

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-044**

**PROPRIETARY NAME REVIEW(S)**

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> October 11, 2006	<b>DESIRED COMPLETION DATE:</b> February 2, 2007	<b>OSE CONSULT #:</b> 2006-462
<b>DATE OF DOCUMENT:</b> May 31, 2006 and July 24, 2006	<b>PDUFA DATE:</b> March 31, 2007	
<b>TO:</b> Mary Parks, M.D., Director, Division of Metabolism and Endocrine Products, HFD-510		
<b>THROUGH:</b> Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support		
<b>FROM:</b> Tselaine Jones Smith, PharmD, Safety Evaluator Division of Medication Errors and Technical Support		
<b>PRODUCT NAME:</b> Janumet (Sitagliptin Phosphate and Metformin Hydrochloride) Tablets 50 mg/500 mg and 50 mg/1000 mg	<b>NDA SPONSOR:</b> Merck	
<b>NDA #:</b> 22-044		

**RECOMMENDATIONS:**

1. DMETS does not recommend the use of the proprietary name, Janumet.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Janumet, acceptable from a promotional perspective.
4. DMETS recommends that the Division contact Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee, for proper guidance on this salt nomenclature issue as outlined in Section II of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-796-0080.

**Division of Medication Errors and Technical Support (DMETS)  
Office of Surveillance and Epidemiology  
HFD-420; WO 22; Mail Stop 4447  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME, LABEL AND LABELING REVIEW**

**DATE OF REVIEW:** December 11, 2006

**NDA #:** 22-044

**NAME OF DRUG:** **Janumet**  
(Sitagliptin Phosphate and Metformin Hydrochloride) Tablets  
50 mg/500 mg and 50 mg/1000 mg

**NDA HOLDER:** Merck

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Metabolism and Endocrine Products (HFD-510), for assessment of the proprietary name, Janumet, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

**PRODUCT INFORMATION**

Janumet contains two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin phosphate and metformin hydrochloride. 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 dosage of Janumet should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of 100 mg sitagliptin and 2000 mg metformin. Janumet should be given twice daily with meals, with gradual dose escalation. The starting dose should be based on the patient's current regimen. Janumet will be supplied as 50 mg/500 mg and 50 mg/1000 mg tablets.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3,4</sup> for existing drug names which sound-alike or look-alike to Janumet to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the

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<sup>1</sup> MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

<sup>4</sup> Phonetic and Orthographic Computer Analysis (POCA)

U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. The Saegis<sup>6</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

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

1. DDMAC finds the proprietary name, Janumet, acceptable from a promotional perspective.
2. The Expert Panel identified the following twenty proprietary names that were thought to have the potential for confusion with Janumet: Sinemet, Januvia, Avandamet, Jantoven, Anzemet, Janupap, Genapap, Temovate, Tenuate, Janumine, Janimine, Tagamet, Junovan, Tirosint, Sinumist SR, Benemid, PanMist, Prinivil, Penovel and Genhemat.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Janumet with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Janumet (see page 4). These prescriptions were optically scanned and one prescription was

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Janumet 50/500 mg #15 1 tablet by mouth bid with meals</p>	<p>Janumet 50 mg/500 mg #15 Take 1 tablet by mouth twice a day with meals.</p>
<p><u>Inpatient RX:</u></p> <p>Janumet 50/500mg + tab po q meals</p>	

2. Results:

Seventeen (n= 17) respondents provided interpretations close in spelling to Sinemet. For example, written inpatient, outpatient and voice mail orders were interpreted as Samumet or Samimet, which look and sound similar to Sinemet. Sinemet is a currently marketed U.S. product that is indicated for the treatment of Parkinson's disease. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Janumet, twenty names were identified as having the potential to look and sound similar to Janumet: Sinumist SR, Jantoven, Anzemet, Janupap, Genapap, Temovate, Tenuate, Janumine, Janimine, Tagamet, Junovan, Tirosint, Benemid, PanMist, Prinivil, Penovel, Genhemat, Sinemet, Januvia and Avandamet.

DMETS conducted prescription studies to simulate the prescription ordering process. Although there was no positive finding where an exact interpretation of Sinemet, seventeen respondents from the Janumet study misinterpreted the name as Samumet or Samimet, which look and sound similar to Sinemet, an already existing U.S. marketed drug product.

Upon initial review of the aforementioned names, it was determined that sixteen names lacked convincing look-alike and sound-alike similarities with Janumet. In addition to there not being additional information on the drug name or the drug being taken off the market, the products also had numerous differentiating product characteristics such as product strength, indication for use, frequency of administration, prescription status, patient population and/or dosage formulation. The seventeenth name, Sinumist SR, has some visual similarity to Janumet. However, the differences in product characteristics such as indication, strength, dose, and patient population minimize the risk of confusion.

The remaining three (n=3) names, Sinemet, Januvia and Avandamet, are described in Table 1 which includes their available dosage forms and their usual doses. Upon further analysis Avandamet was considered to have minimal risk of confusion. The reason this name was discarded and considered acceptable is described in Table 1. The remaining names of concern are Sinemet and Januvia which are discussed in detail below.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other??
Janumet	Sitagliptin phosphate/Metformin Hydrochloride Tablets 50 mg/500 mg and 50 mg/1000 mg	Twice daily with meals, with a gradual dose escalation to reduce the gastrointestinal side effects due to metformin	
Sinemet	Carbidopa/Levodopa Tablets 10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg	Initial: Carbidopa 50 mg/levodopa 100 mg three times a day  Dosage adjustment: alternate tablet strengths may be substituted according to individual carbidopa/levodopa requirements	
Januvia	Sitagliptin Phosphate Tablets: 25 mg, 50 mg, and 100 mg	200 mg once daily (monotherapy) 100 mg once daily (combination therapy with metformin HCl) Januvia is given without regard to food	
Avandamet	Rosiglitazone and Metformin HCl Tablets 1 mg/500 mg, 2 mg/500 mg and 4 mg/500 mg 2 mg/1000 mg and 4 mg/1000 mg	Initial dose should be based on current dose of rosiglitazone and/or metformin; daily dose should be divided and given with meals	<ul style="list-style-type: none"> <li>• Strengths of rosiglitazone (Avandamet) and sitagliptin (Janumet)</li> <li>• Sound of first two syllables (Avanda- vs. Janu)</li> </ul>

1. Sinemet look-alike similarities to Janumet

DMETS believes Sinemet is problematic because it poses strong orthographic characteristics to Janumet making it difficult to differentiate the two names when scripted. This similarity increases the likelihood for confusion between the two drugs which can lead to medication errors. Moreover, postmarketing experience has shown that when names are very similar, product differences may not necessarily prevent medication errors from occurring between the products.

Sinemet and Janumet can look-alike when scripted because of the similarity of the beginning letters ('S' vs. 'J') and the middle letters ('-ine-' vs. '-anu-'). In addition, both names have the same ending letters ('-met'), thereby making the two names difficult to differentiate in writing.

*Sinemet 10mg/100mg*  
*Janumet 50mg/100mg*

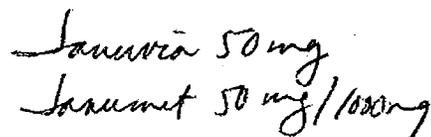
Sinemet and Janumet differ in frequency of administration (three times a day vs. twice a day) and indication (Parkinson's disease vs. Type 2 diabetes). However, Sinemet and

Janumet share overlapping dosage forms (tablets). Additionally, both products are combination products where the strengths are expressed for both active ingredients and their denominators are numerically similar (10 mg/100 mg, 25 mg/100 mg vs. 50 mg/1000 mg). Post marketing experience has shown that products that share these characteristics are more likely to be confused with each other in the marketplace thereby contributing to medication errors. For example, in the Institute of Safe Medication Practices (ISMP<sup>†</sup>) Med-E.R.R.S. August 2004 survey "Prescribing Combination Products", practitioners indicated that both strengths for combination products are not always written regardless of whether both ingredients vary (24%) or if one ingredient has a fixed dosage strength and the other ingredient has a variable dosage strength (49%). Thus, if patients inadvertently receive Sinemet instead of Janumet, they can experience palpitations, arrhythmias, spasms and hypotension or hypertension. Conversely, if patients inadvertently receive Janumet instead of Sinemet, they can experience hypoglycemia. Furthermore, Janumet contains metformin which can increase the patients risk for lactic acidosis. Metformin has the following black box warning: "Lactic acidosis is a rare, but serious, metabolic complication that can occur from the metformin accumulation during treatment with Janumet; when it occurs, it is fatal in approximately 50% of cases."

Thus, because of their visual similarity, similarity in dosage form and both products being combination products with similar numerical strengths, DMETS does not believe these products should be co-marketed.

2. Januvia look-alike similarities to Janumet

DMETS believes Januvia is too similar on appearance to Janumet. This similarity stems from the shared prefix 'Janu' and similarities in the ending letters '-vi-' in Januvia and '-me-' in Janumet when scripted. Although the upstroke of the letter 't' at the end of Janumet may help to differentiate the two names, postmarketing experience has shown that names with differences in their endings ('-ia' vs. '-et') are overlooked, trail off or unrecognizable and may not necessarily prevent medication errors from occurring between the products. Avandia vs. Avandamet are illustrations of such errors.



The image shows two lines of handwritten text in cursive. The first line reads "Januvia 50mg" and the second line reads "Janumet 50mg/1000mg". The handwriting is fluid and somewhat slanted, illustrating the visual similarity between the two drug names and their dosages.

Januvia and Janumet share the same active ingredient (sitagliptin phosphate), indication (type 2 diabetes), auxiliary instructions (take with food), dosage form and similar strengths of sitagliptin phosphate (50 mg). Januvia is a single ingredient (sitagliptin) product expressed as 50 mg and dosed once daily whereas Janumet is a combination active ingredient (sitagliptin and metformin) expressed as 50 mg/500 mg and 50 mg/1000 mg and is dosed twice daily.

Although there is a difference in the expression of strength and dose between the two products, postmarketing experience has shown errors with products that have similar product characteristics as those mentioned above. For example, there has been confusion between Avandia and Avandamet (OSE Review #05-0050) due to identical indication of use, similar name prefixes, shared active ingredient and strength (rosiglitazone: 1 mg,

<sup>†</sup> ISMP August 2004 Question-ERR<sup>®</sup> survey on Prescribing Combination Products: <http://www.med-errs.com/Question/Resulterr0408.asp>

2 mg, and 4 mg), dosage form and proximity on pharmacy shelves. Similarly, DMETS anticipates errors between Janumet and Januvia because they overlap in strength (50 mg), auxiliary dosing instructions (take with food), shared active ingredient (sitagliptin), similar proprietary name prefixes ('Janu-') and route of administration. In addition, both Januvia and Janumet are manufactured by Merck.

Furthermore, Janumet will be placed in close proximity to Januvia on pharmacy shelves, thereby increasing the risk of errors. Thus, if patients inadvertently receive Janumet instead of Januvia, they will be subject to the inappropriate treatment for diabetes. Moreover, if patients are already on metformin, they may be at increased risk for lactic acidosis due to the additional metformin contained in Janumet. Metformin has the following black box warning: "Lactic acidosis is a rare, but serious, metabolic complication that can occur from the metformin accumulation during treatment with Janumet; when it occurs, it is fatal in approximately 50% of cases." On the other hand, if patients receive Januvia instead of Janumet, they are subject to the inappropriate treatment for type 2 diabetes due to the lack of metformin treatment in Januvia.

Based on the similar names and product characteristics between Januvia and Janumet, along with post-marketing experience with similar diabetes products, DMETS does not recommend the use of the name Janumet.

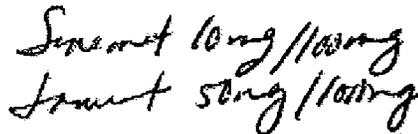
## II. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name Janumet because of its visual similarity to Sinemet and Januvia. Additionally, the labels and labeling were reviewed from a medication error perspective and recommendations are provided below.

### A. Sinemet look-alike similarities to Janumet

DMETS believes Sinemet is problematic because it poses strong orthographic characteristics to Janumet making it difficult to differentiate the two names when scripted. This similarity increases the likelihood for confusion between the two drugs which can lead to medication errors. Moreover, postmarketing experience has shown that when names are very similar, product differences may not necessarily prevent medication errors from occurring between the products.

Sinemet and Janumet can look-alike when scripted because of the similarity of the beginning letters ('S' vs. 'J') and the middle letters ('-ine-' vs. '-anu-'). In addition, both names have the same ending letters ('-met'), thereby making the two names difficult to differentiate in writing.



The image shows two lines of handwritten text in cursive. The first line reads "Sinemet 10mg/100mg" and the second line reads "Janumet 50mg/100mg". The handwriting is very similar, with the 'S' in Sinemet and 'J' in Janumet both starting with a similar loop, and the middle letters '-ine-' and '-anu-' being written in a way that makes them look alike.

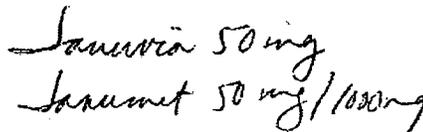
Sinemet and Janumet differ in frequency of administration (three times a day vs. twice a day) and indication (Parkinson's disease vs. Type 2 diabetes). However, Sinemet and Janumet share overlapping dosage forms (tablets). Additionally, both products are combination products where the strengths are expressed for both active ingredients and their denominators are numerically similar (10 mg/100 mg, 25 mg/100 mg vs. 50 mg/1000 mg). Post marketing experience has shown that products that share these characteristics are more likely to be confused with each other in the marketplace thereby contributing to medication errors. For example, in the Institute

of Safe Medication Practices (ISMP<sup>†</sup>) Med-E.R.R.S. August 2004 survey “Prescribing Combination Products”, practitioners indicated that both strengths for combination products are not always written regardless of whether both ingredients vary (24%) or if one ingredient has a fixed dosage strength and the other ingredient has a variable dosage strength (49%). Thus, if patients inadvertently receive Sinemet instead of Janumet, they can experience palpitations, arrhythmias, spasms and hypotension or hypertension. Conversely, if patients inadvertently receive Janumet instead of Sinemet, they can experience hypoglycemia. Furthermore, Janumet contains metformin which can increase the patients risk for lactic acidosis. Metformin has the following black box warning: “Lactic acidosis is a rare, but serious, metabolic complication that can occur from the metformin accumulation during treatment with Janumet; when it occurs, it is fatal in approximately 50% of cases.”

Thus, because of their visual similarity, similarity in dosage form and both products being combination products with similar numerical strengths, DMETS does not believe these products should be co-marketed.

B. Januvia look-alike similarities to Janumet

DMETS believes Januvia is too similar on appearance to Janumet. This similarity stems from the shared prefix ‘Janu’ and similarities in the ending letters ‘-vi-’ in Januvia and ‘-me-’ in Janumet when scripted. Although the upstroke of the letter ‘t’ at the end of Janumet may help to differentiate the two names, postmarketing experience has shown that names with differences in their endings (‘-ia’ vs. ‘-et’) are overlooked, trail off or unrecognizable and may not necessarily prevent medication errors from occurring between the products. Avandia vs. Avandamet are illustrations of such errors.



The image shows two lines of handwritten text in cursive. The first line reads "Januvia 50mg" and the second line reads "Janumet 50mg/1000mg". The handwriting is somewhat slanted and the letters are closely spaced, illustrating the visual similarity between the two drug names and their dosages.

Januvia and Janumet share the same active ingredient (sitagliptin phosphate), indication (type 2 diabetes), auxiliary instructions (take with food), dosage form and similar strengths of sitagliptin phosphate (50 mg). Januvia is a single ingredient (sitagliptin) product expressed as 50 mg and dosed once daily whereas Janumet is a combination active ingredient (sitagliptin and metformin) expressed as 50 mg/500 mg and 50 mg/1000 mg and is dosed twice daily.

Although there is a difference in the expression of strength and dose between the two products, postmarketing experience has shown errors with products that have similar product characteristics as those mentioned above. For example, there has been confusion between Avandia and Avandamet (OSE Review #05-0050) due to identical indication of use, similar name prefixes, shared active ingredient and strength (rosiglitazone: 1 mg, 2 mg, and 4 mg), dosage form and proximity on pharmacy shelves. Similarly, DMETS anticipates errors between Janumet and Januvia because they overlap in strength (50 mg), auxiliary dosing instructions (take with food), shared active ingredient (sitagliptin), similar proprietary name prefixes (‘Janu-’) and route of administration. In addition, both Januvia and Janumet are manufactured by Merck.

Furthermore, Janumet will be placed in close proximity to Januvia on pharmacy shelves, thereby increasing the risk of errors. Thus, if patients inadvertently receive Janumet instead of Januvia,

<sup>†</sup> ISMP August 2004 Question-ERR<sup>®</sup> survey on Prescribing Combination Products: <http://www.med-errs.com/Question/Resulterr0408.asp>

they will be subject to the inappropriate treatment for diabetes. Moreover, if patients are already on metformin, they may be at increased risk for lactic acidosis due to the additional metformin contained in Janumet. Metformin has the following black box warning: "Lactic acidosis is a rare, but serious, metabolic complication that can occur from the metformin accumulation during treatment with Janumet; when it occurs, it is fatal in approximately 50% of cases." On the other hand, if patients receive Januvia instead of Janumet, they are subject to the inappropriate treatment for type 2 diabetes due to the lack of metformin treatment in Januvia.

Based on the similar names and product characteristics between Januvia and Janumet, along with post-marketing experience with similar diabetes products, DMETS does not recommend the use of the name Janumet.

DMETS reviewed the labels and labeling from a safety perspective and have identified the following areas of possible improvement, which might minimize potential user error.

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. DMETS acknowledges that the sponsor is 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,
- d. The colors representing the product strength are being used interchangeably on the sample labels and stock labels (see below). Revise in order to ensure that there is consistency with the font colors of the different strengths.

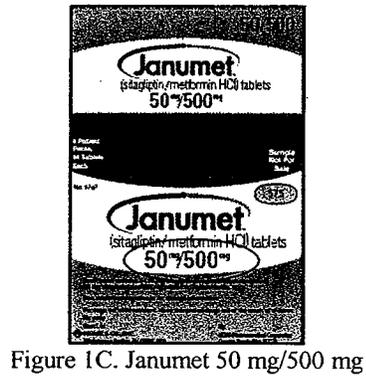
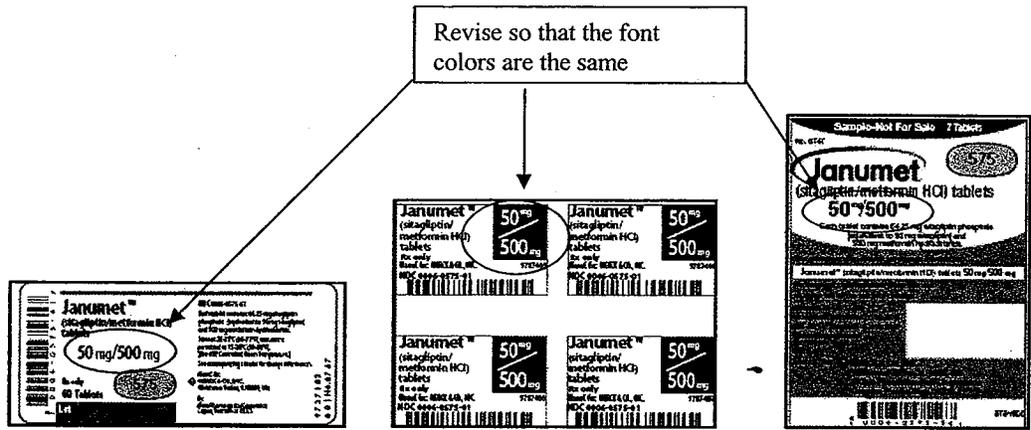


Figure 1C. Janumet 50 mg/500 mg

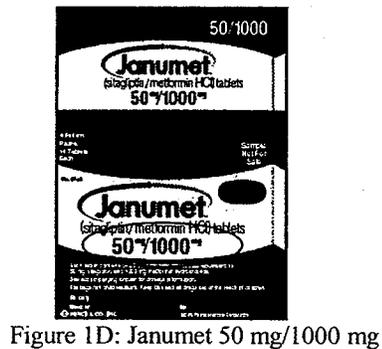
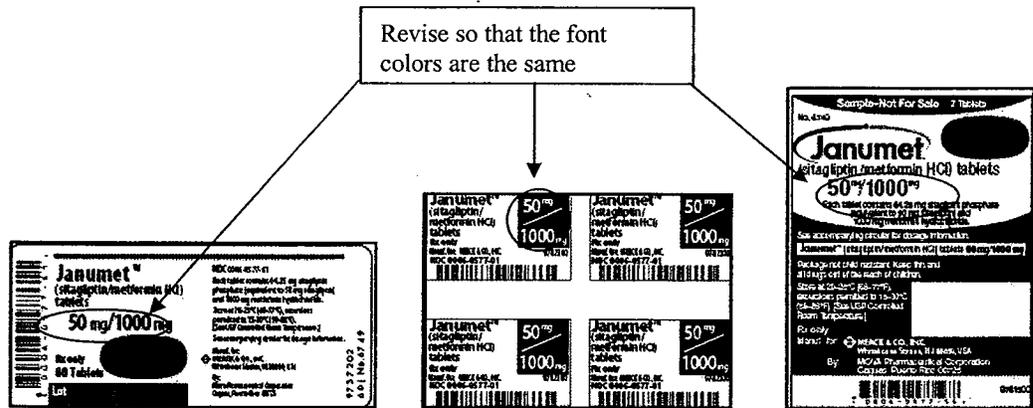
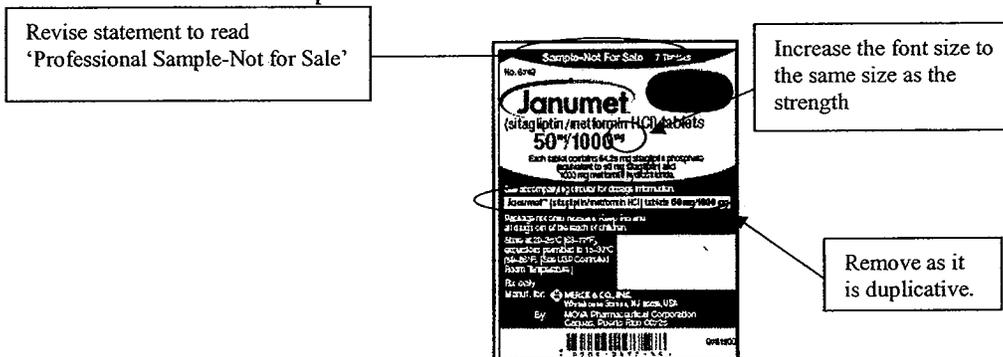


Figure 1D: Janumet 50 mg/1000 mg

5. CONTAINER LABEL (Professional Sample — i)

- a. See COMMENTS 1a, 1c, 1d and 2a.
- b. Delete the graphic encircling the proprietary name, Janumet, as it distorts the appearance of the proprietary name.
- c. The principal display panel includes “No. 674X”. However, this information is not identified as to what it represents. Delete this information as it may be misinterpreted as the strength or the net quantity or clearly identify what each of these number represents.
- d. DMETS cannot discern from the presentation whether the — container is a bottle, blister, or pouch. If this is a pouch, ensure that the proprietary name, established name, strength, and expiration date remain intact after the pouch is open. Additionally, if this is a blister configuration, please ensure that this information is intact even after each and every tablet has been removed from the packaging configuration.
- e. Revise the statement ‘Sample-Not For Sale’ to read ‘Professional Sample – Not for sale’ and increase the prominence of the statement.



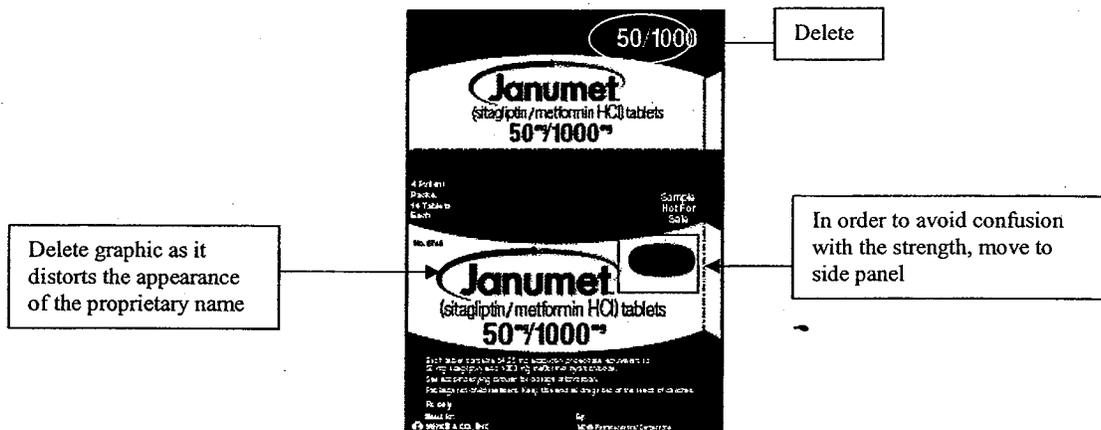
- f. Increase the font size of the unit designation to the same size as that of the strength.
- g. DMETS notes that the strength is presented twice on the principal display panel. Delete the presentation of this information (in the white box) as it is duplicative.

6.

See Comments 5b, 5d and 5f.

7. CARTON LABELING (Professional Sample-4 Patient Packs)

- a. See COMMENTS 1a, 1c, 1d, 2a, 5b, 5c, 5e and 5f.
- b. DMETS notes that the strength is presented twice on both the principal display panel and on the side panels. Additionally, expression of strength is presented without a unit designation (i.e., mg). Delete the expression of strength without the unit designation as it is duplicative and incomplete.



I. INSERT LABELING

See COMMENT 2a.

J. PATIENT INFORMATION SHEET

See COMMENT 2a.

Appears This Way  
On Original

**Appendix A**

<b>Inpatient</b>	<b>Outpatient</b>	<b>Voice</b>
Samimet	Samimet	Samimet
Sanumet	Sanumet	Sanumet
Samimet	Samimet	Samimet
Janunet	Janunet	Janunet
Ianumet	Ianumet	Ianumet
Jamumet	Jamumet	Jamumet
Lamimet	Lamimet	Lamimet
Samimet	Samimet	Samimet
Lamunet	Lamunet	
Sanumet	Sanumet	
Lanumet	Lanumet	
Samimet		
Sanumet		
Samimet		
Janunet		
Ianumet		
Jamumet		
Lamimet		

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Tselaine Jones-Smith  
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
3/15/2007 02:02:01 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
3/15/2007 02:26:14 PM  
DRUG SAFETY OFFICE REVIEWER

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**REQUEST FOR CONSULTATION**

(Division/Office):

Mail: OSE, DSRCS, Attention: Nancy Clark

FROM:

**Lina AlJuburi, Regulatory Project Manager, DMEP  
WO Bldg #22, Room 3103  
Ph#: 301-796-1168**

DATE February 27, 2007	IND NO. N/A	NDA NO. 22-044	TYPE OF DOCUMENT NDA Labeling: PPI	DATE OF DOCUMENT February 5, 2007
NAME OF DRUG Janumet (sitagliptin phosphate and metformin FDC) Tablet		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG antidiabetic	DESIRED COMPLETION DATE March 20, 2007
NAME OF FIRM: Merck & Co., Inc.				

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                    |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                           |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                      |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                               |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>New PPI</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  |   |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input checked="" type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

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|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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**COMMENTS/SPECIAL INSTRUCTIONS:**

Janumet (sitagliptin phosphate and metformin FDC) Tablet is for the treatment of type 2 diabetes.  
Please review the patient product information (PPI) for this NDA (document attached to this consult request form.)  
The NDA was submitted electronically as an eCTD submission and can be found in the edr.  
User fee goal date: Saturday, March 31, 2007  
Feel free to contact me with any questions. Many thanks, Lina

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

4 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF SURVIELLANCE AND EPIDEMIOLOGY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> March 22, 2007	<b>DESIRED COMPLETION DATE</b> March 27, 2007 <b>PDUFA DATE:</b> March 31, 2007	<b>OSE CONSULT #:</b> 2007-666
<b>TO:</b> Mary Parks, M.D. Director, Division of Metabolism and Endocrinology Products HFD-510		
<b>THROUGH:</b> Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support		
<b>FROM:</b> Tselaine Jones Smith, PharmD, Safety Evaluator Division of Medication Errors and Technical Support		
<b>PRODUCT NAME:</b> <b>Janumet</b> (Sitagliptin Phosphate/Metformin Hydrochloride) 70 mg/1000 mg and 100 mg/1000 mg	<b>NDA SPONSOR:</b> Merck	
<b>NDA #:</b> 22-044		
<b>RECOMMENDATIONS:</b>  In order to minimize potential errors with the use of Janumet, DMETS continues to recommend implementation of the label and labeling revisions as outlined in our previous review (OSE Consult # 2006-462). At this time, Merck & Co., Inc has not provided persuasive evidence to diminish our safety concerns with regards to the labels and labeling.  DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-796-0080.		

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

**LABEL AND LABELING REVIEW**

**DATE OF REVIEW:** March 26, 2007

**NDA #:** 22-044

**NAME OF DRUG:** **Janumet**  
(Sitagliptin Phosphate/Metformin Hydrochloride)  
50 mg/1000 mg and 100 mg/1000 mg

**NDA HOLDER:** Merck

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for re-assessment of the recommended revisions to their labels and labeling for Janumet. The labels and labeling were previously reviewed by DMETS (OSE # 2006-462, dated December 11, 2006) from a safety perspective. The sponsor submitted a rebuttal to DMETS on March 22, 2007. This review will evaluate the concerns noted in the March 22<sup>nd</sup> letter.

**PRODUCT INFORMATION**

Janumet contains two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin phosphate and metformin hydrochloride. 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 dosage of Janumet should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of 100 mg sitagliptin and 2000 mg metformin. Janumet should be given twice daily with meals, with gradual dose escalation. The starting dose should be based on the patient's current regimen. Janumet will be supplied as 50 mg/500 mg and 50 mg/1000 mg tablets.

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## II. RISK ASSESSMENT:

DMETS notes that the sponsor based many of its justifications for the Janumet labels and labeling on the FDA approved Januvia. Please note that from a medication error perspective, DMETS has remained consistent in our recommendations for the labels and labeling for both Janumet and Januvia. Specifically, DMETS refers the sponsor to an e-mail dated October 5, 2006 in which the Division submitted comments regarding revisions to the labels and labeling for Januvia. At the time of the email submission, the Division requested a response from the sponsor. To our knowledge, the Division did not receive feedback from the sponsor prior to approval.

Furthermore, DMETS is inclined to believe that the sponsor's reluctance to change their labels may be due in part to the production of the labels prior to submitting the name, labels and labeling to the FDA for review and comments. The pre-production of labels and labeling prior to the FDA having an opportunity to comment on the name, labels and labeling poses numerous risks in regards to drug safety and can lead to post-marketing medication errors.

The sponsor has requested a re-consideration of the recommended revisions to their labels and labeling for Janumet. The sponsor's comments are followed by the DMETS response below.

### 1. General Comments

- a. **Merck fully agrees with the importance of providing healthcare practitioners with the ability to distinguish the labels and labeling between JANUVIA and JANUMET. We believe that the JANUMET labels and labeling, as submitted, have been designed in such a way as to ensure clear differentiation from other marketed products, including JANUVIA, so as to minimize any potential confusion.**

DMETS Response:

DMETS acknowledges the sponsor has attempted to differentiate the labels and labeling between Januvia and Janumet. However, we do not believe this differentiation is adequate to minimize errors. Postmarketing evidence has shown that products that share the same active ingredient and the same prefixes have resulted in selection error due to their close proximity to each other on pharmacy shelves. For example, post-marketing experience has shown errors between Avandia and Avandamet. Even though both products had distinct labels and labeling, Avandia was dispensed instead of Avandamet and vice-versa. These reports illustrate that errors can occur between combination products and the parent product that contains the single ingredient. While DMETS believes that the sponsor has made an adequate attempt to distinguish the Janumet labels and labeling from those of Januvia, we continue to believe that education prior to launch, during launch and during postmarketing are critical in order to minimize confusion between Januvia and Janumet.

- b. **The 60 count bottle is a complementary bottle representing a one month supply of JANUMET. Consistent with industry and Merck practice, these are typically provided to physicians only periodically, and are not the standard sample package configuration (which for JANUMET does consist of a one-week supply). Therefore, Merck proposes to retain the 60 count bottle configuration.**

Therefore, we continue to recommend decreasing the size of the graphic and relocating it to the side panel in order to decrease confusion with the strength and/or net quantity.

- d. **Merck currently applies an internal strength colorcoding algorithm for all US marketed (trade/stock) products. This system was developed to reduce medication errors through the use of pre-defined color coding to differentiate strengths of the same product. Our intention is to minimize dispensing errors by pharmacy staff when different strengths within a product family are stocked next to each other on the pharmacy shelf.**

**Although Merck does not employ the same color algorithm to promotional labeling, we do strive to ensure ready labeling differentiation among different strengths of a given product. Because physician samples and trade/stock labels are distributed in different settings (i.e., trade/stock labels are used in hospital/commercial pharmacies, while physician samples are used within healthcare provider offices), we believe that the use of different color algorithms across trade and physician sample labeling lines for a given product family does not increase the risk of dispensing errors. Merck proposes to retain the physician sample labeling as submitted.**

**Within the trade labeling family for JANUMET, FDA noted the use of different font colors for the product strength on the bottle and hospital unit cell labeling. The strength text on the bottles appears in positive type, while that on the unit cells is white knock-out text printed on a colored background consistent with the trade color algorithm discussed above. With respect to the trade labeling, Merck agrees to revise the fonts of the product strength on the hospital unit cells and associated cartons to positive type, consistent with our current color-coding algorithm.**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

2. **Container Labels (50 mg/500 mg; 50 mg/1000 mg: 60, 180 and 1000 count)**

- a. **Merck believes that the inclusion of the statement "See accompanying circular for dosage information." on the packaging for this product, as submitted, is compliant with the requirements for "Statement of Dosage" as specified in 21 CFR §201.55. In the case of this product, Merck wishes to direct the user to the accompanying circular in order to provide more informative dosage information than can be readily provided in the space available on the label or carton of the package. In such cases, 21CFR §201.55 includes provisions indicating that the dosage statement requirement would be met by a statement such as "See package insert for dosage information." Please note that this is consistent with recently approved package labeling for JANUVIA, as well as other FDA-approved products.**

DMETS Response:

Although DMETS believes that there is adequate space for a Usual Dosage Statement we accept the sponsors statement "See accompanying circular for dosage information." on the labels and labeling as being compliant with 21 CFR §201.55.

- b. **The net quantity statements on the bottle labels are actually smaller than the established name. The net quantity appears in 8 point font, while the established name is displayed in 9.7 point font. Merck proposes to retain the bolding of the net quantity statement to retain its ready visibility to pharmacy personnel. This is consistent with recently approved JANUVIA labeling.**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

- c. **The NDC number text is presented prominently in the top third of the principal display, preceded by "NDC" for compliance with 21CFR§207.35(b)(3)(i)and (ii). Further, the font size used for the product strength is substantially larger and more prominent than that of the NDC number. As such, Merck proposes to retain the NDC number text as submitted.**

DMETS Response:

DMETS acknowledges that the sponsor is compliant with 21CFR§207.35(b)(3)(i)and (ii).

- d. **The numbers "XXXX | No. 674X" and the group of numbers above or to the right of these represent the tablet count, the 4-digit Merck Product Number, and the labeling component number. These are internal numbers which help Merck to correctly identify and control the product and its associated printed packaging components. Note that on round bottle labels, there is no side or back panel to which this information can be relocated. Merck proposes to retain the information as it is widely used within the Company for product control.**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

3. **Container Label (Unit-Dose Blister)**

- a. **The 7-digit numbers beginning with a "9" are Merck's standard component numbers, applied to all printed packaging components in accordance with Good Manufacturing Practices as addressed in 21CFR §211Subpart G; Packaging and Labeling Control. Each label has a unique component number consisting of a 5-digit "root" number and a 2-digit revision code (odometer). The component number clearly distinguishes between labels for different products and strengths, and also between different versions of the same label or labeling. Placement of the component number on each individual label also complies with Merck's current label standards and packaging equipment templates where the component number may be optically read on the packaging line. This allows electronic or electromechanical equipment to conduct an examination for correct labeling during or after completion of finishing operations.**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

- b. **"Tablets" is considered part of the established product name and is consistent with the name presentation on other approved Merck product unit cell labels. Merck proposes to retain as "tablets".**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

4. Carton Labeling (Unit-Dose Carton, 50-count)

- a. Please refer to Merck responses to 1a, 1d, and 2b as they apply to carton labeling as well.

DMETS Response:

See DMETS comments 1a, 1d and 2b.

- b. **The font size of the net quantity statement "50" is substantially smaller and less prominent than that used for the strength. This text is also physically separated from the strength on the carton, such that Merck feels it does not detract from the strength presentation. Merck proposes to retain the bolding of the net quantity statement to retain its visibility to pharmacy personnel. Please note that this is consistent with recently approved JANUVIA labeling.**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

- c. **The NDC number text is presented prominently in the top third of the principal display and preceded by "NDC" for compliance with 21CFR §207.35(b)(3)(i). Further, the font size used for the established name and strength are substantially larger than that of the NDC number. As such, Merck proposes to retain the current size and location of this text.**

DMETS Response:

DMETS accepts and acknowledges Merck's proposal.

5. Container Label (Professional Sample 7-count)

- a. Please refer to Merck responses to 1a, 1c, and 1d.

DMETS Response:

See DMETS comments 1a, 1c and 1d.

- b. **The proprietary name is in the same color and size throughout its depiction. Merck does not agree that the graphic encircling the proprietary name distorts the appearance of the proprietary name, given the differentiated proprietary name versus other agents, the generic name prominently displayed immediately underneath, and the dosing further displayed. Merck proposes to retain the depiction of the proprietary name as submitted. Please note that it is common industry practice to use proprietary names which contain graphical elements on physician sample packaging, including the recently approved depiction of the proprietary name for JANUVIA. Additionally, this may actually aid healthcare practitioners in distinguishing products during dispensing of samples.**

DMETS Response:

DMETS continues to find the graphic encircling the proprietary name to be distracting and more prominent than the established name. Additionally, this should not be used as a form of identity for the drug product. Practitioners need to know the name and not identify products based on graphics. DMETS recommends deleting this graphic entirely.

- e. **Merck believes that "Sample-Not for Sale" complies with the applicable regulation, 21CFR§203.38(c), in that it clearly denotes its status as a drug sample. Please note that this phrase is used on all approved Merck professional labeling. The relative prominence of "Sample-Not for Sale" is similar to that on the recently approved JANUVIA professional labeling. Further increasing the prominence of this statement may serve to distract from the established name and strength information. As such, Merck proposes to retain the statement as present on the filed labeling.**

DMETS Response:

DMETS acknowledges that the sponsor is compliant with 21CFR§203.38(c) and agrees that the sponsor can retain this statement on its sample labels and labeling.

- f. **Merck chose to employ a different font size for the units of strength (i.e., "mg") relative to the numeric strength (i.e., 50/ 500) in order to make the strength display more readable for this combination product. The use of mixed font sizes is common practice, as it allows the eye to be drawn to the information which is most critical to the selection of the correct numeric dose by the dispenser. As such, Merck proposes to retain the existing designation.**

DMETS Response:

DMETS disagrees with the sponsor's explanation for retaining the existing presentation of the unit designation. The current presentation is too small to read and should be consistent in size with the strength in order to improve readability. The readability of the unit designation is as equal in importance as that of the strength in the selection process.

- g. **The information in the white box was placed here in order to meet the requirement described in 5.d. Therefore, it cannot be deleted. Please refer to the 5d. response.**

DMETS Response:

See DMETS comment 5d.

DMETS accepts and acknowledges the placement of the information in the white box. However, the current presentation is too small to read and may be overlooked. In addition, the placement of this information on the label does not ensure that each blister is labeled with the proprietary name, strength, lot number, expiration date, and distributor should tablets become separated from the blister card. DMETS continues to recommend that the sponsor label each blister with the proprietary name, established name, strength, lot number, expiration date, and distributor.

6. **Pouch Overwrap (Cellophane 7-count)**

- a. **Please refer to Merck responses to 5b and 5f. 5d is not relevant to the pouch overwrap as it is not the primary product container/packaging. This pouch encloses the blister cards within the carton.**

DMETS Response:

See DMETS comments 5b and 5f.

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Denise Toyer  
3/29/2007 05:32:29 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
3/29/2007 05:37:09 PM  
DRUG SAFETY OFFICE REVIEWER

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Date: March 19, 2007

From: Ilan Irony, M.D.

Subject: NDA 22-044, Original Submission; Merck and Company, Inc. Product: sitagliptin / metformin FDC

Through: Mary Parks, M.D., director, DMEP/ODE2

To: NDA 22-044 File in DFS

### **Background**

After the DFS filing of the Medical Officer's review of sitagliptin / metformin FDC original New Drug Application 22-044, the Division of Medication Errors and Technical Support (DMETS) recommended against the use of the proprietary name Janumet for the sitagliptin / metformin FDC. The recommendation was based primarily on findings from potential sound-alike and look-alike prescription confusion with Sinemet, a currently marketed product indicated for the treatment of Parkinson's disease.

### **The Clinical Review Team decision regarding DMETS recommendation on the proprietary name Janumet**

Although the dosage form (tablet) is common to both, Sinemet (Carbidopa / Levodopa tablets) is marketed at dose strengths of 10 mg / 100 mg, 25 mg / 100 mg and 25 mg / 250 mg tablets, and these must be taken three times daily. The dose strengths proposed for Janumet are 50 mg / 500 mg and 50 mg / 1000 mg to be administered twice daily.

Therefore, there are no overlapping dose strengths between the 2 products.

It is very difficult to anticipate confusion during dispensing of a prescription when handwriting is difficult to read or the dose strength is written in incomplete form. The health care provider has the responsibility for writing (or typing) clear and complete prescriptions, including complete dose strengths.

The Clinical Review Division decided to accept the proprietary name Janumet, proposed by the applicant.

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This is our review of the DMETS recommendation to  
reject the Janumet trade name

Mary Parks  
3/20/2007 10:57:17 AM  
MEDICAL OFFICER

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