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*APPLICATION NUMBER:*

**22-350**

**OTHER REVIEW(S)**

**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS  
SAFETY TEAM  
MEMO TO THE FILE**

**NDA/Submission #/Submission type:** 22-350/000/NDA 1

**Product Name:** ONGLYZA (saxagliptin)

**Application submission date:** 30 June 2008

**Safety team reviewer:** Amy G. Egan, M.D., M.P.H.

**Safety review completion date:** 30 July 2009

**Action goal date:** 30 July 2009

**Reason for Review:** New PPI

**Items Reviewed:** PI/PPI/CDTL memo

**Synopsis of Findings:** Saxagliptin is a depeptidyl peptidase-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Safety issues identified during the review cycle or based on experience with other drugs in the class include severe hypersensitivity reactions and severe cutaneous reactions; hepatotoxicity; pancreatitis; decreased lymphocyte counts; and infections. In addition, a safety requirement for all new antidiabetic drugs, including saxagliptin, is to rule out an unacceptably increased risk of ischemic cardiovascular events. This is consistent with the December 2008 Guidance to Industry, entitled Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. All of these safety concerns are being adequately addressed in 3 post-marketing required studies/trials – a cardiovascular safety trial and 2 epidemiological studies.

The sponsor's PPI provides basic information about saxagliptin in patient friendly language which has been reviewed and approved by DRISK. There are no significant safety issues identified in the PI or PPI that would suggest that a Medication Guide would be more appropriate or that a REMS would be needed.

**Determination:**

**REMS triggered:** Y  I

**If yes (Y) or indeterminate (I), was submission referred to the SRT?:** Y N

**Date submitted:**

**Date response received:**

**SRT response:**

**If no (N), why not?:**

**If no (N), please check one (or more) of the following reasons below:**

**No significant safety issue identified**

**Only editorial changes made**

**Changes pertain only to proper use of a device**

**Other:**

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

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/s/

AMY G EGAN  
07/30/2009



Karen A. Hicks, M.D.  
Division of Cardiovascular and Renal Products, HFD-110

Food and Drug Administration  
10903 New Hampshire Avenue, Building 22, Room 4182  
Silver Spring, MD 20993-0002  
Tel: (301) 796-1089  
FAX: (301) 796-9841

**Memorandum**

**FROM:** Karen A. Hicks, M.D., Medical Officer  
Division of Cardiovascular and Renal Products

**THROUGH:** Norman L. Stockbridge, M.D., Ph.D., Director  
Division of Cardiovascular and Renal Products

**TO:** Julie Marchick and Rachel Hartford  
Project Managers  
Division of Metabolism and Endocrinology Products (HFD-510)  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

and

Hylton Joffe, M.D.  
Diabetes Team Leader  
Division of Metabolism and Endocrinology Products (HFD-510)

**SUBJECT:** Draft CV Outcomes Study Design Concept Document D1680C0003 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 4 Trial to Evaluate the Effect of Saxagliptin on the Incidence of Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes," dated April 17, 2009 (BMS Document No. 930035959) (NDA 22,350 Saxagliptin)

**DATE RECEIVED:** April 24, 2009

**DATE COMPLETED:** July 15, 2009

**Materials Reviewed:**

1. Draft CV Outcomes Study Design Concept Document D1680C0003 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 4 Trial to Evaluate the Effect of Saxagliptin on the Incidence of Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes," dated April 17, 2009 (BMS Document No. 930035959)

## OVERALL RECOMMENDATIONS

1. The sponsor has provided only a brief synopsis for the proposed postmarketing cardiovascular safety trial. We recommend that the sponsor submit the final protocol and statistical analysis plan, along with the Clinical Event Committee Charter, as soon as possible. The Division of Cardiovascular and Renal Products would be happy to review these materials upon receipt.

## COMMENTS TO BE TRANSMITTED TO SPONSOR

We have completed our review of your submission dated April 17, 2009, including your Draft Outcomes Study Design Concept Document D1680C003 entitled, "A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 4 Trial to Evaluate the Effect of Saxagliptin on the Incidence of Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes" and have the following comments and recommendations:

1. Please clarify the individual definitions for moderate and severe renal insufficiency.
2. You propose the following regional allocation:
  - United States (15-20%)
  - South America and Canada (40-45%)
  - Europe (15-20%)
  - Asia/Australia (10-15%)

Additionally, you state key subgroups of interest will be African-Americans, US patients of Hispanic ethnicity, and elderly/very elderly men and women.

- a. We recommend that the regional allocation for the United States is increased to approximately 30% or greater.
  - b. Please clarify regional allocation for South America and Canada separately.
  - c. Please clarify regional allocation for Asia and Australia separately.
3. Please incorporate in the final protocol the events of special interest that will also be followed in this study such as pancreatitis, hepatic toxicity, fractures, hypersensitivity, skin lesions, and lymphocyte reduction.
  4. In the trial, you propose to include a restriction on the use of thiazolidinediones (TZDs) in the study design to avoid a possible imbalance in the occurrence of first CV events (MACE and heart failure) if a greater number of subjects in the placebo are initiated on TZDs, compared to the saxagliptin treatment group. Furthermore, after randomization, TZDs will be added for glycemic control only if necessary. (Internal Comment: Defer specific comment to DMEP)

## 5. Study Recommendations

- a. Prior to initiating the study, please submit the following information to the Review Division:
  1. Proposed protocol
  2. Definitions for all protocol endpoints and events of special interest
  3. Case Report Form
  4. Clinical Endpoints Committee (CEC) charter, including algorithms to be used for endpoint events such as determination of myocardial infarction
  5. Statistical Analysis Plan
  
- b. In general, the Division recommends that the following endpoints are adjudicated:
  - Death
    - All Cause Mortality
    - Cardiovascular Death
    - Non-Cardiovascular Death
  
  - Acute Coronary Syndrome
    - Myocardial Infarction
    - Hospitalization for Unstable Angina
  
  - Cerebrovascular Events
    - Cerebrovascular Event (Stroke)
      - i. Ischemic (Non-hemorrhagic)
      - ii. Hemorrhagic
      - iii. Unknown
    - Transient Ischemic Attack
  
  - Coronary Revascularization Procedures
    - Coronary Artery Bypass Graft Surgery
    - Percutaneous Coronary Intervention
  
  - Hospitalization for Heart Failure
  
  - Stent Thrombosis (clinical adjudication)
    - Data needed
      - i. Name of device (Bare metal stent versus Drug eluting stent) as well as stent diameter and length
      - ii. Coronary reference vessel diameter (RVD) and lesion length
      - iii. Date of implantation
      - iv. Date of stent thrombosis
      - v. Indication for index PCI [ACS (indicate STEMI, non-STEMI, or UAP), non-ACS]
      - vi. Did patient have multivessel disease?
      - vii. Did patient undergo multivessel (three-vessel disease) or left main treatment?
      - viii. Left ventricular function
      - ix. Overlapping stents
      - x. Bifurcation lesion stenting
      - xi. Bypass graft (arterial or venous conduit) stenting
      - xii. Presence or absence of renal disease based on glomerular filtration rate as determined by the Cockcroft-Gault Equation
      - xiii. Was patient on dual antiplatelet therapy (yes/no), and if not, date of aspirin or P2Y12 inhibitor discontinuation?

- c. Other endpoints of interest that do not require formal adjudication include
- Hospitalization for other CV causes
    - Pulmonary embolus
    - Ruptured Aortic Aneurysm
  - Carotid Artery Revascularization (surgical versus percutaneous)
  - Other Peripheral Vascular Revascularization (lower extremity, renal, mesenteric, iliac, subclavian, and aortic etc.) (surgical versus percutaneous)
  - Lower Extremity Amputation
  - Hospitalization for Cardiac Arrhythmia (specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement)
- d. In your study, investigators should inquire about the interim occurrence of cardiovascular events at each study visit through the use of a boxed check-list, and these results should be noted in the study schedule. For patients hospitalized for cardiovascular events, all pertinent hospital records, electrocardiograms, imaging studies, and laboratory results should be obtained for the purpose of adjudication. If a patient dies during the study, autopsy reports should be requested. Endpoint Event Investigator Reporting forms and CEC Adjudication forms should also be comprised of boxed check-lists.

Source documents needed for the following events include but are not limited to

1. Death
  - a. Autopsy (if performed)
  - b. Code summary (if available)
  - c. Death/discharge summary (if death occurred in-hospital)
2. Myocardial Infarction/Hospitalization for Unstable Angina/Stent Thrombosis
  - a. Admission History and Physical
  - b. ECG tracings (at baseline and time of event)
  - c. Cardiac markers (troponin/CK-MB results with units and ULN)
  - d. Other laboratory reports, if requested
  - e. Procedure reports (Cardiac catheterization, PCI, CABG)
  - f. Discharge Summary
3. Stroke or TIA
  - a. Neurology Consult
  - b. Imaging reports (MRI, CT, or other imaging report)
  - c. Discharge Summary
4. Coronary Revascularization Procedures
  - a. Procedure reports (Cardiac catheterization, PCI, CABG)
  - b. Discharge Summary

5. Hospitalization for Heart Failure
  - a. Admission History and Physical
  - b. ECG tracings (at baseline and time of event)
  - c. Cardiac markers (troponin/CK-MB results with units and ULN)
  - d. Other laboratory reports (e.g., BNP)
  - e. Chest X-Ray report
  - f. Discharge Summary
  
6. Acute Pancreatitis
  - a. Imaging reports
  - b. Discharge Summary
  
- e. At the time of the submission of the Clinical Study Report, please include verbatim terms in the adverse events data set.
  
- f. All of the prospectively collected cardiovascular events should be reviewed by the Clinical Endpoints Committee (CEC), as discrepancies between investigator-reported and adjudicated events may arise. With the clinical study report, the sponsor should submit data sets for both the investigator-reported and CEC adjudicated cardiovascular events. Additionally, the sponsor should submit the following 5 listings:
  - All investigator-reported CV events
  - All CEC-adjudicated CV events
  - All investigator-reported CV events that were also adjudicated by the CEC to be events
  - All investigator-reported CV events that were not thought to be events by the CEC (“downgrades”)
  - All CEC-adjudicated CV events that were not considered to be events by the investigator (“upgrades”)
  
- g. In addition to CEC adjudication of triggered events, we recommend searching the following standardized MedDRA queries (SMQs) for other possible cardiovascular events that may also require adjudication:
  1. Myocardial Infarction
  2. Ischaemic Heart Disease
  3. Cardiac Arrhythmias
  4. Cardiac Failure
  5. Embolic and Thrombotic Events
  6. Shock
  7. Torsade de pointes/QT prolongation
  8. Cerebrovascular Disorders
  9. Central Nervous System Haemorrhages and Cerebrovascular Accidents
  10. Vasculitis
  
- h. The Division also recommends searching the following system organ classes (SOCs), high level terms (HLT), lower level terms (LLTs), and preferred terms (PTs) for cardiovascular events that may also require adjudication:
  1. SOC: Cardiac Disorders
  2. SOC: General Disorders and Administration Site Conditions
  3. SOC: Injury, Poisoning, and Procedural Complications
  4. SOC: Investigations
  5. SOC: Musculoskeletal and Connective Tissue Disorders
  6. SOC: Nervous System Disorders
  7. SOC: Respiratory, Thoracic, and Mediastinal Disorders
  8. SOC: Surgical and Medical Procedures

9. SOC: Vascular Disorders
10. LLT: Cerebral Revascularization Synangiosis (search value: revascularization)
11. LLT: Coronary Revascularization (search value: revascularization)
12. LLT: Peripheral Revascularization (search value: revascularization)
13. LLT: Renal Revascularization (search value: revascularization)
14. LLT: Transmyocardial Revascularization (search value: revascularization)
15. LLT: Acute myocardial ischemia (search value: myocardial ischemia)
16. LLT: ECG signs of myocardial ischemia (search value: myocardial ischemia)
17. LLT: Myocardial ischemia (search value: myocardial ischemia)
18. LLT: Myocardial ischemia recurrent (search value: myocardial ischemia)
19. LLT: Silent myocardial ischemia (search value: myocardial ischemia)
20. PT: Acute Myocardial Infarction (search value: myocardial infarction)
21. PT: Myocardial Infarction (search value: myocardial infarction)
22. PT: Post Procedural Myocardial Infarction (search value: myocardial infarction)
23. PT: Silent Myocardial Infarction (search value: myocardial infarction)

**Review:**

**NDA 22,350 Saxagliptin (BMS-477118)**

**Background:** Saxagliptin is a dipeptidyl dipeptidase-4 (DPP4) inhibitor developed for the treatment of type 2 diabetes mellitus. The New Drug Application (NDA 22,350) was submitted to the Division of Metabolism and Endocrinology Products on June 30, 2008. On April 1, 2009, there was an Advisory Committee Meeting to discuss the safety and efficacy of saxagliptin. The Advisory Committee voted to approve saxagliptin but recommended that the sponsor conduct a post-marketing cardiovascular outcomes trial. The sponsor submits this draft design concept paper for the CV outcomes trial and expects to finalize the protocol in September 2009.

**Protocol Number:** D1680C0003

**Sponsor:** Bristol-Myers Squibb Company

**Investigators:** Pending

**Site(s) of Investigation:** Pending. Regional allocation is expected to be 15-20% from US, 40-45% from South America and Canada, 15-20% from Europe, and 10-15% from Asia/Australia. Key subgroups of interest will include African-Americans, US patients of Hispanic ethnicity, and elderly/very elderly men and women.

**Reviewer Comments:**

1. *We recommend that US enrollment in this trial is increased to approximately 30%*
2. *The sponsor should clarify the percentage of patients expected to be enrolled from Canada separately from South America and should also clarify the percentage of patients expected to be enrolled from Asia separately from Australia.*

**IRB Approval:** Pending

**Title:** "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 4 Trial to Evaluate the Effect of Saxagliptin on the Incidence of Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes," dated April 17, 2009 (BMS Document No. 930035959)

**Indication:** Treatment of type 2 diabetes mellitus (T2DM)

**Study Design:** This is a multicenter, randomized, double-blind, placebo controlled Phase 4 study to evaluate the effect of saxagliptin on the incidence of major adverse cardiovascular events.

**Hypothesis:**

Saxagliptin reduces the risk of experiencing a cardiovascular (CV) event in subjects with type 2 diabetes mellitus and additional CV risk factors.

The study plans to address two questions:

1. Do the results of the study exclude an unacceptable risk of MACE for saxagliptin, based on the criteria established by the December 2008 FDA Guidance?
2. Is treatment with saxagliptin (added to usual care) associated with a reduction in the risk of MACE compared to usual care only.

**Objectives:**

**Primary:** The primary objective is to assess the time to first event for the composite endpoint of major adverse CV events (MACE, including CV death, non-fatal myocardial infarction, and non-fatal stroke) during treatment with saxagliptin compared with placebo when added to current care, in patients with T2DM.

MACE is to be adjudicated by an independent Clinical Endpoints Committee (CEC), using prospectively defined criteria without knowledge of treatment group assignment.

**Safety:** The safety objective is to evaluate the safety and tolerability of saxagliptin by assessment of overall adverse events, adverse events of special interest, laboratory tests including renal function, blood pressure, and body weight.

**ENDPOINTS:**

**Primary:** The primary endpoint is major adverse cardiovascular events (MACE), defined as CV death, non-fatal myocardial infarction (MI), and non-fatal stroke)

**Reviewer Comment:** *The primary endpoint should be MACE defined as CV death, non-fatal MI, OR non-fatal stroke.*

**Number of Patients:** Approximately 10,100 randomized patients (631 primary endpoint events). During the course of the trial, the sample size may be increased to achieve 631 primary endpoint events if the rate of CV events is lower than anticipated.

**Duration of Study:** This is an event-driven trial. The sponsor estimates that the total duration of the trial will be 5 years. The trial duration may be increased to achieve 631 primary endpoint events if the rate of CV events is lower than anticipated.

**Timelines:**

Finalized Protocol: September 2009

First patient first visit: 2Q2010

Last patient last visit: 2Q2015

Clinical Study Report: 4Q2015

**Inclusion Criteria (Must be present) (Reproduced from Sponsor, pages 9-10)**

1. Written, informed consent
2. Diagnosed with T2DM based on the current American Diabetes Association (ADA) guidelines
3. A1C  $\geq$  6.5% (based on a documented laboratory measurement in the previous 3 months)
4. High risk for a CV event defined as at least one of the following
  - a. Clinically evident CV disease defined by prior history of ischemic heart disease (e.g., unstable angina, stable angina, MI, need for revascularization), and/or peripheral vascular disease (e.g., intermittent claudication), and/or stroke; and/or
  - b. Multiple risk factors (treated or non treated) for CV disease in addition to T2DM

**Exclusion Criteria (Cannot be present) (Reproduced from Sponsor, page 10)**

1. Pregnant or breast-feeding patients
2. Contraindication to therapy as outlined in the saxagliptin product information
3. Involvement in the planning and conduct of the study (applies to both AstraZeneca and Bristol-Myers Squibb staff or staff at the study site)

4. Previous randomization in the present study
5. Participation in a clinical study within 60 days of Visit 1
6. Any conditions that, in the opinion of the investigator, may render the subject unable to complete the study including non-CV disease with likely fatal outcome within 5 years
7. Individuals at risk for poor protocol or medication compliance
8. Current or previous (within 6 months) treatment with an incretin based therapy such as DPP4 inhibitors and or glucagon-like peptide (GLP)-1 mimetics
9. Acute vascular (cardiac or stroke) event < 2 months prior to randomization

**Dosage/Administration:** Subjects will undergo a screening evaluation following an 8-hour fast. Subjects who cannot complete all screening procedures may return within 7 days to complete them. Eligible subjects will be randomized in a 1:1 ratio to receive either saxagliptin 5 mg (or 2.5 mg for patients with moderate or severe renal insufficiency) or placebo for a double-blind treatment period of 48 months. Those subjects who develop moderate to severe renal impairment during the course of the trial will have the dose of study drug blindly adjusted to either saxagliptin 2.5 mg or matching placebo, depending on their originally assigned treatment group.

For patients with moderate or severe renal impairment, or end-stage renal disease (creatinine clearance [CrCl]  $\leq$  50 mL/min, approximately corresponding to serum creatinine levels of  $\geq$  1.7 mg/dL in men and  $\geq$  1.5 mg/dL in women), the dose of saxagliptin should be adjusted from 5 mg to 2.5 mg.

During the randomized treatment period, patients will be encouraged to follow diet and life-style modifications, and treatment guidelines with respect to glycemic monitoring and control as well as the use of concomitant medications to minimize cardiovascular risk, such as antihypertensive agents, low dose aspirin, and lipid lowering agents are to be followed.

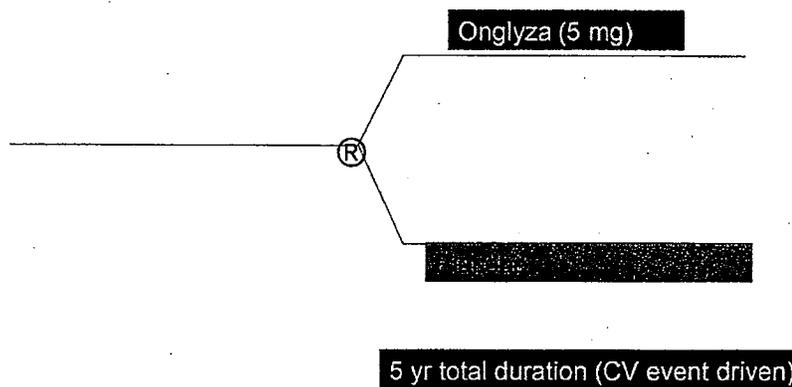
Patients will return for office visits every 6 months for evaluation of the primary endpoint, assessment of treatment compliance, and study drug distribution.

Telephone follow-up will be conducted at 3-month intervals between office visits.

Every 12 months, subjects will undergo a physical examination and laboratory testing.

The study design is displayed in Figure 1. Since this is an event-driven trial, the 5 year trial duration may be modified if the rate of CV events is lower than expected.

**Figure 1. Study Design (D1680C0003)**



(Sponsor, Figure 2.1, page 5)

Background and rescue treatments to be used in this study will include metformin, sulfonylureas, and both short and long-acting insulins. After randomization, thiazolidinediones (TZDs) may be added for glycemic control only if thought to be necessary. The sponsor plans to include a restriction on the use of TZDs in the study design to avoid a possible imbalance in the occurrence of first CV events (MACE and heart failure) if a greater number of subjects in the placebo arm are initiated on TZDs, compared to the saxagliptin treatment group.

Subjects may not be initiated on DPP4 inhibitors or GLP1 mimetics during this trial.

**Reviewer Comments:**

1. *Per discussion with DMEP, an action will be taken on saxagliptin later in July 2009. Saxagliptin, 5 mg daily, is expected to be the maximum dose approved for human use.*
2. *The sponsor should clarify the individual definitions for moderate and severe renal insufficiency*

**Informed Consent:** Not included with submission.

**Schedule of Evaluations/Procedures:** Not included in submission.

**Safety Evaluation:** The study will have a Clinical Events Committee (CEC) and a data safety monitoring board (DSMB)

**Withdrawal Criteria/Stopping Criteria:** Not discussed.

Subjects who discontinue study medication will continue to be followed in the trial for CV events.

**Definition of Lost-to-Follow-Up:**

1. Inability to reach the patient after 3 documented phone calls, faxes, or e-mails
2. Inability to contact the patient through patient locator agencies (if allowed per national regulation); and
3. Lack of response by the patient to one letter sent by registered/certified mail

All attempts to contact the patient are to be documented in the patient's medical records.

**Statistical Analysis:** Sample size calculations (10,100 patients to yield 631 primary endpoint events) include the following assumptions:

1. 2% event rate at 1 year on placebo
2. 2 year accrual period
3. 3 year minimum follow-up period
4. 2.5% 1-sided level of statistical significance

to rule out an increased CV risk of 1.30 for saxagliptin, compared to placebo, with 91% power.

Superiority of saxagliptin can also be tested at the 4.95% 2-sided significance level if a hazard ratio (HR) of at most 0.855 is observed for saxagliptin:placebo, representing a 14.5% reduction in risk. With 631 events, the sponsor estimates there would be 90% power for testing superiority if the true HR was 0.77 and 85% power for testing superiority if the true HR was 0.79.

One or more interim analyses are to be performed, and stopping criteria will be prespecified for either unanticipated efficacy or an unsuspected safety risk.

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/s/

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Karen Hicks  
7/15/2009 12:45:04 PM  
MEDICAL OFFICER

Norman Stockbridge  
7/15/2009 02:19:35 PM  
MEDICAL OFFICER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Date:** June 24, 2009

**To:** Mary Parks, MD, Director  
Division of Metabolism and Endocrinology Products

**Through:** Melina Griffis, RPh, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis

**From:** Anne Crandall, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

**Subject:** Label and Labeling Review

**Drug Name(s):** Onglyza (Saxagliptin) Tablets 2.5 mg and 5 mg

**Application Type/Number:** NDA 22-350

**Applicant/sponsor:** Bristol-Myers Squibb

**OSE RCM #:** 2009-994

## **1 INTRODUCTION**

The Division of Medication Error Prevention and Analysis (DMEPA) completed a label and labeling review for Onglyza (OSE RCM #2008-967) on February 11, 2009 in which we made recommendations regarding the proposed container labels and labeling. In a submission dated April 29, 2009 the Applicant submitted their revisions addressing DMEPA's requested changes.

## **2 MATERIALS REVIEWED**

DMEPA reviewed our previous proprietary name and labeling review for Onglyza (OSE review # 2008-967, dated February 11, 2009) and we also reviewed the revised labels submitted by the Applicant dated April 29, 2009. See Appendix A for pictures of the revised labels.

## **3 DISCUSSION**

The Applicant has revised the container labels and blister labeling according to our recommendations, however, the size of the 5 mg strength designation on the physician sample pack is small and should be increased.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The Applicant has satisfactorily revised the labels per our February 11, 2009 request. Please forward the remaining additional comment to the Applicant.

If you further questions or need clarification, please contact Mildred Wright, OSE Project Manager, at 301-796-1027.

### **4.1 COMMENTS TO THE APPLICANT**

The size of the 5 mg strength designation on the physician sample pack is small and should be increased and should be similarly displayed as the strength on the trade container labels.

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/s/

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Melina Griffis  
6/24/2009 08:20:04 AM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
6/24/2009 12:51:05 PM  
DRUG SAFETY OFFICE REVIEWER

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

**Memorandum**

**Date:** March 25, 2009  
**To:** Rachel E. Hartford, Regulatory Health Project Manager, DMEP  
**From:** Kendra Jones, Regulatory Review Officer, DDMAC  
Sam Skariah, Regulatory Review Officer, DDMAC  
**Through:** Robert Dean, Group Leader, DDMAC  
Sangeeta Vaswani, Group Leader, DDMAC  
**Subject:** NDA 22-350  
DDMAC labeling comments for (saxagliptin)

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**Prescribing Information and Patient Labeling**

DDMAC has reviewed the proposed Prescribing Information and Patient Labeling for saxagliptin. DDMAC's comments are provided directly on the marked up version of the document attached. Additionally, DDMAC notes the inclusion of the saxagliptin Carton and Container Labels in the EDR. DDMAC offers the following comments on the proposed Carton Label:

Carton Label (5mg < > Carton Label (5mg < > )

b(4)

1. ...  
C

b(4)

If you have any questions on the comments provided, please contact Sam Skariah at 301-796-2774 or [Sam.skariah@fda.hhs.gov](mailto:Sam.skariah@fda.hhs.gov) or Kendra Jones at 301-796-3917 or [Kendra.jones@fda.hhs.gov](mailto:Kendra.jones@fda.hhs.gov).

40 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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/s/

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Sam Skariah  
3/25/2009 02:53:58 PM  
DDMAC PROFESSIONAL REVIEWER