

cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death [see Data]. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

Risk Summary

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of OPDIVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older.

8.6 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-use vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune

response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. Based on a population pharmacokinetic (PK) analysis using data from 909 patients, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (V_{ss}) is 8.0 L (30.4%), and geometric mean elimination half-life (t_{1/2}) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Specific Populations: Based on a population PK analysis using data from 909 patients, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m²; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m²; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m²; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function [see Use in Specific Populations (8.6)].

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST) [see Use in Specific Populations (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *M. tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

Trial 1 was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either OPDIVO administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m² every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m² every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in Trial 1 and in whom the minimum duration of follow up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with OPDIVO, the median age was 58 years (range: 25-88), 65% of patients were male, 98% were white, and the ECOG PS was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were objective responses in patients with and without BRAF V600 mutation positive-melanoma.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) is available as follows:

Carton Contents	NDC
40 mg/4 mL single-use vial	0003-3772-11
100 mg/10 mL single-use vial	0003-3774-12

Store OPDIVO under refrigeration at 2°C to 8°C (36°F-46°F). Protect OPDIVO from light by storing in the original package until time of use. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions* (5.1)].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see *Warnings and Precautions* (5.2)].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see *Warnings and Precautions* (5.3)].
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [see *Warnings and Precautions* (5.4)].
- Hypothyroidism and Hyperthyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism and hyperthyroidism [see *Warnings and Precautions* (5.5)].

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests [see *Warnings and Precautions* (5.3, 5.4, 5.5, 5.6)].

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.7), *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO [see *Use in Specific Populations* (8.3)].

Advise women not to breastfeed while taking OPDIVO [see *Use in Specific Populations* (8.2)].

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

1321663

MEDICATION GUIDE
OPDIVO® (op-DEE-voh)
(nivolumab)
injection

Read this Medication Guide before you start receiving OPDIVO and before each infusion. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OPDIVO?

OPDIVO is a medicine that may treat your melanoma by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Symptoms of pneumonitis may include:

- new or worsening cough
- chest pain
- shortness of breath

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach-area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruise more easily than normal
- feeling less hungry than usual

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Hormone gland problems (especially the thyroid, pituitary, and glands). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- dizziness or fainting
- hair loss
- feeling cold
- constipation
- voice gets deeper

Problems in other organs. Signs of these problems include:

- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness

Getting medical treatment right away may keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid medicines and delay or completely stop treatment with OPDIVO, if you have severe side effects.

What is OPDIVO?

OPDIVO is a prescription medicine used to treat a type of skin cancer called melanoma

OPDIVO may be used when your melanoma:

- has spread or cannot be removed by surgery (advanced melanoma)

and,

- after you have tried a medicine called ipilimumab and it did not work or is no longer working

and,

- if your tumor has an abnormal "BRAF" gene, and you have also tried a different medicine called a BRAF inhibitor, and it did not work or is no longer working.

It is not known if OPDIVO is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before receiving OPDIVO?

Before you receive OPDIVO, tell your healthcare provider if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung, or breathing problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant.
- OPDIVO can harm your unborn baby.
- Females who are able to become pregnant should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed
- It is not known if OPDIVO passes into your breast milk
- Do not breastfeed during treatment with OPDIVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

How will I receive OPDIVO?

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 60 minutes.
- OPDIVO is usually given every 2 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects. See "What is the most important information I should know about OPDIVO?"

The most common side effects of OPDIVO include:

- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OPDIVO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OPDIVO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about OPDIVO, talk with your healthcare provider. You can ask your healthcare provider for information about OPDIVO that is written for health professionals.

For more information, call 1-855-673-4861 or go to www.OPDIVO.com.

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

1321663

Issued December 2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

BLA ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) dated July 30, 2014, received July 30, 2014, submitted under section 351 of the Public Health Service Act for Opdivo (nivolumab) Injection for Intravenous Infusion.

We acknowledge receipt of your amendments dated August 29, 2014; September 11, 17, 24, 26 (2), 30, 2014; October 6, 7, 9, 10, 17, 23, 28, 2014; November 3, 7, 10, 11, 12, 14, 17, 19, 20, 24, 2014; December 1 (2), 2, 3 (2), 4, 5, 8, 10, 11, 16, 18, 20, 2014.

LICENSING

We have approved your BLA for Opdivo effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Opdivo under your existing Department of Health and Human Services U.S. License No.1713. Opdivo is indicated for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Opdivo drug substance at Lonza Biologics, Incorporated in Portsmouth, NH. The final formulated product will be manufactured, filled, labeled, and packaged at Bristol-Myers Squibb Holdings Pharma, Ltd., in Manatí, Puerto Rico. You may label your product with the proprietary name Opdivo and will market it in 40 mg and 100 mg single-use vials.

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DATING PERIOD

The dating period for Opdivo shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 24 months from the date of manufacture when stored at 2-8°C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Opdivo to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Opdivo, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on November 3, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes,

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designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125554.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Opdivo (nivolumab) was not referred to an FDA advisory committee because: this biologic is not the first in its class; the clinical trial design is acceptable; the application did not raise significant safety or efficacy issues; and the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated December 10, 2014. This requirement, along with required completion dates, is listed below.

This postmarketing trial is subject to the reporting requirements of 21 CFR 601.70:

- 2838-1 Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

Final Report Submission: December 31, 2016

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart E Postmarketing Requirement(s).**”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

Drug Substance Specification Assessment:

- 2838-2 To re-evaluate nivolumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

The timetable you submitted on December 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: October 31, 2016

Drug Product Specification Assessment:

- 2838-3 To re-evaluate nivolumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

The timetable you submitted on December 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: October 31, 2016

Improvements To Methods Assessment (HCP Assay):

- 2838-4 To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the nivolumab drug substance release program. The analytical procedure, validation report, proposed specification acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.

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The timetable you submitted on December 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: March 31, 2016

Improvements To Methods Assessment (CE-SDS Method):

- 2838-5 To optimize and re-validate a non-reduced CE-SDS method that has improved reproducibility. The analytical procedure, validation report, any proposed changes to specification acceptance criteria, and the data used to set the proposed acceptance criteria will be provided in the final study report

The timetable you submitted on December 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: March 31, 2016

Improvements To Endotoxin Limits (Drug Substance):

- 2838-6 Re-evaluate and tighten the endotoxin limits for the following in-process samples: post-intermediate-filtration, prior-to-transfer of the clarified bulk, Tank T-701 end of hold, and protein A load. Re-evaluate and tighten the endotoxin limits for the following additional samples: all product-contact buffers, end-of-first-cycle equilibration and end of-last cycle post-wash samples for the protein A, HIC, CEX chromatography columns.

The timetable you submitted on December 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: April, 30, 2016

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70, you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report,"** or **"Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

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You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please notify the Regulatory Project Manager for this application within two weeks of receipt of this letter.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better

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understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Meredith Libeg, Senior Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPDIVO safely and effectively. See full prescribing information for OPDIVO.

OPDIVO (nivolumab) injection, for intravenous use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

OPDIVO is a human programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1, 14)

DOSAGE AND ADMINISTRATION

Administer 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL and 100 mg/10 mL solution in a single-use vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Immune-mediated adverse reactions: Administer corticosteroids based on the severity of the reaction. (5.1, 5.2, 5.3, 5.4, 5.6)

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold for moderate or severe and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate and permanently discontinue for severe or life-threatening serum creatinine elevation. (5.4)
- Immune-mediated hypothyroidism and hyperthyroidism: Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. (5.5)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reaction ($\geq 20\%$) was rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OPDIVO® (nivolumab) is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor [see *Clinical Studies* (14)].

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.2 Dose Modifications

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Withhold OPDIVO for any of the following:

- Grade 2 pneumonitis [see *Warnings and Precautions* (5.1)]
- Grade 2 or 3 colitis [see *Warnings and Precautions* (5.2)]
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN [see *Warnings and Precautions* (5.3)]
- Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline [see *Warnings and Precautions* (5.4)]
- Any other severe or Grade 3 treatment-related adverse reactions [see *Warnings and Precautions* (5.6)]

Resume OPDIVO in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue OPDIVO for any of the following:

- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis [see *Warnings and Precautions* (5.1)]
- Grade 4 colitis [see *Warnings and Precautions* (5.2)]
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN [see *Warnings and Precautions* (5.3)]
- Creatinine greater than 6 times ULN [see *Warnings and Precautions* (5.4)]
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks

- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of OPDIVO

2.3 Preparation and Administration

Visually inspect drug product solution for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 574 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.9% (5/574) of patients receiving OPDIVO. No cases of fatal pneumonitis occurred in Trial 1; all five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: one with Grade 3 and five with Grade 2 pneumonitis. The median time to onset for the six cases was 2.2 months (range: 25 days-3.5 months). In two patients, pneumonitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 pneumonitis led to interruption or permanent discontinuation of OPDIVO in the remaining four patients. All six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day); immune-mediated pneumonitis improved to Grade 0 or 1 with corticosteroids in all six patients. There were two patients with Grade 2 pneumonitis that completely resolved (defined as improved to Grade 0 with completion of corticosteroids) and OPDIVO was restarted without recurrence of pneumonitis.

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis [*see Dosage and Administration (2.2)*].

5.2 Immune-Mediated Colitis

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: five patients with Grade 3 and one patient with Grade 2 colitis. The median time to onset of immune-mediated colitis from initiation of OPDIVO was 2.5 months (range: 1-6 months). In three patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis led to interruption or permanent discontinuation of OPDIVO in the remaining three patients. Five of these six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.4 months (range: 3 days-2.4 months) preceding corticosteroid taper. The sixth patient continued on low-dose corticosteroids started for another immune-mediated adverse reaction. Immune-mediated colitis improved to Grade 0 with corticosteroids in five patients, including one patient with Grade 3 colitis retreated after complete resolution (defined as improved to Grade 0 with completion of corticosteroids) without additional events of colitis. Grade 2 colitis was ongoing in one patient.

Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold OPDIVO for Grade 2 or 3 immune-mediated colitis. Permanently discontinue OPDIVO for Grade 4 colitis or for recurrent colitis upon restarting OPDIVO [see *Dosage and Administration* (2.2)].

5.3 Immune-Mediated Hepatitis

In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs. 12%), alkaline phosphatase (22% vs. 13%), ALT (16% vs. 5%), and total bilirubin (9% vs. 0). Immune-mediated hepatitis, defined as requirement for corticosteroids and no clear alternate etiology, occurred in 1.1% (3/268) of patients receiving OPDIVO: two patients with Grade 3 and one patient with Grade 2 hepatitis. The time to onset was 97, 113, and 86 days after initiation of OPDIVO. In one patient, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. In two patients, OPDIVO was withheld. All three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4-15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids in two patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted OPDIVO and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of OPDIVO.

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.4 Immune-Mediated Nephritis and Renal Dysfunction

In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction (defined as $\geq$ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology) occurred in 0.7% (2/268) of patients at 3.5 and 6 months after OPDIVO initiation, respectively. OPDIVO was permanently discontinued in both patients; both received high-dose corticosteroids (at least 40 mg prednisone equivalents). Immune-mediated nephritis resolved and did not recur with continuation of corticosteroids in one patient. Renal dysfunction was ongoing in one patient.

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue OPDIVO. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold OPDIVO and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

5.5 Immune-Mediated Hypothyroidism and Hyperthyroidism

In Trial 1, where patients were evaluated at baseline and during the trial for thyroid function, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. The median time to onset was 2.5 months (range: 24 days-11.7 months). Seventeen of the 21 patients with hypothyroidism received levothyroxine. Fifteen of 17 patients received subsequent OPDIVO dosing while continuing to receive levothyroxine.

Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. The median time to onset in OPDIVO-treated patients was 1.6 months (range: 0-3.3 months). Four of five patients with Grade 1 hyperthyroidism and two of three patients with Grade 2 hyperthyroidism had documented resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism.

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.

5.6 Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of OPDIVO-treated patients in Trial 1: pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis.

Across clinical trials of OPDIVO administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome.

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate

corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event [see *Dosage and Administration* (2.2)].

5.7 Embryofetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis [see *Warnings and Precautions* (5.1)]
- Immune-Mediated Colitis [see *Warnings and Precautions* (5.2)]
- Immune-Mediated Hepatitis [see *Warnings and Precautions* (5.3)]
- Immune-Mediated Nephritis and Renal Dysfunction [see *Warnings and Precautions* (5.4)]
- Immune-Mediated Hypothyroidism and Hyperthyroidism [see *Warnings and Precautions* (5.5)]
- Other Immune-Mediated Adverse Reactions [see *Warnings and Precautions* (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the WARNINGS and PRECAUTIONS section and below reflect exposure to OPDIVO in Trial 1, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m² every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m² every 3 weeks [see *Clinical Studies* (14)]. The median duration of exposure was 5.3 months (range: 1 day-13.8+ months) with a median of eight doses (range: 1 to 31) in OPDIVO-treated patients and was 2 months (range: 1 day-9.6+ months) in chemotherapy treated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

Clinically significant adverse reactions were also evaluated in 574 patients with solid tumors enrolled in two clinical trials receiving OPDIVO at doses of 0.1 to 10 mg/kg every 2 weeks,

supplemented by immune-mediated adverse reaction reports across ongoing clinical trials [see *Warnings and Precautions* (5.1, 5.6)].

In Trial 1, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV.

The study population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% white, baseline ECOG performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated LDH at baseline (51% vs. 38%).

OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to less than 5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.

Table 1 summarizes the adverse reactions that occurred in at least 10% of OPDIVO-treated patients. The most common adverse reaction (reported in at least 20% of patients) was rash.

Table 1: Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 1)

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Percentage (%) of Patients				
Skin and Subcutaneous Tissue Disorders				
Rash ^a	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	17	0	6	0

Table 1: Selected Adverse Reactions Occurring in $\geq 10\%$ of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of $\geq 5\%$ [All Grades] or $\geq 2\%$ [Grades 3-4]) (Trial 1)

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Percentage (%) of Patients				
Infections and Infestations				
Upper respiratory tract infection ^b	11	0	2.0	0
General Disorders and Administration Site Conditions				
Peripheral edema	10	0	5	0

^a Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, and dermatitis acneiform.

^b Upper respiratory tract infection is a composite term which includes rhinitis, pharyngitis, and nasopharyngitis.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

Skin and Subcutaneous Tissue Disorders: exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis.

Table 2: Selected Laboratory Abnormalities Increased from Baseline Occurring in $\geq 10\%$ of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of $\geq 5\%$ [All Grades] or $\geq 2\%$ [Grades 3-4]) (Trial 1)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline ^a			
	OPDIVO		Chemotherapy	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased AST	28	2.4	12	1.0
Increased alkaline phosphatase	22	2.4	13	1.1
Hyponatremia	25	5	18	1.1
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2.0	6	0

^a Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range 252 to 256 patients) and chemotherapy group (range 94 to 96 patients).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Of 281 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-product antibodies, 24 patients (8.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in two patients (0.7%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-product binding antibody development based on the population pharmacokinetic and exposure-response analyses.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with OPDIVO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action [see *Clinical Pharmacology* (12.1)] and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. In animal reproduction studies, administration of nivolumab to

cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death [see Data]. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

Risk Summary

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of OPDIVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older.

8.6 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-use vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune

response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. Based on a population pharmacokinetic (PK) analysis using data from 909 patients, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (V_{ss}) is 8.0 L (30.4%), and geometric mean elimination half-life (t_{1/2}) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Specific Populations: Based on a population PK analysis using data from 909 patients, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m²; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m²; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m²; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function [see Use in Specific Populations (8.6)].

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST) [see Use in Specific Populations (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

Trial 1 was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either OPDIVO administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m² every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m² every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in Trial 1 and in whom the minimum duration of follow up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with OPDIVO, the median age was 58 years (range: 25-88), 65% of patients were male, 98% were white, and the ECOG PS was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were objective responses in patients with and without BRAF V600 mutation positive-melanoma.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) is available as follows:

Carton Contents	NDC
40 mg/4 mL single-use vial	0003-3772-11
100 mg/10 mL single-use vial	0003-3774-12

Store OPDIVO under refrigeration at 2°C to 8°C (36°F-46°F). Protect OPDIVO from light by storing in the original package until time of use. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions* (5.1)].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see *Warnings and Precautions* (5.2)].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see *Warnings and Precautions* (5.3)].
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [see *Warnings and Precautions* (5.4)].
- Hypothyroidism and Hyperthyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism and hyperthyroidism [see *Warnings and Precautions* (5.5)].

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests [see *Warnings and Precautions* (5.3, 5.4, 5.5, 5.6)].

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.7), *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO [see *Use in Specific Populations* (8.3)].

Advise women not to breastfeed while taking OPDIVO [see *Use in Specific Populations* (8.2)].

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

U.S. License No. 1713

1321663

MEDICATION GUIDE
OPDIVO® (op-DEE-voh)
(nivolumab)
injection

Read this Medication Guide before you start receiving OPDIVO and before each infusion. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OPDIVO?

OPDIVO is a medicine that may treat your melanoma by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Symptoms of pneumonitis may include:

- new or worsening cough
- chest pain
- shortness of breath

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach-area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruise more easily than normal
- feeling less hungry than usual

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Hormone gland problems (especially the thyroid, pituitary, and glands). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- dizziness or fainting
- hair loss
- feeling cold
- constipation
- voice gets deeper

Problems in other organs. Signs of these problems include:

- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness

Getting medical treatment right away may keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid medicines and delay or completely stop treatment with OPDIVO, if you have severe side effects.

What is OPDIVO?

OPDIVO is a prescription medicine used to treat a type of skin cancer called melanoma

OPDIVO may be used when your melanoma:

- has spread or cannot be removed by surgery (advanced melanoma)

and,

- after you have tried a medicine called ipilimumab and it did not work or is no longer working

and,

- if your tumor has an abnormal "BRAF" gene, and you have also tried a different medicine called a BRAF inhibitor, and it did not work or is no longer working.

It is not known if OPDIVO is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before receiving OPDIVO?

Before you receive OPDIVO, tell your healthcare provider if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung, or breathing problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant.
- OPDIVO can harm your unborn baby.
- Females who are able to become pregnant should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed
- It is not known if OPDIVO passes into your breast milk
- Do not breastfeed during treatment with OPDIVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

How will I receive OPDIVO?

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 60 minutes.
- OPDIVO is usually given every 2 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects. See "What is the most important information I should know about OPDIVO?"

The most common side effects of OPDIVO include:

- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OPDIVO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OPDIVO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about OPDIVO, talk with your healthcare provider. You can ask your healthcare provider for information about OPDIVO that is written for health professionals.

For more information, call 1-855-673-4861 or go to www.OPDIVO.com.

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

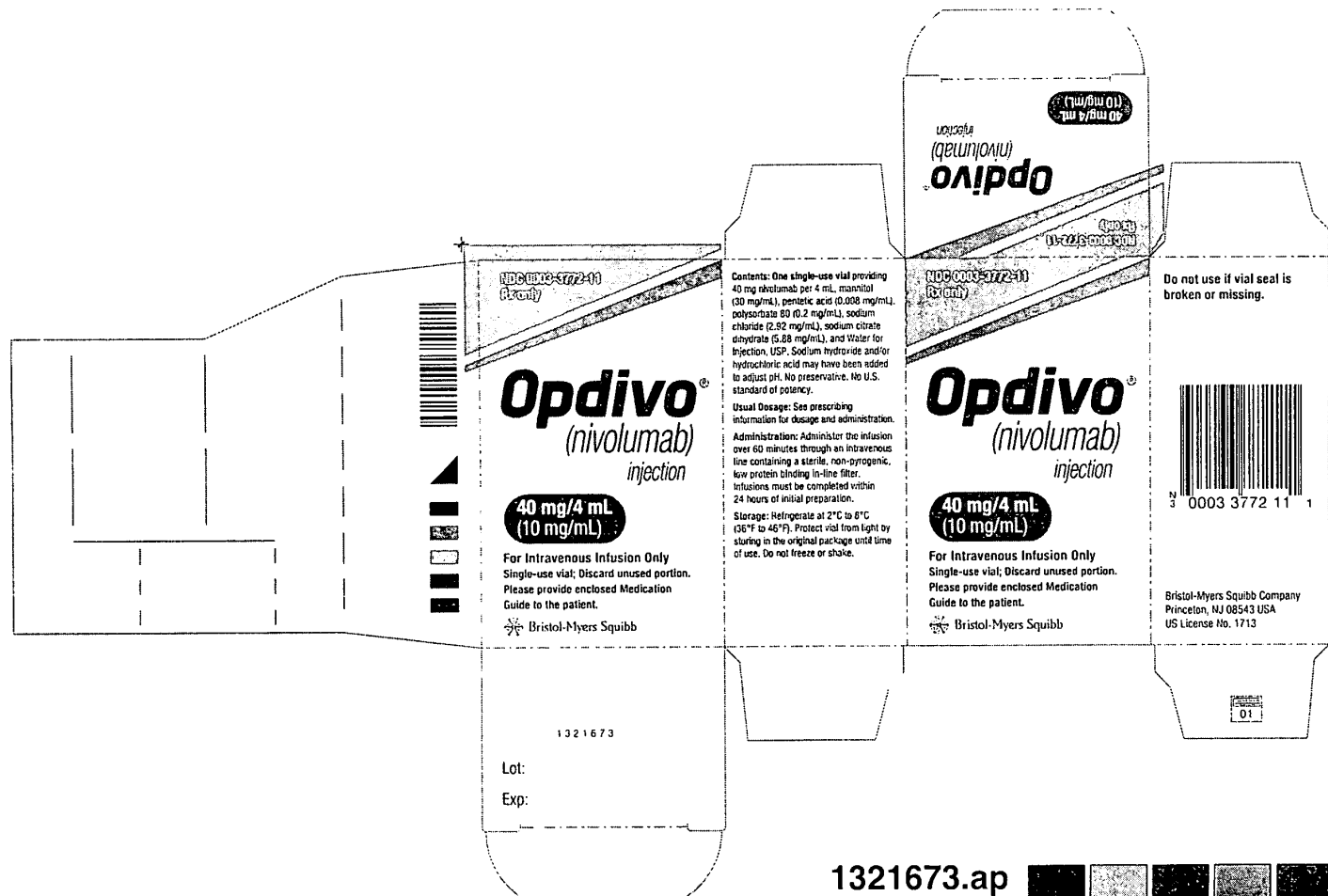
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

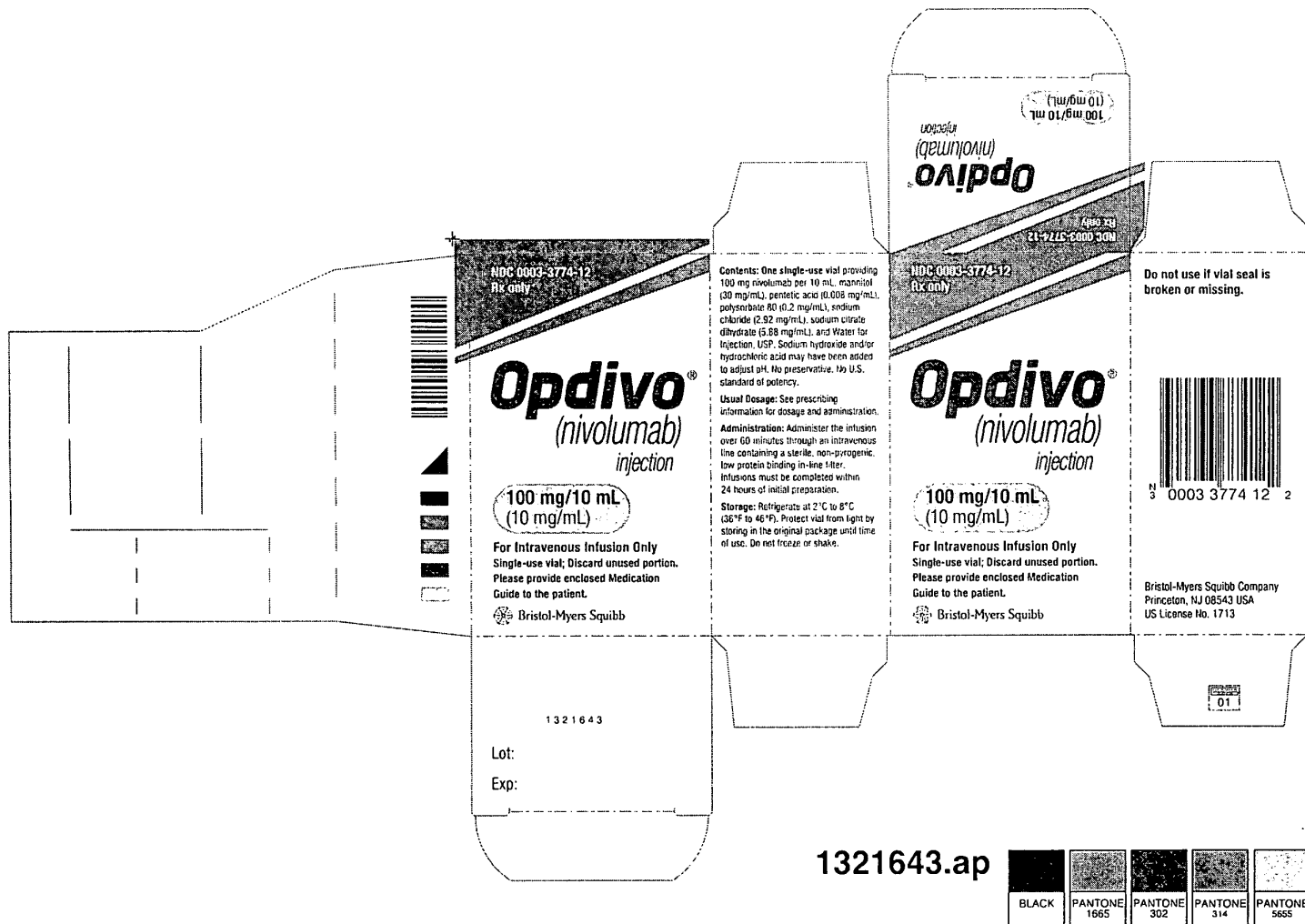
U.S. License No. 1713

1321663

Issued December 2014



Reference ID: 3677021



Reference ID: 3677021

NDC 0003-3772-11
Rx only

Opdivo[®]
(nivolumab)
injection

40 mg/4 mL
(10 mg/mL)

For Intravenous Infusion Only
Single-use vial; Discard unused portion.

See prescribing information for dosage and administration.

Refrigerate at 2°C to 8°C (36°F to 46°F).
Protect vial from light by storing in the original package until time of use. Do not freeze or shake.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

US License No. 1713



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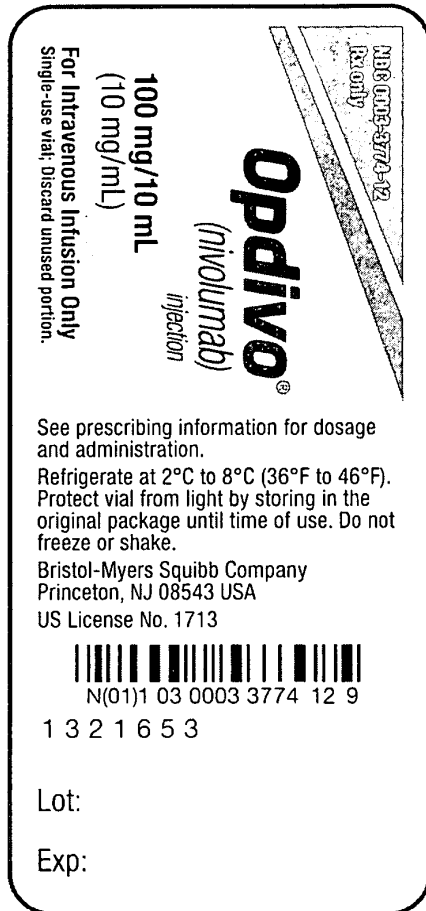
Lot:

Exp:

Exhibit 6
Atty Docket No. 3338.0180003/ELE-C-K

Best Available Copy

Reference ID: 3677021



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

/s/

RICHARD PAZDUR
12/22/2014

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,008,449 B2
APPLICATION NO. : 11/913217
DATED : August 30, 2011
INVENTOR(S) : Alan J. Korman et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

Item (75), Inventors:

Change "Changyu Wang, Fremont, CA" to -- Changyu Wang, Union City, CA --.

Change "Bingliana Chen" to -- Bingliang Chen --.

Claim 1:

Column 125, line 60, change "SEO" to -- SEQ --.

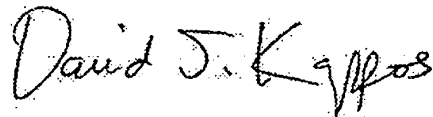
Claim 2:

Column 125, line 65, change "CDR3domains" to -- CDR3 domains --.

Claim 23:

Column 132, line 34, change "claim 5" to -- claim 8 --.

Signed and Sealed this
Twentieth Day of December, 2011



David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
Certificate

Patent No. 8,008,449 B2

Patented: August 30, 2011

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without any deceptive intent, improperly sets forth the inventorship.

Accordingly, it is hereby certified that the correct inventorship of this patent is: Alan J. Korman, Piedmont, CA (US); Mohan Srinivasan, San Jose, CA (US); Changyu Wang, Fremont, CA (US); Mark J. Selby, San Francisco, CA (US); Bingliana Chen, Alameda, CA (US); and Josephine M. Cardarelli, San Carlos, CA (US); Haichun Huang, San Carlos, CA (US).

Signed and Sealed this Eleventh Day of November 2014.

EDAN ORGAD
Supervisory Patent Examiner
Art Unit 2414
Technology Center 2400



United States
Patent and
Trademark Office

Patent Bibliographic Data				02/12/2015 11:57 AM	
Patent Number:	8008449		Application Number:	11913217	
Issue Date:	08/30/2011		Filing Date:	01/29/2009	
Title:	HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS				
Status:	8th year fee window opens: 08/30/2018			Entity:	LARGE
Window Opens:	N/A	Surcharge Date:	N/A	Expiration:	N/A
Fee Amt Due:	Window not open	Surchg Amt Due:	Window not open	Total Amt Due:	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	02/11/2015 Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---				
Address for fee purposes:	Sterne, Kessler, Goldstein & Fox P.L.L.C 1100 New York Avenue NW Washington DC 20005				
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 100052

Medarex, Incorporated
Attention: Geoffrey Nichol, M.D.
Senior Vice President, Product Development
519 route 173 West
Bloomsbury, NJ 08804

Dear Dr. Nichol:

The Center for Drug Evaluation and Research has received your Investigational New Drug Application (IND). The following product name and IND number have been assigned to this application. They serve only to identify it and do not imply that this Center either endorses or does not endorse your application.

IND NUMBER: 100052 ^{100052 LH/7/25/06}

SPONSOR: Medarex, Incorporated

PRODUCT NAME: Human Monoclonal Antibody (MDX-1106) to PD-1 receptor

DATE OF SUBMISSION: June 28, 2006

DATE OF RECEIPT: June 29, 2006

TREATMENT USE: Treatment of patients with recurrent or treatment-refractory malignancies

This above IND number should be used to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND. Please provide an original and two copies of every submission to this file. Please include three originals of all illustrations which do not reproduce well.

You may not initiate studies in humans until 30 days after the date of receipt shown above. If this office notifies you, verbally or in writing, of serious deficiencies that require correction before human studies can begin, you will continue to withhold such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory. If such a clinical hold is placed on this file, you will be notified in writing of the reasons for placing the IND on hold.

You are responsible for compliance with applicable portions of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). The

REC'D 2450466

IND 100052
Page 2

CFR is available through several sources including our web site at <http://www.fda.gov/cder/regulatory/default.htm>. The following points regarding obligations of an IND sponsor are included for your information only, and are not intended to be comprehensive.

Progress reports are required at intervals not exceeding one year and are due within 60 days of the application anniversary date [21 CFR 312.33]. Any unexpected fatal or immediately life-threatening reaction associated with use of this product must be reported to this Division by telephone or facsimile transmission no later than seven calendar days after initial receipt of the information. All serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, must be reported, in writing, to this Division and to all investigators within fifteen calendar days after initial receipt of this information [21 CFR 312.32].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank <http://clinicaltrials.gov/> and <http://prsinfo.clinicaltrials.gov/>. If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

Upon receipt of this acknowledgement letter, you may either obtain supplies of the investigational drug or ship it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold. In addition, prior to use of each new lot of the investigational biologic in clinical trials, submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58, copies available upon request). If such studies have not been conducted in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. Information on environmental assessments is available in the guidance "Environmental Assessment of Human Drugs and Biologics." This document is available on the internet at

IND 100052
Page 3

<http://www.fda.gov/cder/guidance/index.htm> or may be requested from the Office of Training and Communications, Division of Drug Information at (301) 827-4570.

Each submission to this IND must be provided in triplicate, an original and two copies. Please include three originals of all illustrations which do not reproduce well. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Telephone inquiries concerning this IND should be made directly to me at (301) 796-2320. If we have any comments after we have reviewed this submission, we will contact you.

Sincerely yours,

{See appended electronic signature page}

Melanie Pierce
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 100052	MEDAREX	Human monoclonal Antibody (MDX-1106) to PD-1 receptor

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

/s/

MELANIE PIERCE
07/17/2006



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

BLA ACKNOWLEDGEMENT

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Opdivo (nivolumab) Injection for Intravenous Infusion,
40 mg/4 ml (10 mg/mL) vial, 100 mg/10 ml (10 mg/mL) vial

Date of Application: July 30, 2014

Date of Receipt: July 30, 2014

Our Secondary Tracking Number (STN): BLA 125554

Proposed Use: For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

BLA 125554
Page 2

The BLA Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Monica L. Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

MONICA L HUGHES
08/12/2014

Significant Activities During the Applicable Regulatory Review Period

Activity	IND or BLA	Date
Filed IND 100052	IND 100052	28-JUN-2006
Filed IND Commitment Letter for Protocol MDX1106-01; Amended Protocol MDX1106-01	IND 100052	25-JUL-2006
Received FDA Acknowledgement Letter for IND 100052	IND 100052	17-JUL-2006
Filed Response to FDA Comments Dated 24-JUL-2006	IND 100052	26-JUL-2006
Filed Pharm/Tox Report	IND 100052	03-AUG-2006
Amended Protocol MDX1106-01	IND 100052	17-AUG-2006
Responded to FDA Request – CMC	IND 100052	20-OCT-2006
Amended Protocol MDX1106-01 – New Investigator and Changed Investigator Information	IND 100052	23-OCT-2006
Filed Pharm/Tox Report (2 volumes)	IND 100052	25-JAN-2007
Amended Protocol MDX1106-01 – New Investigator	IND 100052	24-MAY-2007
Filed Pharm/Tox Report (4 volumes)	IND 100052	29-JUN-2007
Filed Investigator's Brochure Version 2	IND 100052	31-JUL-2007
Amended Protocol MDX1106-01 – New Investigator	IND 100052	14-AUG-2007
Filed Annual Report	IND 100052	09-OCT-2007
Filed Safety Report	IND 100052	22-JAN-2008
Filed Safety Report	IND 100052	06-FEB-2008
Filed Non-Clinical Expedited Safety Report	IND 100052	20-MAR-2008

Activity	IND or BLA	Date
Filed Safety Report	IND 100052	15-APR-2008
Amended Protocol MDX1106-01	IND 100052	30-APR-2008
Filed Safety Report – Clinical Summary of MDX1066-01	IND 100052	28-MAY-2008
Filed Safety Report	IND 100052	18-JUN-2008
Filed New Protocol – MDX1066-03	IND 100052	29-JUL-2008
Filed Response to FDA Comments of 15-AUG-2008	IND 100052	29-AUG-2008
Amended Protocol MDX1066-03	IND 100052	29-SEP-2008
Filed Annual Report	IND 100052	08-OCT-2008
Amended Protocol MDX1066-03 – New Investigator	IND 100052	11-NOV-2008
Filed Safety Report	IND 100052	30-DEC-2008
Amended CMC	IND 100052	12-MAR-2009
Amended Protocol MDX1106-03 – New Investigator	IND 100052	20-MAR-2009
Filed Response to FDA Request of 22-JAN-2009 – CMC	IND 100052	15-APR-2009
Filed Pharm/Tox Report (3 volumes)	IND 100052	09-JUN-2009
Filed Safety Report	IND 100052	31-JUL-2009
Amended Protocol MDX1106-01 – New Investigator	IND 100052	14-AUG-2009
Filed Notification of Change in Sponsorship to BMS	IND 100052	02-SEP-2009
Amended Protocol MDX1106-03 – New Investigators	IND 100052	14-SEP-2009

Activity	IND or BLA	Date
Filed Notification of Change in Sponsor Ownership to BMS	IND 100052	24-SEP-2009
Filed Annual Report	IND 100052	13-OCT-2009
Filed Safety Report	IND 100052	20-OCT-2009
Amended Protocol MDX1106-01 – New Investigator	IND 100052	18-NOV-2009
Filed Safety Report	IND 100052	08-DEC-2009
Filed Safety Report	IND 100052	07-JAN-2010
Amended Protocol MDX1106-03 – New Investigators, Change Investigators	IND 100052	29-JAN-2010
Filed Safety Report	IND 100052	17-FEB-2010
Amended Protocol MDX1106-03 – Change Investigator	IND 100052	08-MAR-2010
Filed Safety Report	IND 100052	07-APR-2010
Amended Protocol MDX1106-03	IND 100052	22-APR-2010
Filed Administrative Letter – Protocol MDX1106-03; Amend Protocol MDX1106-01	IND 100052	04-JUN-2010
Filed Safety Report	IND 100052	28-JUN-2010
Amended CMC	IND 100052	22-JUL-2010
Filed Safety Report	IND 100052	27-AUG-2010
Filed Safety Report	IND 100052	17-SEP-2010
Filed Safety Report	IND 100052	05-OCT-2010
Filed Safety Report	IND 100052	04-NOV-2010
Filed Safety Report	IND 100052	02-DEC-2010
Amended Protocol MDX1106-03 – Update Investigator Information	IND 100052	09-DEC-2010

Activity	IND or BLA	Date
Filed Safety Report	IND 100052	28-FEB-2011
Filed Safety Report	IND 100052	17-MAR-2011
Amended CMC	IND 100052	21-MAR-2011
Amended CMC	IND 100052	29-APR-2011
Amended Protocol CA209-003 – New Investigator	IND 100052	27-MAY-2011
Filed Safety Report	IND 100052	29-JUN-2011
Filed Annual Report	IND 100052	26-JUL-2011
Filed Request for End of Phase I/Development Meeting	IND 100052	16-SEP-2011
Filed Safety Report	IND 100052	12-OCT-2011
Filed Briefing Book for End of Phase I/Development Meeting	IND 100052	04-NOV-2011
Filed Briefing Document for End of Phase II CMC Meeting	IND 100052	06-JAN-2012
Filed Safety Report	IND 100052	25-JAN-2012
Filed Safety Report	IND 100052	28-FEB-2012
Correspondence with FDA – Sent CTA-A Quality	IND 100052 & IND 115195	16-MAR-2012
Filed Safety Report	IND 100052	20-MAR-2012
Filed Updated Preliminary Data from Ongoing Phase I Study CA209-003 and Request for Type A Meeting	IND 100052	11-MAY-2012
Filed Melanoma Administrative Split from Existing IND to IND 115195	IND 100052	13-JUN-2012
Filed Request for Type A Meeting	IND 115195	18-JUN-2012

Activity	IND or BLA	Date
Amended Protocol CA209-003 – Updated Investigator	IND 100052	20-JUN-2012
Correspondence – FDA Contact Report – Updated IND 115195 (Melanoma)	IND 115195	22-JUN-2012
Filed New Preliminary Melanoma Data	IND 115195	16-JUL-2012
Filed Annual Report	IND 100052	24-JUL-2012
Filed Safety Report	IND 100052 & IND 115195	06-SEP-2012
Filed Safety Report	IND 100052 & IND 115195	14-SEP-2012
Filed Annual Report	IND 100052 & IND 115195	25-SEP-2012
Amended Protocol CA209-003 – Investigator Updates	IND 100052	17-OCT-2012
Amended Protocol – Added Protocol CA209-037	IND 115195	17-OCT-2012
Amended Protocol – Added Protocol CA209-066	IND 115195	22-OCT-2012
Filed Safety Report	IND 100052 & IND 115195	24-OCT-2012
Filed Safety Report	IND 100052 & IND 115195	16-NOV-2012
Amended Protocol CA201-037 – Added New Investigator	IND 115195	14-DEC-2012
Filed Safety Report	IND 100052 & IND 115195	22-JAN-2013
Filed Pharm/Tox Report	IND 100052	22-FEB-2013
Amended Protocol CA209003	IND 100052	18-MAR-2013
Filed Safety Report	IND 100052 & IND 115195	17-APR-2013
Filed Request for Pre-BLA Meeting	IND 100052	26-APR-2013
Amended Protocol CA209003	IND 100052	23-MAY-2013
Amended Protocol CA209003	IND 100052	13-JUN-2013

Activity	IND or BLA	Date
Filed Safety Report	IND 100052 & IND 115195	16-JUL-2013
Amended Protocol CA209003 – New and Updated Investigator Information	IND 100052	17-JUL-2013
Filed Safety Report	IND 100052 & IND 115195	28-AUG-2013
Amended Protocol CA209003	IND 100052	06-SEP-2013
Amended Protocol CA209037	IND 115195	16-OCT-2013
Amended Protocol CA209003	IND 100052	18-OCT-2013
Filed Safety Report	IND 100052 & IND 115195	07-NOV-2013
Filed Safety Report	IND 100052 & IND 115195	10-DEC-2013
Amended Protocol CA209003	IND 100052	08-JAN-2014
Filed Safety Report	IND 100052 & IND 115195	14-JAN-2014
Filed Safety Report	IND 100052 & IND 115195	18-FEB-2014
Amended Protocol CA209003 – Updated Investigator Information	IND 100052	03-MAR-2014
Filed Safety Report	IND 100052 & IND 115195	19-MAR-2014
Filed Safety Report	IND 100052 & IND 115195	17-APR-2014
Filed Safety Report	IND 100052 & IND 115195	21-MAY-2014
Amended Protocol CA209037 and CA209066	IND 115195	23-May-2014
Filed Safety Report	IND 100052 & IND 115195	11-JUN-2014
Amended Protocol CA209037	IND 115195	26-JUN-2014
Amended CMC	IND 100052	10-JUL-2014
Filed List of Clinical Investigators Who Participated in Studies CA209037 and MDX1066-03/CA209003	IND 115195	17-JUL-2014

Activity	IND or BLA	Date
Filed BLA and Received FDA Acknowledgement	BLA 125554	30-JUL-2014
Filed Amendment in Response to 09-SEP-2014 FDA Request for Information	BLA 125554	11-SEP-2014
Filed Amendment in Response to 12-SEP-2014 FDA Request for Information	BLA 125554	17-SEP-2014
Filed Amendment in Response to 17-SEP-2014 FDA Request for Information	BLA 125554	23-SEP-2014
Filed Amendment regarding Testing site and Amendment in Response to 24-SEP-2014 FDA Request for Information	BLA 125554	26-SEP-2014
Filed Amendment in Response to 25-SEP-2014 FDA Request for Information	BLA 125554	30-SEP-2014
Filed Amendment in Response to 03-OCT-2014 FDA Request for Information	BLA 125554	07-OCT-2014
Filed Amendment in Response to 25-SEP-2014 FDA Request for Information – Risk Management Plan; and Amendment to Presubmission – CMC	BLA 125554	10-OCT-2014
Filed Amendment – Product Labeling	BLA 125554	17-OCT-2014
Filed Amendment in Response to 01-OCT-2014 FDA Request for Information – Clinical Pharmacology	BLA 125554	23-OCT-2014
Filed Amendment – 90 Day Safety Update and Clinical Update	BLA 125554	28-OCT-2014
Filed Amendment in Response to 28-OCT-2014 FDA Request for Information – Revised Container and Carton Product Labeling	BLA 125554	03-NOV-2014
Filed Amendment in Response to 31-OCT-2014 and 04-NOV-2014 FDA Request for Information – Clinical and Statistics	BLA 125554	07-NOV-2014

Activity	IND or BLA	Date
Filed Amendment in Response to 28-OCT-2014 and 07-NOV-2014 FDA Request for Information – Clinical and Statistics	BLA 125554	10-NOV-2014
Filed Amendment in Response to 03-NOV-2014 FDA Request for Information – Clinical	BLA 125554	11-NOV-2014
Filed Amendment in Response to 07-NOV-2014 FDA Request for Information – Clinical	BLA 125554	12-NOV-2014
Filed Amendment in Response to 06-NOV-2014 FDA Request for Information – CMC	BLA 125554	14-NOV-2014
Filed Amendment in Response to 12-NOV-2014 FDA Request for Information – Clinical	BLA 125554	17-NOV-2014
Filed Amendment in Response to 07-NOV-2014 FDA Request for Information – CMC	BLA 125554	19-NOV-2014
Filed Amendment in Response to 18-NOV-2014 FDA Request for Information – Clinical	BLA 125554	20-NOV-2014
Filed Amendment in Response to 20-NOV-2014 FDA Request for Information – Clinical	BLA 125554	24-NOV-2014
Filed Amendment in Response to 20-NOV-2014 and 21-NOV-2014 FDA Request for Information – CMC; and Amendment in Response to 26-NOV-2014 FDA Request for Information – Clinical	BLA 125554	01-DEC-2014
Filed Amendment in Response to 26-NOV-2014, 29-NOV-2014, and 01-DEC-2014 FDA Request for Information – Clinical	BLA 125554	02-DEC-2014
Filed Amendment in Response to 25-NOV-2014 FDA Request for Information – CMC	BLA 125554	03-DEC-2014
Filed Amendment in Response to 02-DEC-2014 and 03-DEC-2013 FDA Request for Information - Clinical	BLA 125554	04-DEC-2014
Filed Amendment in Response to 03-DEC-2013 FDA Request for Information – Clinical	BLA 125554	05-DEC-2014

Activity	IND or BLA	Date
Filed Amendment in Response to 04-DEC-2014 and 05-DEC-2014 FDA Request for Information – Clinical, CMC, and Labeling	BLA 125554	08-DEC-2014
Filed Amendment in Response to 08-DEC-2014 and 09-DEC-2014 FDA Request for Information – Clinical, Labeling, and Other	BLA 125554	10-DEC-2014
Filed Amendment in Response to 05-DEC-2014 FDA Request for Information – CMC	BLA 125554	11-DEC-2014
Filed Amendment in Response to 02-DEC-2014, 10-DEC-2014, and 14-DEC-2014 FDA Request for Information – Clinical, CMC, and Labeling	BLA 125554	16-DEC-2014
Filed Amendment in Response to 16-DEC-2014 and 17-DEC-2014 FDA Request for Information – Clinical and Product Labeling	BLA 125554	18-DEC-2014
Filed Amendment in Response to 19-DEC-2014 FDA Request for Information – CMC and Final Draft Product Labeling	BLA 125554	20-DEC-2014
Filed Final Draft Product Labeling (Word Format)	BLA 125554	22-DEC-2014
FDA Approval Letter	BLA 125554	22-DEC-2014

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,008,449 B2
APPLICATION NO. : 11/913217
DATED : August 30, 2011
INVENTOR(S) : Korman et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Item (75) Inventor is corrected to read:
--Alan J. Korman, Piedmont, CA (US);
Mohan Srinivasan, San Jose, CA (US);
Changyu Wang, Fremont, CA (US);
Mark J. Selby, San Francisco, CA (US);
Bingliana Chen, Alameda, CA (US);
Josephine M. Cardarelli, San Carlos, CA (US); and
Haichun Huang, San Carlos, CA (US)--.

Signed and Sealed this
Third Day of March, 2015



Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,008,449 B2
APPLICATION NO. : 11/913217
DATED : August 30, 2011
INVENTOR(S) : Korman et al.

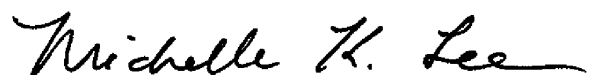
Page 1 of 1

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Title Page, Item (75) Inventor is corrected to read:
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Mohan Srinivasan, San Jose, CA (US);
Changyu Wang, Fremont, CA (US);
Mark J. Selby, San Francisco, CA (US);
Bingliang Chen, Alameda, CA (US);
Josephine M. Cardarelli, San Carlos, CA (US); and
Haichun Huang, San Carlos, CA (US)--.

This certificate supersedes the Certificate of Correction issued March 3, 2015.

Signed and Sealed this
Twenty-first Day of April, 2015



Michelle K. Lee
Director of the United States Patent and Trademark Office



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Food & Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

JAN 17 2016

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 8,008,449 was filed on February 13, 2015, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, OPDIVO™ (nivolumab), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to Ali Salimi at (571) 272-0909 (telephone) or (571) 273-0909 (facsimile) or by e-mail at ali.salimi@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Eldora L. Ellison
Sterne, Kessler, Goldstein & Fox P.L.L.C
1100 New York Avenue NW
Washington DC 20005



Department of Health and Human Services

Public Health Service

APR 26 2016

Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002

Re: OPDIVO
Patent No. 8,008,449
Docket No. FDA-2016-E-0616

The Honorable Michelle K. Lee
UnderSecretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Lee:

This is concerning the application for patent term extension for U.S. Patent No. 8,008,449 filed by E.R. Squibb & Sons, LLC and Ono Pharmaceutical Co., Ltd, under 35 U.S.C. 156. The human biological product claimed by the patent is OPDIVO (nivolumab), which was assigned biologics license application (BLA) No. 125554.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. 156(f)(1).

The BLA was approved on December 22, 2014, which makes the submission of the patent term extension application on February 13, 2015, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

 Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Eldora L. Ellison and Ji-Eun Kim
Sterne Kessler Goldstein & Fox PLLC
1100 New York Ave. NW
Washington, DC 20005



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Food & Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

SEP 13 2016

Attention: Beverly Friedman

Dear Sir:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 8,008,449. The application was filed on February 13, 2015, under 35 U.S.C. § 156.

The patent claims a product which has been subject to review under the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to Ali Salimi at (571) 272-0909 (telephone) or (571) 273-0909 (facsimile) or by e-mail at ali.salimi@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Eldora L. Ellison
Sterne, Kessler, Goldstein & Fox P.L.L.C
1100 New York Avenue NW
Washington DC 20005

RE: OPDIVO® (nivolumab)
Docket No. FDA-2016-E-0616

practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on the format and content of PBPK analyses. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Electronic Access

Persons with access to the Internet may obtain the draft guidance at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <https://www.regulations.gov>.

III. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collection of information in 21 CFR 314.50(d) has been approved under OMB control number 0910–0001.

Dated: November 29, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–28971 Filed 12–1–16; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2016–E–0616]

Determination of Regulatory Review Period for Purposes of Patent Extension; OPDIVO

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for OPDIVO and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of the U.S. Patent and Trademark Office (USPTO), Department of Commerce, for the extension of a patent which claims that human biological product.

DATES: Anyone with knowledge that any of the dates as published (see the **SUPPLEMENTARY INFORMATION** section) are incorrect may submit either electronic

or written comments and ask for a redetermination by January 31, 2017. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by May 31, 2017. See “Petitions” in the **SUPPLEMENTARY INFORMATION** section for more information.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- **Federal eRulemaking Portal:** <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else’s Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- **Mail/Hand delivery/Courier (for written/paper submissions):** Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA–2016–E–0616 for “Determination of Regulatory Review Period for Purposes of Patent Extension; OPDIVO.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly

viewable at <https://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- **Confidential Submissions—**To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6250, Silver Spring, MD 20993, 301–796–3600.

SUPPLEMENTARY INFORMATION:

I. Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years

so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human biological products, the testing phase begins when the exemption to permit the clinical investigations of the biological product becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human biological product and continues until FDA grants permission to market the biological product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of USPTO may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human biological product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human biologic product OPDIVO (nivolumab). OPDIVO is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Subsequent to this approval, the USPTO received a patent term restoration application for OPDIVO (U.S. Patent No. 8,008,449) from E.R. Squibb & Sons, LLC and Ono Pharmaceutical Co., Ltd., and the USPTO requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated April 26, 2016, FDA advised the USPTO that this human biological product had undergone a regulatory review period and that the approval of OPDIVO represented the first permitted commercial marketing or use of the product. Thereafter, the USPTO requested that FDA determine the product's regulatory review period.

II. Determination of Regulatory Review Period

FDA has determined that the applicable regulatory review period for OPDIVO is 3,071 days. Of this time, 2,925 days occurred during the testing phase of the regulatory review period, while 146 days occurred during the

approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective:* July 28, 2006. The applicants claim July 29, 2006, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was July 28, 2006, which was the first date after receipt of the IND that the investigational studies were allowed to proceed.

2. *The date the application was initially submitted with respect to the human biological product under section 351 of the Public Health Service Act (42 U.S.C. 262):* July 30, 2014. FDA has verified the applicants' claim that the biologics license application (BLA) for OPDIVO (BLA 125554) was initially submitted on July 30, 2014.

3. *The date the application was approved:* December 22, 2014. FDA has verified the applicants' claim that BLA 125554 was approved on December 22, 2014.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the USPTO applies several statutory limitations in its calculations of the actual period for patent extension. In the application for patent extension, these applicants seek 552 days of patent term extension.

III. Petitions

Anyone with knowledge that any of the dates as published are incorrect may submit either electronic or written comments and ask for a redetermination (see **DATES**). Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must be timely (see **DATES**) and contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Submit petitions electronically to <https://www.regulations.gov> at Docket No. FDA–2013–S–0610. Submit written petitions (two copies are required) to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Dated: November 23, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–28917 Filed 12–1–16; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–E–5107]

Determination of Regulatory Review Period for Purposes of Patent Extension; TRESIBA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for TRESIBA and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of the U.S. Patent and Trademark Office (USPTO), Department of Commerce, for the extension of a patent which claims that human drug product.

DATES: Anyone with knowledge that any of the dates as published (in the **SUPPLEMENTARY INFORMATION** section) are incorrect may submit either electronic or written comments and ask for a redetermination by January 31, 2017. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by May 31, 2017. See "Petitions" in the **SUPPLEMENTARY INFORMATION** section for more information.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- **Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you



FDA U.S. FOOD & DRUG
ADMINISTRATION

DEC 07 2016

Re: OPDIVO
Patent No.: 8,008,449
Docket No.: FDA-2016-E-0616

The Honorable Michelle K. Lee
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Lee:

This is in regard to the application for patent term extension for U.S. Patent No. 8,008,449, filed by E.R. Squibb & Sons, LLC (Squibb) and Ono Pharmaceutical Co., Ltd. (Ono), under 35 U.S.C. section 156 *et seq.* We have reviewed the dates contained in the application and have determined the regulatory review period for OPDIVO (nivolumab), the human biological product claimed by the patent.

The total length of the regulatory review period for OPDIVO is 3,071 days. Of this time, 2,925 days occurred during the testing phase and 146 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this biologic product became effective: July 28, 2006.

The applicants claim July 29, 2006, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was July 28, 2006, which was the first date after receipt of the IND that the investigational studies were allowed to proceed.

2. The date the application was initially submitted with respect to the human biological product under section 351 of the Public Health Service Act: July 30, 2014.

FDA has verified the applicant's claim that the biologics license application (BLA) for OPDIVO (BLA 125554) was initially submitted on July 30, 2014.

3. The date the application was approved: December 22, 2014.

FDA has verified the applicant's claim that BLA 125554 was approved on December 22, 2014.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002
www.fda.gov

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a stylized, flowing script.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research
Food and Drug Administration

cc: Eldora L. Ellison and Ji-Eun Kim
Sterne Kessler Goldstein & Fox PLLC
1100 New York Ave. NW
Washington, DC 20005



SEP 20 2017

Re: OPDIVO
Patent No. 8,008,449
Docket No. FDA-2016-E-0616

Acting Director
United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director:

This is in regard to the patent term extension application for U.S. Patent No. 8,008,449 filed by E.R. Squibb & Sons, LLC and Ono Pharmaceutical Co., Ltd under 35 U.S.C. § 156. The patent claims OPDIVO (nivolumab), a human biological product reviewed in biologics license application (BLA) 125554.

In the December 2, 2016, issue of the Federal Register (81 Fed. Reg. 87044), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before May 31, 2017, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6250
Silver Spring, MD 20993
www.fda.gov

USPTO – Patent No. 8,008,449
E.R. Squibb & Sons, LLC and Ono Pharmaceutical Co., Ltd
OPDIVO
Page 2

cc: Eldora L. Ellison and Ji-Eun Kim
Sterne Kessler Goldstein & Fox PLLC
1100 New York Ave. NW, Suite 600
Washington, DC 20005



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Eldora L. Ellison
Sterne, Kessler, Goldstein & Fox P.L.L.C
1100 New York Avenue NW
Washington DC 20005

In Re: Patent Term Extension
Application for
U.S. Patent No. 8,008,449

NOTICE OF FINAL DETERMINATION

MAR 14 2018

A determination has been made that U.S. Patent No. 8,008,449, claims of which cover biological human product known by tradename OPDIVO® (nivolumab), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 552 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 552 days.

The period of extension, if calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of December 2, 2016 (81 Fed. Reg. 87044), would be 679 days. Under 35 U.S.C. § 156(c):

$$\begin{aligned}\text{Period of Extension} &= \text{RRP} - \text{PGRRP} - \text{DD} - \frac{1}{2} (\text{TP} - \text{PGTP})^1 \\ &= 3,071 - 1,860 - 0 - \frac{1}{2} (2,925 - 1,860) \\ &= 679 \text{ days (1.9 years)}\end{aligned}$$

Since the regulatory review period began July 28, 2006, before the patent issued (August 30, 2011), only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). (From July 28, 2006, to and including August 30, 2011, is 1,860 days; this period is subtracted from the number of days occurring in the testing phase according to the FDA determination of the length of the regulatory review period.) No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

¹ Consistent with 35 U.S.C. § 156(c), “RRP” is the total number of days in the regulatory review period, “PGRRP” is the number of days of the RRP which were on and before the date on which the patent issued, “DD” is the number of days of the RRP that the applicant did not act with due diligence, “TP” is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and “PGTP” is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of $\frac{1}{2} (\text{TP} - \text{PGTP})$.

However, the 14 year exception of 35 U.S.C. § 156(c)(3) operates to limit the term of the extension in the present situation, because it provides that the period remaining in the term of the patent measured from the date of approval of the approved product plus any patent term extension cannot exceed fourteen years. The period of extension calculated above, 679 days, would extend the patent from June 19, 2027, to April 28, 2029, which is beyond the 14-year limit (the approval date is December 22, 2016, thus the 14 year limit is December 22, 2028). The period of extension is thus limited to 552 days, by operation of 35 U.S.C. § 156(c)(3). Accordingly, the period of extension is the number of days to extend the term of the patent from its original expiration date, June 19, 2027, to and including December 22, 2028, or 552 days.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	8,008,449
Granted:	August 30, 2011
Original Expiration Date ² :	June 19, 2027
Applicant:	Korman et al.
Owner of Record:	E.R. Squibb & Sons, L.L.C. and Ono Pharmaceutical Co., Ltd.
Title:	HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS
Product Trade Name:	OPDIVO ® (nivolumab)
Term Extended:	552 days
Expiration Date of Extension:	December 22, 2028

²Subject to the provisions of 35 U.S.C. § 41(b).

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

Telephone inquiries related to this determination should be directed to Ali Salimi at (571) 272-0909.



Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: OPDIVO® (nivolumab)
Docket No.: FDA-2016-E-0616



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Eldora L. Ellison
Sterne, Kessler, Goldstein & Fox P.L.L.C
1100 New York Avenue NW
Washington DC 20005

In Re: Patent Term Extension
Application for
U.S. Patent No. 8,008,449

SEP 11 2018

Dear Ms. Ellison:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 8,008,449 for a period of 552 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to patent expiration dates as necessary.

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-0909, or by e-mail at ali.salimi@uspto.gov.

Ali Salimi
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

RE: OPDIVO® (nivolumab)
Docket No.: FDA-2016-E-0616

Attention: Beverly Friedman

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68) PATENT NO. : 8,008,449
(45) ISSUED : August 30, 2011
(75) INVENTOR : Korman et al.
(73) PATENT OWNER : E.R. Squibb & Sons, L.L.C. and Ono
Pharmaceutical Co., Ltd.
(95) PRODUCT : OPDIVO ® (nivolumab)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 8,008,449 based upon the regulatory review of the product OPDIVO ® (nivolumab) by the Food and Drug Administration. According to United States Patent and Trademark Office records, the original expiration date of the patent as of the date of issuance of this certificate is June 19, 2027. Because it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 552 days

subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.



I have caused the seal of the United States Patent and Trademark Office to be affixed this 6th day of September 2018.

Andrei Iancu

Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office