WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS See full prescribing information for complete boxed warning. YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

YERVOY® 5 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 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.

Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody (IgG1κ) produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipients with known effect:

Each ml of concentrate contains 0,1 mmol sodium, which is 2,30 mg sodium.

Contains sugar (mannitol): 107 mg per 10 ml vial and 426 mg per 40 ml vial

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Infusion

YERVOY is a sterile, preservative-free, clear to slightly opalescent, colourless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent to white particulates and has a pH of 7,0 and an osmolarity of 260-300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YERVOY is indicated for the treatment of previously treated unresectable or metastatic melanoma in adults.

4.2 Posology and method of administration

YERVOY should be administered under the supervision of healthcare professionals experienced in the treatment of cancer.

Posology:

Adults:

The recommended induction regimen of **YERVOY** is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessment of tumour response to **YERVOY** should be conducted only after completion of induction therapy.

Additional treatment with **YERVOY** (re-treatment with four doses) may be considered for patients who develop progressive disease (PD) after prior complete or partial response (CR or PR) or after stable disease (SD) lasting longer than 3 months from the first tumour assessment.

The recommended re-treatment regimen of **YERVOY** is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions.

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, must be assessed during treatment with **YERVOY** (see Tables 1A, 1B, and section 4.4).

Paediatric patients:

The safety and efficacy of **YERVOY** in paediatric patients have not been established.

Permanent discontinuation of treatment or omission of doses:

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 section 4.4). Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Guidelines for permanent discontinuation or omission of scheduled doses are described in **Tables 1A** and **1B**.

Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1A: 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 section 4.4 for detailed management guidelines).	
Severe or life-threatening adverse reactions	**NCI-CTCAE v4 Grade[a]**
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	• Grade 3 or 4 diarrhoea or colitis
Hepatic: 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: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	• Grade 4 rash or Grade 3 pruritus
Neurologic:	Grade 3 or 4 motor or sensory neuropathy

New onset or worsening severe motor or sensory neuropathy **Other organ systems[b]:** (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, diabetes, transverse myelitis)	• ≥ Grade 3 immune-related reactions[c] • ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy • Grade 4 diabetes • All grades of immune-related transverse myelitis

[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 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.

Table 1B: When to withhold dose of YERVOY	
Withhold YERVOY dose[a] in patients with the following immune-related adverse reactions. See section 4.4 for detailed management guidelines.	
Mild to moderate immune-related adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea 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. 2. If resolution occurs, resume therapy[d].
Hepatic:	

Grade 2[b] elevation in AST, ALT, or total bilirubin	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 return to baseline does not occur.
Skin: Moderate to severe (Grade 3)[b] skin rash or (Grade 2) widespread/intense pruritus regardless of aetiology	
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 Grade 3 diabetes	
Neurological: 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. 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.

Special populations

Paediatric population

The safety and efficacy of **YERVOY** in the paediatric population have not been established. Very limited data are available.

Elderly

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years).

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 section 5.2).

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 section 5.2). **YERVOY** must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.

Method of administration

YERVOY is for intravenous use. The recommended infusion period is 90 minutes.

YERVOY can be used for intravenous administration without dilution or may be diluted in sodium chloride 9 mg/ml (0,9 %) solution for injection or glucose 50 mg/ml (5 %) solution for injection to concentrations between 1 and 4 mg/ml.

YERVOY must not be administered as an intravenous push or bolus injection.

For instructions on the preparation and handling of the medicine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Immune-related reactions

YERVOY is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine or other organ systems.

While most immune-related adverse reactions occurred during the induction period, onset months after the last dose of YERVOY has also been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, liver function test (LFT) elevations, rash and endocrinopathy must be considered inflammatory and YERVOY-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

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

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, **YERVOY** should be withheld and

corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction that occurs as a consequence of combination therapy, a taper of at least 1-month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction.

Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Immune-related gastrointestinal reactions

YERVOY is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported (see section 4.8).

Patients must be 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. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration. Post-marketing cases of cytomegalovirus (CMV) infection/reactivation have been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate aetiologies.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per NCI-CTCAE v4 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 (e.g. abdominal pain or blood in stools) may remain on **YERVOY** therapy. Symptomatic treatment (e.g. 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 (e.g. 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 section 4.2).

- **YERVOY** must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately. 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. Addition of an alternative immunosuppressive medicine to the corticosteroid regimen should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including Cytomegalovirus (CMV) infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial and parasitic aetiology). 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 (see the prescribing information for infliximab).

Immune-related hepatotoxicity

YERVOY is associated with serious immune-related hepatotoxicity, including fatal hepatic failure (see section 4.8).

In patients who received **YERVOY** 3 mg/kg monotherapy in MDX010-20, the 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, the 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 section 4.2). Elevations in LFTs may develop in the absence of clinical symptoms.

Increases in aspartate transaminase (AST) and alanine transaminase (ALT) or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, tumour progression, or concomitant medication,

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 Grade 2 transaminase or total bilirubin elevation, the scheduled dose of **YERVOY** should be withheld, and LFTs must be monitored until resolution. Upon improvement, **YERVOY** may be resumed (see section 4.2).
- For patients with Grade 3 or 4 transaminase or total bilirubin elevation, treatment must be permanently discontinued (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg daily or equivalent) should be initiated immediately. In such patients, LFTs must be monitored until normalisation. Once symptoms have resolved and LFTs show sustained improvement or return to baseline, the initiation of corticosteroid taper should be based on clinical judgment. Tapering 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 medicine 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 (see the prescribing information for mycophenolate mofetil).

Immune-related skin adverse reactions

YERVOY is associated with serious skin adverse reactions that may be immune-related. Rare cases of toxic epidermal necrolysis (TEN) (including Steven Johnson Syndrome) have been observed, some with fatal outcome. Rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported in clinical trials and during post-marketing use (see section 4.8).

DRESS presents as a rash with eosinophilia associated with one or more of the following features: fever, lymphadenopathy, facial oedema, and internal organ involvement (hepatic, renal, pulmonary).

DRESS may be characterized by a long latency (two to eight weeks) between medicine exposure and disease onset.

Hypersensitivity skin reactions have been reported following a switch from **YERVOY** to vemurafenib or PD1-inhibitors or when **YERVOY** was combined with one of these medicines.

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 %) after discontinuing **YERVOY**, with a median time from onset to resolution of 5 weeks (range 0,6 to 29 weeks).

YERVOY-induced rash and pruritus should be managed based on severity:

- Patients with a mild to moderate (Grade 1 or 2) rash may remain on **YERVOY** therapy with symptomatic treatment (e.g. 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 (e.g. prednisone 1 mg/kg once daily or equivalent).
- For patients with a severe (Grade 3) rash, the scheduled dose of **YERVOY** should be withheld. If initial symptoms improve to mild (Grade 1) or resolve, **YERVOY** therapy may be resumed (see section 4.2).
- **YERVOY** must be permanently discontinued in patients with a very severe (Grade 4) rash or severe (Grade 3) pruritus (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled,

initiation of corticosteroid taper should be based on clinical judgment. Tapering 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 prior cancer immune stimulatory therapy.

Immune-related neurological adverse reactions

YERVOY is associated with serious immune-related neurological adverse reactions. Fatal Guillain-Barré syndrome has been reported in clinical trials.

Myasthenia gravis-like symptoms have also been reported (see section 4.8). Patients may present with muscle weakness. Sensory neuropathy may also occur.

Post-marketing cases of transverse myelitis have been reported during treatment with **YERVOY**. Patients should be monitored for signs and symptoms suggestive of myelitis.

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 medication 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, the patient may resume **YERVOY** (see section 4.2).
- **YERVOY** must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to **YERVOY** (see section 4.2). Patients must be treated according to institutional guidelines for management of sensory neuropathy, and intravenous corticosteroids (e.g. 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 section 4.2).

Immune-related endocrinopathy

YERVOY can cause inflammation of the endocrine system organs, manifesting as hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism, Type 1 diabetes mellitus and diabetic ketoacidosis (see sections 4.2 and 4.8), 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, behavioural changes, electrolyte disturbances, and hypotension. Adrenal crisis (acute adrenal failure) as a cause of the patient's symptoms must be excluded. Clinical experience with **YERVOY**-associated endocrinopathy is limited.

For 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 intravenous corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for the 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 (e.g. 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 section 4.2). 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.

For symptomatic diabetes, **YERVOY** should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. **YERVOY** must be permanently discontinued for life-threatening diabetes.

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

Other immune-related adverse reactions

The following 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, haemolytic 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. Cases of Vogt-Koyanagi-Harada syndrome and serous retinal detachment have been reported post-marketing (see section 4.8). In addition, cases of severe graft-versus-host disease (GVHD), some with fatal outcome, have been reported in the post-marketing setting in patients who had undergone prior allogeneic stem cell transplant (see section 4.8). The benefit of treatment with **YERVOY** versus the possible risk should be considered in these patients.

If severe (Grade 3 or 4), these reactions may require immediate systemic high-dose corticosteroid therapy and discontinuation of **YERVOY** (see section 4.2). For **YERVOY**-related uveitis, iritis, serous retinal detachment or episcleritis, topical corticosteroid eye drops should be considered as medically indicated. Transient vision loss has been reported in patients with **YERVOY**-related ocular inflammations.

YERVOY *as monotherapy or in combination with a PD-1 or PD-L1 inhibitor*

Haemophagocytic lymphohistiocytosis (HLH) has been reported in relation to **YERVOY** therapy. The adverse reaction mostly responded well to treatment with corticosteroids. In most reported cases prior or concurrent therapy with a PD-1 or PD-L1 inhibitor has occurred. Caution should be taken when **YERVOY** is given following or in combination with a PD-1 or PD-L1 inhibitor.

Infusion reaction

Severe infusion reactions have been reported in clinical trials of **YERVOY** (see section 4.8). In case of a severe or life-threatening 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 and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Disease specific precautions

Immune-related pneumonitis

Infections and disease-related aetiologies should be ruled out in patients with signs and symptoms suggestive of immune-related pneumonitis and patients must be monitored for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes.

Mycobacterium tuberculosis infection

The monitoring and screening of patients for Mycobacterium tuberculosis infection and reactivation is recommended.

BCG infection

The monitoring of events of systemic BCG infection in patients with urothelial cancer, previously treated with BCG for immunotherapy is recommended.

Melanoma

Patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the pivotal clinical trials.

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 trials. **YERVOY** is a T-cell potentiator that enables the immune response (see section 5.1) 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.

Patients on controlled sodium diet

Each ml of this medicine 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 due to increased toxicity.

Sequential administration with vemurafenib

In a Phase 2 trial, the sequential treatment with vemurafenib followed by 10 mg/kg **YERVOY** in patients with BRAF-mutated metastatic melanoma showed a higher incidence of Grade 3+ skin adverse reactions than with **YERVOY** alone. Caution should be used when **YERVOY** is administered following prior vemurafenib.

Paediatric population

Limited, but no long-term, safety data is available on the use of **YERVOY** in adolescents 12 years of age and older.

Only very limited data are available in children younger than 12 years of age.

The safety and efficacy of **YERVOY** in paediatric patients have not been established.

4.5 Interaction with other medicines and other forms of interaction

YERVOY (ipilimumab) is a human monoclonal antibody that is not metabolised by cytochrome P450 enzymes (CYPs) or other metabolising enzymes.

A drug-interaction study in adults of ipilimumab administered alone and in combination with chemotherapy (dacarbazine or paclitaxel/carboplatin) was conducted evaluating interaction with CYP isozymes (particularly CYP1A2, CYP2E1, CYP2C8, and CYP3A4) in patients with treatment-naïve advanced melanoma. No clinically relevant pharmacokinetic drug-drug interaction was observed between **YERVOY** and paclitaxel/ carboplatin, dacarbazine or its metabolite, 5-aminoimidazole-4-carboxamide (AIC).

Other forms of interactions

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** (see section 4.8), patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

Pregnancy

There are no data on the use of **YERVOY** in pregnant women. Animal reproduction studies have shown reproductive toxicity (see section 5.3). Human IgG1 crosses the placental barrier. The potential risk of treatment to the developing foetus is unknown.

YERVOY should not be used during pregnancy. Women of childbearing potential should use highly effective contraception.

Lactation

Ipilimumab has been shown to be present at very low levels in milk from cynomolgus monkeys treated during pregnancy. It is unknown whether ipilimumab is secreted in human milk. Secretion of IgGs in human milk is generally limited and IgGs have a low oral bioavailability. Significant systemic exposure of the infant is not

expected and no effects on the breastfed newborn/infant are anticipated. However, because of the potential for adverse reactions in nursing infants, **YERVOY** should not be used in women breastfeeding their infants.

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

4.7 Effects on ability to drive and use machines

YERVOY has minor influence on the ability to drive and use machines.

Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that **YERVOY** does not adversely affect them.

4.8 Undesirable effects

Summary of safety profile

YERVOY has been administered to approximately 10 000 patients in a clinical program evaluating its use with various doses and tumour types. Unless otherwise specified, the data below reflect exposure to **YERVOY** at 3 mg/kg in clinical trials of melanoma. In the Phase 3 study MDX010-20, 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. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of **YERVOY** (see section 4.4 for management of immune-related adverse reactions).

In patients who received 3 mg/kg **YERVOY** monotherapy in MDX010-20, the most frequently reported adverse reactions (≥ 10 % of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased

appetite, and abdominal pain. The majority were mild to moderate (Grade 1 or 2). **YERVOY** therapy was discontinued for adverse reactions in 10 % of patients.

Tabulated list of adverse reactions

Adverse reactions reported in patients with advanced melanoma who were treated with **YERVOY** 3 mg/kg in clinical trials (n= 767) and from post-marketing surveillance are presented. These reactions are presented by system organ class and by frequency.

Frequencies are defined as:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from available post-marketing data).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. 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.

Adverse reactions in patients with advanced melanoma treated with YERVOY 3 mg/kg [a]

Infections and infestations	
Common	sepsis[b], urinary tract infection, respiratory tract infection
Uncommon	septic shock[b], pneumonia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopenia, thrombocytopenia, neutropenia
Uncommon	haemolytic anaemia[b], eosinophilia
Not known	haemophagocytic lymphohistiocytosis (HLH)[e]

Immune system disorders	
Uncommon	hypersensitivity
Very rare	anaphylactic reaction (shock)
Not known	solid organ transplant rejection[e]
Endocrine disorders	
Common	hypopituitarism (including hypophysitis)[c], hypothyroidism[c]
Uncommon	adrenal insufficiency[c], secondary adrenocortical insufficiency[d], hyperthyroidism[c], hypogonadism
Rare	autoimmune thyroiditis[d], thyroiditis[d]
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalaemia, weight decreased, hyponatraemia
Uncommon	alkalosis, hypophosphataemia, tumour lysis syndrome, hypocalcaemia[d]
Rare	type 1 diabetes mellitus (including diabetic ketoacidosis)[h]
Psychiatric disorders	
Common	confusional state, depression
Uncommon	mental status changes, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy, cranial neuropathy, brain oedema, peripheral neuropathy
Uncommon	Guillain-Barré syndrome[b,c], meningitis (aseptic), autoimmune central neuropathy (encephalitis)[d], syncope, ataxia, tremor, myoclonus, dysarthria
Rare	myasthenia gravis[d]
Not known	myelitis (transverse myelitis)[e]
Eye disorders	

Common	blurred vision, eye pain
Uncommon	uveitis[c], vitreous haemorrhage, iritis[c], eye oedema[d], blepharitis[d], reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Rare	Vogt-Koyanagi-Harada syndrome[e], serous retinal detachment
Cardiac disorders	
Common	dysrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy[b], peripheral ischaemia, orthostatic hypotension
Rare	temporal arteritis[d]
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, cough, allergic rhinitis
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis
Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea, constipation, abdominal pain
Common	gastrointestinal haemorrhage, colitis[b,c], gastroesophageal reflux disease, mucosal inflammation[d], gastroenteritis, stomatitis
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c], peritonitis (infectious)[b], diverticulitis, pancreatitis (autoimmune), enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus[d], proctitis[d]
Rare	coeliac disease
Hepatobiliary disorders	
Common	abnormal hepatic function
Uncommon	hepatic failure[b,c], hepatitis, hepatomegaly, jaundice

Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus[c]
Common	dermatitis, erythema, vitiligo, urticaria, eczema[d], alopecia, night sweats, dry skin
Uncommon	toxic epidermal necrolysis (including Stevens Johnson syndrome)[b,c], leukocytoclastic vasculitis, skin exfoliation, hair colour changes[d]
Rare	erythema multiforme[d], psoriasis[d], Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)[d]
Not known	pemphigoid
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[f]
Common	arthralgia, myalgia, muscle spasms, arthritis
Uncommon	polymyalgia rheumatica, myositis[d], muscular weakness[d]
Rare	polymyositis[d]
Renal and urinary disorders	
Common	renal failure[b]
Uncommon	glomerulonephritis[c], autoimmune nephritis[d], renal tubular acidosis, haematuria[d], cystitis noninfective[g], proteinuria[d]
Reproductive system and breast disorders	
Uncommon	amenorrhoea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia, oedema, pain
Common	chills, asthenia, influenza-like illness (symptoms)[d]
Uncommon	multi-organ failure[b,c], systemic inflammatory response syndrome[d], infusion related reaction
Investigations	

Common	increased alanine aminotransferase[c], increased aspartate aminotransferase[c], increased blood bilirubin, increased blood alkaline phosphatase[d], increased lipase[c]
Uncommon	increased gamma-glutamyltransferase[d], increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotropin, increased blood amylase[c], positive antinuclear antibody[d], decreased blood testosterone
Rare	decreased blood thyroid stimulating hormone[d], decreased thyroxine[d], abnormal blood prolactin[d]

[a] Frequencies are based on pooled data from 9 clinical trials investigating the **YERVOY** 3 mg/kg dose in melanoma.

[b] Including fatal outcome.

[c] Additional information about these potentially inflammatory adverse reactions is provided in "Description of selected adverse reactions" and section 4.4. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.

[d] Data outside the 9 completed clinical trials in melanoma were included in frequency determinations.

[e] Post-marketing event (also see section 4.4)

[f] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain

[g] Reported in clinical trials and in the post-marketing setting

[h] Type 1 diabetes mellitus that may be associated with diabetic ketoacidosis

Additional adverse reactions not listed above have been reported in patients who received other doses (either < or > 3 mg/kg) of **YERVOY** in clinical trials of melanoma. These additional reactions occurred at a frequency of < 1 % unless otherwise noted: meningism, myocarditis, pericardial effusion, cardiomyopathy, autoimmune

hepatitis, erythema nodosum, autoimmune pancreatitis, hyperpituitarism, hypoparathyroidism, infectious peritonitis, episcleritis, scleritis, Raynaud's phenomenon, palmar-plantar erythrodysaesthesia syndrome, cytokine release syndrome, sarcoidosis, decreased blood gonadotrophin, leukopenia, polycythaemia, lymphocytosis, ocular myositis, and neurosensory hypoacusis.

Description of selected adverse reactions

Except where noted, data for the following selected adverse reactions are based on patients who received either **YERVOY** 3 mg/kg monotherapy (n = 131) or **YERVOY** 3 mg/kg in combination with gp100 (n = 380) in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20).

Immune-related gastrointestinal reactions

YERVOY is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in < 1 % of patients who received **YERVOY** 3 mg/kg in combination with gp100.

In the **YERVOY** 3 mg/kg monotherapy group, diarrhoea and colitis of any severity were reported in 27 % and 8 %, respectively. The frequency of severe (Grade 3 or 4) diarrhoea and severe (Grade 3 or 4) colitis was 5 % each.

The median time to onset of severe or fatal (Grade 3 to 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 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). In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration.

Immune-related hepatotoxicity

YERVOY is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in < 1 % of patients who received **YERVOY** 3 mg/kg monotherapy.

Increases in AST and ALT of any severity were reported in 1 % and 2 % of patients, respectively. There were no reports of severe (Grade 3 or 4) AST or ALT elevation. Time to onset of moderate to severe or fatal (Grade 2 to 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. In clinical trials, liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

In patients receiving **YERVOY** at a higher than recommended dose in combination with dacarbazine, immune-related hepatotoxicity occurred more frequently than in patients receiving **YERVOY** 3 mg/kg monotherapy.

Immune-related skin adverse reactions

YERVOY is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis (including SJS) has been reported in < 1 % of patients who received **YERVOY** in combination with gp100. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been rarely reported with **YERVOY** in clinical studies and during post-marketing use. Incidental cases of pemphigoid have been reported during post-marketing use.

In the **YERVOY** 3 mg/kg monotherapy group, rash and pruritus of any severity were each reported in 26 % of patients. **YERVOY**-induced rash and pruritus were predominantly mild (Grade 1) or moderate (Grade 2) and responsive to symptomatic therapy. The median time to onset of moderate to severe or fatal (Grade 2 to 5) skin adverse reactions was 3 weeks from start of treatment (range 0,9 to 16 weeks). 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).

Immune-related neurological reactions

YERVOY is associated with serious immune-related neurological reactions. Fatal Guillain-Barré syndrome has been reported in < 1 % of patients who received **YERVOY** 3 mg/kg in combination with gp100. Myasthenia gravis-like symptoms have also been reported in < 1 % of patients who received higher doses of **YERVOY** in clinical trials.

Immune-related endocrinopathy

In the **YERVOY** 3 mg/kg monotherapy group, hypopituitarism of any severity was reported in 4 % of patients. Adrenal insufficiency, hyperthyroidism, and hypothyroidism of any severity were each reported in 2 % of patients.

The frequency of severe (Grade 3 or 4) hypopituitarism was reported in 3 % of patients. There were no reports of severe (Grade 3 or 4) adrenal insufficiency, hyperthyroidism, or hypothyroidism. Time to onset of moderate to very severe (Grade 2 to 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 hormone replacement therapy.

Immunogenicity

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected

adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 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 overdose, side effects will be exacerbated and exaggerated. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC11

Pharmacological classification: A 30.1 Antibodies

Mechanism of action

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab is a T-cell potentiator that specifically blocks the inhibitory signal of CTLA-4, resulting in T-cell activation, proliferation and lymphocyte infiltration into tumours, leading to tumour cell death. The mechanism of action of ipilimumab is indirect, through enhancing T-cell mediated immune response.

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period.

In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA-DR^+ $CD4^+$ and $CD8^+$ T cells was observed after treatment with ipilimumab, 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 ipilimumab.

5.2 Pharmacokinetic properties

The pharmacokinetics of ipilimumab were studied in 785 patients with advanced melanoma who received induction doses ranging from 0,3 to 10 mg/kg administered once every 3 weeks for 4 doses. C_{max}, C_{min} and AUC of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index 1,5 fold or less. Ipilimumab steady-state was reached by the third dose. Based on 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 Cmin achieved at steady-state with a 3 mg/kg induction regimen was 19,4 µg/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 or dacarbazine, performance status, HLA-A2*0201 status, mild hepatic impairment, renal impairment, immunogenicity, and previous 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 was independent of prior systemic anti-cancer therapy and increased with higher ipilimumab Cminss plasma concentrations.

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild and moderate renal impairment did not influence the clearance of ipilimumab. Clinical and pharmacokinetic data with pre-existing severe renal impairment are limited; the potential need for dose adjustment cannot be determined.

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. Clinical and pharmacokinetic data with pre-existing moderate hepatic impairment are limited; the potential need for dose adjustment cannot be determined. No patients with pre-existing severe hepatic impairment were identified in clinical studies.

Paediatric patients:

The safety and efficacy of **YERVOY** in paediatric patients have not been established.

5.3 Preclinical safety data

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently (~3 %) and included colitis (which resulted in a single

fatality), dermatitis, and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate). A decrease in the weight of the thyroid and testes was seen in unknown.

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 similar to or higher than those associated with the clinical dose of 3 mg/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, developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed *in utero* to ipilimumab. 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. The relationship of these malformations to treatment is unclear.

Studies to evaluate the mutagenic and carcinogenic potential of ipilimumab have not been performed. Fertility studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tris 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

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

Unopened vial

3 years

After opening

From a microbiological point of view, once opened, the medicine should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 and 4 mg/ml) has been demonstrated for 24 hours at 25 °C and 2 °C to 8 °C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours in a refrigerator (2 °C to 8 °C) or at room temperature (25 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

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

Do not freeze.

For storage conditions after first opening or dilution of the medicine, see section 6.3.

For single use only. Discard any unused portion.

6.5 Nature and contents of container

10 ml of 5 mg/ml sterile concentrate in a clear, colourless vial (Type I glass) with a grey stopper (coated butyl rubber) and a light blue flip-off seal (aluminium). Pack size of 1.

OR

40 ml of 5 mg/ml sterile concentrate in a clear, colourless vial (Type I glass) with a grey stopper (coated butyl rubber) and a purple flip-off seal (aluminium). Pack size of 1.

6.6 Special precautions for disposal

PREPARE INFUSION USING ASEPTIC TECHNIQUE.

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose:

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).

Preparing the infusion:

Take care to ensure aseptic handling when you prepare the infusion.

YERVOY can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe;

or

- after diluting to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the **YERVOY** concentrate, you can use either:
  - sodium chloride 9 mg/ml (0,9 %) solution for injection; or
  - 50 mg/ml (5 %) glucose solution for injection

STEP 1

- Allow the appropriate number of vials of **YERVOY** to stand at room temperature for approximately 5 minutes.
- Inspect the **YERVOY** concentrate for particulate matter or discoloration. **YERVOY** concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of **YERVOY** concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous bag (PVC or non-PVC).
- If applicable, dilute with the required volume of sodium chloride 9 mg/ml (0,9 %) solution for injection or 50 mg/ml (5 %) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/ml (0,9 %) solution for injection or 50 mg/ml (5 %) glucose solution for injection. Gently mix the infusion by manual rotation.

Administration

The **YERVOY** infusion must not be administered as an intravenous push or bolus injection.

Administer the **YERVOY** infusion intravenously over a period of 90 minutes.

The **YERVOY** infusion should not be infused at the same time in the same intravenous line with other medicines.

Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0,2 µm to 1,2 µm).

The **YERVOY** infusion is compatible with:

- Glass, polyvinyl chloride (PVC) and non-PVC intravenous bags
- PVC intravenous extension/administration sets
- Polyethersulfone (0,2 µm to 1,2 µm) and nylon (0,2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0,9 %) solution for injection or 50 mg/ml (5 %) glucose solution for injection at the end of the infusion.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd*

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8. REGISTRATION NUMBER

47/30.1/0522

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 October 2014

10. DATE OF REVISION OF THE TEXT

24 July 2025

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