

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125377Orig1s000**

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

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

FINAL REMS REVIEW

**Date:** March 24, 2011

**To:** Patricia Keegan, M.D., Director  
Division Biologic Oncology Products (DBOP)

**Through:** Claudia Karwoski, Pharm.D. Director  
Division of Risk Management (DRISK) *Claudia Karwoski*  
3/24/11

**From:** **Scientific Lead**, Risk Management Analyst (RMA)  
Joyce Weaver, Pharm.D., DRISK *Joyce Weaver*  
**Team Leader**, Suzanne Robottom, Pharm.D., DRISK *Suzanne Robottom*  
Kate Heinrich, M.A., Health Education Reviewer, DRISK *Kate Heinrich*  
3/24/11

**Subject:** Review of Risk Evaluation and Mitigation Strategy

**Drug Name:** Yervoy (ipilimumab)

**Therapeutic Class:** Human cytotoxic T-lymphocyte antigen-4 (CTLA-4)-  
blocking monoclonal antibody

**Dosage and Route:** 3 mg/kg intravenously every 3 weeks for four doses

**Application Type/Number:** BLA 125377

**Applicant:** Bristol-Myers Squibb Company

**OSE RCM #:** 2010-1503

## **1 INTRODUCTION**

The FDA is reviewing an application for ipilimumab (Yervoy), a fully human anticytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody with a mechanism of action of T-cell potentiation, for the treatment of advanced pre-treated melanoma. The applicant submitted a REMS proposal consisting of a Medication Guide, a communication plan, and a timetable for submission of assessments.

Ipilimumab causes immune-mediated adverse events, including severe events. Immune-mediated adverse events occurred in most study subjects in the pivotal phase 3 trial, and severe events occurred in 10% of patients. Some of these events were fatal. The autoimmune adverse events result from increased immune activity that can manifest in any body system, most frequently the gastrointestinal tract, liver, skin, endocrine system, and nervous system. The events can manifest during treatment with ipilimumab, or after the course of treatment has been completed, and the events can escalate quickly into severe events. These events are managed by withholding ipilimumab, and, in some cases, by administering corticosteroids.

This application is receiving priority review. It originally had a PDUFA goal date of December 25, 2010. This date was extended to March 26, 2011 because the applicant submitted a major amendment to the application.

## **2 MATERIALS REVIEWED**

We reviewed the following portions of the June 25, 2010 ipilimumab submission:

- Proposed REMS and REMS Supporting Document, submissions of June 25, 2010, March 14, 2011, March 15, 2011
- The applicant's submission of January 20, 2011 replying to FDA's preliminary comments on the REMS
- Draft labeling submitted March 14, 2011

## **3 RESULTS OF REVIEW OF PROPOSED YERVOY RISK EVALUATION AND MITIGATION STRATEGY**

### **3.1 Goal**

The goal of the YERVOY REMS is to inform healthcare providers about the serious risks associated with YERVOY, and the management of the reactions, including risks of severe and fatal immune-mediated adverse reactions such as fatal immune-mediated enterocolitis (including gastrointestinal perforation), fatal immune-mediated hepatitis (including hepatic failure), fatal immune-mediated toxicities of skin (including toxic epidermal necrol

### **3.2 REMS Elements**

### 3.2.1 Communication Plan

The REMS for ipilimumab includes a communication plan to healthcare providers (HCPs) expected to prescribe, administer, or provide care for patients receiving ipilimumab. This includes oncologists, surgical oncologists, oncology nurses, oncology pharmacists, infusion nurses, emergency department physicians, gastroenterologists, endocrinologists, hepatologists, neurologists, dermatologists, and health-system pharmacists.

The communication is divided into two tiers, one tier for oncology practitioners, and another tier for non-oncology practitioners who might be involved in the management of the patients receiving ipilimumab. The oncology audience comprises the healthcare providers who manage patients with advanced melanoma (oncologists, surgical oncologists, oncology nurses, oncology pharmacists and infusion nurses) and cancer treatment infusion center. This audience will receive the following in a mailing and by electronic communication prior to launch and every six months for three years thereafter:

- a. *A Dear Healthcare Provider Letter* informing healthcare providers about the incidence, type, severity and management of immune-mediated adverse reactions caused by YERVOY
- b. *The Immune-Mediated Adverse Reaction Management Guide*
- c. *The Patient Wallet Card*
- d. *The Nursing Immune-Mediated Adverse Reaction Symptom Checklist*

The non-oncology practitioners who may be involved in the care of patients receiving ipilimumab include gastroenterologists, dermatologists, endocrinologists, emergency room physicians, hepatologists, and health-system pharmacists. This audience will be contacted by electronic communication only at or shortly after product launch and then every six months for three years. The communication will include the Dear Healthcare Provider Letter and the Immune-Mediated Side Effects Management Guide. The non-oncology practitioners will not receive hardcopy mailings of the materials.

The communication materials will be available for seven years in electronic format on a REMS website. The communication package will be distributed annually at the Bristol-Myers Squibb booth at the meeting of the American Society of Clinical Oncology starting June 2011 in Chicago, Illinois. Hard copies of the communication materials will be available to the oncology audience for seven years.

### 3.2.2 Timetable for Submission of Assessments

Bristol-Myers Squibb Company will submit REMS Assessments to FDA 18 months, 3 years, and 7 years from the date of approval of the REMS.

### **3.3 REMS Assessment Plan**

The REMS assessment reports will include the following:

- a An evaluation of healthcare providers' (HCPs) understanding of the serious risks of YERVOY (ipilimumab) and the management of the immune-mediated adverse reactions caused by YERVOY
- b With regard to assessment of the communication plan:
  - i The date of product launch and the launch of the communication plan
  - ii The date(s) of mailing and number of recipients of the Dear Healthcare Provider (DHCP) letter and the communication package
  - iii The number of mailings returned
  - iv The sources of the recipient lists
  - v The number of new prescribers prescribing YERVOY /new facilities purchasing YERVOY during the reporting period. Of the new prescribers/purchasers, the number supplied with the communication materials within the required timeframe; the number not supplied with communication materials within the required timeframe; the reasons for the failure to deliver communication materials within the required timeframe.
- c Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.
- d Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.
- e An analysis of post-marketing cases of immune-mediated adverse events reported for YERVOY that result in the patient's death, including an analysis of the length and reasons for any reported delay in recognition and treatment of the events.

The sponsor has agreed to submit the survey methodology and survey instruments for FDA review at least 90 days before the evaluation using the survey is conducted.

## **4 DISCUSSION/CONCLUSION**

The use of a communication plan-based REMS instead of an ETASU-based REMS was discussed at the Safety First Steering Committee meeting February 3, 2011. The committee advised the REMS team that the use of such a communication plan-based REMS instead of ETASU was appropriate.

A draft of the safety-related labeling was prepared in a 6-hour labeling meeting between the FDA review team and the applicant held March 9, 2011. Prior to this meeting, it was not clear that the labeling (and therefore the REMS) could offer specific advice to healthcare providers on the management the immune-mediated

adverse events. Agreement was reached during the March 9 meeting on the appropriate management of these events supported by the clinical trial data, specifically, when the trial data supported advice to temporarily or permanently withhold ipilimumab, and when the trial data supported the use of corticosteroids. This information has been incorporated into the REMS materials.

The Medication Guide, originally proposed as part of this REMS, was removed from the REMS in accordance with the February 2011 draft *Guidance for Industry, Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*.

## **5 RECOMMENDATION**

The REMS submitted March 24, 2011 is acceptable. The REMS should be approved.

**ATTACHMENTS** (REMS document and all appended materials.)

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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 ONCOLOGY DRUG PRODUCTS  
DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS

**BLA:** STN 125377  
**Products:** Yervoy (ipilimumab),  
injection, for intravenous use  
**APPLICANT:** Bristol-Myers Squibb  
**FROM:** Jeff Summers  
**DATE:** March 23, 2011

*JK Summers*  
*3/23/11*

This is an addendum to the previously written REMS memorandum of August 30, 2010. The Draft Guidance for Industry titled, "Medication Guides – Distribution Requirements and Inclusion in RISK Revaluation and Mitigation Strategies (REMS)", now allows the Agency to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS or required as labeling but not part of a REMS. We have determined based on the guidance and the criterion therein that a Medication Guide is not required as part of the ipilimumab REMS; therefore, the initially drafted REMS memo has been revised to remove the Medication Guide as part of the REMS requirement. In addition, this memo updates the REMS goal language to be consistent with the boxed warning in the package insert. The Office of Surveillance and Epidemiology was consulted on the updated language.

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 Yervoy (ipilimumab) to ensure that the benefits of the drug outweigh the risk of severe and fatal immune-mediated adverse reactions such as fatal immune-mediated enterocolitis (including gastrointestinal perforation), fatal immune-mediated hepatitis (including hepatic failure), fatal immune-mediated toxicities of skin (including toxic epidermal necrolysis), fatal

nervous system toxicity, and endocrinopathies, and the management of the reactions, associated with Yervoy (ipilimumab). In reaching this determination, we considered the following:

A. The estimated size of the population likely to use the drug involved:

According to data from the Surveillance Epidemiology and End Results (SEER) program (2000-2007, SEER 17), age adjusted incidence rates for invasive melanoma for all (ages, races, and sexes) for 2007 was 20.43 per 100,000 people. SEER data (2002-2006) documented incidence rates for invasive melanoma among Caucasian individuals in the United States of 28.9/100,000 men and 18.7/100,000 women per year. It is estimated that 68,130 men and women (38,870 men and 29,260 women) will be diagnosed with, and 8,700 men and women will die of, melanoma of the skin in 2010. Regional and distant (metastatic) disease comprises 12% of the cases diagnosed; therefore approximately 8,000 patients develop advanced (unresectable Stage III and Stage IV) melanoma annually. There are no other alternative therapies that have been demonstrated to have an overall survival benefit in advanced melanoma, hence, approximately 8,000 to 10,000 patients in the US are general candidates for ipilimumab therapy, as indicated.

B. The seriousness of the disease or condition that is to be treated with the drug:

Advanced melanoma is generally considered incurable with 5 year survival rates of less than 10% and median survival of 6 to 12 months

C. The expected benefit of the drug with respect to such disease or condition:

Ipilimumab-containing regimens demonstrated a statistically significant advantage in OS. The hazard ratio (HR) for comparison of OS between the ipilimumab monotherapy and gp100 groups was 0.66 (95% CI: 0.51, 0.87; p = 0.0026). The result was consistent with the HR for comparison between the ipilimumab+gp100 group and the gp100 group (HR 0.68 [95% CI: 0.55, 0.85; p = 0.0004].

D. The expected or actual duration of treatment with the drug:

Ipilimumab therapy is indicated as one intravenous infusion over 90 minutes administered every three weeks for a total of four infusions

(b) (4)

(b) (4)

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:

The serious adverse drug reactions caused by ipilimumab that were identified during clinical development are immune related adverse reactions including hepatitis, colitis,

and endocrinopathies. Ipilimumab caused fatal hepatitis and fatal colitis. Ipilimumab also caused severe hypophysitis with subsequent life threatening adrenal crisis. The background incidence of these specific immune mediated adverse reactions cannot be estimated, however, these rates would be low, as cancer patients are treated with immunosuppressive drugs that would be anticipated to further reduce the already extremely low incidence rate in the general population. The immune-related adverse reactions caused by ipilimumab can also be caused by non-immune mediated mechanisms such as sepsis or direct drug induced hepatic toxicity and require specialized tests to differentiate the etiological mechanism, thereby confounding any attempt to determine accurate background incidence rates of these toxicities in cancer patients. Ipilimumab also causes immune-related skin (pruritis, rash and peeling) and neurologic (motor and sensory neuropathies) toxicity.

F. Whether the drug is a new molecular entity.

Ipilimumab is a new molecular entity and will be the first drug to augment T-cell immune responses by blocking signaling through the CTLA-4 receptor.

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

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

REMS INTERIM REVIEW #2

**Date:** February 15, 2011

**To:** Patricia Keegan, M.D., Director  
Division Biologic Oncology Products (DBOP)

**Through:** Claudia Karwoski, Pharm.D. Director *Claudia Karwoski*  
Division of Risk Management (DRISK) *2/15/11*

**From:** **Scientific Lead**, Risk Management Analyst (RMA) *J. Weaver 2/15/11*  
Joyce Weaver, Pharm.D., DRISK  
**Team Leader**, Suzanne Robottom, Pharm.D., DRISK

**Subject:** Risk Evaluation and Mitigation Strategy (REMS)

**Drug Name (Established Name):** Yervoy (ipilimumab)

**Therapeutic Class:** Human cytotoxic T-lymphocyte antigen-4 (CTLA-4)-  
blocking monoclonal antibody

**Dosage and Route:** 3 mg/kg intravenously every 3 weeks for four doses for  
induction

**Application Type/Number:** BLA 125377

**Applicant:** Bristol-Myers Squibb Company

**OSE RCM #:** 2010-1503

## **1 EXECUTIVE SUMMARY**

This document reviews the status of the proposed risk evaluation and mitigation strategy (REMS) for ipilimumab to address the risk of autoimmune adverse events.

The applicant has proposed a REMS comprising a Medication Guide, a communication plan, and a timetable for submission of assessments. The REMS materials focus on communicating the intervention protocols developed during the clinical development program. The division has requested data from the sponsor to clarify the appropriate management of the adverse events. If these protocols are supported by the clinical data requested by the division, we agree with incorporating the protocols into the REMS. If data do not support the protocols, or if data are not available, DRISK does not recommend including specific management recommendations into the REMS.

Without data supporting the management of the autoimmune adverse events, the REMS can inform prescribers about the possibility of these events, but should not advise prescribers about the management of the events.

## **2 BACKGROUND**

The FDA is reviewing an application for ipilimumab (Yervoy), a fully human anticytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody with a mechanism of action of T-cell potentiation, for the treatment of advanced pre-treated melanoma. The applicant submitted a REMS proposal consisting of a Medication Guide, a communication plan, and a timetable for submission of assessments.

Ipilimumab causes autoimmune adverse events, including severe events. Autoimmune adverse events occurred in most study subjects in the pivotal phase 3 trial, and severe events occurred in 10% of patients. Some of these events were fatal. The autoimmune adverse events result from increased immune activity that can manifest in any body system, most frequently the gastrointestinal tract, liver, skin, endocrine system, and nervous system. The events can manifest during treatment with ipilimumab, or after the course of treatment has been completed, and the events can escalate quickly into severe events.

This application is receiving priority review. It originally had a PDUFA goal date of December 25, 2010. This date was extended to March 26, 2011 because the applicant submitted a major amendment to the application.

## **3 MATERIALS REVIEWED**

We reviewed the following portions of the June 25, 2010 ipilimumab submission:

- Proposed REMS
- REMS Supporting Document
- Module 2.5 (clinical overview)
- Summary of Clinical Safety
- Appendix E (management algorithm for treatment of immune events)

- Draft labeling

Additionally, we reviewed the following:

- Draft labeling of January 25, 2011, incorporating FDA edits
- The applicant's submission of January 21, 2011, responding to an FDA request for information regarding the time to onset and time to resolution of autoimmune events.
- The applicant's submission of January 20, 2011 replying to FDA's preliminary comments on the REMS

## **4 RESULTS OF REVIEW**

### **4.1 OVERVIEW OF THE PERTINENT ASPECTS OF THE CLINICAL PROGRAM**

Overall, 3,450 subjects had received ipilimumab in clinical testing prior to the June 2010 submission. In the pivotal phase 3 trial, ipilimumab was studied in a randomized, double-blind, multicenter study comparing ipilimumab monotherapy, ipilimumab in combination with a melanoma peptide vaccine, gp100 peptide vaccine, and gp100 peptide vaccine monotherapy in HLA-A2\*0201-positive patients with previously treated unresectable Stage III or IV melanoma. The primary objective of the study was the overall survival of subjects receiving ipilimumab + gp100 peptide vaccine compared with the survival of those subjects receiving gp100 peptide vaccine alone. A total of 676 subjects from twelve countries entered the study. About one-half of the study subjects were from the United States. Ipilimumab was dosed at 3 mg per kg of body weight administered intravenously every three weeks for a total of four doses for induction. Survival was increased in the ipilimumab subjects compared to the subjects receiving ipilimumab + gp100 peptide vaccine group or the subjects receiving gp100 peptide vaccine alone (median survival advantage exceeded three months for patients receiving ipilimumab).

### **4.2 SAFETY CONCERN**

#### **Autoimmune adverse events**

Ipilimumab causes autoimmune adverse events that can be severe, even fatal. In the pivotal trial, eight patients died secondary to autoimmune adverse events. These events are inflammatory in nature, and are based on the T-cell potentiation mechanism of action of ipilimumab. The most frequently affected body systems in clinical testing were the gastrointestinal (GI) system and the skin. GI effects ranged from diarrhea to GI perforation. Such GI effects occurred in nearly 30% of study subjects in the pivotal efficacy trial. Bowel perforation contributed to four subject deaths in the pivotal efficacy trial.

Skin reactions range from rash and pruritus to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Skin effects occurred in over 40% of patients in the pivotal efficacy trial. Fatalities secondary to skin reactions occurred in clinical testing of ipilimumab.

Other body systems can be affected by the adverse events, including the neurological system (Guillain-Barré syndrome, myasthenia gravis), the endocrine system (hypophysitis, hypopituitarism, adrenal insufficiency), and the liver (hepatitis, hepatic failure). A subject died secondary to hepatic failure in the pivotal trial, and another subject died secondary to Guillain-Barré syndrome.

Holding of scheduled doses and symptomatic management of the autoimmune adverse events is proposed by the applicant to be appropriate if the events are mild and self-limited. For persistent or more severe autoimmune adverse events, use of high-dose corticosteroids is proposed.

According to the applicant's response to the FDA's inquiry regarding the timing of the autoimmune adverse events, the events developed as early as a fraction of a week after the first dose of ipilimumab for skin, gastrointestinal, neuropathic, and endocrine events, and three weeks for hepatic events. The time to resolution of the events ranged from a fraction of a week to years.

The applicant has not submitted a response to FDA's information request regarding the impact of holding doses and the impact of intervention with immunosuppressant drugs to manage these events.

#### **4.3 APPLICANT'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY<sup>1</sup>**

##### **4.3.1 Goals**



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<sup>1</sup> The sponsor has agreed to FDA-proposed changes to the REMS (see our review and comments dated December 14, 2010), but they have not submitted a revised REMS proposal incorporating the changes. The FDA-proposed changes did not change the basic structure of the proposed REMS.

[Redacted] (b) (4)

*Reviewers note: The applicant agreed to change the goals to the goals listed below as conveyed in the FDA's preliminary comments on the REMS, dated January 3, 2011. If the applicant submits data supporting the management of the events, the management of these events should be included in the goals; e.g., "Inform HCPS about the serious risks associated with Yervoy and appropriate management. These risks include...."*

[Redacted] (b) (4)

#### **4.3.2 Medication Guide**

A Medication Guide will be enclosed in each carton of Yervoy. The carton will include a notice to dispense the Medication Guide to each patient prior to each infusion.

#### **4.3.3 Communication Plan**

The applicant proposes that the REMS include a communication plan for healthcare providers. [Redacted] (b) (4)

[Redacted]

The applicant plans to distribute communication materials [Redacted] (b) (4)

[Redacted]

*Reviewers note: The applicant agreed to streamline the communication materials as outlined in our December 13, 2010 review. The applicant also agreed to rename [Redacted] (b) (4) the Patient Wallet Card. Note that if the communication plan does not include medical management of the events, some of these pieces would be modified or removed from the REMS.*

#### **4.3.4 Elements to Assure Safe Use**

The REMS does not include elements to assure safe use. [Redacted] (b) (4)

[Redacted]

(b) (4)

*Reviewers note: The ipilimumab REMS was discussed at the February 3, 2011 meeting of the Safety First Steering Committee. The committee agreed that ETASU would not be required for this REMS.*

#### **4.3.5 Implementation System**

Because the REMS proposal does not include elements to assure safe use, the proposal also does not include an implementation system.

#### **4.3.6 Timetable for Submission of Assessments**

(b) (4)

#### **4.3.7 Information Needed for Assessment**

(b) (4)

## **5. DISCUSSION**

The applicant stated that the management recommendations for autoimmune adverse events were developed during the clinical trials. Management of GI toxicity was developed after the start of the pivotal Phase 3 trial. The recommendations for managing autoimmune hepatitis, skin, and neurological events were developed during the conduct of the supportive Phase 2 studies. The division sent questions to the sponsor regarding the management protocols, including classification of mild, moderate, and severe autoimmune adverse events, the data regarding delaying doses for toxicity, omitting doses for toxicity, the data regarding permanently discontinuing ipilimumab for toxicity, the impact of intervention with steroids and other immunosuppressants, and the criteria for determining that an event is refractory to treatment with steroids.

The division has requested the following information from the applicant regarding severe autoimmune enterocolitis and gastrointestinal perforation:

- The clinical study/CRF report lacks sufficient detail to determine how often in Study 1 pts with Grade 2 colitis or diarrhea had doses delayed and for how long. It is also unclear whether corticosteroids were initiated in what proportion of subjects with grade 2 enterocolitis, whether there is a difference in time to resolution or completeness of resolution in patients whose doses were withheld compared to those where doses were withheld and corticosteroids were initiated. Provide data to support recommendation in product labeling.

- We do not agree with the methods used in deriving time to resolution. Events such as diarrhea and colitis should be considered same events. Update label and provide data for all subjects who received Yervoy in study 1. Reanalyze using the definition from Table 3.
- What is the maximum allowable delay time before the drug was supposed to be discontinued, as per MDX10-20 protocol?
- Please provide patient IDs for all patient with severe diarrhea or enterocolitis in Study 1 who received high dose IV steroids and those that did not. Compare/contrast time to symptom treatment resolution between those treated with and without high-dose corticosteroids.
- Justify this statement by providing data (specific case studies, patients ID numbers, narratives) where a withdrawal of steroids over less than a month resulted in recurrence of symptoms. Provide dose and duration of IV steroid use for all subjects treated for severe or fatal enterocolitis in Study 1.
- After what duration was a patient considered steroid refractory? Provide subject IDs and duration of high dose steroid use in Study 1. Provide subject IDs of all patients considered steroid refractory. C

The division posed similar questions and made similar comments for other autoimmune events (i.e., hepatitis, dermatitis, neuropathy, endocrinopathy). The requested information is critical if the REMS materials is to provide meaningful specific advice regarding the management of these adverse events. Without the requested information, the REMS can function to inform the prescribers of the side effect profile, but the REMS will not be able to help inform prescribers how to manage the events. (b) (4)

## 6 CONCLUSION

High level OSE comments regarding the REMS were sent to the applicant, and the applicant has responded to the comments. The applicant did not resubmit the REMS because labeling negotiations critical to the REMS are ongoing. As appropriately noted by the applicant, the details of the REMS are contingent on the results of the labeling negotiations. The labeling negotiations include a request for data regarding the management of the autoimmune reactions. We cannot determine the scope and content of the REMS and move forward in finalizing the REMS until such time as the information from the applicant has been received and labeling negotiations to a large extent have been settled. If these protocols are supported by the clinical data requested by the division, we agree with incorporating the protocols into the REMS. If data do not support the

protocols, or if data are not available, DRISK does not recommend including specific management recommendations into the REMS.

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

**DRISK INTERIM REMS REVIEW**

**REMS Comments Set #1**

**Date:** December 13, 2010

**To:** Patricia Keegan, M.D., Director  
Division Biologic Oncology Products (DBOP)

**Through:** Claudia Karwoski, Pharm.D. Director  
Division of Risk Management (DRISK)

*Claudia Karwoski*  
12/15/10

**From:** Scientific Lead, Risk Management Analyst (RMA)  
Joyce Weaver, Pharm.D., DRISK  
Team Leader, Suzanne Robottom, Pharm.D., DRISK

*J. Weaver*  
12/13/2010  
*[Signature]*  
12/14/10

**REMS Review Team**

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**Subject:** Interim REMS Review Comments Set #1 for Ipilimumab

**Drug Name:** Yervoy (ipilimumab)

**Therapeutic Class:** Human cytotoxic T-lymphocyte antigen-4 (CTLA-4)-  
blocking monoclonal antibody

**Dosage and Route:** 3 mg/kg intravenously every 3 weeks for four doses

**Application Type/Number:** BLA 125377

**Applicant:** Bristol-Myers Squibb Company

**OSE RCM #:** 2010-1503

## INTERIM REMS REVIEW COMMENTS

### 1 Materials Reviewed

We reviewed the REMS proposal submitted by the applicant on June 25, 2010:

### 2 Introduction and Background

Ipilimumab is a fully human anticytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody with a mechanism of action of T-cell potentiation. The Agency is reviewing an application for ipilimumab for the treatment of advanced melanoma. In the application for approval, the applicant submitted a REMS proposal consisting of a Medication Guide and a communication plan.

Ipilimumab causes severe immune-related adverse events, including severe events that occur in 10-13% of patients. In clinical testing some of these events were fatal. The immune-related adverse events result from increased immune activity that manifests in numerous body systems, including gastrointestinal tract, liver, skin, endocrine system, and nervous system. The events can manifest during treatment with ipilimumab, or after the course of treatment has been completed, and the events can escalate quickly into severe events requiring intervention with immunosuppressant drugs to manage the patients.

### 3 Summary of Applicant's Proposed REMS

The applicant proposes a REMS comprised of a Medication Guide, and a communication plan for healthcare providers.

(b) (4)

The applicant plans to distribute communication materials

(b) (4)

K

(b) (4)

### 4 Recommendations for the Review Division

DRISK met with DBOP to discuss the value

(b) (4)

The language in the Medication Guide will be reviewed separately. This review will commence when a substantially complete label is available.

The comments below are based on DRISK's preliminary review of the REMS proposal for ipilimumab. We recommend that the following comments on the ipilimumab REMS proposal be sent to the applicant. Please request that the applicant respond to these comments within 14 days.

## **5 Recommendations for the Applicant**

We have reviewed the submission and have the following comments. Be aware that we anticipate additional comments as your application undergoes further review.

### **1. REMS goals: Change the goals of the REMS to the following.**

The goals of the REMS <sup>(b)</sup><sub>(4)</sub> are

(b) (4)

(b) (4)

## 2. Communication Plan

a. It is not clear what contact database list will be used to derive the mailing list for the providers to receive the *Dear Healthcare Provider Letter*. Clarify how the names and addresses of these providers will be determined. This information should be included in the REMS Supporting Document. Provide estimate on the numbers of providers by specialty you plan to target. Clarify what material new prescribers and infusion sites will receive.

b. The REMS should specify the targets of the communication plan, including each prescriber specialty, each specific professional association, each medical oncology association, each oncology and nursing association, each infusion association, and the other specialty associations you reference. For each named target, the communication plan should state clearly which educational pieces the target will receive, the manner of delivery, and the timeframe for delivery. In order to reach as many healthcare providers as possible, we suggest disseminating the DHCP letters through various media. For example, in addition to hardcopy the letter could be sent electronically. If you do not choose to use electronic mailings, provide a rationale for this decision.

c. You propose using prescriber orders for ipilimumab to identify prescribers to whom you will communicate the risk information for ipilimumab. Provide more information how this will work, especially regarding the time that will lapse between the date the prescriber orders ipilimumab and the date the prescriber will receive the training on the risks of ipilimumab. How will you ensure that prescribers are offered the training promptly?

d. Describe how you propose to handle orders placed by organizations rather than prescribers (e.g., infusion centers or hospitals). How will the prescribers using these supplies be trained?

e. A definite time period, including initiation date, interval, and end date, is needed in your communication plan for all communication activities. (b) (4)

(b) (4) We recommend sending the letter within a set timeframe, for example, within 60 days of approval of ipilimumab or in conjunction with product launch, whichever is sooner. This information should be included in the REMS.

f. The REMS document states that the *Dear Healthcare Provider Letter* will be distributed at launch and then every six months for three years following launch. (b) (4)

(b) (4) The timeframe in the REMS Supporting Document should be corrected.

g. We recommend streamlining the following materials into one concise document for providers:

(b) (4)

This new streamlined document should be included with the *Dear Healthcare Provider Letter* mailing to the primary target audience as defined in the REMS Supporting Document.

h. The following piece should be removed from the REMS communication plan:

(b) (4)

i. The (b) (4) should be renamed; we suggest "Patient Wallet Card."

i. The following language should be modified as recommended in all materials:

(b) (4)

k. The basis of the management recommendations should be included in the communication materials.

(b) (4)

m. As the communication materials will be maintained on a website, we recommend a stand alone REMS dedicated website.

(1) We recommend that you include a prominent link on the product website's homepage for REMS materials. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote ipilimumab or any other

Bristol-Myers Squibb product. Only the separate webpage(s) and/or link will be considered a component of the Communication Plan.

(2) The landing page of the separate REMS link should contain background information on the REMS, as well as safety information, along with the REMS communication materials.

This page should include a prominent header to communicate the risks associated with ipilimumab and addressed through the REMS.

We recommend the following language as background information on the REMS landing page:



### **3. Timetable for Submission of Assessments**

The Timetable for Submission of Assessments should include the following standard language:

Bristol-Myers Squibb Company will submit REMS Assessments to FDA (b) (4) (b) (4) from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for the

assessment. Bristol-Myers Squibb will submit each assessment so that it will be received by the FDA on or before the due date.

#### **4. REMS Supporting Document**

Revise the REMS Supporting Document to be consistent with all changes made to the REMS document and materials.

#### **5. The REMS assessment plan**



#### **7. General Comments**

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.

If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document. However, changes must be noted using PDF mark-up tools.

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF ONCOLOGY DRUG PRODUCTS  
DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS**

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**BLA:** STN 125377  
**Products:** Yervoy (ipilimumab),  
injection, for intravenous use  
**APPLICANT:** Bristol-Myers Squibb  
**FROM:** Jeff Summers  
**DATE:** August 30, 2010

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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 Yervoy (ipilimumab) to ensure that the benefits of the drug outweigh the risks of three major immune-related toxicities identified during the clinical development of ipilimumab: 1) risk for fatal colitis; 2) risk for fatal hepatitis; and 3) risk for severe and potentially fatal hypopituitarism. In reaching this determination, we considered the following:

A. The estimated size of the population likely to use the drug involved:

According to data from the Surveillance Epidemiology and End Results (SEER) program (2000-2007, SEER 17), age adjusted incidence rates for invasive melanoma for all (ages, races, and sexes) for 2007 was 20.43 per 100,000 people. SEER data (2002-2006) documented incidence rates for invasive melanoma among Caucasian individuals in the United States of 28.9/100,000 men and 18.7/100,000 women per year. It is estimated that 68,130 men and women (38,870 men and 29,260 women) will be diagnosed with, and 8,700 men and women will die of, melanoma of the skin in 2010. Regional and distant (metastatic) disease comprises 12% of the cases diagnosed; therefore approximately 8,000 patients develop advanced (unresectable Stage III and Stage IV) melanoma annually. There are no other alternative therapies

that have been demonstrated to have an overall survival benefit in advanced melanoma, hence, approximately 8,000 to 10,000 patients in the US are general candidates for ipilimumab therapy, as indicated.

B. The seriousness of the disease or condition that is to be treated with the drug:

Advanced melanoma is generally considered incurable with 5 year survival rates of less than 10% and median survival of 6 to 12 months

C. The expected benefit of the drug with respect to such disease or condition:

Ipilimumab-containing regimens demonstrated a statistically significant advantage in OS. The hazard ratio (HR) for comparison of OS between the ipilimumab monotherapy and gp100 groups was 0.66 (95% CI: 0.51, 0.87;  $p = 0.0026$ ). The result was consistent with the HR for comparison between the ipilimumab+gp100 group and the gp100 group (HR 0.68 [95% CI: 0.55, 0.85;  $p = 0.0004$ ].

D. The expected or actual duration of treatment with the drug:

Ipilimumab therapy is indicated as one intravenous infusion over 90 minutes administered every three weeks for a total of four infusions. (b) (4)

(b) (4)

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:

The serious adverse drug reactions caused by ipilimumab that were identified during clinical development are immune related adverse reactions including hepatitis, colitis, and endocrinopathies. Ipilimumab caused fatal hepatitis and fatal colitis. Ipilimumab also caused severe hypophysitis with subsequent life threatening adrenal crisis. The background incidence of these specific immune mediated adverse reactions cannot be estimated, however, these rates would be low, as cancer patients are treated with immunosuppressive drugs that would be anticipated to further reduce the already extremely low incidence rate in the general population. The immune-related adverse reactions caused by ipilimumab can also be caused by non-immune mediated mechanisms such as sepsis or direct drug induced hepatic toxicity and require specialized tests to differentiate the etiological mechanism, thereby confounding any attempt to determine accurate background incidence rates of these toxicities in cancer patients. Ipilimumab also causes immune-related skin (pruritis, rash and peeling) and neurologic (motor and sensory neuropathies) toxicity.

F. Whether the drug is a new molecular entity.

Ipilimumab is a new molecular entity and will be the first drug to augment T-cell immune responses by blocking signaling through the CTLA-4 receptor.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Yervoy (ipilimumab). FDA has determined that Yervoy (ipilimumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Yervoy (ipilimumab). FDA has determined that Yervoy (ipilimumab) is a product for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Yervoy (ipilimumab).

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