

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125431Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 14, 2014

Reviewer(s): Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst
Division of Risk Management (DRISK)

Kate Heinrich Oswell, MA, Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D., Division Director, DRISK

Subject: Review of the amended proposed REMS received April 13, 2014

Drug Name(s): Albiglutide

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 2 mg, subcutaneous, once every seven days

Application Type/Number: BLA 125431

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2013-279

1 INTRODUCTION

This document reviews the amended proposed risk evaluation and mitigation strategy (REMS) for albiglutide for injection sent to the Agency on April 11, 2014 and April 13, 2014. GlaxoSmithKline (GSK) is seeking approval for albiglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The Agency has determined that, like other drugs in this class of glucagon like peptide-1 (GLP-1) receptor agonist, in addition to labeling including a boxed warning, a communication plan (CP) REMS to communicate the risks of pancreatitis and medullary thyroid cancer (MTC) is necessary to maintain a favorable risk to benefit balance for albiglutide.

DRISK comments on the REMS were sent to the sponsor April 10, 2014. The sponsor replied to the comments and submitted a revised REMS and a revised REMS Supporting Document April 11, 2014, and revised REMS materials April 13, 2014.

The REMS submission is acceptable, and the REMS can be approved.

2 MATERIALS REVIEWED

We reviewed the following:

- GlaxoSmithKline amended proposed REMS package, submitted April 11, 2014 and April 13, 2014.

Previous DRISK review related to the original submission:

- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on October 16, 2013.
- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on March 18, 2014.
- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on April 4, 2014
- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on April 10, 2014

3 RESULTS OF REVIEW

The sponsor accepted our markup from the April 10, 2014 review. The sponsor had additional minor edits to the REMS materials.

3.1 REMS

The REMS to be approved is a CP with the following components.

Goal

The goal of the Tanzeum REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis associated with Tanzeum by:

- Informing healthcare providers (HCPs) about the potential risk of medullary thyroid carcinoma associated with Tanzeum
- Informing HCPs about the risk of acute pancreatitis associated with Tanzeum

Communication pieces

The communication pieces include a REMS Letter for Healthcare Providers, a REMS Letter for Professional Societies, a REMS Factsheet to accompany the letters and to be distributed by GSK representatives in visits to discuss Tanzeum, and a REMS website.

Timetable for Submission of Assessments

The sponsor will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the REMS approval.

3.2 ASSESSMENT PLAN

The REMS assessment plan includes the following:

- a) REMS communication plan activities:
 - (1) Number of healthcare providers and professional societies targeted by the REMS.
 - (2) Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the healthcare providers did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - (3) Number of REMS Factsheets distributed to healthcare providers during the 12 months after product launch.
 - (4) Date when REMS website went live and number of total and unique site visits during the assessment period.
- b) Evaluation of healthcare providers' understanding of:
 - (1) The potential risk of medullary thyroid cancer.
 - (2) The risk of pancreatitis.
 - (3) The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.
 - (4) Appropriate albiglutide patient population characteristics.
- c) Safety surveillance
 - (1) Albiglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.).
 - (2) Evaluation and postmarketing case reports of pancreatitis.
 - (3) Evaluation and postmarketing case reports of medullary thyroid cancer.
 - (4) Any other relevant data and analysis employed to assess if the albiglutide REMS is meeting its goals.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

4 CONCLUSION/RECOMMENDATION

The REMS is acceptable.

DRISK recommends approval of the REMS.

ATTACHMENTS

Tanzeum REMS

Tanzeum REMS Letters

Tanzeum REMS Factsheet

Tanzeum REMS website

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/s/

JOYCE P WEAVER
04/14/2014

CLAUDIA B MANZO
04/14/2014
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

NDA/BLA #s: BLA 125431
Products: TANZEUM (albiglutide) injection, 30 and 50 mg
APPLICANT: GlaxoSmithKline LLC
FROM: Curtis Rosebraugh, M.D., M.P.H.
DATE: March 30, 2014

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for TANZEUM (albiglutide) to ensure that the benefits of the drug outweigh the potential serious risk of medullary thyroid carcinoma identified in non-clinical studies of other (GLP)-1 receptor agonists and a signal of a serious risk of acute pancreatitis, including necrotizing pancreatitis, identified in the clinical trial data for TANZEUM (albiglutide) and in post-marketing reports for other approved glucagon-like peptide (GLP)-1 receptor agonists. In reaching this determination, we considered the following:

- A. In 2010 diabetes affected 25.8 million people in the United States, of which 18.8 million were diagnosed and 7.0 million were undiagnosed.¹ Type 2 diabetes is thought to account for 90 to 95 percent of all diagnosed cases in adults.² In 2012, approximately 670,000 patients in the United States filled prescriptions in retail pharmacies for one of the two approved (GLP)-1 receptor agonists.³

¹ <http://www.cdc.gov/diabetes/pubs/factsheet11/fastfacts.htm>; accessed March 28, 2014.

² <http://ndep.nih.gov/diabetes-facts/>; accessed March 28, 2014.

³ Hampp C, Borders-Hemphil V, Money DG, Wysowski DK. Use of Antidiabetic Drugs in the U.S., 2003-2012. *Diabetes Care*. 2014 Mar 12. [Epub ahead of print].

- B. Patients with type 2 diabetes who require anti-diabetic medication for glycemic control are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated.
- C. TANZEUM (albiglutide) has been shown to achieve a mean placebo-adjusted reduction in hemoglobin A1c over 52 weeks of approximately 0.8-1.0%. Some of the complications listed above can be prevented or delayed with good glycemic control. TANZEUM (albiglutide) is an option for those individuals who are inadequately treated with lifestyle modification and other anti-diabetic therapies.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risks of medullary thyroid carcinoma and acute pancreatitis, TANZEUM (albiglutide) is associated with the following other adverse effects, including serious hypoglycemia when used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, gastrointestinal adverse events such as nausea and diarrhea, and hypersensitivity.
- F. TANZEUM (albiglutide) is a new molecular entity.

The elements of the REMS will be a communication plan and a timetable for submission of assessments of the REMS.

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/s/

MEHREEN HAI
04/14/2014

JEAN-MARC P GUETTIER
04/14/2014
Signing on behalf of Dr. Jennifer R. Pippins.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 10, 2014

Reviewer(s): Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst
Division of Risk Management (DRISK)

Kate Heinrich Oswell, MA, Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Subject: Review of the amended proposed REMS submitted on April 9, 2014

Drug Name(s): Albiglutide

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 2 mg, subcutaneous, once every seven days

Application Type/Number: BLA 125431

Submission Number: Sequence number 57, received April 9, 2014

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2013-279

1 INTRODUCTION

This review provides comments on the amended proposed risk evaluation and mitigation strategy (REMS) for albiglutide for injection submitted on April 9, 2014. GlaxoSmithKline (GSK) is seeking approval for albiglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The Agency has determined that, like other drugs in this class of glucagon like peptide-1 (GLP-1) receptor agonist, in addition to labeling including a boxed warning, a communication plan (CP) REMS to communicate the risks of pancreatitis and medullary thyroid cancer (MTC) is necessary to maintain a favorable risk to benefit balance for albiglutide.

DRISK comments on the REMS were sent to the sponsor April 4, 2014. The sponsor replied to the comments and submitted a revised REMS, revised REMS documents, and a revised REMS Supporting Document April 9, 2014.

2 MATERIALS REVIEWED

We reviewed the following:

- GlaxoSmithKline amended proposed REMS, submitted April 9, 2014

Previous DRISK review related to the original submission:

- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on October 16, 2013.
- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on March 18, 2014.
- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on April 4, 2014

3 RESULTS OF REVIEW

The sponsor accepted most of our markup from the April 4, 2014 review, but introduced additional language into the REMS that must be deleted. For clarity, additional detail should be included in the REMS Supporting Document about the REMS Assessment Plan.

4 COMMENTS FOR DMEP

Forward the following comments and edited documents to GSK and ask them to submit the entire REMS, REMS Supporting Document, and REMS materials within 1 day.

5 COMMENTS FOR THE SPONSOR

We acknowledge your April 9, 2014 response to our comments on your REMS submission for albiglutide, and we have the following revisions and comments. Please make the indicated changes and resubmit the REMS, REMS materials, and REMS Supporting Document. Provide versions of all documents in Word, and include both clean and track changes versions. We remind you that language in all REMS materials must reflect the approved final labeling. The REMS has not completed clearance within the Agency, and additional changes may be necessary.

REMS Document:

1. Remove [REDACTED] (b) (4) from the REMS document.
2. Remove the placeholder for the day in the date approved on the REMS document.

3. Remove “Tanzeum” as shown in the markup.

REMS Supporting Document:

4. Add a summary list of the REMS Assessment Plan.

ATTACHMENTS

Revised REMS and REMS Supporting Document

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/s/

JOYCE P WEAVER
04/10/2014

CYNTHIA L LACIVITA
04/11/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 4, 2014

Reviewer(s): Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst
Division of Risk Management (DRISK)

Kate Heinrich Oswell, MA, Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D., Division Director, DRISK

Subject: Review of the amended proposed REMS submitted on March 25, 2014

Drug Name(s): Albiglutide

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 2 mg, subcutaneous, once every seven days

Application Type/Number: BLA 125431

Submission Number: Sequence number 56, received March 25, 2014

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2013-279

1 INTRODUCTION

This review provides comments on the amended proposed risk evaluation and mitigation strategy (REMS) for albiglutide for injection submitted on March 25, 2014. GlaxoSmithKline (GSK) is seeking approval for albiglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The Agency has determined that, like other drugs in this class of glucagon like peptide-1 (GLP-1) receptor agonist, in addition to labeling including a boxed warning, a communication plan (CP) REMS to communicate the risks of pancreatitis and medullary thyroid cancer (MTC) is necessary to maintain a favorable risk to benefit balance for albiglutide.

DRISK comments on the REMS were sent to the sponsor March 18, 2014. The sponsor replied to the comments and submitted a revised REMS, revised REMS documents, and a revised REMS Supporting Document March 25, 2014.

This review is written by the Division of Risk Management (DRISK), in consultation with the Office of Prescription Drug Promotion (OPDP).

2 MATERIALS REVIEWED

We reviewed the following:

- GlaxoSmithKline amended proposed REMS, submitted March 25, 2014¹³ submission.
- OPDP REMS Consult Review; signed in DARRTS on March 19, 2014 by Jones, K.

Previous DRISK review related to the original submission:

- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on October 16, 2013.
- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on March 18, 2014.

3 RESULTS OF REVIEW

The sponsor did not accept some of our previous markup from the March 18, 2014 review, and the sponsor posed the following questions in the March 25, 2014 submission:

1. Regarding distribution of the REMS Factsheet by “GSK representatives,” GSK interprets this section as US-based sales and /or medical representatives during the first product/promotional discussions for TANZEUM with US-based HCPs likely to prescribe TANZEUM. Does FDA agree?

Reviewer comment: We agree that GSK’s interpretation is correct, and the positions at GSK can be named in the REMS document.

2. Also, GSK interprets the distribution of the Factsheet to include by hand, by fax, or by email during a two-way conversation/exchange occurring with a US-based HCP about TANZEUM in person, over the telephone, via a live meeting, video, or email. Does FDA agree?

Reviewer comment: We agree that GSK’s interpretation is correct, except that the Factsheet should also be distributed with any other materials, even if the HCP is unable to interact with the representative in person.

The sponsor reinserted the (b) (4) information and the adverse event reporting information into the Factsheet.

Reviewer comment: We do not agree with inclusion of the (b) (4) We agree with the inclusion of the adverse event reporting information.

DRISK has revisions and comments to relay to the sponsor.

4 COMMENTS FOR THE REVIEWING DIVISION

DRISK notes that OPDP provided the following comments:

REMS letter for Healthcare Professionals, REMS letter for Professional Societies, and REMS Fact Sheet

- OPDP is concerned that the section of these REMS materials entitled “**Indication**” (bolded emphasis original) implies that this is the full indication for Tanzeum; however, it omits material information from the full indication, which includes the limitations of use for Tanzeum. OPDP recommends revising the “**Indication**” (bolded emphasis original) section of these REMS materials to also communicate the **full** indication, which includes the limitations of use for Tanzeum.

DRISK Response: DRISK did not completely accept OPDPs recommendation. We did not include the limitations of use that do not relate to any risks the Tanzeum REMS program is in place to mitigate. However we have included the two limitations of use in the materials where they relate to the REMS risks.

REMS letter for Healthcare Professionals, REMS letter for Professional Societies and Website Landing Page

“**Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with other glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TANZEUM causes thyroid C-cell tumors, including MTC in humans.” (bolded emphasis original)

- OPDP is concerned that this presentation minimizes the risks associated with Tanzeum by omitting important material information from the regarding thyroid C-cell tumors. OPDP recommends revising this presentation to include this important material in a manner consistent with the Warnings and Precautions section of the draft PI. Specifically, the Warnings and Precautions section of the draft PI states, (b) (4)

[REDACTED]

“**Acute Pancreatitis.** In clinical trials, there were more cases of acute pancreatitis among patients treated with TANZEUM than among patients treated with comparators.” (bolded emphasis original)

- OPDP is also concerned that this presentation omits important material information regarding acute pancreatitis from the Warnings and Precautions section of the draft PI. The Warnings and Precautions section of the draft PI states, (b) (4)

***DRISK Response:** DRISK does not agree with providing comprehensive messaging in the REMS letters or the website landing page. The purpose of the REMS letters and website is to concisely relay the main risk messages from the REMS program, while providing access to other resources for more comprehensive risk information about the REMS program for the audience. Communication experts have advised that having too much text heavy information in DHCP Letters is not an effective way to communicate the risks of the REMS. Therefore, the letters include either a web link to the REMS factsheet (sent through email) or the factsheet is enclosed (sent through mail). The factsheet is also contained on the REMS website. The REMS factsheet contains more complete risk messaging from the PI about the REMS risks in a more user friendly manner. Therefore we have modified the REMS letters and website to be brief in regard to messaging and include a more inviting looking REMS factsheet for the audience to find out more complete risk information.*

5 COMMENTS FOR THE SPONSOR

We acknowledge your March 25, 2014 response to our comments on your REMS submission for albiglutide, and we have the following revisions and comments. Please make the indicated changes and resubmit the REMS, REMS materials, and REMS Supporting Document. Provide versions of all documents in Word, and include both clean and track changes versions. We remind you that language in all REMS materials must reflect the approved final labeling. The REMS has not completed clearance within the Agency, and additional changes may be necessary.

REMS Document:

1. You asked the following, “Regarding distribution of the REMS Factsheet by “GSK representatives,” GSK interprets this section as US-based sales and /or medical representatives during the first product/promotional discussions for TANZEUM with US-based HCPs likely to prescribe TANZEUM. Does FDA agree?”

FDA Reply: We agree that your interpretation is correct, and the positions at GSK that will conduct this activity can be named in the REMS document. Edit the REMS document to include the appropriate positions at GSK:

A REMS Factsheet will made available to healthcare providers and distributed through GSK sales and medical representatives during the initial discussion for TANZEUM with healthcare providers during the first 12 months after approval of this REMS.

REMS Supporting Document:

2. Under section 3.1.2 *Factsheet*, the third paragraph makes reference to the (b) (4) being a part of the information included in the REMS Factsheet. We have removed the (b) (4) information from the REMS Factsheet. Therefore (b) (4) information should be removed from your Supporting Document in this section.

REMS Letters to HCPs and Professional societies (print and email)

3. Per FDA comments sent on March 18, 2014, retain the subject of the emails: “Risk of Medullary Thyroid Carcinoma and Acute Pancreatitis with Tanzeum (albiglutide).”
4. Per FDA comments sent on March 18, 2014, retain the following sentence under the bullet “Potential Risk of Medullary Thyroid Carcinoma (MTC)”:
“It is unknown whether TANZEUM causes thyroid C-cell tumors, including MTC in humans.”
5. Include the following statement in bold font, as a new paragraph before the statement concerning the factsheet:
“Because of these risks, TANZEUM is not recommended as first-line therapy for patients inadequately controlled on diet and exercise.”
6. Revise the following sentence in the printed letters to both the healthcare providers and the professional societies to read:
(b) (4)
7. Revise the following sentence in the emailed letters to both the healthcare providers and the professional societies to read:
“A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is available at www.tanzeumrems.com.”
8. The FDA has already reviewed and accepted the appearance of the email versions of the REMS Letters, including logos, coloring and graphics in GSK’s submission on December 5, 2013. Removal of these items makes the email less inviting to read and minimizes association of risk messages with Tanzeum. Retain the logos, coloring and graphics on the emailed versions of the REMS Letters.

REMS Factsheet

9. We have the following edits to your REMS Factsheet:

- Added specific symptoms of thyroid tumors to be consistent with the PI
- Added language to the indication concerning one of the limitations of use
- Added the Tanzeum logo back onto the Factsheet
- Added the purple font back to the headings
- Accepted GSK's change to include the adverse event information
- Removed the (b) (4) FDA is no longer including this information in other REMS materials for similar drugs in this class.
- Modified formatting so that factsheet is now two pages. Spacing was increased to improve readability.

10. You asked the following in your March 25, 2014 letter, "... GSK interprets the distribution of the Factsheet to include by hand, by fax, or by email during a two-way conversation/exchange occurring with a US-based HCP about TANZEUM in person, over the telephone, via a live meeting, video, or email. Does FDA agree?"

FDA Reply: We agree that your interpretation is correct, except that the factsheet should also be distributed with any other Tanzeum materials, even if the HCP is unable to interact with the representative in person (e.g., if the prescriber is too busy to meet in person, and the representative is leaving written materials for the prescriber in lieu of speaking with the prescriber).

11. Retain the logos and coloring on this factsheet so that the REMS Factsheet does not look like a black and white document, with minimal association with Tanzeum. See revised REMS Factsheet attached.

REMS Website

12. Retain the Tanzeum logo on the Tanzeum REMS website.

13. Remove the following statement from the website as it is not necessary and redundant:

(b) (4)

14. Per FDA comments sent on March 18th, 2014, revise the website to include the following risk information:

Under "Potential Risk of Medullary Thyroid Carcinoma (MTC)", include the sub-bullets:

"Thyroid C-cell tumors have been observed in rodent studies with other glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TANZEUM causes thyroid C-cell tumors, including Medullary Thyroid Carcinoma in humans."

15. Under "Acute Pancreatitis", include the sub-bullet:

"In clinical trials, there were more cases of acute pancreatitis among patients treated with

TANZEUM than among patients treated with comparators.

16. Revise the following statement to read: “A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is available in the box to the right. “

ATTACHMENTS

Revised REMS Tanzeum Factsheet

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review Addendum

Date: March 18, 2014

Reviewer(s): Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst
Division of Risk Management (DRISK)

Kate Heinrich Oswell, MA, Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Subject: Review of the amended proposed REMS submitted on December 18, 2013

Drug Name(s): Albiglutide

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 2 mg, subcutaneous, once every seven days

Application Type/Number: BLA 125431

Submission Number: Sequence number 45, received December 18, 2013

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2013-279

1 INTRODUCTION

This review provides comments on the amended proposed REMs for albiglutide for injection submitted on December 18, 2013. GlaxoSmithKline (GSK) is seeking approval for albiglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The Agency has determined that, like other drugs in this class of glucagon like peptide-1 (GLP-1) receptor agonist, in addition to labeling including a boxed warning, a communication plan (CP) REMS to communicate the risks of pancreatitis and medullary thyroid cancer (MTC) is necessary to maintain a favorable risk to benefit balance for albiglutide.

DRISK comments on the REMS were sent to the sponsor October 25, 2013. The sponsor replied to the comments and submitted a revised REMS, revised REMS documents, and a revised REMS Supporting Document December 18, 2013.

2 MATERIALS REVIEWED

GlaxoSmithKline amended proposed REMS, submitted December 18, 2013 submission.

Previous DRISK review related to the original submission:

- Weaver J., DRISK REMS Review for BLA 125431. Signed in DARRTS on October 16, 2013.

3 RESULTS OF REVIEW

The sponsor responded appropriately to most comments. DRISK has additional revisions and comments to relay to the sponsor.

4 COMMENTS FOR THE SPONSOR

We acknowledge your December 19, 2013 response to our comments on your REMS submission for albiglutide, and we have the following revisions and comments. Please make the indicated changes and resubmit the REMS, REMS materials, and REMS Supporting Document. Provide versions of all documents in Word. We remind you that language in all REMS materials must reflect the approved final labeling. The REMS has not completed clearance within the Agency, and additional changes may be necessary.

REMS Materials:

REMS Letters to HCPs and Professional societies (print and email)

We have made minor edits to the REMS letters to provide more information concerning each risk. See track changes to your REMS Letters to HCPs and Professional Societies (print and email versions) attached.

REMS Factsheet

We have made edits to the REMS Factsheet removing information that is not directed related to the REMS goals and risks to narrow the focus of this communication piece. See track changes to your REMS Factsheet attached.

REMS Website

We have made minor edits to the REMS letters to provide more information concerning each risk. See track changes to your REMS Website attached.

REMS Assessment Plan

We agree with your comment that [REDACTED] (b) (4) are not part of the communication materials, and the item should be removed from the REMS Assessment Plan:

[REDACTED] (b) (4)

Make the change to the REMS Assessment Plan in the REMS Supporting Document.

ATTACHMENTS

Revised REMS materials

- Tanzeum REMS letter for Healthcare Providers
- Tanzeum REMS letter for professional societies
- Tanzeum Factsheet
- Tanzeum Professional Societies and Healthcare Providers emails
- Tanzeum REMS Website

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**Department of Health and Human Services
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Risk Evaluation and Mitigation Strategy (REMS) Review

Date: October 16, 2013

Reviewer(s): Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst
Division of Risk Management (DRISK)

Kate Heinrich Oswell, MA, Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D., Director, DRISK

Drug Name(s): Albiglutide

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 2 mg, subcutaneous, once every seven days

Application Type/Number: BLA 125431

Submission Number: Original submission /Seq. No. 0000 (1)

Applicant/sponsor: GlaxoSmithKline

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EXECUTIVE SUMMARY

This review documents DRISK's evaluation of need for a Risk Evaluation and Mitigation Strategy (REMS) for albiglutide. GlaxoSmithKline (GSK) is seeking approval for albiglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). At the time this document was written, FDA's review of the data submitted by the applicant in support of the efficacy and safety of albiglutide was still ongoing. DRISK will reassess the need for additional risk management measures once FDA reviewers complete their assessment of the benefits and risks associated with albiglutide.

Albiglutide is a glucagon like peptide-1 (GLP-1) receptor agonist. GLP-1 is an endogenous gastrointestinal hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas. FDA-approved GLP-1 receptor agonists include exenatide (Byetta, Bydureon) and liraglutide (Victoza). FDA required a REMS for these drugs to address the risks for pancreatitis (Byetta, Bydureon, and Victoza), the potential risk for thyroid C-cell tumors (Bydureon and Victoza), and the potential risk of renal failure (Byetta).

Efficacy and safety of albiglutide were studied in eight clinical trials. The trials included both placebo control and comparisons to other anti-diabetic therapies; i.e., glimepiride, insulin, liraglutide, pioglitazone, and sitagliptin. A total of 2,365 patients with T2DM received treatment with albiglutide in these trials. The trials showed superiority over placebo, non-inferiority to insulin glargine, insulin lispro, sitagliptin and glimeperide active control, and superiority to glimeperide. Non-inferiority to pioglitazone was not established.

The most commonly reported treatment emergent adverse events were diarrhea, injection site reactions, and nausea. Acute pancreatitis occurred in six patients who received albiglutide. One case of pancreatic cancer occurred in a patient treated with albiglutide. Two cases of thyroid cancer occurred in clinical testing, including one case of papillary thyroid cancer and one case of medullary thyroid cancer (MTC).

The applicant submitted a REMS to address the risks of pancreatitis and MTC. The proposed REMS includes a communication plan (CP) consisting of letters to healthcare providers (HCPs) and professional societies and a website.

DRISK has determined that, like other drugs in this class, in addition to labeling including a boxed warning, a CP REMS to communicate the risks of pancreatitis and MTC is necessary to maintain a favorable risk to benefit balance for albiglutide. A CP REMS for albiglutide will inform HCPs of the risks of pancreatitis and MTC, will have no negative impact on patient access to the drug, and there is no burden to the healthcare system resulting from the implementation of a CP REMS. The CP proposed by DRISK includes REMS communications (i.e., brief, risk message-focused letters for HCPs and professional societies), a REMS Factsheet, and a REMS website. These CP tools are revised versions of tools previously employed in other REMS for GLP-1 receptor agonists; the revisions are based on the experience gained from the assessments of other REMS. DRISK determined that although a Medication Guide (MG) would likely be useful as part of albiglutide's label, its inclusion as part of the REMS is not necessary. Based on the available safety information, DRISK determined that a REMS with elements to assure safe use (ETASU) is not required to maintain the risk to benefit balance of albiglutide.

1 INTRODUCTION

This review documents DRISK's evaluation of need for a Risk Evaluation and Mitigation Strategy (REMS) for albiglutide. GlaxoSmithKline is seeking approval for albiglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Because the Agency's review of the application is ongoing, this initial review of the risk mitigation required could be amended, depending on the results of the ongoing review. DRISK will reassess the need for additional risk management measures once FDA reviewers complete assessment of the benefits and risks associated with albiglutide.

Albiglutide is not approved for use in any country. An application was filed March 2013 for European consideration.

1.1 BACKGROUND

Albiglutide is a glucagon like peptide-1 (GLP-1) receptor agonist. GLP-1 is an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas. Endogenous GLP-1 has a beneficial impact on the metabolism of nutrients, stimulates insulin release from the pancreatic islets, suppresses glucagon secretion, delay gastric emptying, reduces body weight, slows gastric emptying, reduction of food intake, and increase in satiety. GLP-1 levels are reduced in patients with T2DM but their response to exogenous GLP-1 remains intact.

Albiglutide is supplied as a solution for subcutaneous injection to be taken once weekly. It is supplied in two strengths, 30mg and 50mg, in single-use pens.

*GLP-1 Receptor Agonists Safety Concerns.*¹ Byetta (exenatide), Bydureon (exenatide extended-release), and Victoza (liraglutide) are labeled for pancreatitis based on postmarketing data. Bydureon and Victoza have boxed warnings for the potential risk of thyroid C-cell tumors. Victoza causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. Bydureon causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. FDA required the implementation of REMS for all 3 approved GLP-1 receptor agonists.

1.2 REGULATORY HISTORY

Following are regulatory milestones for this application:

- **January 14, 2013:** BLA received for albiglutide
- **March 14, 2013:** BLA filed.
- **June 19, 2013:** Mid-cycle meeting.
- **July 11, 2013:** Mid-cycle communication sent to sponsor. The important issues relayed in the letter were chemistry, manufacturing, and controls (CMC) issues
- **August 1, 2013:** Sponsor notified that the July 12, 2013 CMC submission constitutes a major amendment, extending the review clock 3 months.
- **April 14, 2014:** PDUFA date.

¹ Byetta, Bydureon, and Victoza product labels.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Albiglutide proposed REMS and REMS supporting document, submitted with the application.
- Albiglutide draft labeling, submitted with the application.
- Albiglutide summary of clinical studies, submitted with the application.
- Reviewer slides and handouts from mid-cycle review meeting for albiglutide, dated June 19, 2013.
- Dr. Amarilys Vega review of proposed REMS for lixisenatide, NDA 204961, dated August 21, 2013.

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

Efficacy and safety of albiglutide were studied in eight clinical trials. The trials included both placebo control and comparisons to other anti-diabetic therapies; i.e., glimepiride, insulin, liraglutide, pioglitazone, and sitagliptin. A total of 2,365 patients with T2DM received treatment with albiglutide in these trials. The trials showed superiority over placebo, non-inferiority to insulin glargine, insulin lispro, sitagliptin and glimeperide active control, and superiority to glimeperide. Non-inferiority to pioglitazone was not established.

3.1 SAFETY

Fatalities: Overall, fatalities in patients receiving albiglutide in clinical trials were similar to fatalities in patients in the comparator groups. Twenty deaths (0.9%) occurred in patients receiving albiglutide in the clinical trials compared to 22 deaths (1%) in patients in the comparator groups.

Cancer: One case of metastatic pancreatic cancer occurred in a patient receiving albiglutide. One case of bile duct cancer that might have had a pancreatic primary also occurred in a patient receiving albiglutide. A case of papillary thyroid cancer occurred in a patient receiving albiglutide.

Pancreatitis: Six patients (1.6/1000 patient-years) experienced pancreatitis judged to be likely or possibly related to albiglutide. One of the cases of pancreatitis was fatal. Two of 408 (7.1/1000 patient-years) receiving the comparator drug, liraglutide, experienced pancreatitis. No cases of pancreatitis occurred in the 2122 patients who received other comparator drugs in the trials.

Drug-induced liver injury (DILI): One case of possible DILI occurred in a patient receiving albiglutide. The case was confounded by gallstones, but a causal role for albiglutide was not ruled out.

Other adverse events occurring more frequently in patients receiving albiglutide: Other events occurring more frequently in patients receiving albiglutide were pneumonia (0.4% vs 0.1%), atrial fibrillation (0.4% vs 0.1%), and appendicitis (0.2% vs 0%).

4 REMS FOR OTHER GLP-1 RECEPTOR AGONISTS

The safety profile of all currently FDA-approved GLP-1 receptor agonists (Victoza [liraglutide], Byetta [exenatide], and Bydureon [exenatide]) includes the risk of pancreatitis, including fatal events. Victoza and Bydureon have the additional risk for thyroid C-cell tumor and Byetta has a potential risk of renal failure, sometimes requiring hemodialysis and renal transplantation. A REMS with a communication plan (CP) was required by FDA for each of the approved GLP-1 receptor agonists. The REMS messages addressed by the REMS for the 3 FDA-approved GLP-1 receptor agonists are

similar with the exception of the potential risk of renal failure associated with Byetta and the fact that Byetta is not associated with thyroid C-cell tumor.

Byetta's CP consisted of a Dear Healthcare Professional (DHCP) letter directed to potential prescribers informing them of the risks of Byetta and a REMS website. Victoza's CP consisted of: (1) a DHCP letter, 2) Direct Mail letter, (3) Highlighted Information for Prescribers (to be mailed with the Direct Mail letter), and a REMS website. Bydureon's CP consisted of a DHCP letter, Highlighted Information for Prescribers, and a REMS webpage. Byetta was released from its REMS because, after receiving the first REMS assessment report, FDA considered that the REMS was meeting its goals.

5 RATIONALE FOR A REMS

A REMS has been required for the other members of this class of drugs to mitigate risks of pancreatitis and thyroid C-cell tumors. These risks extend to albiglutide. The applicant's proposed labeling includes a boxed warning for thyroid C-cell tumors. The risk of pancreatitis is listed in the Warnings and Precautions section of the labeling. It appears that, in addition to labeling including a boxed warning, a CP REMS to communicate the risk of pancreatitis and the potential risk of thyroid C-cell tumors is necessary to maintain a favorable benefit:risk balance for albiglutide.

The CP proposed by DRISK includes REMS communications (i.e., brief, risk message-focused letters for HCPs and professional societies), a REMS Factsheet, and a REMS website. These CP tools are revised versions of tools previously employed in other REMS for GLP-1 receptor agonists; the revisions are based on the experience gained from the assessments of other REMS. DRISK has no conclusive evidence of the effectiveness of the implementation of CP REMS in communicating a risk message but it presumes that making this information accessible to HCPs will increase the probability of informing them about the risks associated to albiglutide.

Key albiglutide CP REMS messages must be consistent with the product labeling and may include the following: (1) albiglutide is associated with the risk of acute pancreatitis; (2) HCPs must consider other antidiabetic therapies in patients with a history of pancreatitis, gallstones, alcoholism, and high blood triglycerides; (3) patients should be monitored for signs and symptoms of pancreatitis when treated with albiglutide; (4) if pancreatitis is suspected, albiglutide should be discontinued; (5) if pancreatitis is confirmed, albiglutide should be discontinued and not be restarted; and (6) patients must be counseled to be aware of the signs and symptoms of acute pancreatitis (i.e., severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting) and of the importance of reporting these to their physicians as soon as possible.²

HCPs are the target of the REMS messages, thus, DRISK determined that although it is important to include a Medication Guide (MG) as part of albiglutide's label, its inclusion as part of the REMS is not necessary. In addition, DRISK determined that a REMS with elements to assure safe use (ETASU) is not required to maintain the risk:benefit balance of albiglutide.

6 REMS PROPOSED BY THE SPONSOR AND DRISK'S COMMENTS

The applicant submitted a proposed REMS comprising a CP.

6.1 GOALS

The applicant proposed the following goal for the REMS:

² This list must be consistent with the approved product labeling and is likely to be revised during the BLA review process.

- [REDACTED] (b) (4)

Reviewer comment: We propose the following goal statement—

The goal of the TRADENAME REMS is to mitigate the risk of pancreatitis and the potential risk of medullary thyroid cancer associated with TRADENAME by:

- *informing healthcare providers (HCP) about the risk of acute pancreatitis associated with TRADENAME*
- *informing HCP about the potential risk of medullary thyroid cancer associated with TRADENAME.*

6.2 REMS ELEMENTS

Communication Plan: The applicant proposed implementation of a CP including the following tools:

- [REDACTED] (b) (4)

- The American Academy of Family Physicians (AAFP)
- The American College of Physicians (ACP)
- The American Medical Association (AMA)
- The American College of Osteopathic Family Physicians (ACOFP)
- The American Academy of Nurse Practitioners (AANP)
- The American Academy of Physician Assistants (AAPA)
- The American College of Clinical Pharmacy (ACCP)
- The American Society of Health-System Pharmacists (ASHP)
- The American Pharmacists Association (APhA)
- The American Association of Clinical Endocrinologists (AACE)
- The Endocrine Society (ENDO)
- The American Diabetes Association (ADA)
- The American Association of Diabetes Educators (AADE)
- The Association of Managed Care Pharmacy (AMCP)
- The National Association of Managed Care Physicians (NAMCP)

The letter will be provided to MedWatch at the same time it is disseminated to the professional societies.

The letter would be distributed within 60 days of product launch, and again 6 months after product launch.

- [REDACTED] (b) (4)
- *Albiglutide REMS website* – a REMS-specific website housing the REMS, [REDACTED] (b) (4), the Highlighted Information for Prescribers, and the product labeling, including a Medication Guide would be maintained for a year following product approval.

Reviewer comment: The CP proposed by DRISK includes REMS communications (i.e., concise risk message-focused letters for HCPs and professional societies), a REMS Factsheet, and a REMS website. These CP tools are revised versions of tools previously employed in other REMS for GLP-1 receptor agonists; the revisions are based on the experience gained from the assessments of other REMS and feedback from FDA’s Health Professional Organization Conference (October 2012). The change to the tools were made to provide a concise risk message and to improve the format for electronic letters; making this information more accessible to HCPs will increase the probability that prescribers will be able to receive and view risks messages associated to albiglutide. An increase in awareness of the REMS materials may result in improvements in prescribers’ knowledge of the risks associated with albiglutide.

- (1) *REMS letters* – replace [REDACTED] (b) (4) with concise, risk-focused REMS letters addressed to HCPs and relevant Professional Societies. DRISK proposes having print versions and email-friendly versions of these letters with the objective of improving the communication of the risk message among the growing HCP population of hand-held device users. Data from the assessment of other GLP-1 receptor agonist REMS programs suggest that HCPs’ awareness of REMS materials and knowledge about the risks communicated by the REMS increase after repeated mailings of the DHCP letter. Repeated communications may contribute to the letter dissemination of the risk message to HCPs. Consequently, DRISK proposes that REMS communications be sent within 60 days of product approval or at the time of product launch, whichever is sooner, 1 year after product launch, and again 2 years after product launch. The need for additional letters can be determined based on REMS assessment findings. The subject of the emails should be, “Risk of acute pancreatitis and potential risk of medullary thyroid cancer with albiglutide.” The outside of the mailed envelopes should state, “FDA Required REMS Safety Information”; it should be printed in red, bolded and a minimum of size 14 font. It may be printed on two lines and should be boxed.
- (2) *REMS Factsheet for HCPs* – development of a REMS Factsheet for HCPs to be distributed by the applicants’ sales and/or medical representatives during the first discussion of albiglutide with all HCPs detailed/visited during the first 12 months after product launch. The objective of the REMS Factsheet is to enhance the communication of the REMS messages by serving as an easily accessible reminder. This REMS Factsheet must be in a user-friendly format, including coloring, and logos from albiglutide’s REMS program; include bullets, boxes, and bold text to highlight important information; should have plenty of white space and a font size of at least 12; and a heading that should read: FDA Required TRADENAME REMS Safety Information.
- (3) *REMS website* – all REMS Communications, a downloadable version of the REMS Factsheet, the USPI, and Medication Guide should be available via a REMS-specific link from the albiglutide website for the duration of the REMS.

REMS CP materials must be consistent with the approved product label and include all key albiglutide CP REMS messages as listed in section 6.1 above, if applicable

Timetable for Submission of REMS Assessments: The Applicant proposed to submit REMS Assessments to the FDA at years (b) (4) from the date of approval of the initial REMS.

Reviewer comment: DRISK proposes submission of albiglutide REMS assessment reports at 18 months, 3 years, and 7 years from the date of the approval of the REMS. This will allow for assessment of the 12-month communication and is consistent with the assessment timelines described in the statute.

6.3 REMS ASSESSMENT PLAN

The proposed REMS assessment plan includes the following:

- An analysis of healthcare providers' understanding of the risk of acute pancreatitis and medullary thyroid cancer including identification, and need for prompt evaluation of possible cases of pancreatitis, and understanding of the appropriate albiglutide patient population characteristics.
- A description of specific measures to be taken to increase awareness if the assessment of HCPs indicates that prescriber awareness is not adequate.
- A narrative summary of all reported cases of medullary thyroid cancer and acute pancreatitis during the reporting period.
- Drug use patterns (e.g., patient demographics, duration of therapy, extent, and concomitant antidiabetic therapies).
- Based on information reported, an assessment of whether the REMS is meeting its goal and whether modification of the REMS is needed.

Reviewer comment: FDA recommends the albiglutide REMS assessment report must include but not be limited to the following items—

1. *REMS communication plan activities:*

- a. *Number of HCPs and professional societies targeted by the REMS.*
- b. *Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.*
- c. *Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.*
- d. *Date when REMS website went live and number of total and unique site visits during the assessment period.*

2. *Evaluation of HCPs' understanding of:*

- a. *The potential risk of MTC*
- b. *The risk of pancreatitis*
- c. *The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.*
- d. *Identification and treatment of acute pancreatitis after initiation of albiglutide.*
- e. *Appropriate albiglutide patient population characteristics*

3. *Safety surveillance*

- a. *Albiglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)*
 - b. *Evaluation and postmarketing case reports of pancreatitis*
 - c. *Evaluation and postmarketing case reports of MTC*
 - d. *Any other relevant data and analysis employed to assess if the albiglutide REMS is meeting its goals*
4. *The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification*

7 CONCLUSIONS AND RECOMMENDATIONS

DRISK determined that the potential risk of MTC and the risk of pancreatitis associated with albiglutide require management with a CP REMS in addition to labeling with a boxed warning.

At this point in the BLA review process, MTC and pancreatitis are the only risks to be included in this REMS; evidence to support inclusion of other serious risks in the REMS may surface during the BLA review process. DRISK will reassess the need for revisions to the risk management measures once FDA reviewers complete their assessment of the benefits and risks associated with albiglutide.

DRISK revised the REMS documents proposed by the applicant and recommends the Division of Metabolism and Endocrinology Products sends the applicant the comments included in section 8 below.

8 COMMENTS FOR THE SPONSOR

We acknowledge your submission of a proposed REMS for albiglutide (December 20, 2012) and have the following revisions and comments:

- 1) At this point in the BLA review process, MTC and pancreatitis are the only risks to be included in this REMS; evidence to support inclusion of other serious risks in the REMS may surface during the remaining BLA review process.
- 2) Goal statement: the goal statement was restated for clarity as follows:
 - i) The goal of the TRADENAME REMS is to mitigate the risk of pancreatitis and the potential risk of medullary thyroid cancer associated with TRADENAME by:
 - (1) informing healthcare providers (HCP) about the risk of acute pancreatitis associated with TRADENAME
 - (2) informing HCP about the potential risk of medullary thyroid cancer associated with TRADENAME.
- 3) Key albiglutide CP REMS messages must be consistent with the product's final labeling and may include the following, as applicable:
 - a) Albiglutide is potentially associated with the risk of MTC
 - b) HCPs must consider other anti-diabetic therapies in patients with a personal or family history of MTC, and in patients with Multiple Endocrine Neoplasia Syndrome type 2 (MEN 2).
 - c) Albiglutide is associated with the risk of acute pancreatitis.

- d) Patients should be monitored for signs and symptoms of pancreatitis when treated with albiglutide.
- e) If pancreatitis is suspected, albiglutide should be discontinued.
- f) If pancreatitis is confirmed, albiglutide should be discontinued and not be restarted.
- g) Patients must be counseled to be aware of the signs and symptoms of acute pancreatitis (i.e., severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting), and the signs and symptoms of MTC, and of the importance of reporting these to their physicians as soon as possible.

4) REMS document – a revised version of the REMS document is attached.

5) Communication Plan – the REMS should include the following communication tools:

i) REMS letters, REMS Factsheet, and a REMS website.

- (1) REMS Letters—Replace (b) (4) with concise, risk-focused REMS letters addressed to HCPs and relevant Professional Societies. FDA proposes having the REMS letters formatted in two different ways: print and electronic versions. The electronic version of the REMS letters should be email- and handheld device-friendly. The objective of these changes is to improve the communication of the risk message among the growing HCP population of hand-held device users. The subject of the emails should be “Risk of Medullary Thyroid Carcinoma and Acute Pancreatitis with Eperzan (albiglutide)”. The outside of the mailed envelopes should state: "FDA Required REMS Safety Information: it should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:



See proposed print and electronic REMS letter templates attached.

- (2) (b) (4)—Replace proposed (b) (4) with a new REMS Factsheet for HCPs. This REMS Factsheet must be in a user-friendly format, including coloring, and any logos from Eperzan's REMS program; include bullets, boxes, and bold text to highlight important information; should have plenty of white space and a font size of at least 12; be printed on thicker card stock paper; be only one sheet with information on both sides of paper and heading should read: FDA Required Eperzan REMS Safety Information.

Key messages to include on fact sheet include: boxed warning information, including risk of medullary thyroid carcinoma, risk of acute pancreatitis, contraindications, patient counseling on symptoms of thyroid tumors and acute pancreatitis, and brief REMS explanation.

- (3) REMS Website—Ensure the REMS website, is independent of link to the promotional and/or commercial website and non-REMS materials about the product. Do not

include [REDACTED] (b) (4). The REMS website should also be accessible directly through a search engine. The REMS website, including all REMS materials (REMS letters, REMS factsheet) will be available for the duration of the REMS.

(i) Submit screen shots and actual layout for the Eperzan REMS website

We remind you to use bullets, moderate white space, shorter line lengths, and fewer lines of text when possible when developing your website. The following is a link to helpful guidelines developed by HHS that you may consider in developing your website.

http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes

See proposed REMS website template attached.

- 6) Timetable for submission of REMS assessments – revise the timetable for submission of assessments of albiglutide REMS assessment reports to 18 months, 3 years, and 7 years from the date of the approval of the REMS. This will permit assessment of the 12-month communication, and is consistent with the assessment timelines described in the statute.
- 7) REMS assessment plan: the albiglutide REMS assessment report must include but not be limited to the following items—
 - a) REMS communication plan activities:
 - (1) Number of HCPs and professional societies targeted by the REMS.
 - (2) Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - (3) Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.
 - (4) Date when REMS website went live and number of total and unique site visits during the assessment period.
 - b) Evaluation of HCPs’ understanding of:
 - (1) The potential risk of MTC
 - (2) The risk of pancreatitis
 - (3) The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.
 - (4) Identification and treatment of acute pancreatitis after initiation of albiglutide.
 - (5) Appropriate albiglutide patient population characteristics
 - c) Safety surveillance
 - (1) Albiglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)
 - (2) Evaluation and postmarketing case reports of pancreatitis
 - (3) Evaluation and postmarketing case reports of MTC

- (4) Any other relevant data and analysis employed to assess if the albiglutide REMS is meeting its goals
- d) The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification
 - e) The inclusion of REMS assessment report synopsis or executive summary is helpful in the Agency's review of the REMS Assessment Reports.
- 8) Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- 9) Product marketing materials generally are not appropriate to educate about product risks.
- 10) Please submit all planned materials (e.g., proposed communications, education materials, and REMS website) identified within the plan that will be necessary to implement your proposal.
- 11) We recommend pre-testing all REMS materials.
- 12) Update the REMS Supporting Document to reflect all the changes to the REMS, REMS appended materials, and REMS assessment plan.
- 13) HCP survey: Submit for review the detailed plan you propose to use to evaluate prescribers' understanding about the safe use of albiglutide. You may submit the proposed plan after approval of the REMS; however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of albiglutide.
- a) Recruit respondents using a multi-modal approach.
 - b) Explain how often you perform non-respondent follow-up or reminders. If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value. Explain how you select recruitment sites. Submit for review any recruitment advertisements.
 - c) Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of prescriber knowledge for each key risk(s).
 - d) Define the expected number of prescribers to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
 - e) Ensure the sample is demographically representative of the prescriber population regardless of the condition for which they prescribe it.
 - f) When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, and geographically.
 - g) List the inclusion criteria for prescribers.
 - h) Submit any screener instruments, and describe any quotas of sub-populations used.
 - i) Explain how you administer surveys and the intended frequency. Offer respondents multiple options for completing the survey. Explain how you train surveyors.

- j) Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
- k) Submit for review the introductory text used to inform respondents about the purpose of the survey. Tell potential respondents that their answers will not affect their ability to prescribe albiglutide, and that their answers and personal information will be kept confidential and anonymous. All text, including questions and answers, are to be non-promotional in language and tone.
- l) Clarify in your methodology that respondents are eligible for one wave of the survey only.
- m) Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). You may stratify the data by any relevant variable, and also in aggregate. Submit all methodology and instruments utilized with your assessments.
- n) The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating HCPs' knowledge of the risks and safe use associated with albiglutide. The assessment does not assess HCPs' comprehension of the educational materials. Do not offer respondents an opportunity to read or see any educational materials (e.g., prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.
- o) Submit for review the survey instruments (e.g., questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
- p) Ensure the HCP knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials. Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Answer options should include an appropriate number of foils. Ensure each question has an "I don't know" answer option. Randomize the order of the multiple choice responses on each survey.
- q) Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions. Do not allow respondents the opportunity or ability to go back to previous questions in the survey. Explain if and when any education will be offered for incorrect responses.

ATTACHMENTS

Revised REMS Document

Sample of REMS Letters

- REMS Letter for HCP (print version)
- REMS Letter for HCP (email version)
- REMS Letter for Professional Societies (print version)
- REMS Letter for Professional Societies (email version)

Sample of REMS Website

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

/s/

JOYCE P WEAVER
10/16/2013

CLAUDIA B MANZO
10/16/2013
concur