# PRODUCT MONOGRAPH

Pr YERVOY®

Ipilimumab for injection

Intravenous Infusion, 5 mg ipilimumab / mL

10 mL and 40 mL vials

Antineoplastic

Bristol-Myers Squibb Canada
Montreal Canada

Date of Authorization:
December 12, 2017



Control No.: 201987

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Pr YERVOY®

Ipilimumab for injection

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Intravenous infusion | 50 mg ipilimumab / 10 mL (5 mg/mL)<br>200 mg ipilimumab / 40 mL (5 mg/mL) | None.<br>For a complete listing of nonmedicinal ingredients, see DOSAGE FORMS, COMPOSITION AND PACKAGING section. |

### Description

YERVOY (ipilimumab for injection) is a recombinant, fully human monoclonal antibody that binds to and blocks human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

### INDICATIONS AND CLINICAL USE

- YERVOY (ipilimumab for injection) is indicated for the treatment of unresectable or metastatic melanoma, as a single agent.
- YERVOY in combination with OPDIVO® (nivolumab) is indicated for the treatment of unresectable or metastatic melanoma in previously untreated adults.
    - Relative to OPDIVO (nivolumab) monotherapy, an increase in progression-free survival for the combination of YERVOY with OPDIVO (nivolumab) is established only in patients with low tumour PD-L1 expression (based on the predefined expression level of < 5%).
    - An improvement in survival has not yet been established, and **this combination therapy was authorized under the Notice of Compliance with conditions (NOC/c) pathway for OPDIVO.**
    - When using YERVOY in combination with OPDIVO (nivolumab), consult Product Monograph for OPDIVO (nivolumab) for further information on this drug.

**Geriatrics (≥ 65 years of age):**

Of the 131 patients treated with YERVOY 3 mg/kg monotherapy in the study MDX-010-20, 30% were 65 years of age or older. No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (<65 years).

**Pediatrics (< 18 years of age):**

The efficacy and safety of YERVOY in pediatric patients have not been established [see ADVERSE REACTIONS, Clinical Trial Adverse Reactions (Pediatrics), and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

## CONTRAINDICATIONS

YERVOY (ipilimumab for injection) is contraindicated in patients who are hypersensitive to ipilimumab or to any ingredient in the formulation or component of the container [see DOSAGE FORMS, COMPOSITION AND PACKAGING].

YERVOY is also contraindicated in patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life-threatening [see WARNINGS AND PRECAUTIONS].

When using YERVOY in combination with OPDIVO (nivolumab), consult Product Monograph for OPDIVO (nivolumab) for further information on this drug.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**YERVOY should be administered under the supervision of physicians experienced in the treatment of cancer.**

**YERVOY can cause severe and fatal immune-mediated adverse reactions, including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, endocrinopathy, as well as toxicities in other organ systems.** While most of these reactions occurred during the induction period, onset months after the last dose has been reported [see WARNINGS AND PRECAUTIONS].

**Early diagnosis and appropriate management are essential to minimize life-threatening complications**. Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions; clinical chemistries (e.g., electrolytes, liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests) should be evaluated at baseline and before each dose. Diarrhea, increased stool frequency, bloody stool, liver function test elevations, rash, and endocrinopathies must be considered immune-mediated and YERVOY-related, unless an alternate etiology has been identified.

**For severe immune-mediated adverse reactions, YERVOY should be permanently**

**discontinued; systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for treatment** [see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION].

## General

**YERVOY should be administered under the supervision of physicians experienced in the treatment of cancer.**

When using YERVOY in combination with OPDIVO (nivolumab), consult Product Monograph for OPDIVO (nivolumab) for further information on this drug.

YERVOY is an immune-potentiator and can cause inflammatory adverse reactions resulting from increased or excessive immune activity (immune-mediated adverse reactions), likely to be related to its mechanism of action. Immune-mediated adverse reactions, sometime fatal, can involve any organ systems, although more commonly manifest in gastrointestinal tract, liver, skin, endocrine, and nervous systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Signs and symptoms suggestive of immune-mediated adverse reactions may be non-specific and should be considered YERVOY-related, unless an alternate etiology is identified. Most immune-mediated adverse reactions occurred during the induction period; however, onset months after the last dose of YERVOY has also been reported.

YERVOY-specific management guidelines for immune-mediated adverse reactions are described below. Due to the mechanism of the inflammatory reactions observed with YERVOY, systemic high-dose corticosteroids with or without additional immunosuppressive therapy may be required for management of severe immune-mediated adverse reactions. A summary of high-dose corticosteroid use in patients who had severe to fatal immune-mediated adverse reactions is presented in Adverse Reactions (Table 3).

### Immune-mediated Enterocolitis

In Study MDX-010-20, severe, life-threatening, or fatal immune-mediated enterocolitis (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3–5) occurred in 34 (7%) YERVOY-treated patients, and moderate enterocolitis (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) occurred in 28 (5%) YERVOY-treated patients. Across all YERVOY-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 4 (0.8%) patients died as a result of complications, and 26 (5%) patients were hospitalized for severe enterocolitis.

The median time to onset was 7.4 weeks (range 1.6–13.4) after the initiation of YERVOY and the median number of doses prior to onset was 3 (range 1-4) for patients with Grade 3-5 enterocolitis. The median time to onset was 6.3 weeks (range 0.3–18.9) and the median number of doses prior to onset was 3 (range 1-4) for patients with Grade 2 enterocolitis.

Twenty-nine patients (85%) with Grade 3–5 enterocolitis were treated with high-dose (≥40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 2.3 weeks (ranging up to 13.9 weeks) followed by corticosteroid taper. Of the 29 patients with Grade 3–5 enterocolitis who received high-dose corticosteroids, 21 (72%) experienced complete resolution, 1 (3%) experienced improvement to Grade 2 severity, and 7 (24%) experienced no improvement to ≤ Grade 2 severity (including 2 [7%] with fatal outcome). Of the 28 patients with moderate enterocolitis, 13 (46%) were not treated with systemic corticosteroids, 8 (29%) were treated with <40 mg prednisone or equivalent per day for a median duration of 5.1 weeks, and 7 (25%) were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Among the 28 patients with Grade 2 enterocolitis, 22 (79%) experienced complete resolution, 3 (11%) improved, and 3 (11%) did not improve.

Infliximab was administered to 6 of the 62 patients (10%) with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids. In these patients, infliximab was administered once or twice usually at a dose of 5 mg/kg. All 6 patients treated with infliximab achieved resolution of their enterocolitis.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Management recommendations for diarrhea or colitis are based on severity of symptoms (per NCI-CTCAE v4 severity grading classification). Patients with mild-to-moderate (Grade 1 or 2) diarrhea (an increase of up to 6 stools per day) or suspected mild-to-moderate colitis (eg, abdominal pain or blood in stools) may remain on YERVOY. Symptomatic treatment (eg, loperamide, fluid replacement) and close monitoring are advised.

Permanently discontinue YERVOY in patients with severe (Grade 3 or 4) diarrhea or colitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients [see DOSAGE AND ADMINISTRATION].

Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for 5-7 days, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent. If resolution to Grades 0-1 or return to baseline occurs, YERVOY may be resumed [see DOSAGE AND ADMINISTRATION].

**Immune-mediated Hepatitis**

YERVOY is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials.

In MDX-010-20, severe, life-threatening, or fatal hepatotoxicity (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] elevations of more than 5 times the upper limit of normal or total bilirubin elevations more than 3 times the upper limit of normal; Grade 3–5) occurred in 8 (2%) YERVOY-treated patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 (2.5%) patients experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology for hepatotoxicity was not ascertained in all patients but in some instances did include immune-mediated hepatitis. Among the 8 patients with Grade 3-5 hepatitis, the median number of YERVOY doses prior to onset was 3 (range 1-4).

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue YERVOY in patients with Grade 3 or 4 transaminase or bilirubin elevation and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Once symptoms have resolved and liver function tests (LFTs) show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

Withhold YERVOY in patients with Grade 2 transaminase or total bilirubin elevation and LFTs must be monitored until resolution. Upon improvement, YERVOY may be resumed [see DOSAGE AND ADMINISTRATION].

**Immune-mediated Dermatitis**

In Study MDX-010-20, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) YERVOY-treated patients. One (0.2%) patient died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 (12%) patients with moderate (Grade 2) dermatitis.

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 3.1 weeks and ranged up to 17.3 weeks from the initiation of YERVOY. The median number of YERVOY doses prior to onset was 2 (range 1-4) for patients with Grade 2-5 dermatitis.

Seven (54%) YERVOY-treated patients with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 14.9 weeks followed

by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to 15.6 weeks. The other patient had no improvement.

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 2.1 weeks, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four (70%) patients with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue YERVOY in patients with very severe (Grade 4) rash, (including Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations) or severe (Grade 3) pruritus. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

Withhold YERVOY dosing in patients with severe (Grade 3) signs and symptoms. If initial symptoms improve to mild (Grade 1) or resolve, YERVOY may be resumed [see DOSAGE AND ADMINISTRATION].

Patients with a mild-to-moderate (Grade 1 or 2) skin adverse reaction may remain on YERVOY therapy with symptomatic treatment (eg, antihistamines). Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

Caution should be used when considering the use of YERVOY in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy.

**Immune-mediated Neuropathies**

In Study MDX-010-20, one case of fatal Guillain-Barré syndrome and one case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (Grade 3 or 4, interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold YERVOY dosing in patients with moderate (Grade

2) neuropathy (not interfering with daily activities). If neurologic symptoms resolve to baseline, YERVOY may be resumed [see DOSAGE AND ADMINISTRATION].

**Immune-mediated Endocrinopathies**

In Study MDX-010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3–4) occurred in 9 (1.8%) YERVOY-treated patients. All 9 patients had hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and one case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY. The median number of doses prior to onset was 4 (range 1-4) for patients with Grade 2-5 endocrinopathy.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

If pituitary imaging or laboratory tests of endocrine function are abnormal, withhold YERVOY dosing. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy [see DOSAGE AND ADMINISTRATION].

**Other Immune-mediated Adverse Reactions, Including Ocular Manifestations**

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients in Study MDX-010-20: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for YERVOY, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing. Vogt-Koyanagi-Harada syndrome (VKH) also known as uveo-meningitis syndrome is a rare multisystem disease of presumed autoimmune cause affecting pigmented tissues containing melanin. It is characterized by chronic uveitis, poliosis (decrease or absence of melanin in head hair), alopecia, dysacousia (a condition in which ordinary sounds produce discomfort or pain), vitiligo, and signs of meningeal irritation.

Permanently discontinue YERVOY for clinically significant or severe (Grade 3 or 4) immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy [see DOSAGE AND ADMINISTRATION].

**Infusion Reaction**

There were isolated cases of severe infusion reaction in clinical trials and postmarketing use. In case of a severe infusion reaction, YERVOY infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive YERVOY with close monitoring.

**Patients Requiring Immunosuppressive Therapy for Life-Threatening Disease or Condition**

Patients who require systemic immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance were not evaluated in clinical studies. Ipilimumab is a T-cell potentiator that enables the immune response [see ACTION AND CLINICAL PHARMACOLOGY – Mechanism of Action] and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. YERVOY should not be administered in patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life-threatening [see CONTRAINDICATIONS].

**Patients with ocular melanoma or active central nervous metastases**

The safety and efficacy of YERVOY were not established in patients with ocular melanoma or active central nervous metastases.

**Patients on controlled sodium diet**

Each mL of this medicinal product contains 0.1 mmol (or 2.30 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

**Concurrent administration with vemurafenib**

The concurrent administration of YERVOY and vemurafenib is not recommended. In a Phase 1

trial, asymptomatic Grade 3 LFT elevations (ALT/AST with or without total bilirubin) were reported in 6 of 10 patients treated with the combination of YERVOY (3 mg/kg) and vemurafenib (960 mg or 720 mg twice daily) administered concurrently These results do not impact the currently approved use of YERVOY as monotherapy (see CLINICAL TRIALS).

**Patient Counseling Information**

Patients should be advised to report immediately any signs or symptoms suggestive of immune-mediated adverse reactions as described in WARNINGS AND PRECAUTIONS. The importance of reporting any worsening of symptoms or severity should be emphasized. Patients should be strongly advised not to treat any of these symptoms with over-the-counter medications without consultation with a health care provider.

Because of potential adverse reactions such as fatigue [see ADVERSE REACTIONS], patients should be advised to use caution when driving or operating machinery.

**Hepatic**

The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Clinical experience with YERVOY is limited in patients with transaminase levels 5 times ULN or greater or bilirubin levels greater than 2 times ULN at baseline and must be administered with caution in these patients [see CLINICAL TRIALS]. In the population pharmacokinetic analysis of data from clinical studies concerning patients with metastatic melanoma, the covariate pre-existing mild hepatic impairment did not influence the CL parameter in the population PK model of ipilimumab and on this basis, no specific dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin [TB] >1.0 × to 1.5 × the upper limit of normal [ULN] or AST >ULN) [see ACTION AND CLINICAL PHARMACOLOGY].

**Renal**

The safety and efficacy of YERVOY have not been studied in patients with renal impairment. In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, the covariate pre-existing mild and moderate renal impairment did not influence the CL parameter in the population PK model of ipilimumab and on this basis, no specific dose adjustment is necessary. [see ACTION AND CLINICAL PHARMACOLOGY].

**Special Populations**

**Pregnant Women:**

Animal reproduction studies have shown reproductive toxicity [see TOXICOLOGY].

Based on its mechanism of action and data from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth

weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY.

Human IgG1 is known to cross the placental barrier; therefore, ipilimumab has the potential to be transmitted from the mother and cause harm to the developing fetus. YERVOY should not be used during pregnancy unless the potential benefits justify the potential risks to the fetus.

**Nursing Women:**

Ipilimumab has been shown to be present at very low levels in milk from cynomolgus monkeys treated during pregnancy. It is not known whether ipilimumab is secreted in human milk. However, because human IgG1 is known to be secreted in human breast milk, there is potential for ipilimumab to be passed from mother to nursing child. Women who are taking YERVOY should not breast-feed.

**Geriatrics (≥ 65 years of age):**

Of the 131 patients treated with YERVOY 3 mg/kg monotherapy, 30% were 65 years of age or older. No overall differences in safety or efficacy were reported between the elderly patients (≥ 65 years) and younger patients (<65 years).

**Pediatrics (< 18 years of age):**

The efficacy and safety of YERVOY in pediatric patients have not been established [see ADVERSE REACTIONS, Clinical Trial Adverse Reactions (Pediatrics), and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

**Monitoring and Laboratory Tests**

Liver function tests must be assessed at baseline and before each dose of ipilimumab. In addition, thyroid function test should be performed and electrolytes monitored before each dose. Patients should be closely monitored during treatment for signs and symptoms indicative of immune-mediated adverse reactions including, but not limited to, adrenal insufficiency, hypophysitis, increased frequency of bowel movements, diarrhea, abdominal pain, mucus or blood in stool with or without fever, peritoneal signs, ileus; elevated transaminase and bilirubin levels; rash, pruritus; muscle weakness (unilateral or bilateral), sensory alterations, paresthesia; headache, fatigue, mental status changes, unusual bowel habits, hypotension; eye pain, and visual disturbances.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Unless otherwise specified, the data described below reflect exposure to YERVOY at 3 mg/kg in previously treated patients with unresectable or metastatic melanoma from a Phase 3 study (Study MDX-010-20: YERVOY monotherapy n=131; YERVOY in combination with an investigational gp100 peptide vaccine [gp100] n=380). Patients in this study received a median of 4 doses (range 1 to 4 doses).

When using YERVOY in combination with OPDIVO (nivolumab), consult Product Monograph for OPDIVO (nivolumab) for further information on this drug.

### Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

YERVOY is most commonly associated with adverse reactions resulting from increased or excessive immune activity (see WARNINGS AND PRECAUTIONS for guidance on management of immune-mediated adverse reactions). Most of these adverse reactions, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of YERVOY (see WARNINGS AND PRECAUTIONS).

In patients who received 3 mg/kg YERVOY monotherapy in Study MDX-010-20, the most frequently reported adverse reactions (occurring at ≥10%) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain (Table 1). The majority of adverse reactions were mild to moderate (Grade 1 or 2). YERVOY therapy was discontinued for adverse reactions in 10% of patients; colitis and diarrhea were the most common adverse reactions that led to discontinuation of YERVOY therapy.

Table 1 presents adverse reactions reported in at least 1% of patients treated with YERVOY 3 mg/kg in the pivotal study MDX-010-20.

**Table 1: Adverse Reactions Reported in at least 1% of Patients Treated with YERVOY 3 mg/kg in MDX-010-20 (During Induction)**

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | **YERVOY 3 mg/kg n=131** | | YERVOY 3 mg/kg+gp100 [a] n=380 | | gp 100[a] n=132 | |
| **System Organ Class/ Preferred Term** | **Any Grade** | **Grade 3/4** | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| **Gastrointestinal Disorders** | | | | | | |
| Diarrhea | **35 (27)** | **6 (5)** | 111 (29) | 13 (3) | 18 (14) | 1 (0.8) |
| Nausea | **30 (23)** | **0** | 71 (19) | 1 (0.3) | 23 (17) | 0 |
| Vomiting | **16 (12)** | **0** | 34 (9) | 1 (0.3) | 9 (7) | 1 (0.8) |
| Abdominal pain | **14 (11)** | **0** | 38 (10) | 1 (0.3) | 9 (7) | 0 |
| Colitis | **10 (8)** | **7 (5)** | 19 (5) | 11 (3) | 1 (0.8) | 0 |
| Constipation | **3 (2)** | **0** | 17 (4) | 0 | 2 (2) | 0 |
| Gastrointestinal hemorrhage | **2 (2)** | **0** | 8 (2) | 1 (0.3) | 1 (0.8) | 0 |
| Gastroesophageal reflux disease | **1 (0.8)** | **0** | 4 (1) | 0 | 3 (2) | 0 |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | |
| Pruritus | **34 (26)** | **0** | 69 (18) | 1 (0.3) | 14 (11) | 0 |
| Rash | **34 (26)** | **1 (0.8)** | 77 (20) | 6 (2) | 8 (6) | 0 |
| Erythema | **7 (5)** | **0** | 18 (5) | 1 (0.3) | 4 (3) | 0 |
| Alopecia | **2 (2)** | **0** | 3 (0.8) | 0 | 0 | 0 |
| Night sweats | **2 (2)** | **0** | 7 (2) | 0 | 0 | 0 |
| Vitiligo | **2 (2)** | **0** | 13 (3) | 0 | 1 (0.8) | 0 |
| Dermatitis | **1 (0.8)** | **0** | 5 (1) | 1 (0.3) | 0 | 0 |
| Urticaria | **1 (0.8)** | **0** | 9 (2) | 0 | 1 (0.8) | 0 |
| Dry skin | **0** | **0** | 6 (2) | 0 | 2 (2) | 0 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | **31 (24)** | **6 (5)** | 89 (23) | 10 (3) | 26 (20) | 2 (2) |
| Pyrexia | **11 (8)** | **0** | 41 (11) | 1 (0.3) | 9 (7) | 0 |
| Chills | **7 (5)** | **0** | 12 (3) | 1 (0.3) | 6 (5) | 0 |
| Asthenia | **6 (5)** | **2 (2)** | 15 (4) | 0 | 5 (4) | 1 (0.8) |
| Injection Site Reaction | **5 (4)** | **0** | 185 (49) | 5 (1) | 50 (38) | 0 |
| Edema | **5 (4)** | **1 (0.8)** | 11 (3) | 0 | 2 (2) | 0 |

**Table 1: Adverse Reactions Reported in at least 1% of Patients Treated with YERVOY 3 mg/kg in MDX-010-20 (During Induction)**

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | **YERVOY 3 mg/kg n=131** | | YERVOY 3 mg/kg+gp100 [a] n=380 | | gp 100[a] n=132 | |
| **System Organ Class/ Preferred Term** | **Any Grade** | **Grade 3/4** | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Pain | **2 (2)** | **0** | 8 (2) | 0 | 4 (3) | 0 |
| **Metabolism and Nutrition Disorders** | | | | | | |
| Decreased appetite | **15 (11)** | **0** | 39 (10) | 1 (0.3) | 8 (6) | 1 (0.8) |
| Dehydration | **2 (2)** | **0** | 7 (2) | 1 (0.3) | 1 (0.8) | 0 |
| Hypokalemia | **1 (0.8)** | **0** | 4 (1) | 0 | 0 | 0 |
| **Musculoskeletal Disorders** | | | | | | |
| Musculoskeletal pain | **6 (5)** | **0** | 33 (9) | 4 (1) | 10 (8) | 1 (0.8) |
| Arthralgia | **5 (4)** | **1 (0.8)** | 12 (3) | 0 | 4 (3) | 0 |
| Myalgia | **5 (4)** | **0** | 24 (6) | 0 | 3 (2) | 0 |
| Muscle spasms | **1 (0.8)** | **0** | 5 (1) | 0 | 2 (2) | 0 |
| **Vascular Disorders** | | | | | | |
| Flushing | **6 (5)** | **0** | 8 (2) | 0 | 0 | 0 |
| Hypotension | **4 (3)** | **2 (2)** | 6 (2) | 1 (0.3) | 1 (0.8) | 0 |
| Hot flush | **1 (0.8)** | **0** | 4 (1) | 0 | 4 (3) | 0 |
| **Investigations** | | | | | | |
| Decreased weight | **4 (3)** | **0** | 10 (3) | 0 | 2 (2) | 0 |
| Increased ALT | **2 (2)** | **0** | 3 (0.8) | 2 (0.5) | 2 (2) | 0 |
| Decreased blood corticotrophin | **2 (2)** | **1 (0.8)** | 0 | 0 | 0 | 0 |
| Increased AST | **1 (0.8)** | **0** | 4 (1) | 1 (0.3) | 1 (0.8) | 0 |
| **Endocrine Disorders** | | | | | | |
| Hypopituitarism | **5 (4)** | **4 (3)** | 5 (1) | 4 (1) | 0 | 0 |
| Adrenal insufficiency | **2 (2)** | **0** | 2 (0.5) | 2 (0.5) | 0 | 0 |
| Hyperthyroidism | **2 (2)** | **0** | 3 (0.8) | 0 | 0 | 0 |
| Hypothyroidism | **2 (2)** | **0** | 6 (2) | 1 (0.3) | 2 (2) | 0 |
| **Nervous System Disorders** | | | | | | |
| Headache | **6 (5)** | **1 (0.8)** | 30 (8) | 2 (0.5) | 8 (6) | 1 (0.8) |

**Table 1: Adverse Reactions Reported in at least 1% of Patients Treated with YERVOY 3 mg/kg in MDX-010-20 (During Induction)**

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | **YERVOY 3 mg/kg n=131** | | YERVOY 3 mg/kg+gp100 [a] n=380 | | gp 100[a] n=132 | |
| **System Organ Class/ Preferred Term** | **Any Grade** | **Grade 3/4** | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Dizziness | **1 (0.8)** | **0** | 7 (2) | 0 | 5 (4) | 0 |
| Lethargy | **0** | **0** | 4 (1) | 0 | 1 (0.8) | 0 |
| Peripheral sensory neuropathy | **0** | **0** | 9 (2) | 0 | 2 (2) | 0 |
| **Respiratory, Thoracic, and Mediastinal Disorders** | | | | | | |
| Cough | **4 (3)** | **0** | 12 (3) | 1 (0.3) | 2 (2) | 0 |
| Dyspnea | **2 (2)** | **1 (0.8)** | 6 (2) | 1 (0.3) | 3 (2) | 1 (0.8) |
| **Blood and Lymphatic Disorders** | | | | | | |
| Anemia | **2 (2)** | **0** | 20 (5) | 2 (0.5) | 2 (2) | 1 (0.8) |
| **Eye Disorders** | | | | | | |
| Blurred vision | **3 (2)** | **0** | 4 (1) | 0 | 2 (2) | 0 |
| Uveitis | **2 (2)** | **0** | 1 (0.3) | 0 | 1 (0.8) | 0 |
| **Hepatobiliary Disorders** | | | | | | |
| Abnormal hepatic function | **2 (2)** | **1 (0.8)** | 3 (0.8) | 0 | 4 (3) | 3 (2) |
| **Renal and Urinary Disorders** | | | | | | |
| Renal failure | **2 (2)** | **1 (0.8)** | 0 | 0 | 1 (0.8) | 0 |
| **Neoplasms Benign, Malignant and Unspecified** | | | | | | |
| Tumor pain | **2 (2)** | **0** | 4 (1) | 0 | 1 (0.8) | 0 |

a Combination of YERVOY+gp100 is not a recommended regimen. gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

The following additional adverse reactions were reported in less than 1% of patients treated with YERVOY 3 mg/kg monotherapy or in combination with gp100 in Study MDX-010-20 (excluding immune-mediated adverse reaction terms presented in Table 2):

0.1-<1%: gastrointestinal perforation, intestinal perforation, large intestine perforation, peritonitis, infusion related reaction, multi-organ failure, hypophosphatemia, tumor lysis syndrome, hyponatremia, arthritis, angiopathy, orthostatic hypotension, increased blood bilirubin, abnormal liver function test, increased lipase, increased blood amylase, decreased blood cortisol, increased blood creatinine, increased blood thyroid stimulating hormone,

polymyalgia rheumatica, peripheral neuropathy, tremor, ataxia, brain edema, cranial neuropathy, Guillain-Barré syndrome, hemolytic anemia, leukocytoclastic vasculitis, toxic epidermal necrolysis (including Stevens Johnson Syndrome), hypogonadism, respiratory failure, allergic rhinitis, acute respiratory distress syndrome, neutropenia, thrombocytopenia, eye pain, foreign body sensation in eyes, conjunctivitis, iritis, vitreous hemorrhage, reduced visual acuity, hepatitis, hepatic failure, hepatomegaly, jaundice, sepsis, septic shock, urinary tract infection, lower respiratory infection, gastroenteritis, upper respiratory tract infection, depression, libido decreased, confusional state, mental status changes, paraneoplastic syndrome, amenorrhea, myoclonus, atrial fibrillation, arrhythmia, and hypersensitivity.

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions by YERVOY treatment group from Study MDX-010-20.

**Table 2: Severe to Fatal Immune-mediated Adverse Reactions in MDX-010-20 (During Induction)**

| | **Number (%) of Patients** | |
|---|---|---|
| | **YERVOY 3 mg/kg n=131** | YERVOY 3 mg/kg+gp100[a] n=380 |
| **Any Immune-mediated Adverse Reaction** | **19 (15)** | 47 (12) |
| **Enterocolitis**[b,c] | **9 (7)** | 25 (7) |
| **Hepatotoxicity**[b] | **1 (0.8)** | 7 (2) |
| **Dermatitis**[b] | **3 (2)** | 10 (3) |
| **Neuropathy**[b] | **1 (0.8)** | 1 (0.3) |
| **Endocrinopathy** | **5 (4)** | 4 (1) |
| Hypopituitarism | **5 (4)** | 4 (1) |
| Adrenal insufficiency | **0** | 2 (0.5) |
| **Other** | | |
| Pneumonitis | **0** | 1 (0.3) |
| Meningitis | **0** | 1 (0.3) |
| Nephritis | **1 (0.8)** | 0 |
| Eosinophilia[d,e] | **1 (0.8)** | 0 |
| Pericarditis[b,d] | **0** | 1 (0.3) |

a Combination of YERVOY+gp100 is not a recommended regimen. gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.
b Including fatal outcome.
c Including intestinal perforation.
d Underlying etiology not established.
e Occurred after induction.

Five patients experienced immune-mediated adverse reactions with onset greater than 2 months after the last dose of YERVOY. All had previously experienced similar immune-mediated

adverse reactions while on study, of which 4 were treated with corticosteroids. One of these 5 patients died due to large intestine perforation approximately 5 months after the last dose of YERVOY and at least 1 month after receiving dacarbazine and temozolomide. Another patient experienced severe enterocolitis and moderate dermatitis approximately 3 months and 4.5 months, respectively, after the last dose of YERVOY; both of these adverse reactions completely resolved. Immune-mediated adverse reactions in the remaining 3 patients were of moderate intensity and included hypothyroidism, enterocolitis, and dermatitis with onset between 2.5 and 10.5 months after the last dose of YERVOY.

Five patients developed new immune-mediated adverse reactions while receiving high-dose corticosteroid treatment for an earlier immune-mediated adverse reaction. Of the 5 patients, 3 developed a new immune-mediated adverse reaction on the day of the initiation of the high-dose corticosteroids, and 2 developed a new immune-mediated adverse reaction after 1 and 4 days of treatment.

A summary of severe to fatal immune-mediated adverse reactions, including treatment outcome for patients who received high-dose corticosteroids or infliximab, is presented in Table 3.

**Table 3: High-Dose Systemic Corticosteroid Administration in Patients with Grade 3-5 Immune-mediated Adverse Reactions: Patients Receiving Either YERVOY-containing Regimen (n=511)**

| | **Number (%) with Grade 3-5 Immune-mediated Adverse Reaction (n=511)** | **Number Receiving High-dose Corticosteroids/ Number with Grade 3-5 Immune-mediated Adverse Reaction (%)** |
|---|---|---|
| **Grade 3-5 Immune-mediated Adverse Reactions** | **66 (13%)** | **44/66 (67%)** |
| *Immune-mediated Enterocolitis* | 34 (7%) | 29/34 (85%) |
| *Immune-mediated Hepatitis* | 8 (2%) | 2/8 (25%) |
| *Immune-mediated Dermatitis* | 13 (3%) | 7/13 (54%) |
| *Immune-mediated Neuropathy* | 2 (0.4%) | 1/2 (50%) |
| *Immune-mediated Endocrinopathy* | 9 (2%) | 6/9 (67%) |
| *Other immune-mediated Adverse Reactions* | 4 (0.8%) | 2/4 (50%) |
| **Treatment Discontinuation Due to Grade 3-5 Immune-mediated Adverse Reactions**[a] | **Number Discontinuing/Number with Grade 3-5 Immune-mediated Adverse Reaction (%)** | |
| *Immune-mediated Enterocolitis* | 17/34 (50%) | |
| *Immune-mediated Hepatitis* | 2/8 (25%) | |
| *Immune-mediated Dermatitis* | 1/13 (8%) | |
| *Immune-mediated Neuropathy* | 0 | |
| *Immune-mediated Endocrinopathy* | 1/9 (11%) | |
| *Other immune-mediated Adverse Reactions* | 2/4 (50%) | |

**Table 3: High-Dose Systemic Corticosteroid Administration in Patients with Grade 3-5 Immune-mediated Adverse Reactions: Patients Receiving Either YERVOY-containing Regimen (n=511)**

| Clinical Outcomes Following Treatment with High-Dose Corticosteroids | Number Resolved or Not Resolved/Number Receiving High-Dose Corticosteroids (%) | | | | | |
|---|---|---|---|---|---|---|
| | | Not Resolved - Last Grade Reported | | | | |
| | Resolved | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Fatal |
| *Immune-mediated Enterocolitis* | 21/29[b] (72%) | 0 | 1/29 (3%) | 4/29 (14%) | 1/29 (3%) | 2/29 (7%) |
| *Immune-mediated Hepatitis* | 2/2 (100%) | 0 | 0 | 0 | 0 | 0 |
| *Immune-mediated Dermatitis* | 6/7 (86%) | 0 | 0 | 0 | 0 | 1/7[c] (14%) |
| *Immune-mediated Neuropathy* | 1/1 (100%) | 0 | 0 | 0 | 0 | 0 |
| *Immune-mediated Endocrinopathy* | 3/6[d] (50%) | 0 | 1/6 (17%) | 1/6 (17%) | 0 | 0 |
| *Other Immune-mediated Adverse Reactions* | 2/2 (100%) | 0 | 0 | 0 | 0 | 0 |
| **Clinical Outcomes Following Treatment with infliximab** | **Number Resolved or Not Resolved/Number Receiving Infliximab (%)** | | | | | |
| | | Not Resolved- Last Grade Reported | | | | |
| | Resolved | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Fatal |
| *Immune-mediated Enterocolitis* | 6/6 (100%) | 0 | 0 | 0 | 0 | 0 |

a With or without high-dose corticosteroids

b One of the 21 patients had a resolution of enterocolitis following corticosteroid therapy but died 4 months later (5 months after the last dose of YERVOY) due to large intestine perforation. The patient had received two chemotherapies after discontinuation of YERVOY and before experiencing the fatal large intestine perforation.

c One patient had toxic epidermal necrolysis for which the last recorded severity grade after corticosteroid therapy was Grade 4. This patient subsequently died from acute respiratory distress syndrome (ARDS). Of note, this patient had lung metastasis at baseline and was diagnosed with Grade 4 pneumonia prior to the onset of the ARDS event. This case was included as a fatal immune-mediated dermatitis event in Table 3 since the contribution of toxic epidermal necrolysis to the fatal outcome could not be ruled out.

d Three of the 6 cases of immune-mediated endocrinopahy did not resolve. Two unresolved cases are captured in the table. An additional patient had a resolution (Grade 0) per the investigator assessment but was considered not resolved because the patient required long-term hormone replacement therapy.

*Deaths*

In patients who received either YERVOY monotherapy (n=131) or YERVOY in combination with gp100 (n=380) in MDX-010-20, there were 8 deaths (1.6%) due to immune-mediated adverse reactions: 2 (1.5%) occurred in the YERVOY monotherapy group (large intestine perforation and hepatic failure) and 6 (1.6%) in the YERVOY in combination with gp100 group (toxic epidermal necrolysis with acute respiratory distress syndrome; colitis with gastrointestinal perforation; intestinal perforation; multi-organ failure due to peritonitis; Guillain-Barré syndrome; and pericardial effusion [pericarditis]).

An additional 5 (1.0%) YERVOY-related deaths were reported: 2 (1.5%) in the YERVOY monotherapy group (angiopathy; infection and renal failure with septic shock) and 3 (0.8%) in the YERVOY in combination with gp100 group (sepsis; myelofibrosis; severe colitis and hyponatremia associated with fatal sepsis).

Other Studies

The safety profile of YERVOY 3 mg/kg in chemotherapy-naïve patients pooled across Phase 2 and 3 clinical trials (n= 75; treated) and in treatment-naïve (i.e., naïve to chemotherapy, BRAF inhibitors or immunotherapy) patients in a retrospective observational study (n= 120) was similar to that in previously treated advanced melanoma.

The following serious adverse reactions were also reported in patients with advanced melanoma treated with YERVOY in clinical studies (regardless of dose or regimen; n=1498 unless otherwise noted). Adverse reactions presented elsewhere in this section are excluded.

**Gastrointestinal disorders**

*0.1%–<1%* – pancreatitis

<0.1% - oesaphagitis[a], large intestinal ulcer, pancreatitis (autoimmune)[a], mucosal inflammation[a], peritonitis (infectious)[a]

**General Disorders and Administration Site Conditions**

<0.1% - Influenza-like Illness (symptoms)[a], systemic inflammatory response syndrome[a]

**Investigations**

<0.1% - Increased blood alkaline phosphatase[a], increased gamma-glutamyltransferase[a], abnormal blood prolactin[a]

**Endocrine disorders**

<0.1% – autoimmune thyroiditis, hyperpituitarism, secondary adrenocortical insufficiency

**Metabolism and nutrition disorders**

<0.1% – alkalosis

**Hepatobiliary disorders**

0.1% – <1% – autoimmune hepatitis

**Nervous system disorders**

0.1% –<1% – dysarthria

<0.1% – meningism, myasthenia gravis[a], meningitis (aseptic)[a], autoimmune central neuropathy (encephalitis)[a] , optic neuritis[a]

**Blood and lymphatic system disorders**

<0.1% – polycythemia

**Respiratory, thoracic and mediastinal disorders**

0.1% – <1% – lung infiltration

**Musculoskeletal and connective tissue disorders**

<0.1% - polymyositis,[a] myositis[a]

**Eye disorders**

<0.1% – episcleritis, eye edema, scleritis, ocular myositis[a]

**Renal and urinary disorders**

0.1%–<1% – hematuria

<0.1% – autoimmune nephritis, proteinuria, renal tubular acidosis

**Vascular disorders**

<0.1% – peripheral ischemia, Raynaud's phenomenon, temporal arteritis, vasculitis

**Immune System Disorders**

<0.1% - sarcoidosis[a]<0.01% - anaphylactic reaction (shock)[a]

**Cardiac disorders**

<0.1% – cardiomyopathy, myocarditis, pericardial effusion (pericarditis)[a]

**Ear disorders**

<0.1% - neurosensory hypoacusis[a]

[a] Reported in clinical studies outside the completed clinical trials in melanoma.

Additional adverse reactions have been reported in clinical trials of melanoma. These additional reactions all occurred at a frequency of <1%: Eczema, syncope, hair colour changes and cytokine release syndrome.

### Clinical Trial Adverse Reactions (Pediatrics)

Two pediatric studies, NCI17458/CA184070 and CA184178, were conducted including 45 subjects aged from 2.4 to 21.8 years old who had advanced solid tumors including melanoma. Four dose levels of YERVOY were investigated: 1, 3, 5 or 10 mg/kg, administered every 3 weeks for 4 doses. Among all the study subjects, 32 were aged 12 years and older and 5 of them were treated at dose level of 3 mg/kg. Decreased lymphocyte count, prolonged activated partial thromboplastin time (APTT), hyperglycemia and pleural effusion were observed in these 2 studies, in addition to the ARs reported in adult patients. Due to the limited pediatric data, the safety of YERVOY in children has not been fully established. In children and adolescents 12 years of age and older, the incidences of severe (Grade 3 or 4) adverse reactions and severe (Grade 3 or 4) immune-mediated adverse reactions were numerically higher at certain dose levels among pediatric subjects than those in adults. Hepatic, pancreatic, gastrointestinal immune-mediated adverse reactions and autoimmune disorders could be the most common severe (Grade 3 or 4) immune-mediated adverse reactions in pediatric subjects. No data pooling was conducted for children younger than 12 years.

### Immunogenicity

Less than 2% of patients with advanced melanoma who received YERVOY in Phase 2 and 3 clinical studies developed antibodies against ipilimumab. None of these patients had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Neutralizing antibodies against ipilimumab were not detected. Overall, no apparent association was observed between antibody development and adverse reactions.

### Post-market Adverse Drug Reactions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been very rarely reported with YERVOY in post-marketing use.

Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing

## DRUG INTERACTIONS

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes. In a drug interaction study of YERVOY administered alone and in combination with chemotherapy (dacarbazine or paclitaxel/carboplatin) in patients with treatment-naïve advanced melanoma, ipilimumab did not have an observable, clinically relevant effect on the pharmacokinetics of substrates of CYP1A2, CYP2E1, CYP2C8, and CYP3A4 when coadministered with substrates of these CYP isozymes

(i.e., paclitaxel/carboplatin, dacarbazine or its metabolite, 5-aminoimidazole-4-carboxamide (AIC)).

Except for treatment of immune-mediated adverse reactions, systemic immunosuppressants, including systemic corticosteroids, should be avoided as they could interfere with the pharmacodynamic activity of ipilimumab.

The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with ipilimumab, patients who require concomitant anticoagulant therapy should be monitored closely [see ADVERSE REACTIONS].

When using YERVOY in combination with OPDIVO (nivolumab), consult Product Monograph for OPDIVO (nivolumab) for further information on this drug.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations:

When using YERVOY in combination with OPDIVO (nivolumab) for unresectable or metastatic melanoma, consult Product Monograph for OPDIVO (nivolumab) for further information, such as recommended dose, dosage adjustment, sequence of administration of each medication and duration of treatment.

### Recommended Dose

The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks to a maximum of four doses, and within 16 weeks of the first dose. Patients should receive the entire induction regimen (four doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumor response to YERVOY should be conducted only after completion of induction therapy.

Liver function tests (LFTs), thyroid function tests, and electrolytes should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-mediated adverse reactions, including diarrhea and colitis, should be assessed during treatment [see WARNINGS AND PRECAUTIONS].

### Recommended Dose Modification

**Table 4 When to withhold dose of YERVOY**

| Withhold scheduled dose[a] of YERVOY for any moderate immune-mediated adverse reactions. | |
|---|---|
| **Any moderate immune-mediated adverse reactions** | **Action** |
| **Gastrointestinal:**<br>Moderate diarrhea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs. | 1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline) and management with corticosteroids is complete.<br>2. If resolution occurs, resume therapy.[d]<br>3. If resolution has not occurred, continue to withhold doses until resolution, then resume |
| **Hepatic**<br>Grade 2[b] elevation in AST, ALT, or total bilirubin. | |

| **Table 4 When to withhold dose of YERVOY** | |
|---|---|
| Withhold scheduled dose[a] of YERVOY for any moderate immune-mediated adverse reactions. | |
| **Any moderate immune-mediated adverse reactions** | **Action** |
| **Endocrine**<br>Symptomatic endocrinopathy. | treatment.[d]<br>4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 or return to baseline does not occur. |
| **Skin:**<br>Severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology. | |
| **Neurological:**<br>Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days) | |
| **Other moderate adverse reactions[c].** | |

[a] No dose reduction of YERVOY is recommended.

[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI-CTCAE v4).

[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. The decision whether to withhold a dose should be based on severity.

[d] Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

| **Table 5 When to permanently discontinue YERVOY** | |
|---|---|
| **Permanently discontinue YERVOY for any of the following:**<br>Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.<br>Failure to complete full treatment course within 16 weeks from administration of first dose. | |
| **Severe or life-threatening adverse reactions, including any of the following:** | **NCI-CTCAE v4[a] Grade** |
| **Gastrointestinal:**<br>Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation. | Grade 3 or 4 diarrhea or colitis. |
| **Hepatic:**<br>Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin, or symptoms of hepatotoxicity. | Grade 3 or 4 elevation in AST, ALT, or total bilirubin. |
| **Skin:**<br>Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations or severe pruritus. | Grade 4 rash or Grade 3 pruritus. |

| Table 5 When to permanently discontinue YERVOY | |
|---|---|
| **Neurologic:**<br>New onset or worsening, severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis. | Grade 3 or 4 motor or sensory neuropathy. |
| **Other organ systems[b]:**<br>Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis).<br>Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy. | ≥ Grade 3 immune-related reactions[c].<br>≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy. |

[a] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI-CTCAE v4).

[b] Any other organ system adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. The decision whether to discontinue YERVOY should be based on severity.

[c] Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

**See WARNINGS AND PRECAUTIONS for detailed management guidelines of immune-mediated adverse reactions.**

## Renal impairment

The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on covariate analysis of renal impairment on the CL parameter, in the population pharmacokinetic model, no specific dose adjustment is considered necessary in patients with mild to moderate renal dysfunction [see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY].

## Hepatic Impairment

The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Based on a covariate analysis of hepatic impairment on the CL parameter, in the population pharmacokinetic model, no specific dose adjustment is considered necessary in patients with mild hepatic impairment [see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY].

## Administration

Ipilimumab solutions must not be administered as an intravenous push or bolus injection. The entire solution of the ipilimumab dose must be infused through a compatible low-protein-binding in-line filter over a 90-minute period (refer to the "Preparation for Administration" section for compatible filters). A separate infusion line must be used for the infusion, and the line must be

flushed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose injection at the end of infusion.

Once opened, the product should be infused or diluted and infused immediately. If not used immediately, the infusion solution (undiluted or diluted between 1 mg/mL and 4 mg/mL) may be stored for up to 24 hours either under refrigeration (2° to 8°C) or at room temperature (20° to 25°C).

**Preparation for Administration**

PREPARE INFUSION USING ASEPTIC TECHNIQUE.

YERVOY Injection (5 mg/mL) may be used for intravenous administration without dilution after transferring to an infusion container using an appropriate sterile syringe, or after diluting with sterile sodium chloride 9 mg/mL (0.9% solution) or 5% dextrose injection solution to a concentration ranging from 1 mg/mL to 4 mg/mL. An in-line, sterile, non-pyrogenic, compatible, low-protein-binding filter must be used for intravenous administration.

Do not shake product.

The drug product should be inspected visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Determine the number of vials of YERVOY (5 mg/mL) needed [see DOSAGE AND ADMINISTRATION]. Allow the vials to stand at room temperature for approximately 5 minutes. Withdraw the required volume of ipilimumab solution using an appropriate sterile syringe and transfer into a sterile, evacuated glass bottle or intravenous bag (PVC or non-PVC).

Ipilimumab 5 mg/mL is compatible with:

- Glass, polyvinylchloride (PVC) and non-PVC bags
- PVC intravenous extension/administration sets
- Polyethersulfone (0.2 micrometer and 1.2 micrometer) and nylon (0.2 micrometer) in-line filters

Partially used vials or empty vials of YERVOY should be discarded in accordance with local requirements.

## OVERDOSAGE

The maximum tolerated dose of YERVOY has not been determined. In case of overdosage, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

CTLA-4 is a key regulator of T cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumor reactive T effector cells which mobilize to mount a direct T-cell immune attack against tumor cells. CTLA-4 blockade can also reduce T regulatory cell function, which may lead to an increase in anti-tumor immune response. Ipilimumab may selectively deplete T regulatory cells at the tumor site, leading to an increase in the intratumoral T effector/T regulatory cell ratio which drives tumor cell death.

### Pharmacodynamics

The pharmacodynamics of YERVOY is not completely understood. In patients with melanoma who received YERVOY, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase occurred in a dose-dependent fashion. In Study MDX-010-20 [see CLINICAL TRIALS], YERVOY at 3 mg/kg given with or without gp100 increased ALC throughout the induction dosing period, but no meaningful change in ALC was observed in the control group of patients who received an investigational gp100 peptide vaccine alone.

In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA-DR+ CD4+ and CD8+ T cells and a mean decrease in the percent of naïve (CCR7+ CD45RA+) CD4+ and CD8+ T cells were observed after treatment with YERVOY, consistent with its mechanism of action. A mean increase in the percent of central memory (CCR7+ CD45RA-) CD4+ and CD8+ T cells and a smaller, but significant, mean increase in the percent of effector memory (CCR7- CD45RA-) CD8+ T cells also was observed after treatment with YERVOY.

### Pharmacokinetics

The pharmacokinetics of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. Of the 785 treated patients, 30 (3.8%) had intensive pharmacokinetic sampling. The data obtained from intensive sampling in 30 patients with advanced melanoma were analyzed using Non-Compartmental Pharmacokinetic Analysis.

**Table 6 Summary Statistics of Pharmacokinetic Parameters from Intensively Sampled Subjects**

| Study Day | T-HALF (day) Mean (SD) [N] | CL (mL/hr/kg) Geo.Mean (95% CI) [N] | Vss (mL/kg) Geo.Mean (95%CI) [N] |
|---|---|---|---|
| 1 | 9.45 (3.17) [18] | 0.218 (0.180,0.265) [15] | 68.3 (57.2,81.6) [15] |
| 43 | 15.44 (6.90) [30] | 0.129 (0.105,0.146) [28] | 62.0 (56.2,68.5) [28] |

Pharmacokinetic parameters are summarized in **Table 6** above. The mean (SD) terminal half-life of ipilimumab was 15.4 (6.90) days, and the mean (95% CI) of CL and volume of distribution at steady state (Vss) were 0.218 (0.180, 0.265) mL/hr/kg for Day 1 and 0.129 (0.105, 0.146) mL/hr/kg for Day 43 and 68.3 (57.2, 81.6) mL/kg for Day 1 and 62.0 (56.2, 68.5) mL/kg, respectively. The small Vss value indicates that ipilimumab is confined primarily to the extracellular fluid volume which is consistent with its large molecular weight. Observed peak and trough mean ipilimumab serum concentrations are reported in **Table 7**.

Peak concentrations (Cmax) and trough concentrations (Cmin) of ipilimumab were found to be dose proportional with the dose range examined. Upon multiple dosing of YERVOY every 3 weeks, systemic accumulation was observed as evident by an accumulation index (AI) 1.37-fold or less for Cmax and Cmin. In addition, 95% of ipilimumab steady-state concentrations are achieved by the fourth dose of YERVOY administrated every 3 weeks.

**Table 7: Summary of Observed Peak (Cmax) and Trough (Cmin) Ipilimumab Serum Concentration Values in Studies (CA184004, CA184007, CA184008, CA184022, CA184024 and CA184078)**

| Parameter | 0.3 mg/kg | 3 mg/kg | 10 mg/kg |
|---|---|---|---|
| Cmax (µg/mL) (Day 1 Dose) | 5.18±1.20 (n=32) | 72.58±105.94 (n=74) | 188.24±44.60 (n=515) |
| Cmax (µg/mL) (Day 43 Dose) | 6.63 ±1.48 (n=31) | 74.78 ±55.85 (n=68) | 227.62 ± 133.78 (n=395) |
| Cmax AI (Day 43/Day1) | 1.37 ±0.772 (n=22) | 1.26 ±0.814 (n=48) | 1.33 ±1.520 (n=332) |
| Cmin (µg/mL) (Day 1 Dose) | NA | NA | 39.2 ±8.2 (n=6) |
| Cmin (µg/mL) (Day 43 Dose) | 2.1 ±1.1 (n=30) | 18.93 ±10.61 (n=63) | 53.094 ±26.01 (n=363) |

**Table 7: Summary of Observed Peak (Cmax) and Trough (Cmin) Ipilimumab Serum Concentration Values in Studies (CA184004, CA184007, CA184008, CA184022, CA184024 and CA184078)**

| Parameter | 0.3 mg/kg | 3 mg/kg | 10 mg/kg |
|---|---|---|---|
| Cmin AI (Day 43/Day1) | NA | NA | 1.36 ± 0.45 (n=3) |

Note : The end of infusion concentration value is taken to be Cmax.
Including all patients who had PK assessment taken from both dense and sparse sampling.

**Special Populations and Conditions**

No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in patients with hepatic or renal impairment.

Cross-study analyses were performed on data from 785 patients with melanoma who received single or multiple infusions of YERVOY at doses of 0.3, 3, or 10 mg/kg. In population pharmacokinetic analyses, the covariate pre-existing mild to moderate renal impairment, mild hepatic impairment, or prior systemic anticancer therapy did not influence the CL parameter in the population PK model of ipilimumab.

*Pediatric Population:*

The efficacy of YERVOY in pediatric patients has not been established. YERVOY has been studied in two trials with a total of 45 pediatric patients of which 17 adolescent patients 12 years of age and older had advanced melanoma.

YERVOY was evaluated in a dose-finding trial in pediatric patients with untreatable, relapsed or refractory solid malignant tumors and in an open label trial in adolescent patients with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma [see ADVERSE REACTIONS, Clinical Trial Adverse Reactions (Pediatrics)].In a population PK analysis using available pooled data from 565 patients from 4 phase 2 adult studies (N=521) and 2 pediatric studies (N=44), the covariate baseline body weight had a positive correlation with the CL parameter in the POPPK model of ipilimumab. This is the justification for dosing on a per weight basis. The covariate of age (2-87 years) had no effect on the CL parameters in the POPPK model of ipilimumab. Dose-normalized exposures (Cmin, Cmax) in adolescents are comparable with that in adults, as shown below. Based on this analysis, the exposure at 3 mg/kg in the adolescent and adult populations is comparable.

**Table 8: Summary of Clearance (CL), Peak (Cmax) and Trough (Cmin) Ipilimumab Serum Concentration Values In Adolescents and Adults from the Population PK Analysis**

| Age range (years) | No Subjects | CL (mL/h) | Cmin** (ug/mL/(mg/kg))* | Cmax** (ug/mL/(mg/kg))* |
|---|---|---|---|---|
| 12 to < 18 | 26 | 8.72 | 6.95 (53%) | 26.7 (26%) |

| | | | | |
|---|---|---|---|---|
| 18 to 87 | 530 | 14.7 | 5.05 (50.1%) | 24 (17.7%) |

(*) Geometric mean, dose normalized (CV%)
(**) The Trough (Cmin) and Peak (Cmax) Ipilimumab concentration at steady state

*Renal Impairment:*

The safety and efficacy of YERVOY have not been studied in patients with renal impairment. In a population pharmacokinetic analysis of patients with metastatic melanoma, the covariate pre-existing mild to moderate renal dysfunction did not influence the CL parameter in the population PK model of ipilimumab, and on this basis, no specific dose adjustment is considered necessary. Clinical and pharmacokinetic data with pre-existing severe renal impairment are limited, and the potential need for dose adjustment in these patients cannot be determined [see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION].

*Hepatic Impairment:*

The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. In a population pharmacokinetic results of patients with metastatic melanoma, the covariate pre-existing mild hepatic impairment (total bilirubin [TB] 1.0 x to 1.5 x ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) did not influence the CL parameter in the population PK model of ipilimumab, and on this basis, no specific dose adjustment is considered necessary. Ipilimumab has not been studied in patients with moderate (TB >1.5 x to 3 x ULN and any AST) or severe hepatic impairment (TB >3 x ULN and any AST) and the influence on clearance, or need for dose adjustment in these patients, cannot be determined; ipilimumab should be administered with caution in these patients. [see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION].

## STORAGE AND STABILITY

YERVOY must be stored refrigerated at 2°C to 8°C with protection from light. Do not freeze. Since YERVOY does not contain preservatives, any unused portion remaining in the vial must be discarded.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

YERVOY is supplied at a nominal concentration of 5 mg/mL ipilimumab in 50-mg and 200-mg single-use vials. Each milliliter contains 5 mg of ipilimumab, 3.15 mg tris hydrochloride, 5.85 mg sodium chloride, 10 mg mannitol, 0.04 mg diethylene triamine pentaacetic acid (DTPA),

0.1 mg polysorbate 80 and Water for Injection, USP at an approximate pH of 7. Sodium hydroxide or hydrochloric acid is added as necessary to adjust pH.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

**Proper name**: Ipilimumab

**Structure:** Ipilimumab is a fully human immunoglobulin (IgG1κ) consisting of four polypeptide chains; two identical heavy chains primarily consisting of 447 amino acids each with two identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds.

**Molecular Formula and Weight:** The predominant product has a molecular formula of C6572 H10126 N1734 O2080 S40 and predicted molecular weight of 147,991 Daltons.

**Physical and Chemical Characteristics:** Ipilimumab drug substance at 5 mg/mL in 20 mM Tris HCl, 0.1 M sodium chloride,1.0% w/v mannitol, 0.1 mM pentetic acid, 0.01% w/v polysorbate 80, pH 7.0, is a clear to slightly opalescent, colorless to pale yellow liquid. Light (few) particulates may be present. The absorptivity for ipilimumab is calculated to be 1.53 mL mg-1 cm-1.

**Product Characteristics**: Ipilimumab for Injection is formulated as a clear, colorless, sterile, non-pyrogenic, single-use, isotonic aqueous solution. Light (few) particulates may be present. Ipilimumab for Injection, 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) are supplied in 10-mL or 50-mL Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a pH of 7.

## CLINICAL TRIALS

Overall survival (OS) benefits of YERVOY at the recommended dose of 3 mg/kg in previously treated patients with unresectable or metastatic melanoma was demonstrated in a Phase 3 study (Study MDX-010-20).

***Study MDX-010-20:*** A Phase 3, double-blind study enrolled patients with unresectable or metastatic melanoma who had previously been treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive YERVOY 3 mg/kg in combination with an investigational gp100 peptide vaccine (gp100), YERVOY 3 mg/kg monotherapy, or gp100 alone.

The study included patients with HLA-A2 *0201 type; this HLA type supports the immune presentation of gp100. Patients were enrolled regardless of their baseline BRAF mutation status. The study excluded patients with active autoimmune disease (or those receiving systemic immunosuppression for organ transplantation), ocular melanoma, primary central nervous system melanoma, active untreated brain metastasis, human immunodeficiency virus (HIV), hepatitis B, hepatitis C, and ECOG performance status > 1. Patients without liver metastasis who had a baseline AST ≥ 2 x ULN, patients with liver metastasis who had a baseline AST > 5 x ULN, and patients with a baseline total bilirubin ≥ 2 x ULN were also excluded.

YERVOY/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for four doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for four doses. Patients with apparent tumor burden increase before completion of the induction period were continued on induction therapy as tolerated if they had adequate performance status. Assessments of tumor response to YERVOY were conducted at 12 and 24 weeks, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

A total of 676 patients were randomized: 137 to the YERVOY monotherapy group, 403 to the YERVOY + gp100 group, and 136 to the gp100 group. The proportions of treated patients who received all 4 doses were 67%, 64%, and 59%, respectively. Median follow-up was 9.5 months (range 0.36-55.06), 9.4 months (range 0.03-54.08), and 6.2 months (range 0.03-44.65), respectively. Baseline characteristics were well balanced across treatment groups. A total of 77 (12%) treated patients had a history of previously treated brain metastases that was clinically stable at study entry. Demographic and baseline disease characteristics are shown in Table 9.

**Table 9: Baseline Characteristics in Study MDX-010-20**

| | **YERVOY 3 mg/kg n=137** | YERVOY 3 **mg/kg+gp100**[a] n=403 | gp100[a] n=136 |
|---|---|---|---|
| Men | **59%** | 61% | 54% |
| Women | **41%** | 39% | 46% |
| Age (median) | **57 years** | 57 years | 57 years |
| M-Stage at study entry (%) | | | |
| M0 | **1%** | 1% | 3% |
| M1a (soft tissue) | **10%** | 9% | 8% |
| M1b (lung) | **16%** | 19% | 17% |
| M1c (all viscera) | **73%** | 71% | 72% |
| ECOG | | | |
| 0 (%) | **53%** | 58% | 51% |
| 1 (%) | **47%** | 41% | 45% |

**Table 9: Baseline Characteristics in Study MDX-010-20**

| | | **YERVOY 3 mg/kg n=137** | YERVOY 3 **mg/kg+gp100**[a] n=403 | gp100[a] n=136 |
|---|---|---|---|---|
| 2 | (%) | **1%** | 1% | 3% |
| 3 | (%) | **0%** | <1% | 0% |
| Elevated Baseline LDH[a] | | **39%** | 37% | 38% |

a Combination of YERVOY+gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

The primary endpoint was overall survival (OS) in the YERVOY + gp100 group vs. the gp100 group. Key secondary endpoints were OS in the YERVOY + gp100 group vs. the YERVOY monotherapy group and in the YERVOY monotherapy group vs. the gp100 group. Other secondary endpoints included best overall response rate (BORR) up to Week 24 and duration of response.

The OS results are shown in Figure 1 and Table 10.

**Figure 1 Overall Survival in Study MDX-010-20**

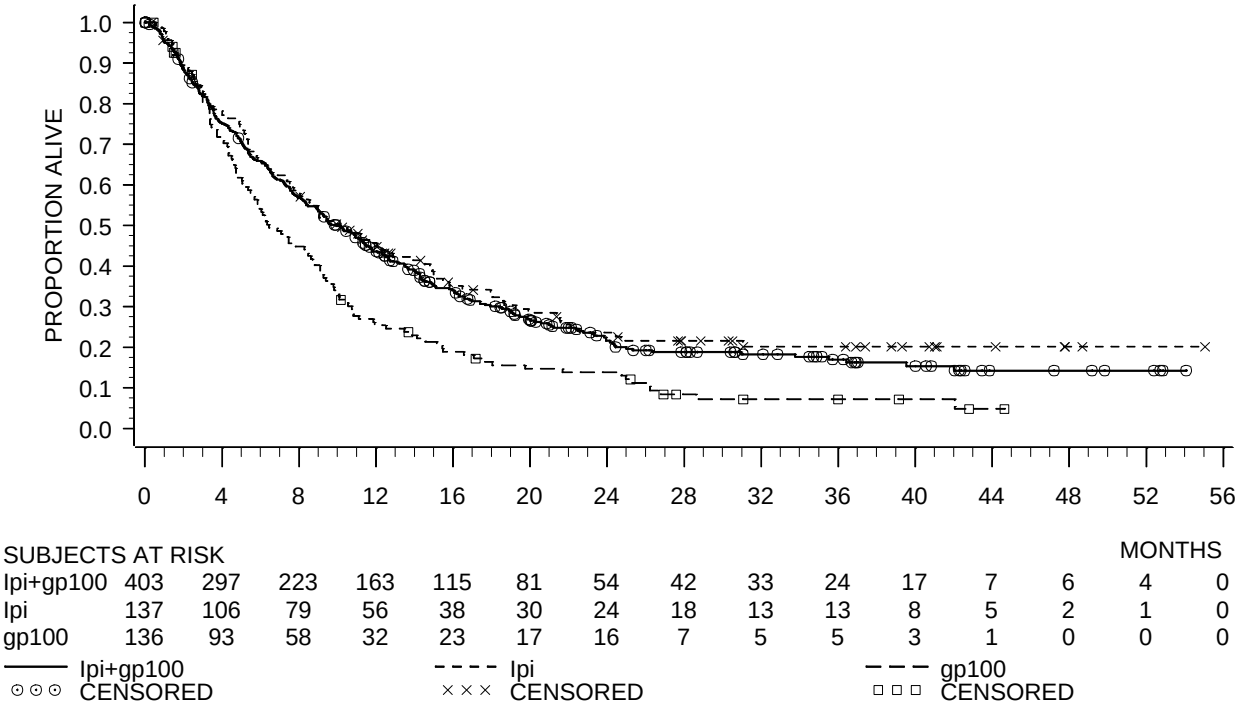

**Table 10: Summary and Comparison of Overall Survival in Study MDX-010-20**

| | **YERVOY 3 mg/kg n=137** | YERVOY 3 mg/kg++gp100[a] n=403 | gp100[a] n=136 |
|---|---|---|---|
| Number of events | **100** | 306 | 119 |
| Median (months) | **10.1** | 10.0 | 6.4 |
| 95% CI for median | **(8.0, 13.8)** | (8.5, 11.5) | (5.5, 8.7) |
| HR vs. gp100 with 95% CI | **0.66 (0.51, 0.87)** [b] | 0.68 (0.55, 0.85) [b] | |
| Log-rank p value vs. gp100 | **0.0026**[b,c] | 0.0004[b] | |
| HR vs. YERVOY with 95% CI | | 1.04 (0.83, 1.30) [b] | |
| Overall Survival at 1 year | **46%** | 44% | 25% |
| Overall Survival at 2 years | **24%** | 22% | 14% |

a Combination of YERVOY+gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

b Cox model for Hazard ratios (HR) and log-rank test p-values were stratified by baseline M-stage at randomization (M0, M1a, M1b vs. M1c) and prior treatment with IL-2 (Yes vs. No).

c P-values for the comparison of the YERVOY monotherapy arm and the gp 100 arm are not been adjusted for multiple comparisons.

Results of best overall response rate and duration of response are presented in Table 11.

**Table 11: Efficacy of YERVOY in Study MDX-010-20**

| | **YERVOY 3 mg/kg n=137** | **YERVOY 3mg/kg+gp100[a] n=403** | gp100 [a] n=136 |
|---|---|---|---|
| BORR[b] (up to Week 24) % (95% CI) | **10.9% (6.3, 17.4)** | 5.7% (3.7, 8.4) | 1.5% (0.2, 5.2) |
| CR (%) | **1.5%** | 0.2% | 0 |
| PR (%) | **9.5%** | 5.5% | 1.5% |
| SD (%) | **17.5%** | 14.4% | 9.6% |
| Median Duration of Response (Range) | **Not Reached (2.8-44.2+)** | 11.5 months (1.9-44.4+) | Not Reached (2.0-5.6+) |

a Combination of YERVOY+gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

b Based on investigator assessment.

***CA184045:*** In a Phase 2, multicenter, open-label study in patients with unresectable Stage III or Stage IV melanoma who had failed or were intolerant to at least 1 prior systemic therapy, a total of 2751 patients were treated with ipilimumab 3 mg/kg. The median number of doses received

during the induction phase was 4 in the overall study group. In the subgroup of patients with Eastern Cooperative Oncology Group performance status ≥ 2 (n=214, 212 subjects with ECOG=2), median number of doses received was 2, and 25% of the patients completed the entire induction regimen (four doses). Seventy-five percent of patients were discontinued from ipilimumab treatment during the induction phase, and disease progression was the most common reason for treatment discontinuation (67% of patients).

***CA184161:*** A Phase 1 study was conducted to investigate the safety of the concurrent administration of vemurafenib and YERVOY in patients with $BRAF^{V600}$-mutated metastatic melanoma not previously treated with CTLA-4 blocking antibodies or with BRAF or MEK inhibitors. Following a 1-month lead-in with monotherapy vemurafenib (960 mg or 720 mg twice daily), patients received combination therapy with YERVOY (3 mg/kg IV every 3 weeks) and vemurafenib administered concurrently. Of the 10 patients who received the combination regimen, 6 developed Grade 3 elevation of ALT/AST, 1 of which also developed Grade 3 elevation of total bilirubin. All were asymptomatic and reversible with either interruption or permanent discontinuation of the drugs, and/or treatment with corticosteroids [see WARNINGS AND PRECAUTIONS].

For information on clinical studies with YERVOY (ipilimumab for injection) in combination with OPDIVO (nivolumab), consult Product Monograph for OPDIVO (nivolumab).

## TOXICOLOGY

The toxicology studies performed with ipilimumab are summarized in **Table 12**.

### *Repeat-Dose Toxicity*

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was tolerated without adverse effects at doses up to 30 mg/kg/day administered every 3 days for 3 doses (peak serum concentrations ≤ 682 µg/mL), at 10 mg/kg (equivalent to approximately 3 times the human dose on body-weight basis) administered weekly for 1 month (mean AUC (0-168h) and AUC (0-63 days) of 31.6 µg•h/mL and 102.1 µg•h/mL, respectively), at 1 mg/kg administered weekly for 10 weeks, and at doses up to 10 mg/kg/day administered approximately monthly for up to 6 months. In an exploratory pharmacology/toxicity study, 1 of 6 monkeys was euthanatized in moribund condition due to colitis after receiving 2 monthly doses of ipilimumab at 10 mg/kg in combination with 3 vaccines. In another pharmacology study, 1 monkey receiving ipilimumab approximately monthly at 10 mg/kg in combination with another immunomodulatory antibody and vaccines developed dermatitis/rash 4 weeks following a 3 month dosing period, whereas another monkey in this study developed an infusion reaction within minutes following a dose of ipilimumab. Colitis and rash were infrequent events in preclinical studies (~6% of monkeys receiving approximate monthly doses of ipilimumab at 10 mg/kg and 3% of monkeys in all repeat-dose studies). Since the infusion reaction was not reproducible upon a controlled

ipilimumab rechallenge, the drug relationship to this event remains unclear; however, the occurrence of acute cytokine release resulting from a rapid injection rate is possible.

***Reproduction and Development***

Pregnant monkeys received ipilimumab every 21 days from the onset of organogenesis in the first trimester through delivery, at dose levels either 2.6 or 7.2 times higher than the clinical dose of 3 mg/kg of ipilimumab (by AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls. Developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed in utero to ipilimumab 30 mg/kg every 3 weeks. One female infant had unilateral renal agenesis of the left kidney and ureter, and one male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema. The relationship of these malformations to treatment is unclear.

Human IgG1 is known to cross the placental barrier; therefore, YERVOY has the potential to be transmitted from the mother and cause harm to the developing fetus. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY.

YERVOY should not be used during pregnancy unless the potential benefits justify the potential risks to the fetus.

***Impairment of Fertility***

No formal studies of effects of ipilimumab on fertility have been conducted. As part of the routine histopathological examination of organs collected in toxicity studies, the male and female reproductive organs were evaluated, including assessments of sperm and ovum morphology and maturation. There were no histopathologic changes in these organs that could be attributed to ipilimumab. In a chronic 6-month toxicology study using sexually mature monkeys ranging in age from 7 to 8 years, drug-related changes in reproductive organ weights were limited to decreases in absolute and relative testicular (27 to 50%) weights at 10 mg/kg; however, there were no corresponding microscopic changes in these organs. There were no other drug-related changes in male or female reproductive or endocrine organ weights or drug-related microscopic findings in these organs.

In tissue crossreactivity studies, ipilimumab specifically bound to activated lymphocytes expressing CTLA-4 in several normal human and/or cynomolgus monkey tissues (tonsil, gastrointestinal tract, lymphoid system, lung, kidney, liver, skin, and/or peripheral blood). In addition, ipilimumab bound specifically to connective tissue in human and cynomolgus monkey

placenta and to connective tissue in cynomolgus monkey ovary; no specific binding was observed in human ovary. Despite specific binding of ipilimumab to cynomolgus monkey ovarian tissue, no gross or microscopic ovarian findings were observed in ipilimumab toxicity studies conducted in monkeys. Therefore, binding of ipilimumab to connective tissue in cynomolgus monkey ovary is also not expected to have any biological or toxicological relevance, especially since similar binding was not observed with human ovaries.

***Mutagenicity***

Since it is not expected that large recombinant proteins like ipilimumab would interact directly with DNA or other chromosomal materials, genotoxicity studies were not conducted for ipilimumab.

***Carcinogenicity***

No formal animal studies have been performed to establish the carcinogenic potential of ipilimumab. Carcinogenicity studies are generally not needed for oncolytic agents intended for treatment of advanced systemic disease. Despite the development of a fatal lymphoproliferative disorder in CTLA-4 knockout mice, there were no hyperplastic, preneoplastic, or neoplastic lesions in the peripheral blood or lymphoid tissues of ipilimumab-treated monkeys in toxicology studies, despite long-term treatment at a clearly immunostimulatory dose of 10 mg/kg.

Non-clinical studies conducted with CTLA-4 blocking antibodies demonstrated anti-proliferative effects. In mouse tumor models, treatment with CTLA-4 blocking mAbs resulted in the induction of an antitumor immune response able to delay tumor growth or eradicate established tumors. In tumor models where anti-CTLA-4 therapy was ineffective, combination with several therapeutic modalities, including surgery, vaccination, radiotherapy and immunomodulatory agents, demonstrated synergistic effects to control tumor growth.

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| General Toxicity | | | | | |
| **Repeat-Dose Toxicity** IV | 2 weeks (Dosing Days 1, 4, 7 Necropsy Day 14) | Monkey/ Cynomolgus | 2F | 3 | None. |
| **Repeat-Dose Toxicity** IV | 2 weeks (Dosing Days 1, 4, 7 Necropsy Day 14) | Monkey/ Cynomolgus | 2M (3 mg/kg), 2F (10 mg/kg) | 3, 10 | No adverse toxicities occurred. |
| **Repeat-Dose Toxicity** IV | 2 weeks (Dosing Days 1, 4, 7 Necropsy Day 14) | Monkey/ Cynomolgus | 2M (3 mg/kg) 2M, 2F (30 mg/kg) | 3, 30 | There were no adverse drug-related findings, compared to prestudy, or substantial changes in lymphocyte subpopulations. The NOAEL was 30 mg/kg. |
| **Repeat-Dose Toxicity** IV | 1 month (Dosing Days 1, 8, 15, 22 Necropsy Days 24 and 91/92) | Monkey/ Cynomolgus | 5M, 5F | 0, 10[b] | There were no adverse treatment-related effects observed during the study period. The ipilimumab NOAEL was 10 mg/kg (an estimated human exposure multiple of ~2-fold) when administered alone or in combination with 100 mg/kg BMS-663513.Transient ipilimumab-specific antibodies were detected in only 1 of 10 monkeys receiving the combination treatment and in none receiving ipilimumab alone. Following immunization with KLH on Day 10, enhancement of the T-cell-dependent KLH-specific antibody response with ipilimumab alone (3.9 to 4.7x control) and, to a larger extent, in combination with BMS-663513 (6.3 to 7.0x control) was consistent with its T-cell potentiating mechanism of action. |
| **Repeat-Dose Toxicity** IV | 2 months (Dosing Days 1, 29 Necropsy Day 64) | Monkey/ Cynomolgus | 2M, 2F | 0[c], 10 | No adverse toxicities occurred following monthly administration of 10 mg/kg ipilimumab, when administered with or without oligo-CpG on study day 2. Stimulatory effects on antigen-specific (HBsAg) T-cell-dependent antibody response and ex vivo antigen specific intracellular T-cell activation occurred with similar effects as oligo CpG and were consistent with the pharmacologic activity of ipilimumab. No evidence of nonspecific immune-cell activation was observed. |

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| **Repeat-Dose Toxicity** IV | 3 months (Dosing Days 1, 29, 57, 140 Necropsy Day 154) | Monkey/ Cynomolgus | 3M, 3F | 0, 10 | One monkey developed severe colitis and was euthanized moribund on Day 42. Findings preceding death included persistent diarrhea, inappetance, and body-weight loss and agonal changes. Secondary findings included mixed-cell infiltrates in the adrenals, liver, and renal glomeruli, thickened glomerular mesangia, hyperplasia of adrenal cortex, and lymphoid depletion of thymus, spleen, and gut-associated lymphoid tissue. In surviving monkeys, there were no drug-related toxicologic changes. Increased cellular (DTH challenge scores for HbsAg, ~2-fold controls) and humoral (≤~5-fold to SKMel-3 and HBsAg) immune responses, and an increased (≤77%) peripheralblood CD4 central memory T-cell population were observed in monkeys given ipilimumab. |

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| **Repeat-Dose Toxicity** IV | 4 Months (Dosing Days 4, 7, 29, 32, 57, 59, 85, 87) | Monkey/ Cynomolgus | 3M, 3 F (0 mg/kg) 4M, 2F (10 mg/kg) | 0, 10[d] | One monkey receiving ipilimumab at 10 mg/kg developed an infusion reaction immediately after dosing on Day 58 with ipilimumab at 10 mg/kg and SIV DNA vaccines. The monkey stabilized ~45 minutes later. Approximately 5 months later (Day 211), this animal was rechallenged with ipilimumab at 10 mg/kg (without vaccine challenge). Following rechallenge, there were no adverse clinical signs. A second monkey receiving ipilimumab at 10 mg/kg in combination with BMS-663513 and SIV DNA vaccines developed dermatitis/rash in the inguinal area accompanied by peripheral lymphadenopathy on Day 113. Treatment with antihistamine transiently resolved the rash but the rash returned ~ 1 month later and spread to the back of the knees, at which time prednisone treatment was initiated. Findings observed in skin biopsies obtained from the affected area were compatible with a DTH reaction. The drug regimen was well tolerated by all other monkeys on the study. |

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| **Repeat Dose Toxicity** IV | 6 months (Dosing Days 0, 28, 56, 84, 140 Necropsy Day 167/168) | Monkey/ Cynomolgus | 2 or 3/sex | 0, 10 | Drug-related findings were limited to decreases in absolute and relative thyroid (44 to 50%) and testicular (27 to 50%) weights; however, there were no corresponding microscopic changes in these organs. In addition, irritation (slight erythema and edema) was observed after the fourth and fifth doses at the site of subcutaneous injection of SK-mel vaccine in 1 male given ipilimumab and SK-mel. Ipilimumab substantially enhanced the T-cell-dependent antibody response to SK-mel vaccine. Five of 6 animals receiving ipilimumab demonstrated a robust antibody response to SK-mel vaccine, compared to 1 of 6 control animals receiving only SK-mel vaccine. Mean anti-SK-mel antibody levels were substantially higher and mean antibody binding was also relative to vaccine control. The NOAEL following administration of ipilimumab over a period of 6 months was 10 mg/kg. |
| **Combination Toxicity Studies** IV | 1 month (Dosing Days 1, 8, 15, 22 Necropsy Days 30, 59) | Monkey/ Cynomolgus | 5M, 5F | 3/10, 10/50 Ipilimumab/ MDX-1106[e] | At both dose combinations (3/10 or 10/50 mg/kg ipilimumab/MDX-1106), a dose-dependent increase in the incidence of watery feces (accompanied by reduced food consumption and body-weight loss at the high dose); increased spleen weights and decreased thymus weights; partially reversible, dose-related inflammation of the large intestine (colon, cecum, and/or rectum) with secondary decreases in albumin and increases in globulins and neutrophil counts; minimal to mild increases in the size/number of lymphoid follicles and/or marginal zone expansion in the spleen; and minimal to marked decreases in the size and/or cellularity of germinal centers in the spleen and lymph nodes (inguinal, mandibular, mesenteric, colonic, and axillary). At the high combination dosages, there were increases in total circulating T-lymphocyte and T-helper lymphocytes and the death of 1 male monkey on Day 23 was attributed to acute gastric dilatation (bloat). Additional drug-related findings secondary to stress included lymphoid hypocellularity of the cortex and/or medulla of the thymus at both doses and acinar cell degranulation in the pancreas at the high dose only. Effects on the T-cell-dependent antibody response to KLH were consistent with the immunostimulatory activity of ipilimumab and MDX-1106. Following KLH administration on Day 10 (2 days after the second weekly dose), an enhancement of the KLH-specific antibody response (IgM or IgG) was observed at both doses to a similar magnitude (1.4x to 2.5x control for IgM on Days 15 and/or 24 and 2.3x to 3.2x control for IgG on Day 24). |

| **Table 12: Summary of Toxicology Studies** | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| **Product Comparability/ Single-Dose Studies**<br>IV | 1 day | Monkey/ Cynomolgus | 4F | 10<br>Process B[f]<br>Process C[g] | Clinical signs, group mean body weights, qualitative food consumption observations, group mean body temperatures, and physical-examination findings were comparable in monkeys dosed with ipilimumab manufactured using either Process B or Process C. There were no substantial differences in Cmax or AUC parameters or immunogenicity of Process C ipilimumab compared to Process B. |
| **Product Comparability/ Repeat-Dose Toxicity Studies**<br>IV | Once monthly for 3 months<br>Necropsy Day 79<br><br>Once weekly for 10 weeks<br>Necropsy Day 79 | Monkey/ Cynomolgus | 3M, 3F | 10<br>Process A[h]<br>0, 0.1, 1, 10[i]<br>Process B<br><br>1<br>Process A[h] | No adverse toxicities occurred following administration of Process B ipilimumab at 0.1, 1, or 10 mg/kg month for 3 months or 1 mg/kg weekly for 10 weeks, or Process A ipilimumab at 10 mg/kg monthly for 3 months. The NOAEL was considered to be 10 mg/kg for both processes. The pharmacokinetic, immunogenicity, bioactivity (T-cell activation and T-cell-dependent antibody response), and toxicity profiles were comparable for ipilimumab derived from either CHO (Process B) or hybridoma (Process A) cells at exposures approximately equivalent to those used in clinical trials. |
| **Local Tolerance** | | | | | |
| Ipilimumab is administered intravenously in humans. The local tolerance of the drug product, including the current formulation intended for marketing (Process B), was assessed in the intravenous repeat-dose studies in monkeys with ipilimumab as described above. Refer to each of the studies listed above for specific information about these studies and injection site observations. No substantial injection-site irritation was observed in any of the studies. | | | | | |

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| Pre- and Post-natal Development | Once every 21 days from GD20-GD22 until parturition | Monkey/ Cynomolgus | 20F<br>19F<br>20F<br>3F | 0<br>10<br>30<br>-- | Pregnant monkeys received ipilimumab every 21 days from the onset of organogenesis in the first trimester through delivery, at dose levels either 2.6 or 7.2 times higher than the clinical dose of 3 mg/kg of ipilimumab (by AUC). Serum ipilimumab concentrations in the offspring were similar to those in the mothers (infant-to-maternal serum concentration ratios ranged from 1.1 +/- 0.6 to 1.7 +/- 1.1) for up to 3 months post partum. Ipilimumab was shown to be present at very low levels in milk from adult mothers (with mean milk/serum ipilimumab concentration ratios that were 0.002 to 0.003). No treatment-related adverse effects on reproduction were detected during the first 2 trimesters of pregnancy. Maternal pregnancy outcomes for the first 2 trimesters were comparable in control and drug-treated groups. Beginning in the third trimester (≥GD100), the ipilimumab groups experienced increased maternal weight decrements; higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight); and higher incidences of infant mortality in a dose-related manner, compared to controls (21% and 30% for 10 and 30 mg/kg/q3w, respectively; compared to study controls [0%] and historical controls [17.6%]). Some infant mortality in ipilimumab-treated groups could be attributed to prematurity; however, the group mean durations of gestation were comparable in the 3 experimental groups (160, 160, and 155 days in saline, 10, and 30 mg/kg groups, respectively). Developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed in utero to ipilimumab 30 mg/kg every 3 weeks. One female infant had unilateral renal agenesis of the left kidney and ureter, and one male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema. The relationship of these malformations to treatment is unclear. Infants exposed to ipilimumab at 30 mg/kg/q3w had a lower mean body weight (-15% relative to control infant values) at birth. However, the rate of body-weight gain in these infants increased by 3 months of age and mean body weight for the 30 mg/kg/q3w group was comparable to that of the control infants at 6 months. Ipilimumab did not adversely affect the ability of infants to mount a T-cell dependent antibody response to Hepatitis B surface antigen at 6 and 18 weeks of age. There were no adverse effects observed in infants related to ipilimumab-exposure in utero with respect to clinical observations, morphometric measurements, neurobehavioral and skeletal evaluations, clinical pathology, lymphocyte phenotyping, anti-nuclear antibody formation, or serum immunoglobulin levels through 6 months postnatal. |

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| **Other Studies** | | | | | |
| **Tissue Crossreactivity** *In vitro* | 1 hr[j] | Human | n= 3 donors ~36 tissue/donor | 2.5, 10 µg/mL fluoresceinated Ipilimumab (ProcessA) | Ipilimumab specifically bound to lymphocytes expressing CTLA-4 in a few normal human tissues (tonsil, colon, and peripheral blood). No unanticipated cross-reactivities were observed. |
| **Tissue Crossreactivity** *In vitro* | 1 hr[j] | Human | n= 3 donors ~12 tissue/donor | 2, 10 µg/mL fluoresceinated Ipilimumab (Process B) | Ipilimumab specifically bound to lymphocytes expressing CTLA-4 in normal human tonsil, colon, esophagus, small intestine, stomach, lung, kidney, liver, and peripheral blood. No unanticipated cross-reactivities were observed. |
| **Tissue Crossreactivity** *In vitro* | 30 min[j] | Mouse/CD-1, Rat/SD, Rabbit/ New Zealand White, Monkey/ Cynomolgus, Human | 2M, 2F per species ~23 tissues/donor | 1, 10 µg/mL biotinylated MDX-010 | Specific binding of ipilimumab was limited to cynomolgus monkey and human tissues. Specifically, binding occurred to placenta, gastrointestinal tract, lymphoid system, and skin from both species, and to ovarian tissue from cynomolgus monkeys. These data support the species specificity of ipilimumab binding to cynomolgus monkey and human CTLA-4. |

| Table 12: Summary of Toxicology Studies | | | | | |
|---|---|---|---|---|---|
| **Type of Study** | **Treatment Duration** | **Species/ Test System** | **Gender and No. per Group** | **Doses (mg/kg)[a]** | **Noteworthy Findings** |
| **Cytokine Release Studies** *In vitro* | 6 and 24 hr for cytokine release assessment[j]<br>66 hr for proliferation assessment[j] | Human | 10 donors | 0, 0.016, 0.08, 0.4, 2, 10, or 50 µg/well for dry coat assay[k,l]<br>0.08, 0.4, 2, 10, and 50, and 250 µg/ml for antibody capture assay[k,l]<br>2 µg/well IgG1 isotype control for dry coat assay<br>0.4 ug/mL IgG1 isotype control for antibody capture assay | Ipilimumab alone induced minimal proliferation and corresponding cytokine release (primarily IL-2, IL-6, IL-8, and TNF-$\alpha$ at a much lower magnitude of mean peak stimulation indices or SI ranging from 2 to 6)in PBMC from some donors, as compared to the positive control anti-CD28 antibody 5.11A1 (mean SI up to 137). There was no additive or synergistic effect of ipilimumab in combination with BMS-663513. |
| **Cytokine Release Studies** *In vitro* | 4 or 24 hr[j] | Human | 10 donors | 0, 10, 100 µg/mL[m,nt]<br>100 µg/mL IgG1 isotype control | No substantial cytokine release from human PBMC was observed with ipilimumab using this soluble assay format, nor did the addition of MDX-1106 to ipilimumab produce an additive or synergistic effect. |

[a] Unless otherwise specified. For Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

[b] An additional group received ipilimumab at 10 mg/kg in combination with BMS-663513 (immunostimulatory anti-CD137 monoclonal antibody) intravenously at 100 mg/kg.

[c] Control animals received 10 mg/kg of an isotype-matched control human IgG (MAbRSV) specific for respiratory syncytial virus.

[d] An additional group received ipilimumab at 10 mg/kg in combination with BMS-663513 (immunostimulatory anti-CD137 monoclonal antibody) intravenously at 10 mg/kg.

[e] All animals received ipilimumab in combination with MDX-1106, an immunostimulatory anti-PD-1 monoclonal antibody. There were no single agent arms in this study.

[f] Process B (CHO-derived).

[g] 1500-L pilot scale utilizing a higher producing subclone of the Process B master cell bank and modifications to the fermentation and purification processes.

[h] Process A (Hybridoma-derived).

[i] Process B, development grade (Chinese Hamster Ovary-derived).

[j] Duration of incubation with ipilimumab.

[k] Ipilimumab was tested alone or in combination with BMS-663513 (immunostimulatory anti-CD137 monoclonal antibody). The mouse anti-human superagonistic CD28 mAb 5.11A1 (TGN1412 is the IgG4 humanized version of 5.11A1) was also used as a positive control and comparator in these assays at the same concentrations as the test mAbs.

[l] Two immobilization assays were conducted, a dry-coat assay and a captured mAb assay. In the dry coat assay, test mAb (alone or in combination) was immobilized by dry coating it directly to the plates whereas in the captured mAb assay, the test mAb was immobilized by binding to anti-human immunoglobulin previously applied to the plates.

[m] Ipilimumab was tested alone or in combination with MDX-1106 (immunostimulatory anti-PD-1 monoclonal antibody). The mouse anti-human CD3 mAb UCHT-1 was also used as a positive control and comparator in these assays at the same concentrations as the test mAbs.

[n] Test mAb was added in soluble (nonimmobilized) format (alone and in combination) to whole blood in the absence of exogenous antigenic stimuli.

## REFERENCES


**1.** Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Eng J Med. Published online 5 June 2010, and updated June 14 2010.

**PART III: CONSUMER INFORMATION**

**Pr YERVOY® (yur-voi)**
**(ipilimumab for injection)**

**This leaflet is part III of a three-part "Product Monograph" published when YERVOY (ipilimumab for injection) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about YERVOY. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
YERVOY (ipilimumab for injection) is a prescription medicine used to treat melanoma (a kind of skin cancer) that has spread or cannot be removed by surgery. It is for the treatment of melanoma in adults

If your doctor has prescribed YERVOY in combination with OPDIVO® (nivolumab) you should read the leaflets for both medications as they contain different information.

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

**What it does:**
YERVOY helps your immune system attack and destroy cancer cells by your immune cells.

**When it should not be used:**
Do not use YERVOY if you

- are allergic to ipilimumab or any other ingredients in YERVOY
- have an active, very severe condition where your immune system attacks your body (life-threatening autoimmune disease)
- have received an organ transplant

**What the medicinal ingredient is:**
The medicinal ingredient in YERVOY is ipilimumab.

**What the important nonmedicinal ingredients are:**
Tris-hydrochloride, sodium chloride, mannitol, diethylene triamine pentaacetic acid (DTPA) and polysorbate 80.

**What dosage forms it comes in:**
YERVOY 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) are supplied in glass vials.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**Symptoms of serious side effects**
YERVOY acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening.

YERVOY can cause serious side effects in many parts of your body which can lead to death. These serious side effects may include: inflammation of the intestines (colitis) that can cause tears or holes (perforation) in the intestines; inflammation of the liver (hepatitis) that can lead to liver failure; inflammation of the skin that can lead to severe skin reaction (toxic epidermal necrolysis); inflammation of the nerves that can lead to paralysis (Guillain-Barré syndrome); inflammation of hormone glands (especially the pituitary, adrenal, and thyroid glands) that may affect how these glands work; and inflammation of the eyes. Please see complete Important Safety Information for details on signs and symptoms.

These side effects are most likely to begin during treatment; however, side effects can show up months after your last infusion. It is important to tell your doctor immediately if you have, or develop, any of the symptoms listed under **Serious Side Effects, How Often They Happen and What To Do About Them**.

**BEFORE you use YERVOY talk to your doctor or nurse if you:**

- have an active autoimmune disease, such as ulcerative colitis, Crohn's disease, lupus, or sarcoidosis
- have hepatitis
- take steroids or other medicines that lower your immune response
- had a severe skin reaction with a previous cancer therapy which works with your immune system
- take any medicines that stop your blood from clotting (anticoagulants)

**Pregnancy and Breastfeeding:**

- are pregnant or plan to become pregnant. You should not become pregnant while you are getting YERVOY. YERVOY can cause harm or death to your unborn baby.
- must use effective contraception while you are being treated with YERVOY and for at least 3 months after the last dose of YERVOY if you are a women who could become pregnant.
- are breast-feeding. YERVOY may pass into your breast milk. You and your doctor should decide if you will take YERVOY or breast-feed. You should not do both.

Always update your doctor or nurse on your medical conditions.

## INTERACTIONS WITH THIS MEDICATION

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines you obtained without a prescription. Do not start a new medicine before you talk to your doctor.

## PROPER USE OF THIS MEDICATION

YERVOY will be given to you in a hospital or clinic under the supervision of an experienced doctor.

YERVOY is a concentrate for solution for infusion. The amount of YERVOY you will be given will be calculated based on your body weight. Depending on your dose, some or all of the content of the YERVOY vial may be diluted with saline or glucose solution before use. More than one vial may be necessary to obtain the required dose.

It will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 90 minutes.

**Dosage and frequency of administration:**
The recommended dose is 3 mg of ipilimumab per kilogram of your body weight. You will be treated with YERVOY once every 3 weeks for a total of 4 doses as tolerated, depending on your response to treatment.

**Missed Dose:**
It is very important for you to keep all appointments to receive YERVOY. If you miss an appointment, ask your doctor when to schedule your next dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

YERVOY can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

The most common side effects with YERVOY are loss of appetite, diarrhea, feeling sick (nausea) or being sick (vomiting), stomach pain, itching, skin rash, and feeling tired or weak.

YERVOY acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and may be life-threatening. Tears or holes (perforation) in the intestines, liver failure, severe skin reaction (toxic epidermal necrolysis), and paralysis (Guillain-Barré syndrome) have been reported.

**It is important to tell your doctor immediately if you have any of the symptoms listed in the table below or your symptoms get worse.** Your doctor can then give you treatment to prevent more severe complications. Your doctor may give you other medicines in order to reduce your symptoms, delay the next dose of YERVOY, or stop your treatment with YERVOY altogether. **Do not try to treat or diagnose symptoms yourself**. These symptoms are sometimes delayed, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have blood tests before and during treatment.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and call your doctor or pharmacist** |
| | | **Only if severe** | **In all cases** | |
| **Common** *(less than 1 in 10 but more than 1 in 100)* | **Inflammation of the intestines (colitis)**<br>*Symptoms may include:*<br>• diarrhea (loose stools) or more bowel movements than usual. Do not treat the diarrhea yourself.<br>• constipation<br>• blood in stools or dark, tarry, sticky stools<br>• stomach pain (abdominal pain) or tenderness | | √ | |
| **Common** *(less than 1 in 10 but more than 1 in 100)* | **Inflammation of the liver (hepatitis)**<br>*Symptoms may include:*<br>• yellowing of your skin or the whites of your eyes,<br>• dark urine, tiredness, nausea or vomiting, loss of appetite, pain on the right side of your stomach, or bruise easily | | √ | |
| **Common** *(less than 1 in 10 but more than 1 in 100)* | **Inflammation of the skin**<br>*Symptoms may include:*<br>• rash on your skin, mouth blisters, or peeling skin | | √ | |
| **Uncommon** *(less than 1 in 100 but more than 1 in 1000)* | **Inflammation of the nerves**<br>*Symptoms may include:*<br>• weakness of legs, arms or face<br>• numbness or tingling in hands or feet | | √ | |
| **Common** *(less than 1 in 10 but more than 1 in 100)* | **Inflammation of certain glands (pituitary, adrenal glands, or thyroid) so they do not make enough hormone**<br>*Symptoms may include:*<br>• headaches or unusual tiredness or sleepiness<br>• changes in behavior such as less sex drive, being irritable or forgetful<br>• dizziness or fainting | | √ | |
| **Uncommon** *(less than 1 in 100 but more than 1 in 1000)* | **Inflammation in other parts of the body including eyes, kidneys, pancreas, or lung**<br>*Symptoms may include:*<br>• blurry vision, double vision, or other vision problems<br>• eye pain or redness | | √ | |
| **Uncommon** *(less than 1 in 100 but more than 1 in 1000)* | **Infusion reaction**<br>*Symptoms may include:*<br>• shortness of breath or trouble breathing, cough, chest tightness<br>• dizziness, fainting, rapid or weak heartbeat<br>• itching, hives, or feeling warm<br>• swelling of the throat, tongue, or face<br>• hoarse voice, throat tightness or trouble swallowing | | √ | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and call your doctor or pharmacist** |
| | | **Only if severe** | **In all cases** | |
| **Very rare** *(less than 1 in 10,000)* | *Immune Disease (Vogt-Koyanagi-Harada Syndrome)* *Symptoms may include blurry vision, intolerance of bright light or other eye symptoms in combination with*: • neck stiffness, headache • ear ringing, difficulty hearing, dizziness, • flu-like discomfort • skin discoloration, hair loss | | √ | |

*This is not a complete list of side effects. If you have any unexpected effects while taking YERVOY, contact your doctor or pharmacist.*

## HOW TO STORE IT

It is unlikely that you will be asked to store YERVOY yourself. It will be stored in the hospital or clinic where it is given to you.

Keep out of the reach and sight of children.

Do not use YERVOY after the expiry date which is stated on the label and carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.

Do not shake product.

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  **- Fax toll-free to 1-866-678-6789, or**
  **- Mail to: Canada Vigilance Program**
  **Health Canada**
  **Postal Locator 0701D**
  **Ottawa, Ontario**
  **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.bmscanada.ca
or by contacting the sponsor, Bristol-Myers Squibb Canada at:
1-866-463-6267.

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