

PRODUCT INFORMATION

YERVOY[®] (ipilimumab)

5mg per 1mL concentrate solution for infusion

WARNING: IMMUNE-MEDIATED ADVERSE EVENTS

YERVOY therapy should be administered and monitored under the supervision of physicians experienced in the treatment of cancer.

YERVOY can cause severe and life-threatening immune-related adverse reactions (irARs), including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), endocrinopathy (which may not be reversible), neuropathy, as well as irARs in other organ systems [see PRECAUTIONS and DOSAGE AND ADMINISTRATION].

Early diagnosis and appropriate management are essential to minimize life-threatening complications.

NAME OF THE MEDICINE

YERVOY[®] (ipilimumab): 5 mg/mL concentrate solution for infusion

Each 1 mL of concentrate contains 5 mg ipilimumab.
One 10 mL vial contains 50 mg of ipilimumab.
One 40 mL vial contains 200 mg of ipilimumab.

DESCRIPTION

CAS: 477202-00-9. YERVOY (ipilimumab (rch)) is a recombinant, fully human monoclonal antibody that binds to the 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.

YERVOY is a sterile, preservative free liquid for intravenous (IV) administration, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. YERVOY has a pH of 7.0 and an osmolarity of 260-300mOsm/kg. It is supplied at a nominal concentration of 5 mg/mL ipilimumab in 50-mg and 200-mg single-use vials.

Each 1 milliliter contains 5 mg of ipilimumab and 0.1mmol sodium (or 2.30mg sodium).

Inactive ingredients are: trometamol hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride), sodium chloride, mannitol (E421), pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment), water for injections.

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.

Pharmacodynamic effects

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 MDX010-20 (see Clinical Trials), YERVOY given at 3 mg/kg 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 naive (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 were also observed after treatment with YERVOY.

Immunogenicity

Less than 2% of patients with advanced melanoma who received YERVOY in Phase 2 and 3 clinical studies developed antibodies against ipilimumab. None 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 events, or clearance of ipilimumab (see Pharmacokinetics).

PHARMACOKINETICS

The pharmacokinetics of ipilimumab were studied in 785 patients with advanced melanoma who received induction doses of 0.3 mg/kg (n=58), 3mg/kg (n=101), or 10mg/kg (n=369) as monotherapy or 10mg/kg in combination with dacarbazine (n=257). Induction doses were administered once every 3 weeks for 4 doses. C_{max} , C_{min} and AUC of ipilimumab were found to be dose proportional over the dose range examined.

Upon repeated dosing of YERVOY administered every 3 weeks, clearance did not vary over time, and minimal systemic accumulation was observed with an accumulation index of 1.5 or less. Ipilimumab steady-state was reached by the third dose. Based on a population pharmacokinetic analysis, the following mean (percent coefficient of variation) parameters of ipilimumab were obtained: terminal half-life of 15.4 days (34.4%); systemic clearance of 16.8 ml/h (38.1%); and

volume of distribution at steady-state of 7.47-L (10.1%). The mean (percent coefficient of variation) ipilimumab C_{min} achieved at steady-state with a 3mg/kg induction regimen was 19.4µg/ml (74.6%).

Ipilimumab clearance increased with increasing body weight and with increasing lactate dehydrogenase (LDH) at baseline; however, no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis. Ipilimumab clearance was not affected by age (range 23-88 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, mild hepatic impairment, mild to moderate renal impairment, immunogenicity and previous systemic anticancer therapy. The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups.

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

Based on an exposure-response analysis in 497 patients with advanced melanoma, overall survival (OS) was independent of prior systemic anti-cancer therapy.

Renal Impairment

The effect of renal impairment on the clearance of ipilimumab was evaluated in patients with mild (GFR <90 and ≥ 60 mL/min/1.73m²; n=349), moderate (GFR <60 and ≥ 30 mL/min/1.73m²; n=82), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m²; n=4) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m²; n=350) in population pharmacokinetic analyses. No clinically important differences in the clearance of ipilimumab were found between patients with mild to moderate renal impairment and patients with normal renal function (see Precautions: Renal Impairment).

Hepatic Impairment

No clinically important differences in the clearance of ipilimumab were found between patients with mild hepatic impairment (Total Bilirubin 1.0-1.5xULN or AST>ULN as defined using the National Cancer Institute criteria for hepatic dysfunction; n=76) and normal hepatic function (N=708). Ipilimumab has not been studied in patients with moderate (Total Bilirubin > 1.5- 3 xULN and any AST) or severe hepatic impairment (Total Bilirubin > 3x ULN and any AST) (see Precautions: Hepatic impairment).

CLINICAL TRIAL EFFICACY INFORMATION

First line treatment of advanced (unresectable or metastatic) melanoma

Clinical data to support the use of ipilimumab 3mg/kg monotherapy in a first line clinical setting in patients with unresectable or metastatic melanoma is derived from observational clinical data and pooled data sourced from multiple studies. A prospective, randomised, Phase 3 study of ipilimumab 3mg/kg monotherapy has not been performed in this setting.

OS of YERVOY 3mg/kg monotherapy in chemotherapy-naïve patients pooled across Phase 2 and 3 clinical trials (N=78; randomised) and in treatment-naïve patients in two retrospective observational studies (N= 273 and N= 157) were generally consistent. In the two observational studies, 12.1% and 33.1% of the patients had brain metastases at the time of diagnosis. In these studies the estimated 1-

year survival rates were 59.2% (95% CI: 53.0 – 64.8) and 46.7% (95% CI: 38.1-54.9). The estimated 1-year, 2-year and 3-year survival rates for pooled chemotherapy-naïve patients were 54.1% (95% CI: 42.5 – 65.6), 31.6% (95% CI: 20.7 – 42.9) and 23.7% (95% CI: 14.3-34.4), respectively.

Previously treated advanced (unresectable or metastatic) melanoma.

Overall survival advantage (OS) of YERVOY at the recommended dose of 3 mg/kg in patients with previously-treated advanced (unresectable or metastatic) melanoma was demonstrated in a Phase 3 study (MDX010-20). YERVOY has not been investigated in patients with active or a history of serious chronic viral infections, including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Clinical studies excluded patients without liver metastasis who had a baseline AST > 2.5 x ULN or patients with liver metastasis who had a baseline AST greater than > 5 x ULN. Patients with a baseline total bilirubin \geq 3 x ULN were also excluded.

Study MDX010-20

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. All patients in this study were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. BRAF status was not collected at study entry. Patients received YERVOY every 3 weeks for 4 doses as tolerated (induction therapy). Patients with apparent tumour burden increase before completion of the induction period were continued on induction therapy as tolerated if they had adequate performance status. Assessment of tumor response to YERVOY was conducted at approximately Week 12 after completion of induction therapy.

Additional treatment with YERVOY (re-induction therapy) was offered to patients who developed progressive disease (PD) after initial clinical response (partial response [PR] or complete response [CR]) or after stable disease (SD, per the modified WHO criteria) lasting longer than 3 months from the first tumour assessment. 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.

A total of 676 patients were randomized: 137 to the YERVOY monotherapy group, 403 to the YERVOY + gp100 group, and 136 to the gp100 alone group. The majority of patients had received all 4 doses during induction. Thirty-two evaluable patients received a re-induction dose: 8 in the YERVOY monotherapy group, 23 in the YERVOY + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across treatment groups. The median age was 57 years. The majority (71-73%) of patients had M1c stage disease and 37-40% of patients had an elevated LDH at baseline. A total of 77 patients had a history of previously treated brain metastases.

The YERVOY-containing regimens demonstrated a statistically significant advantage over the gp100 group in OS. The hazard ratio (HR) for comparison of OS between the YERVOY

monotherapy and gp100 groups was 0.66 (95% CI: 0.51, 0.87; p = 0.0026). This result was consistent with the HR for comparison between the YERVOY + gp100 group and the gp100 group (HR 0.68 [95% CI: 0.55, 0.85]; p = 0.0004).

The observed OS benefit was consistently demonstrated across subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline LDH, age, gender, and the type and number of prior therapies).

Overall survival results are shown in Figure 1. Median and estimated rates of OS at 1 year and 2 years are presented in Table 1.

Figure 1: Overall Survival in Study MDX010-20

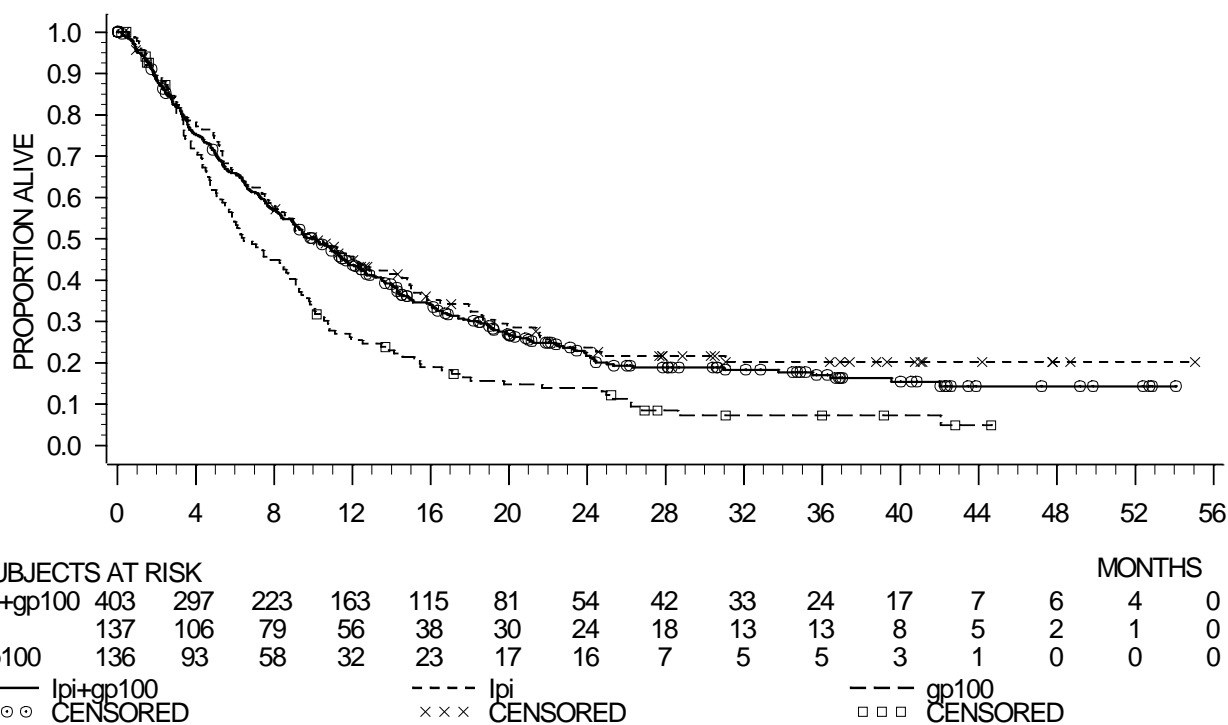


Table 1. Median and estimated rates of OS at 1 year and 2 years.

Table 1: Overall Survival in MDX010-20

	YERVOY 3 mg/kg n= 137	YERVOY 3 mg/kg + gp100 ^a n= 403	gp100 ^a n= 136
Median Months (95% CI)	10 months (8.0, 13.8)	10 months (8.5, 11.5)	6 months (5.5, 8.7)
OS at 1 year % (95% CI)	46% (37.0, 54.1)	44% (38.6, 48.5)	25% (18.1, 32.9)
OS at 2 years% (95% CI)	24% (16.0, 31.5)	22% (17.2, 26.1)	14% (8.0, 20.0)

^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.

In the YERVOY 3 mg/kg monotherapy group, median OS was 22 months and 8 months for patients with SD and those with PD, respectively. At the time of this analysis, medians were not reached for patients with CR or PR.

Efficacy was demonstrated across the primary and secondary endpoints. Additional efficacy results are presented in Table 2.

Table 2: Efficacy of YERVOY in MDX010-20

	YERVOY 3 mg/kg n= 137	YERVOY 3 mg/kg + gp100 ^a n= 403	gp100 ^a n= 136
BORR (up to Week 24) % (95% CI)	10.9% (6.3, 17.4)	5.7% (3.7, 8.4)	1.5% (0.2, 5.2)
YERVOY vs gp100		p= 0.0012	
YERVOY + gp100 vs gp100		p= 0.0433	
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.

Tumour responses were observed as late as 5.5 months from the start of YERVOY therapy.

For patients who required re-induction therapy, the BORR was 38% (3/8 patients) in the YERVOY monotherapy group, 13% (3/23 patients) in the YERVOY + gp100 group, and 0% in the gp100 group. The disease control rate (DCR, defined as CR+PR+SD) was 75% (6/8 patients), 65% (15/23 patients), and 0%, respectively.

The development or maintenance of clinical activity following YERVOY treatment was similar with or without the use of systemic corticosteroids.

Study CA184022

The activity of three doses of YERVOY was investigated in a blinded, randomized Phase 2 study in patients with advanced melanoma. Patients who progressed after or were intolerant to prior therapy were enrolled in the study. A total of 217 patients were randomized to three groups: 0.3 mg/kg (n= 73), 3 mg/kg (n= 72), and 10 mg/kg (n= 72). In this study, some objective responses were observed after initial evidence of tumour burden increase, including new lesions. Clinical response, disease control, and survival were similar regardless of the HLA subtype.

INDICATIONS

YERVOY, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

YERVOY is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions).

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. The most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy and potentially irreversible endocrinopathy.

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 and thyroid functions) should be evaluated at baseline and before each dose.

While most immune-related adverse reactions occurred during the induction period, some immune-related adverse reactions occurred weeks to months after the last dose of YERVOY. Unless an alternate etiology has been identified, diarrhoea, increased stool frequency, bloody stool, liver function test (LFT) elevations, rash, and endocrinopathy must be considered inflammatory and YERVOY-related.

YERVOY should be permanently discontinued for severe immune-mediated adverse reactions and in patients who experience adverse events (Grade 2 protracted, Grade 3 or Grade 4) that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions (see DOSAGE AND ADMINISTRATION).

YERVOY-specific management guidelines for immune-related adverse reactions are described below.

Immune-related gastrointestinal reactions

YERVOY is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in clinical trials (see ADVERSE REACTIONS).

In patients who received YERVOY 3 mg/kg monotherapy in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see Clinical Trials), the median time to onset of severe or fatal (Grade 3-5) immune-related gastrointestinal reactions was 8 weeks (range 5 to 13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution (defined as improvement to mild [Grade 1] or less or to the severity at baseline) occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks).

Patients must be carefully monitored for gastrointestinal signs and symptoms that may be indicative of immune-related colitis or gastrointestinal perforation. Clinical presentation may include diarrhoea, increased frequency of bowel movements, abdominal pain, or haematochezia, with or without fever. Diarrhoea or colitis occurring after initiation of YERVOY therapy must be promptly evaluated to exclude infectious or other alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v3] severity grading classification). Patients with mild to moderate (Grade 1 or 2) diarrhoea (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 therapy. Symptomatic treatment (eg, loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of YERVOY should be withheld, and corticosteroid therapy (eg, prednisone 1 mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, YERVOY may be resumed (see DOSAGE AND ADMINISTRATION).

YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see DOSAGE AND ADMINISTRATION), and high-dose IV corticosteroid therapy should be initiated immediately. (In clinical trials, methylprednisolone 2 mg/kg/day has been used.) Once diarrhoea and other symptoms are controlled, corticosteroid taper should occur over a period of at least 1 month. In clinical trials, rapid tapering (over periods < 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.

The experience from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis is limited. However, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, a single dose of infliximab 5 mg/kg was added unless contraindicated. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected. Refer to the Product Information for infliximab.

Immune-related hepatotoxicity

YERVOY is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials of YERVOY (see ADVERSE REACTIONS).

In patients who received YERVOY 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to severe or fatal (Grade 2-5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. With protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks.

Hepatic transaminase and bilirubin must be evaluated before each dose of YERVOY as early laboratory changes may be indicative of emerging immune-related hepatitis (see DOSAGE AND ADMINISTRATION). Elevations in LFTs may develop in the absence of clinical symptoms. Increases in AST and ALT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, tumour progression, or concomitant medications and monitored until

resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

For patients with elevated AST or ALT in the range of $> 5 \leq 8$ x ULN or total bilirubin in the range of $> 3 \leq 5$ x ULN that is suspected to be related to YERVOY, the scheduled dose of YERVOY should be withheld, and LFTs must be monitored until resolution. After LFT levels improve (AST and ALT ≤ 5 x ULN and total bilirubin ≤ 3 x ULN), YERVOY therapy may be resumed (see DOSAGE AND ADMINISTRATION).

For patients with AST or ALT elevations > 8 x ULN or bilirubin > 5 x ULN that are suspected to be related to YERVOY, treatment must be permanently discontinued (see DOSAGE AND ADMINISTRATION), and systemic high-dose IV corticosteroid therapy (eg, methylprednisolone 2 mg/kg daily or equivalent) should be initiated immediately. In such patients, LFTs must be monitored until normalization. Once symptoms have resolved and LFTs show sustained improvement or return to baseline, corticosteroid taper should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.

For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, mycophenolate mofetil was used in patients without response to corticosteroid therapy, or who had an LFT elevation during corticosteroid tapering that was not responsive to an increase in the dose of corticosteroids. Refer to the Product Information for mycophenolate mofetil.

Immune-related skin adverse reactions

YERVOY is associated with serious skin adverse reactions that may be immune-related. In clinical trials, fatal toxic epidermal necrolysis has been reported (see ADVERSE REACTIONS).

YERVOY-induced rash and pruritus were predominantly mild or moderate (Grade 1 or 2) and responsive to symptomatic therapy. In patients who received YERVOY 3 mg/kg monotherapy in MDX010-20, the median time to onset of moderate to severe or fatal (Grade 2-5) skin adverse reactions was 3 weeks (range 0.9-16 weeks) from start of treatment. With protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

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

YERVOY-induced rash and pruritus should be managed based on severity. Patients with a mild to moderate (Grade 1 or 2) skin adverse reaction may remain on YERVOY therapy with symptomatic treatment (eg, antihistamines). For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids, oral corticosteroid therapy should be initiated (eg, prednisone 1 mg/kg once daily or equivalent).

For patients with a severe (Grade 3) skin adverse reaction, the scheduled dose of YERVOY should be withheld. If initial symptoms improve to mild (Grade 1) or resolve, YERVOY therapy may be resumed (see DOSAGE AND ADMINISTRATION).

YERVOY must be permanently discontinued in patients with a very severe (Grade 4) rash or severe (Grade 3) pruritus (see DOSAGE AND ADMINISTRATION), and systemic high-dose IV corticosteroid therapy (eg, methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled, corticosteroid taper should occur over a period of at least 1 month.

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-related neurological adverse reactions

YERVOY is associated with serious immune-related neurological adverse reactions. In clinical trials, fatal Guillain-Barré syndrome has been reported. Myasthenia gravis-like symptoms have also been reported (see ADVERSE REACTIONS). Patients may present with muscle weakness. Sensory neuropathy may also occur.

Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting > 4 days must be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic syndromes and concomitant medications should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to YERVOY, the scheduled dose should be withheld. If neurologic symptoms resolve to baseline, YERVOY may be resumed (see DOSAGE AND ADMINISTRATION).

YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to YERVOY (see DOSAGE AND ADMINISTRATION). Patients must be treated according to institutional guidelines for management of sensory neuropathy, and intravenous corticosteroids (eg, methylprednisolone 2 mg/kg/day) should be initiated immediately.

Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality (see DOSAGE AND ADMINISTRATION).

Immune-related endocrinopathy

YERVOY can cause inflammation of the endocrine system organs which may be irreversible and require long-term hormone replacement therapy. These events may manifest as hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism (see ADVERSE REACTIONS) and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms must be excluded. Clinical experience with YERVOY-associated endocrinopathy is limited.

In patients who received YERVOY 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to very severe (Grade 2-4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with immunosuppressive therapy and hormone replacement therapy.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of IV corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for presence of sepsis or infections.

If there are signs of adrenal insufficiency but the patient is not in adrenal crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy (eg, dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of YERVOY should be withheld (see DOSAGE AND ADMINISTRATION). It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with YERVOY may be resumed, and corticosteroid taper should occur over a period of at least 1 month.

Other immune-related adverse reactions

The following additional adverse reactions suspected to be immune-related have been reported in patients treated with YERVOY 3 mg/kg monotherapy in MDX010-20: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, hemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with YERVOY 3 mg/kg + gp100 peptide vaccine in MDX010-20 (see ADVERSE REACTIONS).

If severe (Grade 3 or 4), these reactions may require immediate high-dose corticosteroid therapy and discontinuation of YERVOY (see DOSAGE AND ADMINISTRATION). For YERVOY-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

Infusion reaction

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

Patients with autoimmune disease

Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism), including those 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 PHARMACOLOGY) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection.

YERVOY should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In other patients with a history of autoimmune disease, YERVOY should be administered with caution after careful consideration of the potential risk-benefit on an individual basis.

Concurrent administration with vemurafenib

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. Asymptomatic Grade 3 LFT elevations (ALT/AST with or without total bilirubin) were reported in 6 of 10 patients treated with the combination regimen. All were reversible with either interruption or permanent discontinuation of the drugs, and/or treatment with corticosteroids. Based on these data, the concurrent administration of YERVOY and vemurafenib is not recommended outside of a clinical trial. These results do not impact the currently approved use of YERVOY as monotherapy.

HEPATIC IMPAIRMENT

The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild hepatic impairment did not influence the clearance of ipilimumab. No specific dose adjustment is necessary in patients with mild hepatic impairment (see Pharmacokinetics). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see Clinical Trials).

RENAL IMPAIRMENT

The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see Pharmacokinetics).

Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.3 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

EFFECTS ON FERTILITY

Studies to evaluate the effect of ipilimumab on fertility have not been performed. Thus, the effect of YERVOY on male and female fertility is unknown.

USE IN PREGNANCY (Category C)

YERVOY is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

There are no data on the use of ipilimumab in pregnant women. It is not known whether ipilimumab can cause foetal harm when administered to a pregnant woman.

The effects of ipilimumab on prenatal and postnatal development were investigated in a study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through delivery, at exposure (AUC) levels either 3 or 7 times higher than those associated with the clinical dose of 3mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, both ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and infant mortality relative to control animals; these findings were dose-dependent. Additionally, visceral abnormalities were identified in the urogenital system of 2 infants of the 30 mg/kg group. 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 oedema. A no adverse effect level was not identified. Due to the low incidences, the relationship of these malformations to treatment is unclear.

Ipilimumab was detected in the serum of monkey infants at similar levels to their mothers post-partum, likely through *in utero* exposure. Very low levels of ipilimumab were detected in milk. Human IgG1 is known to cross the placental barrier; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

USE IN LACTATION

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 breast milk; however, because human IgG1 is known to be secreted in human breast milk, there is potential for infant exposure to ipilimumab via nursing. A risk to the newborns/infants cannot be excluded. Women who are taking YERVOY should not breast-feed.

PAEDIATRIC USE

The safety and efficacy of YERVOY in children below 18 years have not been established. The use of YERVOY in children or adolescents is not recommended.

GENOTOXICITY AND CARCINOGENICITY

Studies to evaluate the genotoxic and carcinogenic potential of ipilimumab have not been performed.

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, ipilimumab did not have a significant effect on the pharmacokinetics of substrates of CYP1A2, CYP2E1, CYP2C8, and CYP3A4 when coadministered with substrates of these CYP isozymes (dacarbazine or paclitaxel/carboplatin).

Other forms of interaction

Corticosteroids

The use of systemic corticosteroids at baseline, before starting YERVOY, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of YERVOY. However, systemic corticosteroids or other immunosuppressants can be used after starting YERVOY to treat immune-related adverse reactions. The use of systemic corticosteroids after starting YERVOY treatment does not appear to impair the efficacy of YERVOY.

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with YERVOY, patients who require concomitant therapy should be monitored closely.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Because of potential adverse reactions such as fatigue (see ADVERSE REACTIONS), patients should be advised to use caution when driving or operating machinery until they are reasonably certain that YERVOY does not adversely affect them.

PATIENT COUNSELLING INFORMATION

Patients should be advised to report immediately any signs or symptoms suggestive of immune-related events as described in 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.

ADVERSE REACTIONS

YERVOY has been administered to approximately 10,000 patients in a clinical program evaluating its use with various doses and tumor types. Unless otherwise specified, the data described below reflect exposure to YERVOY monotherapy at 3 mg/kg (n= 131) in previously treated patients with advanced melanoma from a Phase 3 study (MDX010-20. See Clinical Trials). Patients received a median of 4 doses (range 1-4).

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

The safety profile of YERVOY 3mg/kg in chemotherapy-naïve patients pooled across Phase 2 and 3 clinical trials (N=75; treated) and in treatment-naïve patients in two retrospective observational studies (N= 273 and N= 157) was similar to that in previously-treated advanced melanoma.

Adverse Events reported in study MDX010-20

In patients who received 3 mg/kg YERVOY monotherapy in MDX010-20, the most frequently reported adverse events ($\geq 10\%$ of patients) were fatigue, diarrhoea, pruritus, rash, decreased appetite, nausea, vomiting, abdominal pain, cough, headache, pyrexia, and insomnia (Table 3). The majority of adverse events were mild to moderate (Grade 1 or 2). YERVOY therapy was discontinued for adverse reactions in 10% of patients.

Adverse events, regardless of causality, reported in $\geq 1\%$ of patients treated with either YERVOY-containing regimen in MDX010-20 are presented in Table 3. This table includes adverse events that occurred at a greater incidence in a YERVOY group than in the gp100 group (before rounding).

These adverse events are presented by system organ class and by frequency.

Table 3: Adverse Events Reported in $\geq 1\%$ of patients treated with YERVOY

System Organ Class/ Preferred Term	Percentage (%) of Patients ^a		
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 ^b n=380	gp100 ^b n=132
Gastrointestinal Disorders			
Diarrhea	33	38	20
Vomiting	24	20	22
Abdominal pain	23	23	23
Colitis	8	6	2
Gastrointestinal haemorrhage	4	6	2
Stomatitis	2	0	1
Dysphagia	2	1	2
Retching	2	1	0
General Disorders and Administration Site Conditions			
Fatigue	42	37	31
Pyrexia	13	21	18
Chills	7	6	5
Injection site reaction	4	50	38
Chest pain	1	2	2
Vaccination site reaction	1	4	4
Skin and Subcutaneous Tissue Disorders			
Pruritus	33	23	11
Rash	30	25	8
Erythema	8	7	5
Vitiligo	3	4	2

Table 3: Adverse Events Reported in $\geq 1\%$ of patients treated with YERVOY

System Organ Class/ Preferred Term	Percentage (%) of Patients ^a		
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 ^b n=380	gp100 ^b n=132
Alopecia	2	3	2
Dry skin	2	3	2
Night Sweats	2	4	3
Dermatitis	2	2	1
Urticaria	1	3	1
Eczema	1	2	0
Skin hypopigmentation	0	1	0
Metabolism and Nutrition Disorders			
Decreased appetite	27	23	22
Hypokalaemia	6	3	2
Hyperglycaemia	4	2	0
Hypoalbuminaemia	3	1	3
Hyponatraemia	2	2	2
Musculoskeletal and Connective Tissue Disorders			
Myalgia	6	7	3
Muscle spasms	2	3	3
Infections and Infestations			
Upper respiratory tract infection	8	5	5
Urinary tract infection	7	3	5
Sepsis	3	1	0
Lower respiratory tract infection	2	3	1
Gastroenteritis	1	2	0
Infectious hepatitis	2	0	0
Oral candidiasis	1	2	2
Cellulitis	0	2	2
Respiratory, Thoracic and Mediastinal Disorders			
Cough	17	16	14
Oropharyngeal pain	2	2	2
Wheezing	2	1	0
Nasal disorder	1	3	1
Sinus congestion	0	1	0
Nervous System Disorders			
Headache	15	18	14

Table 3: Adverse Events Reported in $\geq 1\%$ of patients treated with YERVOY

System Organ Class/ Preferred Term	Percentage (%) of Patients ^a		
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 ^b n=380	gp100 ^b n=132
Lethargy	4	3	2
Tremor	2	1	0
Brain oedema	1	2	1
Cranial neuropathy	1	1	0
Peripheral neuropathy	1	1	1
Aphasia	0	1	1
Vascular Disorders			
Hypotension	8	3	5
Flushing	5	3	1
Hypertension	3	1	0
Haematoma	2	1	2
Venous thrombosis	2	2	1
Thrombosis	1	1	0
Haemorrhage	0	6	1
Lymphoedema	0	3	2
Psychiatric Disorders			
Insomnia	12	9	11
Depression	5	5	5
Anxiety	4	8	8
Decreased libido	2	<1	0
Blood and Lymphatic System Disorders			
Lymphadenopathy	2	1	2
Eosinophilia	2	<1	0
Neutropenia	2	1	2
Thrombocytopenia	1	2	2
Investigations			
Increased blood creatinine	4	1	2
Increased blood bilirubin	2	<1	2
Decreased blood corticotrophin	2	0	0
Increased lipase	1	2	0
Eye Disorders			
Blurred vision	4	4	4
Conjunctivitis	2	2	2
Uveitis	2	<1	1

Table 3: Adverse Events Reported in $\geq 1\%$ of patients treated with YERVOY

System Organ Class/ Preferred Term	Percentage (%) of Patients ^a		
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 ^b n=380	gp100 ^b n=132
Eye pain	1	1	1
Dry eye	0	1	1
Hepatobiliary Disorders			
Abnormal hepatic function	5	3	5
Hepatic failure	2	1	0
Hepatomegaly	2	1	0
Jaundice	0	1	0
Endocrine Disorders			
Hypopituitarism (including hypophysitis)	4	1	0
Hypothyroidism	4	2	2
Adrenal insufficiency	2	1	0
Hyperthyroidism	2	1	0
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)			
Tumour pain	5	4	4
Cancer pain	2	1	1
Cardiac Disorders			
Arrhythmia	3	5	5
Atrial fibrillation	2	1	2
Cardiac failure	2	1	0
Injury, Poisoning and Procedural Complications			
Contusion	2	1	2
Excoriation	2	1	2
Renal and Urinary Disorders			
Renal failure	3	1	2
Haematuria	2	1	2
Immune System Disorders			
Contrast media allergy	2	0	0
Seasonal allergy	2	<1	0

a Incidences presented in this table are based on reports of adverse events regardless of causality.

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

Immune-Related Adverse Reactions in MDX010-20 (Table 4).

Table 4: Immune-Related Adverse Reactions in MDX010-20 (Induction Phase)

	Percentage (%) of Patients		
	YERVOY 3 mg/kg n= 131	YERVOY 3 mg/kg+gp100 ^a n= 380	Gp100 N=132
Any immune-related adverse reactions^b			
Any Grade	60	57	32
Grade 3/4	13	10	3
Gastrointestinal			
Any Grade	28	31	14
Grade 3/4	8	5	1
Colitis	5	3	0
Diarrhoea	5	3	1
Gastrointestinal haemorrhage	0	< 1	0
Intestinal perforation	0	< 1	0
Large intestine perforation	0	1	0
Hepatic			
Any Grade	3	2	4
Grade 3/4	0	1	2
Abnormal hepatic function	0	0	2
Increased ALT	0	1	0
Increased AST	0	< 1	0
Abnormal liver function test	0	< 1	0
Hepatitis	0	< 1	0
Skin			
Any Grade	42	39	17
Grade 3/4	1	2	0
Rash	1	2	0
Dermatitis	0	< 1	0
Erythema	0	< 1	0
Leukocytoclastic vasculitis	0	< 1	0
Pruritus	0	< 1	0
Toxic epidermal necrolysis	0	< 1	0
Neurological			
Any Grade	0	1	0
Grade 3/4	0	< 1	0

Table 4: Immune-Related Adverse Reactions in MDX010-20 (Induction Phase)

	Percentage (%) of Patients		
	YERVOY 3 mg/kg n= 131	YERVOY 3 mg/kg+gp100 ^a n= 380	Gp100 N=132
Meningitis (aseptic)	0	< 1	0
Endocrine			
Any Grade	8	3	2
Grade 3/4	4	1	0
Hypopituitarism	3	1	0
Adrenal insufficiency	0	1	0
Hypogonadism	0	< 1	0
Hypothyroidism	0	< 1	0
Decreased blood corticotrophin	1	0	0
Other organ systems			
Any Grade	4	3	2
Grade 3/4	2	1	1
Glomerulonephritis	1	0	0
Pneumonitis	0	< 1	0
Eosinophilia	0	< 1	0
Hemolytic anaemia	0	< 1	0
Increased lipase	1	1	0
Increased amylase	0	1	1

^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 Includes the following immune-related adverse reactions with fatal outcomes occurring in either YERVOY-containing regimen at a frequency of <1%: gastrointestinal perforation, colitis, hepatic failure, toxic epidermal necrolysis (patient developed Stevens-Johnson syndrome which evolved into toxic epidermal necrolysis), Guillain-Barré syndrome, and multi-organ failure

Adverse reactions observed in Phase 2 studies in patients receiving 3 mg/kg of YERVOY (n=111) were consistent with those in MDX010-20. Rates of immune-related adverse reactions in HLA-A2*0201 positive patients who received YERVOY in MDX010-20 were similar to those observed in the overall clinical program.

Other Adverse Reactions reported in Clinical Trials

In addition, the following adverse reactions were reported in other clinical studies. These additional adverse reactions occurred at a frequency of <1% unless otherwise noted: large intestinal ulcer, oesophagitis, ileus, Myasthenia gravis-like syndrome, erythema multiforme, blepharitis, psoriasis, paraneoplastic syndrome, lymphopenia (1%), leucopenia, thyroiditis, hypoparathyroidism, peripheral sensory neuropathy (2%), dizziness (2%), syncope, myoclonus, vitreous haemorrhage,

reduced visual acuity, foreign body sensation in eyes, hot flush (1%), orthostatic hypotension, pulmonary oedema, allergic rhinitis, constipation (4%), gastroesophageal reflux disease (1%), gastrointestinal perforation, diverticulitis, gastric ulcer, proctitis, skin exfoliation, palmer-plantar erythrodysesthesia syndrome, amenorrhoea, asthenia (3%), pain (3%), weight decrease (4%), increased blood thyroid stimulating hormone, decreased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood testosterone, decreased blood gonadotrophin, decreased thyroxine, cytokine release syndrome and hair colour changes.

Serious Adverse Reactions Reported in Other Clinical Trials

The following serious adverse reactions were also reported in patients with advanced melanoma treated with YERVOY in clinical studies (regardless of dose or regimen). Adverse reactions presented elsewhere in the ADVERSE REACTIONS section are excluded.

Infections and infestations

Uncommon: septic shock

Rare: respiratory tract infection

Blood and lymphatic system disorders

Uncommon: anaemia

Rare: polycythemia

Immune System Disorders

Uncommon: infusion related reaction

Rare: hypersensitivity, sarcoidosis

Very Rare: anaphylactic reaction (shock)

Endocrine disorders

Rare: secondary adrenocortical insufficiency, hyperpituitarism, autoimmune thyroiditis

Metabolism and nutrition disorders

Common: dehydration

Uncommon: hypophosphatemia,

Rare: alkalosis, tumour lysis syndrome

Psychiatric disorders

Rare: confusional state, mental status change

Nervous system disorders

Uncommon: ataxia, dysarthria.

Rare: Guillain-Barré syndrome, meningism, autoimmune central neuropathy (encephalitis)

Eye disorders

Rare: episcleritis, scleritis, iritis, eye oedema, ocular myositis

Ear and labyrinth disorders

Rare: neurosensory hypoacusis

Cardiac disorders

Rare: myocarditis, cardiomyopathy, pericardial effusion (pericarditis)

Vascular disorders

Rare: angiopathy, peripheral ischemia, vasculitis, temporal arteritis, Raynaud's phenomenon,

Respiratory, thoracic and mediastinal disorders

Uncommon: lung infiltration,

Rare: dyspnoea, acute respiratory distress syndrome, respiratory failure

Gastrointestinal disorders

Uncommon: enterocolitis, nausea, pancreatitis (autoimmune), peritonitis (infectious), mucosal inflammation

Hepatobiliary disorders

Uncommon: autoimmune hepatitis

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia, musculoskeletal pain, arthritis

Rare: polymyalgia rheumatica, myositis, polymyositis

Renal and urinary disorders

Uncommon: haematuria

Rare: autoimmune nephritis, proteinuria, renal tubular acidosis

General disorders and administration site conditions

Common: influenza-like illness (symptoms)

Uncommon: multi-organ failure, oedema

Rare: systemic inflammatory response syndrome

Investigations

Common: increased blood alkaline phosphatase

Uncommon: increased gamma-glutamyltransferase

Rare: abnormal blood prolactin

DOSAGE AND ADMINISTRATION

Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, should be assessed during treatment with YERVOY (see Tables 5, 6 and PRECAUTIONS).

Assessments of tumour response to YERVOY should be conducted only after completion of induction therapy. The planned induction course should not be discontinued because of the appearance of new lesions or growth of existing lesions.

The recommended dose of YERVOY is 3mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. Where there is any withholding of a dose, YERVOY should be resumed at a dose of 3mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from the first administration, whichever occurs earlier.

Additional treatment with YERVOY (re-induction with 4 doses) may be considered for patients who develop PD after prior CR or PR or after SD lasting longer than 3 months from the first tumour assessment. The recommended re-induction regimen of YERVOY is 3 mg/kg administered IV over a 90-minute period every 3 weeks for a total of 4 doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions.

Withholding doses or permanent discontinuation

Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see PRECAUTIONS). Dose reduction is not recommended.

YERVOY should be permanently discontinued in patients who:

- experience severe or life-threatening adverse reactions (see Table 5).
- experience adverse events (Grade 2 protracted, Grade 3 or Grade 4) that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors.

YERVOY should be discontinued in patients who are unable to complete a full course of YERVOY (4 doses) within 16 weeks from administration of first dose. Any future re-induction in such patients should not be undertaken if they experienced an adverse event fulfilling the criteria for permanent discontinuation described above.

Guidelines for permanent discontinuation or withholding of doses are described in Tables 5 and 6. Detailed guidelines for the management of immune related adverse reactions are described in PRECAUTIONS. Not adhering to the dose withholding and discontinuation guidelines may increase the risk of severe adverse events.

Table 5 When to Permanently Discontinue YERVOY

Permanently discontinue YERVOY in patients with the following adverse reactions. Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related. See PRECAUTIONS for detailed management guidelines.	
Severe or Life-Threatening Adverse Reactions	NCI-CTCAE v3 Grade^a
Gastrointestinal: Severe symptoms (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 haemorrhage, gastrointestinal perforation)	<ul style="list-style-type: none"> ▪ Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in AST, ALT, or total bilirubin or symptoms of hepatotoxicity	<ul style="list-style-type: none"> ▪ AST or ALT > 8 x ULN or ▪ Total bilirubin > 5 x ULN
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis), rash complicated by full thickness dermal ulceration, or severe widespread pruritus interfering with activities of daily living or requiring medical intervention, or necrotic, bullous, or haemorrhagic manifestations	<ul style="list-style-type: none"> ▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy, Gullain-Barre syndrome, myasthenia gravis	<ul style="list-style-type: none"> ▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems^b: Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis). Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy	<ul style="list-style-type: none"> ▪ ≥ Grade 3 immune-related reactions^c ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy
Adverse reactions that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors.	<ul style="list-style-type: none"> ▪ Grade 2 protracted, Grade 3 or Grade 4 adverse reactions of any kind

^a Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).

^b Any other organ system adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. 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.
ULN = upper limit of normal

Withholding Dose

Withhold YERVOY dose in patients with the following immune-related adverse reactions described in Table 6.

YERVOY should be administered 3-weekly either for all 4 doses OR be completed within 16 weeks from the first dose, whichever occurs earlier. Detailed guidelines for the management of immune related adverse reactions are described in PRECAUTIONS. Not adhering to the dose withholding guidelines may increase the risk of severe adverse events.

Table 6 When to Withhold Dose of YERVOY

Withhold YERVOY dose^a in patients with the following immune-related adverse reactions. See PRECAUTIONS for detailed management guidelines.	
Mild to Moderate Adverse Reactions	Action
<p>Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs</p> <p>Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels</p> <p>Skin: Moderate to severe (Grade 3)^b skin rash or widespread/intense pruritus regardless of etiology</p> <p>Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy</p> <p>Neurological: Moderate (Grade 2)^b unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)</p> <p>Other moderate adverse reactions^c</p>	<ol style="list-style-type: none"> 1. Withhold YERVOY dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs, resume therapy.^d 3. If resolution has not occurred, continue to withhold doses until resolution then resume treatment.^d 4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 (or baseline) does not occur.

^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 3.0 (NCI-CTCAE v3).
^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 of YERVOY should be based on severity.

- ^d Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.
ULN = upper limit of normal

SPECIAL POPULATIONS

Paediatric patients

The safety and efficacy of YERVOY in children below 18 years have not been established. No data are available. The use of YERVOY in children or adolescents is not recommended until further data become available.

Elderly patients.

No overall differences in safety or efficacy were reported between the elderly (≥ 65 years) and younger patients (< 65 years). No specific dose adjustment is necessary in this population.

Renal impairment.

The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see PHARMACOKINETICS).

Hepatic impairment.

The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild hepatic impairment (see Pharmacokinetics). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see Clinical Trials).

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Ipilimumab solutions must not be administered as an IV push or bolus injection. 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% glucose injection at the end of infusion.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. YERVOY should not be infused concomitantly in the same IV line with other medicinal products.

YERVOY may be used for IV 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% glucose injection solution to a concentration ranging from 4 mg/ml to 1 mg/ml. An in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm or 1.2 μm) must be used for IV administration. Care must be taken to ensure aseptic handling when preparing the infusion.

Determine the number of vials of YERVOY needed (see DOSAGE AND ADMINISTRATION).

The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of YERVOY concentrate may be needed to give the total dose for the patient. Each 10 ml vial of YERVOY concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab.

The total ipilimumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
The volume of YERVOY concentrate to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Allow the vials to stand at room temperature for approximately 5 minutes. Withdraw the required volume of ipilimumab solution (5 mg/ml) using an appropriate sterile syringe and transfer into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).

Ipilimumab solution is compatible with:

- Glass, polyvinyl chloride (PVC) and non-PVC bags.
- PVC IV extension/administration sets.
- Polyethersulfone (0.2 µm and 1.2 µm) and nylon (0.2 µm) in-line filters.

EACH VIAL OF YERVOY® IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

Any unused medicinal product or waste material should be discarded in accordance with local requirements.

Prior to administration, the ipilimumab should be inspected visually for particulate matter and discolouration. The vial should be discarded if solution is cloudy, there is pronounced discolouration (solution may have pale yellow colour), or there is foreign particulate matter.

OVERDOSE

The maximum tolerated dose of YERVOY has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

In case of overdosage, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

In the event of an overdose or poisoning contact the Poisons Information Centre on 131126.

PRESENTATION

50 mg of ipilimumab in 10 mL of concentrate solution for infusion is supplied in a vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium light blue “flip off” seal

200 mg of ipilimumab in 40 mL of concentrate solution for infusion is supplied in a vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium purple “flip off” seal

Pack of 1 vial containing 10 mL.

Pack of 1 vial containing 40 mL.

Not all pack sizes may be marketed.

STORAGE AND STABILITY CONDITIONS:

Unopen vial: 36 months

Solution for infusion: The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/mL and 4 mg/mL) has been demonstrated for 24 hours at 25°C and 2°C to 8°C. However, to reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

This medicinal product does not contain any preservatives.

Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

POISONS SCHEDULE: S4

NAME AND ADDRESS OF THE SPONSOR:

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.

AUSTRALIAN REGISTRATION NUMBERS:

YERVOY (ipilimumab): 50mg of ipilimumab in 10mL of concentrate solution for infusion (5mg in 1mL). Pack of one vial containing 10mL. AUST R 174319

YERVOY (ipilimumab): 200mg of ipilimumab in 40mL of concentrate solution for infusion (5mg in 1mL). Pack of one vial containing 40mL. AUST R 174322

DATE OF TGA APPROVAL: 27 June 2011

DATE OF MOST RECENT AMENDMENT: 9 April 2015