and Janumet. The labeling, packaging, and product appearance can aid in the prevention of medication errors with Januvia and Janumet.
- b. We note the availability of a 60 count Sample. Samples are generally made available in smaller quantities. This amount is equivalent to a one month supply of medication making it more like a unit of use bottle for commercial sale rather than a sample. Therefore, we recommend that the quantity of the sample be reduced to a one week supply or less.
- c. The principal display panel contains a graphic with numbers inside a circle. We acknowledge that you are trying to provide healthcare practitioners with identifying characteristics of the tablet; however without identification as to what this graphic indicates, it may be confusing because of its area of placement and its prominence on the label. Postmarketing errors have shown these numbers to be misinterpreted to indicate the strength or net quantity. We recommend decreasing the size of the graphic and relocating it to the side panel in order to decrease confusion with the strength,

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 § 552(b)(5) Deliberative Process

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/s/

Lina Aljuburi
3/16/2007 03:46:58 PM
CSO

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MEMORANDUM

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

DATE: March 20, 2007

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

VIA: Lina AlJuburi, Pharm D., M.S., Regulatory Project Manager
Division of Metabolic and Endocrinology Products

FROM: Sharon R. Mills, B.S.N., R.N., C.C.R.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

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

SUBJECT: DSRCs Review of Patient labeling for Janumet (sitagliptin phosphate monohydrate and metformin hydrochloride) tablet, NDA 22-044.

Background and Summary

The sponsor submitted NDA 22-044 on May 31, 2006 for Janumet as a fixed dose combination tablet containing sitagliptin phosphate monohydrate and metformin hydrochloride. The NME sitagliptin phosphate was approved on October 16, 2006.

See the attached patient labeling (PPI) for our recommended revisions to the draft PPI submitted for Janumet (sitagliptin phosphate monohydrate and metformin hydrochloride) tablets. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have simplified wording where possible, made it consistent with the PI and removed unnecessary information. We have also put this PPI in the patient-friendly format (specified in 21 CFR 208) that we are recommending for all FDA approved patient labeling, although this format is not required for voluntary PPIs. These recommended changes are consistent with current research to improve risk communication to a broad range of audiences including those with lower literacy levels.

These revisions are based on draft product labeling (PI) submitted by the sponsor on February 5, 2007 and then revised by the review division on March 12, 2007. Patient information should always be consistent with the prescribing information. All relevant future changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. A PPI for JANUMET is voluntary. Unless all JANUMET product is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that the patient will receive the PPI. The sponsor should state their intended mechanism for distributing the PPI to patients.
2. The draft PPI submitted by the sponsor has a Flesch Kincaid grade level of 7.4, and a Flesch Reading Ease Score of 62.5. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable. We made changes as discussed above under the section *Background and Summary*.
3. The PI contains a boxed warning about the potential risk of lactic acidosis associated with taking metformin-containing products. This information should be prominently placed at the beginning of the PPI and then may be referenced throughout the PPI as appropriate. Using patient-friendly language, we have placed this information in a box entitled, "What is the most important information that I should know about Janumet?" at the beginning of the PPI. Refer to 21CFR 208.20 (b) (2).
4. Contraindications to use of a product are generally presented in the section of the PPI called "*Who should not take TRADE NAME?*" and reflect the *Contraindications* section of the PI (section 4). We have deleted the third bullet point. Congestive heart failure is not a contraindication; therefore, this information has been moved to "What should I tell my doctor before and during treatment with JANUMET?"
5. The JANUMET boxed warning for lactic acidosis related to metformin indicates that one of the nonspecific symptoms is respiratory distress. Section 17.1 Instructions, tells health practitioners to instruct patients that they should report "unexplained hyperventilation." The sponsor proposes in the PPI the language "trouble breathing." It seems that there is inconsistency in the language between the PI boxed warning and these other areas as noted. Respiratory distress has a broader definition than does hyperventilation. The review division and sponsor should clarify the message that needs to be conveyed to health practitioners and patients with regard to reporting symptoms of respiratory distress. Section 17.1 should be made consistent with the Boxed Warning. The PPI should be revised to be consistent with the PI. Since metformin is available in other fixed dose combination products as well as by itself, we recommend that the review division consider looking at this issue for all metformin-containing products and updating the labels for consistency.

Comments to the review division are ***bolded, underlined and italicized***. We are providing a marked-up and clean copy of the revised document in Word to the review division.

Please call us if you have any questions.

Patient Information
JANUMET™ (jah-NEW-met)
(sitagliptin/metformin HCl)

Tablets

Read the Patient Information that comes with JANUMET¹ before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

IDSRCs Comment: The PI contains a boxed warning about the risk of lactic acidosis associated with metformin. This should be conveyed using patient-friendly language and placed prominently at the beginning of the PPI. The information may be further referenced throughout the PPI as appropriate. See below.]

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/s/

Sharon Mills
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DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
3/20/2007 02:23:02 PM
DRUG SAFETY OFFICE REVIEWER

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Aljuburi, Lina

From: Mills, Sharon
nt: Wednesday, March 28, 2007 5:56 PM
Aljuburi, Lina
cc: Clark, Nancy; Duckhorn, Jodi
Subject: Janumet N22-044 DSRCS responses/modifications to sponsor comments on PPI
Attachments: DSRCS comments to sponsor revisions of 26-Mar-07 final.doc; DSRCS Comments Regarding Merck Response to PPI Comments_3-28-07.doc

Hi Lina,

Here are our track changes in word as well as a separate word document summarizing our comments.

Please let me know if you have any questions.

Thanks,
Sharon



DSRCS comments to sponsor revi...
DSRCS Comments Regarding Merck...

Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
FDA/CDER/OSE/DSRCS
103 New Hampshire Avenue
Bldg. 22, room 4485
Mailstop 4447
Silver Spring, MD 20993-0002
Phone: 301.796.2036
Fax: 301.796.9837
email: sharon.mills@fda.hhs.gov

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

Memorandum

PRE-DECISIONAL AGENCY INFORMATION

Date: March 9, 2007

To: Lina Aljuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrinology Products

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

Subject: Drug: Janumet (sitagliptin/metformin HCl) Tablets
NDA: 22-044

DDMAC has reviewed the proposed product labeling (PI), patient package insert (PPI), and all container labeling for Janumet (sitagliptin/metformin HCl) Tablets and we offer the following comments.

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

Proposed Product Labeling

**Highlights of Prescribing Information Section
Adverse Reactions**

"There were no adverse reactions reported in >5% of patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin. (6.1)"

While the above sentence is included as part of the Adverse Reactions section in the highlights section of the proposed Janumet label, we recommend also including the following relevant adverse reactions from the proposed label into the highlights as well for completeness of this section since they are pertinent, especially to the addition of metformin in this combination drug product.

"The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo was nasopharyngitis."

And

"The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache."

Adverse Reactions - Clinical Trials Experience

"In placebo-controlled trials, in patients with type 2 diabetes mellitus on metformin monotherapy, the addition of sitagliptin 100mg daily was **well tolerated**." (emphasis added) (Page 6, 6.1)

The use of the claim "well tolerated" is promotional tone and is not encouraged because it minimizes the adverse reactions that are associated with the use of Janumet. Therefore, we recommending deleting the use of the terms, "well tolerated" from this and similar sections.

Patient Product Labeling

We have no comments pertaining to this section at this time.

Container Labeling

We have no comments pertaining to this section at this time.

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

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/s/

Kanika Vij
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DDMAC REVIEWER

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