ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) 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 advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

4.2 Posology and method of administration

Treatment must be initiated and supervised by specialist physicians 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. Assessments of tumour response should be conducted only after completion of induction therapy.

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).

Permanent discontinuation of treatment or omission of doses
Management of immune-related adverse reactions may require omission of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy (see section 4.4).

Dose reduction is not recommended. Doses that are omitted due to an adverse reaction must not be replaced.

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 v3 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	▪ 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) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)	▪ ≥ Grade 3 immune-related events[c] ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy

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

[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.

ULN = upper limit of normal

Table 1B When to omit scheduled dose of YERVOY	
Omit YERVOY dose[a] in patients with the following immune-related adverse reactions. See section 4.4 for detailed management guidelines.	
Mild to moderate 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. Omit dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose. 3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule. 4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels	
Skin: Moderate to severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology	
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	
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. Doses that are omitted due to an adverse reaction must not be replaced.

[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. Decision whether to omit a scheduled dose should be based on severity.

ULN = upper limit of normal

Paediatric population

The safety and efficacy of YERVOY in children below 18 years of age have not been established. No data are available. YERVOY should not be used in children below 18 years of age.

Special populations

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

Patients with 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).

Patients with hepatic impairment
The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see section 5.1).

Method of administration

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 handling of the medicinal product 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

Ipilimumab 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 ipilimumab has also been reported. Unless an alternate etiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-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. Ipilimumab-specific management guidelines for immune-related adverse reactions are described below.

Immune-related gastrointestinal reactions

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

In patients who received ipilimumab 3 mg/kg monotherapy in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1), 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 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 ipilimumab 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 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 (e.g. abdominal pain or blood in stools) may remain on ipilimumab. 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 ipilimumab should be omitted 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, ipilimumab may be resumed at the next scheduled dose. Doses omitted due to an adverse reaction must not be replaced (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see section 4.2), and high-dose intravenous corticosteroid therapy should be initiated immediately. (In clinical trials, methylprednisolone 2 mg/kg/day has been used). Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment. 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 (see the Summary of Product Characteristics for infliximab).

Immune-related hepatotoxicity

Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials (see section 4.8).

In patients who received ipilimumab 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 ipilimumab 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 AST and ALT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or medicinal products 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-≤ 8 x ULN or total bilirubin in the range of > 3-≤ 5 x ULN that is suspected to be related to ipilimumab, the scheduled dose of ipilimumab should be omitted, and LFTs must be monitored until resolution. After LFT levels improves (AST and ALT ≤ 5 x ULN and total bilirubin ≤ 3 x ULN), ipilimumab may be resumed at the next scheduled dose. Doses omitted due to an adverse reaction must not be replaced (see section 4.2).

For patients with AST or ALT elevations > 8 x ULN that are suspected to be related to ipilimumab, 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 normalization. Once symptoms have resolved and LFT elevations are normalized, 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 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 (see the Summary of Product Characteristics for mycophenolate mofetil).

Immune-related skin adverse reactions

Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis has been reported in clinical trials (see section 4.8).

Ipilimumab-induced rash and pruritus were predominantly mild or moderate (Grade 1 or 2) and responsive to symptomatic therapy. In patients who received ipilimumab 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).

Ipilimumab-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 ipilimumab 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) skin adverse reaction, the scheduled dose of ipilimumab should be omitted. If initial symptoms improve to mild (Grade 1) or resolve, ipilimumab therapy may be resumed at the next scheduled dose. Doses omitted due to an adverse reaction must not be replaced (see section 4.2).

Ipilimumab 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.

Immune-related neurological reactions

Ipilimumab is associated with serious immune-related neurological adverse reactions. Fatal Guillain-Barré syndrome has been reported in clinical trials (see section 4.8). Myasthenia gravis-like symptoms have also been reported. 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 medicinal products should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to ipilimumab, the scheduled dose should be omitted. If neurologic symptoms resolve to baseline, the patient may resume ipilimumab at the next scheduled dose. Doses omitted due to an adverse reaction must not be replaced (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to ipilimumab (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. Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality (see section 4.2).

Immune-related endocrinopathy

Ipilimumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism, 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 as a cause of the patient's symptoms must be excluded. Clinical experience with ipilimumab-associated endocrinopathy is limited.

For patients who received ipilimumab 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 immunosuppressant 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 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 ipilimumab should be omitted (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.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with ipilimumab 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 additional adverse reactions suspected to be immune-related have been reported in patients treated with ipilimumab 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 ipilimumab 3 mg/kg + gp100 peptide vaccine in MDX010-20 (see section 4.8).
If severe (Grade 3 or 4), these reactions may require immediate high-dose corticosteroid therapy and discontinuation of ipilimumab (see section 4.2). For ipilimumab-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

Special populations

Patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the pivotal clinical trial (see section 5.1).

Infusion reaction

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

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. Ipilimumab 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. Ipilimumab should be

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

Patients on controlled sodium diet

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

Concurrent administration with vemurafenib

In a Phase 1 trial, asymptomatic grade 3 increases in transaminases (ALT/AST > 5 × ULN) and bilirubin (total bilirubin > 3 × ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and vemurafenib is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes, and is not expected to have an effect on CYPs or other drug metabolizing enzymes in terms of inhibition or induction. Therefore, ipilimumab is not expected to have pharmacokinetic-based interactions.

Other forms of interaction

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

Anticoagulants
The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab (see section 4.8), patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of ipilimumab 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 is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

Breast-feeding

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, a decision must be made whether to discontinue breast-feeding or to discontinue from YERVOY therapy taking into account the benefit of breast-feeding for the child and the benefit of YERVOY therapy for the woman.

Fertility

Studies to evaluate the effect of ipilimumab on fertility have not been performed. Thus, the effect of ipilimumab 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 ipilimumab does not adversely affect them.

4.8 Undesirable effects

Summary of safety profile

Ipilimumab has been administered to > 3,000 patients in a clinical program evaluating its use with various doses and tumour types. Unless otherwise specified, the data below reflect exposure to ipilimumab at 3 mg/kg in clinical trials of melanoma. In the Phase 3 study MDX010-20, (see section 5.1), patients received a median of 4 doses (range 1-4).

Ipilimumab 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 ipilimumab (see section 4.4 for management of immune-related adverse reactions).

In patients who received 3 mg/kg ipilimumab 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). *Ipilimumab* 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 ipilimumab 3 mg/kg in clinical trials (n= 767) are presented in Table 2.

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). 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 ipilimumab in MDX010-20 were similar to those observed in the overall clinical program.

Table 2: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg (n= 767)[a]	
Infections and infestations	
Uncommon	sepsis[b], septic shock[b], meningitis, gastroenteritis, diverticulitis, urinary tract infection, upper respiratory tract infection, lower respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopenia
Uncommon	haemolytic anaemia[b], thrombocytopenia, eosinophilia, neutropenia
Immune system disorders	
Uncommon	hypersensitivity
Endocrine disorders	
Common	hypopituitarism (including hypophysitis)[c], hypothyroidism[c]
Uncommon	adrenal insufficiency[c], hyperthyroidism[c], hypogonadism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalemia
Uncommon	hyponatremia, alkalosis, hypophosphatemia, tumour lysis syndrome
Psychiatric disorders	
Common	confusional state
Uncommon	mental status changes, depression, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy
Uncommon	Guillain-Barré syndrome[b,c], syncope, cranial neuropathy, brain oedema, peripheral neuropathy, ataxia, tremor, myoclonus, dysarthria
Eye disorders	
Common	blurred vision, eye pain
Uncommon	uveitis[c], vitreous haemorrhage, iritis[c], reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Cardiac disorders	
Uncommon	arrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy[b], peripheral ischaemia, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, cough
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis, allergic rhinitis
Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea
Common	gastrointestinal haemorrhage, colitis[b,c], constipation, gastroesophageal reflux disease, abdominal pain
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c], peritonitis[b], pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus[d]
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, alopecia, night sweats, dry skin
Uncommon	toxic epidermal necrolysis[b,c], leukocytoclastic vasculitis, skin exfoliation
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, musculoskeletal pain, muscle spasms
Uncommon	polymyalgia rheumatica, arthritis
Renal and urinary disorders	
Uncommon	renal failure[b], glomerulonephritis[c], renal tubular acidosis
Reproductive system and breast disorders	
Uncommon	amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia
Common	chills, asthenia, oedema, pain
Uncommon	multi-organ failure[b,c], infusion related reaction
Investigations	
Common	increased alanine aminotransferase[c], increased aspartate aminotransferase[c], increased blood bilirubin, weight decreased
Uncommon	abnormal liver function test, increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, increased lipase[c], increased blood amylase[c], decreased blood testosterone

a Frequencies are based on pooled data from 9 clinical trials investigating the ipilimumab 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 Reported in recent studies outside the completed clinical trials in melanoma.

Additional adverse reactions not listed in Table 2 have been reported in patients who received other doses (either < or > 3 mg/kg) of ipilimumab in clinical trials of melanoma. These additional reactions all occurred at a frequency of < 1%: meningism, myocarditis, cardiomyopathy, autoimmune hepatitis, erythema multiforme, autoimmune nephritis, myasthenia gravis-like symptoms, autoimmune thyroiditis, hyperpituitarism, secondary adrenocortical insufficiency, hypoparathyroidism, thyroiditis, episcleritis, blepharitis, eye oedema, scleritis, temporal arteritis, Raynaud's phenomenon, proctitis, palmar-plantar erythrodysaesthesia syndrome, psoriasis, haematuria, proteinuria, decreased blood thyroid stimulating hormone, decreased blood gonadotrophin, decreased thyroxine, leukopenia, and polycythaemia.

Description of selected adverse reactions

Except where noted, data for the following selected adverse reactions are based on patients who received either ipilimumab 3 mg/kg monotherapy (n= 131) or ipilimumab 3 mg/kg in combination with gp100 (n= 380) in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

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

In the ipilimumab 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 occurred in most cases (90%), with a median time from onset to resolution (defined as improvement to mild [Grade 1] or less or to

the severity at baseline) 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
Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in < 1% of patients who received ipilimumab 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).

Immune-related skin adverse reactions
Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis has been reported in < 1% of patients who received ipilimumab in combination with gp100 (see section 5.1).

In the ipilimumab 3 mg/kg monotherapy group, rash and pruritus of any severity were each reported in 26% of patients. Ipilimumab-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
Ipilimumab is associated with serious immune-related neurological reactions. Fatal Guillain-Barré syndrome has been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100. Myasthenia gravis-like symptoms have also been reported in < 1% of patients who received higher doses of ipilimumab in clinical trials.

Immune-related endocrinopathy
In the ipilimumab 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 or very 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.

Other immune-related adverse reactions
The following additional adverse reactions suspected to be immune-related have been reported in < 2% of patients treated with ipilimumab 3 mg/kg monotherapy: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with ipilimumab 3 mg/kg in combination with gp100 peptide vaccine.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

In case of overdose, 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.

Mechanism of action

Cytotoxic T-lymphocyte antigen-4 (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.

Pharmacodynamic effects

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase was dose-dependent. In MDX010-20 (see section 5.1), ipilimumab 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 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 also was observed after treatment with ipilimumab.

Immunogenicity

Less than 2% of patients with advanced melanoma who received ipilimumab in Phase 2 and 3 clinical trials 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 reactions.

Clinical trials

The efficacy of ipilimumab at the recommended dose of 3 mg/kg in patients with previously treated advanced (unresectable or metastatic) melanoma was investigated in a Phase 3 study (MDX010-20). Patients with ocular melanoma, primary CNS melanoma, active brain metastases, human immunodeficiency virus (HIV), hepatitis B, and hepatitis C were not included in the pivotal clinical trial. Clinical trials excluded patients with ECOG performance status > 1 and mucosal melanoma. Patients without liver metastasis who had a baseline AST > 2.5 x ULN, patients with liver metastasis who had a baseline AST > 5 x ULN, and patients with a baseline total bilirubin ≥ 3 x ULN were also excluded.

For patients with a history of autoimmune disease, see also section 4.4.

MDX010-20
A Phase 3, double-blind study enrolled patients with advanced (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 ipilimumab 3 mg/kg + an investigational gp100 peptide vaccine (gp100), ipilimumab 3 mg/kg monotherapy, or gp100 alone. All patients were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. Patients received ipilimumab 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 tumour response to ipilimumab was conducted after completion of induction therapy. Additional treatment with ipilimumab (re-induction therapy) was offered to those who developed PD after initial clinical response (PR or CR) or after SD (per the modified WHO criteria) > 3 months from the first tumour assessment. The primary endpoint was overall survival (OS) in the ipilimumab+ gp100 group *vs.* the gp100 group. Key secondary endpoints were OS in the ipilimumab+ gp100 group *vs.* the ipilimumab monotherapy group and in the ipilimumab 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 ipilimumab monotherapy group, 403 to the ipilimumab + gp100 group, and 136 to the gp100 alone group. The majority had received all 4 doses during induction. Thirty-two patients received a re-induction dose: 8 in the ipilimumab monotherapy group, 23 in the ipilimumab + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across 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 lactate dehydrogenase (LDH) at baseline. A total of 77 patients had a history of previously treated brain metastases.

The ipilimumab-containing regimens demonstrated a statistically significant advantage over the gp100 control group in OS. The hazard ratio (HR) for comparison of OS between ipilimumab monotherapy and gp100 was 0.66 (95% CI: 0.51, 0.87; p = 0.0026).

By subgroup analysis, it has been shown that the observed OS benefit was consistent within most of the subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline LDH, age, and sex). However, for women above 50 years of age, the data supporting an OS benefit of ipilimumab treatment were limited. The efficacy of ipilimumab for women above 50 years of age is therefore uncertain. As the subgroups analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data.

Median and estimated rates of OS at 1 year and 2 years are presented in Table 3.

Table 3: Overall survival in MDX010-20

	Ipilimumab n= 137	gp100 [a] n= 136
Median Months (95% CI)	10 months (8.0, 13.8)	6 months (5.5, 8.7)
OS at 1 year % (95% CI)	46% (37.0, 54.1)	25% (18.1, 32.9)
OS at 2 years % (95% CI)	24% (16.0, 31.5)	14% (8.0, 20.0)

[a] gp100 peptide vaccine is an experimental control.

In the ipilimumab 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.

For patients who required re-induction therapy, the BORR was 38% (3/8 patients) in the ipilimumab monotherapy group, and 0% in the gp100 group. The disease control rate (DCR) (defined as

CR+PR+SD) was 75% (6/8 patients) and 0%, respectively. Because of the limited number of patients in these analyses, no definitive conclusion regarding the efficacy of ipilimumab re-induction can be drawn.

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

The European Medicines Agency has waived the obligation to submit the results of studies with YERVOY in all subsets of the paediatric population in the treatment of melanoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ipilimumab was studied in 498 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 for C_{max}, C_{min} and AUC. Ipilimumab steady-state was reached by the third dose administered once every 3 weeks. Based on population pharmacokinetic analysis, the following pharmacokinetic parameters of ipilimumab were obtained: a mean (SD) terminal half-life of 15 (4.62) days; a geometric mean systemic clearance of 15.3 ml/h with percent coefficient of variation (CV%) of 38.5%; and a geometric mean volume of distribution at steady-state of 7.22 l with CV% of 10.5%. The average (±SD) ipilimumab serum trough concentrations achieved at steady-state with a 3 mg/kg induction regimen was 21.8 µg/ml (± 11.2).

Ipilimumab clearance increased with increasing body weight and with increasing LDH at baseline; however no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis. Clearance was not affected by age (range 26-86 years), gender, hepatic function (as measured by albumin and alkaline phosphatase), concomitant use of budesonide, renal function (estimated GFR 22 ml/min or greater), performance status, HLA-A2*0201 status, and prior use of 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.

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 one study without accompanying histopathologic findings; the clinical relevance of this finding is 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 edema. 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 medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial: 3 years

After opening:
Solution for infusion: From a microbiological point of view, once opened, the medicinal product 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 hrs at 25°C and 2 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 (20°C to 25°C).

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

10 ml of sterile concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.
40 ml of sterile concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

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 IV 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. Gently mix the infusion by manual rotation.

Administration:
YERVOY infusion must not be administered as an intravenous push or bolus injection.
Administer the YERVOY infusion intravenously over a period of 90 minutes.

YERVOY infusion should not be infused at the same time in the same intravenous line with other agents. 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).

YERVOY infusion is compatible with:
- PVC infusion 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 medicinal product or waste material should be discarded in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/698/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Lonza Biologics, Inc.
101 International Drive
Portsmouth, NH 03801
United States

Name and address of the manufacturer(s) responsible for batch release

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe YERVOY are provided with the following:
- Healthcare Professional FAQ Brochure

- Patient Information Brochures including Alert Cards

Key elements of the Healthcare Professional FAQ Brochure (Q&A format):

- Brief introduction to ipilimumab (indication and the purpose of this tool).
- List of important immune-related adverse reactions (irARs) and their symptoms, as outlined in section 4.4 of the Summary of Product Characteristics (SmPC):
    - Inflammation of the gastrointestinal tract, such as colitis, which can lead to bowel perforation
    - Inflammation of the liver, such as hepatitis, which can lead to liver failure
    - Inflammation of the skin that can lead to severe skin reaction (toxic epidermal necrolysis)
    - Inflammation of the nerves that can lead to neuropathy
    - Inflammation of the endocrine system. including the adrenal, pituitary, or thyroid glands
    - Inflammation of the eyes
    - Other related irARs (e.g. pneumonitis, glomerulonephritis, multi-organ failure…)
    - Severe infusion reaction

- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and require early intervention, as outlined in the guidelines for the management of immune-related adverse reactions in section 4.4 of the SmPC.
- Importance of evaluating liver function tests (LFTs), TSH and signs/symptoms of irARs before each treatment.
- Follow-up of patients due to late onset (months after treatment) of irARs
- Reminder to distribute the Patient Information Brochure, and to educate patients/caregivers about symptoms of irARs and of the need to report them immediately to the physician.

Key elements for the Patient Information Brochure and Alert Card:

- Brief introduction to ipilimumab indication and the purpose of this tool.
- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and need to be addressed immediately
- Request to inform the physician of all medical conditions before treatment.
- Description of the main symptoms of irARs and the importance of notifying their treating physician immediately if symptoms occur, persist or worsen.
    - Gastrointestinal: diarrhea, bloody stool, abdominal pain, nausea, or vomiting
    - Liver: yellowing of your skin or whites of your eyes
    - Skin: rash, blisters and/or peeling, mouth sores
    - Eye: blurred vision, vision changes, eye pain,
    - General: fever, headache, feeling tired, dizziness or fainting, dark urine, bleeding, weakness, numbness of legs, arms, or faces, changes in behavior, such as less sex drive, being irritable or forgetful
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional first.
- Placeholder including the weblink of the Package Leaflet on the EMA website
- The importance of carrying the detachable wallet-sized Patient Alert Card at all times to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with ipilimumab.

The Marketing Authorisation Holder shall agree the format and content of the above material with the National Competent Authority prior to launch in the Member State.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due Date**
The Marketing Authorisation Holder shall perform a randomized comparison study of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint, based on a CHMP-agreed protocol.	Final study report: 4Q2017

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for solution for infusion
Ipilimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 5 mg ipilimumab.
Each vial contains 50 mg ipilimumab.
Each vial contains 200 mg ipilimumab.

3. LIST OF EXCIPIENTS

Excipients: Tris hydrochloride, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

50 mg/10 ml
200 mg/40 ml

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park - Sanderson Road
Uxbridge UB8 1DH - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/698/001
EU/1/11/698/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml sterile concentrate
Ipilimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 5 mg ipilimumab.
Each vial contains 50 mg ipilimumab.
Each vial contains 200 mg ipilimumab.

3. LIST OF EXCIPIENTS

Excipients: Tris hydrochloride, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

50 mg/10 ml
200 mg/40 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park - Sanderson Road
Uxbridge UB8 1DH - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/698/001
EU/1/11/698/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

YERVOY 5 mg/ml concentrate for solution for infusion
Ipilimumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What YERVOY is and what it is used for

YERVOY contains the active substance ipilimumab, a protein which helps your immune system to attack and destroy cancer cells by your immune cells.

Ipilimumab is used to treat advanced melanoma (a type of skin cancer) in adults. It is used if your cancer has not responded, or if it has stopped responding to earlier treatment.

2. What you need to know before you use YERVOY

You should not be given YERVOY
- if you are **allergic** to ipilimumab or any of the other ingredients of this medicine (listed in Section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions
- Talk to your doctor before using YERVOY.
  - **inflammation of the intestines (colitis)** which can worsen to bleedings or bowel perforation. Signs and symptoms of colitis may include diarrhoea (watery, loose or soft stools), an increased number of bowel movements than usual, blood in your stools or darker-coloured stools, pain or tenderness in your stomach area.
  - **inflammation of the liver (hepatitis)** that can lead to liver failure. Signs and symptoms of hepatitis may include eye or skin yellowing (jaundice), pain on the right side of your stomach area, tiredness.
  - **inflammation of the skin** that can lead to severe skin reaction (toxic epidermal necrolysis). Signs and symptoms of severe skin reaction may include such as skin rash with or without itching, peeling of the skin**,** dry skin.

- **inflammation of the nerves** that can lead to paralysis. Symptoms of nerve problems may include muscle weakness, numbness or tingling in your hands or feet, loss of consciousness or difficulty waking up.

- **inflammation of hormone** producing glands (especially the pituitary, adrenal and thyroid glands) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include headaches, blurry or double vision, tiredness, decreased sexual drive, behavioral changes.

- **inflammation of the eyes**. Signs and symptoms may include redness in the eye, pain in the eye, vision problems or blurry vision.

Tell your doctor immediately if you have any of these signs or symptoms or they get worse. **Do not try to treat your symptoms with other medicines**. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms, omit the next dose of YERVOY, or stop your treatment with YERVOY altogether.
Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during treatment.

Check with your doctor or nurse before you are given YERVOY
- if you have an **autoimmune disease** (a condition where the body attacks its own cells);
- if you have, or have ever had, **chronic viral infection of the liver**, including hepatitis B (HBV) or hepatitis C (HCV);
- if you have **human immunodeficiency virus** (HIV) infection or acquired immune deficiency syndrome (AIDS).

Children
YERVOY should not be used in children below 18 years of age until more information becomes available.

Other medicines and YERVOY
Before you are given YERVOY, tell your doctor
- if you are taking any medicines that suppress your immune system, such as corticosteroids. These medicines may interfere with the effect of YERVOY. However, once you are treated with YERVOY, your doctor may give you corticosteroids to reduce the side-effects that you may have with YERVOY.

- if you are taking any medicines that stop your blood from clotting (anticoagulants). These medicines may increase the likelihood of bleeding in the stomach or intestine, which is a side-effect of YERVOY.

Also tell your doctor if you are taking or have recently taken any other medicines.

Do not take any other medicines during your treatment without talking to your doctor first. Based on early data, the combination of YERVOY (ipilimumab) and Zelboraf (vemurafenib, another drug for the treatment of melanoma) is not recommended due to increased toxicity to the liver.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant, if you are planning to become pregnant, or if you are breast-feeding.

You must not use YERVOY if you are pregnant unless your doctor specifically recommends it. The effects of YERVOY in pregnant women are not known, but it is possible that the active substance, ipilimumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with YERVOY if you are a woman who could become pregnant.

- If you become pregnant while using YERVOY **tell your doctor**.

It is not known whether ipilimumab gets into breast milk. However, significant exposure of ipilimumab to the infant through breast milk is not expected and no effects on the breastfed infant are anticipated. Ask your doctor if you can breast feed during or after treatment with YERVOY.

Driving and using machines
Do not drive or use machines after you have been given YERVOY unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of YERVOY. This can affect your ability to drive or to use machines.

YERVOY contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given YERVOY. It contains 2.3 mg sodium per ml of concentrate.

3. How to use YERVOY

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

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

The amount of YERVOY you will be given will be calculated based on your body weight. Depending on your dose, some or all of the content of the YERVOY vial may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection before use. More than one vial may be necessary to obtain the required dose.

How much YERVOY is given
The recommended dose is 3 mg of ipilimumab per kilogram of your body weight.
You will be treated with YERVOY once every 3 weeks, for a total of 4 doses. You may notice the appearance of new lesions or growth of existing lesions on your skin, which can be expected when you are being treated with YERVOY. Your doctor will continue giving you YERVOY for a total of 4 doses, depending on your tolerance to the treatment.

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

If you stop using YERVOY
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with YERVOY unless you have discussed this with your doctor.

If you have any further questions about your treatment or the use of this medicine, ask your doctor.

4. Possible side effects

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

Be aware of important symptoms of inflammation
YERVOY acts on your immune system and may cause **inflammation** in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening.

The following side effects have been reported in clinical trials:

Very common (may affect more than 1 in 10 people)
- loss of appetite
- diarrhoea, vomiting or feeling sick (nausea)
- skin rash, itching
- feeling tired or weak, reaction at site of injection, fever

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)
- tumour pain
- underactive function of the thyroid gland which can cause tiredness or weight gain, underactive function of the pituitary gland
- dehydration
- confusion
- damage to the nerves (causing pain, weakness and cramps), dizziness, headache,
- blurred vision, pain in the eye
- low blood pressure, temporary redness of the face and neck, feeling of intense heat with sweating and rapid heart beat
- shortness of breath, cough
- bleeding in the stomach or intestine, inflammation of the intestines (colitis), constipation, heartburn, stomach pain
- abnormal function of the liver
- inflammation and redness of the skin, skin colour change in patches (vitiligo), hives (itchy, bumpy rash), hair loss or thinning, excessive sweating at night, dry skin
- pain in muscles and joints, muscle spasms
- shivering, lack of energy, swelling, pain
- weight loss

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)
- serious bacterial infection of the blood (sepsis, septic shock), inflammation around the brain or spinal cord, inflammation of the stomach and intestines, inflammation of bowel wall (causing fever, vomiting and stomach pain), urinary tract infection, infection of the respiratory tract
- a group of symptoms due to cancer in the body such as high blood levels of calcium and cholesterol, and low blood levels of sugar (paraneoplastic syndrome)
- allergic reaction
- underactive function of the adrenal glands, overactive function of the thyroid gland, which can cause rapid heart rate, sweating and weight loss, defect of the glands producing sex hormones
- a group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome).
- changes in mental health, depression, lowered sex drive
- severe and possibly fatal inflammation of the nerves causing pain, weakness or paralysis in the extremities (Guillain-Barré syndrome), fainting, inflammation of the nerves within the brain, excessive accumulation of fluid in the brain,difficulty in coordinating movements (ataxia), shaking, brief involuntary muscle contraction, difficulty in speaking
- inflammation of the eye which causes redness or pain, bleeding in the eye, inflammation of the coloured part of the eye, reduced vision, a foreign body sensation in the eyes, swollen runny eyes
- irregular or abnormal heart beat
- inflammation of the blood vessels, disease of the blood vessels, restriction in the blood supply to the extremities, low blood pressure when standing up
- extreme difficulty in breathing, fluid accumulation in the lungs, inflammation of the lungs, hay fever

- bowel perforation, inflammation of the membrane of the stomach wall, inflammation of the small intestine, inflammation of the bowel or the pancreas, peptic ulcer, inflammation of the food pipe, blockage of the intestines
- liver failure, inflammation of the liver, enlarged liver, yellowing of the skin or eyes (jaundice)
- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)
- inflammation of the muscles causing pain or stiffness in the hip and shoulder, painful joints
- kidney function failure, kidney disease
- absence of menstrual periods
- multi organ dysfunction, reaction related to infusion of the medicine

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

In addition, the following uncommon (may affect up to 1 in 100 people) side effects have been reported in patients who received other doses of YERVOY in clinical trials:
- triad of symptoms (meningism): neck stiffness, intolerance of bright light and headache
- inflammation of the heart muscle, disease of the heart muscle
- antibodies against some of your own body cells causing damage to the the liver or the thyroid gland, the kidney
- inflammation and redness of the skin (erythema multiforme)
- muscle weakness
- overactive pituitary gland
- decreased function of the adrenal glands caused by an underactive hypothalamus (part of the brain)
- decreased function of the parathyroid gland, inflammation of the thyroid gland
- inflammation of the eye, inflammation of the eyelids, swelling of the eye,
- inflammatory disease of blood vessels (most commonly head arteries), poor blood circulation which makes toes and fingers numb or pale
- inflammation of the anus and the rectal wall (marked by bloody stools and a frequent urge to defecate), damage to the tissues of the hands and feet resulting in redness, swelling and blisters
- skin disease characterized by dry red patches covered with scales (psoriasis)

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Changes in test results
YERVOY may cause changes in the results of tests carried out by your doctor. These include:
- a variation in the number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- an abnormal variation of hormones and liver enzyme levels in the blood
- abnormal liver function test
- abnormal levels of calcium, sodium, phosphate or potassium in the blood
- presence of blood or proteins in the urine
- an abnormally high alkalinity of the blood and other body tissues
- kidneys unable to remove acids from blood normally

Reporting of side effects
If you get any side effects**, talk to your doctor.** This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store YERVOY

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

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

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What YERVOY contains

- The active substance is ipilimumab.
  Each ml of sterile concentrate contains 5 mg of ipilimumab.
  Each vial contains either 50 mg or 200 mg of ipilimumab.

- The other ingredients are Tris-hydrochloride, sodium chloride (see section 2 "YERVOY contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What YERVOY looks like and contents of the pack
YERVOY concentrate for solution for infusion is clear to slightly opalescent, colourless to pale yellow and may contain light (few) particulates.

It is available in packs containing either 1 vial of 10 ml or 1 vial of 40 ml.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

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. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

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 IV 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. Gently mix the infusion by manual rotation.

Administration:
YERVOY infusion must not be administered as an intravenous push or bolus injection. Administer the YERVOY infusion intravenously **over a period of 90 minutes**.

YERVOY infusion should not be infused at the same time in the same intravenous line with other agents. 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).

YERVOY infusion is compatible with:
- PVC infusion 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.

Storage conditions and shelf life:
Unopened vial
YERVOY must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. YERVOY should not be frozen.

Do not use YERVOY after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

YERVOY infusion
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 infusion solution (between 1 and 4 mg/ml) has been demonstrated for 24 hours at room temperature (20°C to 25°C) or when refrigerated (2°C to 8°C). If not used immediately, the infusion solution (undiluted or diluted) must be used within 24 hours when stored either under refrigeration (2°C to 8°C) or at room temperature (20°C to 25°C). Other in-use storage time and conditions are the responsibility of the user.

Disposal:
Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.