6509

YERVOY™ 5mg per 1mL

(ipilimumab)

concentrate solution for infusion

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SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM
YERVOY® 5 mg/ml solution for infusion

COMPOSITION
Each vial contains 5 mg/ml ipilimumab.
Inactive ingredients:
Tris-hydrochloride, sodium chloride, mannitol, pentetic acid, polysorbate 80, sodium hydroxide (pH adjustment), hydrochloric acid (pH-adjustment) and water for injection.

PHARMACOLOGICAL CLASSIFICATION
A 30.1 Antibodies

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Ipilimumab is a recombinant, human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa.
Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture by recombinant DNA technology.
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 also was observed after treatment with ipilimumab.

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 four 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 concentration achieved at steady-state with a 3 mg/kg induction regimen was 21,8 µg/ml (± 11,2).

Special Populations:
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 26 to 86 years), gender, hepatic function (as measured by albumin and alkaline phosphatase), concomitant use of oral budesonide, renal function (estimated GFR 22 ml/min or greater), performance status, HLA-A2*0201 status and prior use of systemic anticancer therapy.

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

Elderly patients:
No overall differences in safety or efficacy were reported between the elderly (65 years and over) and younger patients (less than 65 years).

Renal impairment:
The safety and efficacy of **YERVOY** have not been studied in patients with renal impairment.

Hepatic impairment:
The safety and efficacy of **YERVOY** have not been studied in patients with hepatic impairment.

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

CONTRAINDICATIONS
Hypersensitivity to ipilimumab or to any other ingredients in the formulation (see **COMPOSITION**).

WARNINGS AND SPECIAL PRECAUTIONS
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.

Immune-related gastrointestinal reactions
YERVOY is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported (see **SIDE EFFECTS**).
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 **YERVOY** must be promptly evaluated to exclude infectious or other alternate aetiologies. 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:
- 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 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, **YERVOY** may be resumed at the next scheduled dose. Doses omitted due to an adverse reaction should not be replaced.
- **YERVOY** must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis and 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 of corticosteroid therapy) resulted in recurrence of diarrhoea or colitis in some patients. Patients should be evaluated for evidence of gastrointestinal perforation or peritonitis.
  For management of corticosteroid-refractory diarrhoea or colitis, 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 should not be used if gastrointestinal perforation or sepsis is suspected. Refer to the prescribing information for infliximab.

See **DOSAGE AND DIRECTIONS FOR USE – Recommended dose modifications**.

Immune-related hepatotoxicity
YERVOY is associated with serious immune-related hepatotoxicity, including fatal hepatic failure (see **SIDE EFFECTS**).
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.
Serum hepatic transaminases and bilirubin levels must be evaluated before each dose of **YERVOY** because early laboratory changes may be indicative of emerging immune-related hepatitis. 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).
YERVOY should be administered with caution in patients with transaminase levels 5 times ULN or greater or bilirubin levels greater than 3 times ULN at baseline.
- For patients with elevated AST or ALT in the range of > 5 - ≤ 8 x ULN (upper limit of normal) or total bilirubin in the range of > 3 - ≤ 5 x ULN that is suspected to be related to **YERVOY**, the scheduled dose of **YERVOY** should be omitted, and LFTs must be monitored until resolution. After LFT levels improve (AST and ALT ≤ 5 x ULN and total bilirubin ≤ 3 x ULN), **YERVOY** may be resumed at the next scheduled dose. Doses omitted due to an adverse reaction should not be replaced.
- For patients with AST or ALT elevations > 8 x ULN or bilirubin > 5 x ULN that are suspected to be related to **YERVOY**, treatment must be permanently discontinued 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, corticosteroid taper should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.
- For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered.

See **DOSAGE AND DIRECTIONS FOR USE – Recommended dose modifications**.

Immune-related skin adverse reactions
YERVOY is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis has been reported (see **SIDE EFFECTS**).
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) skin adverse reaction 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) skin adverse reaction, the scheduled dose of **YERVOY** should be omitted. If initial symptoms improve to mild (Grade 1) or resolve, **YERVOY** therapy may be resumed at the next scheduled dose. Doses omitted due to an adverse reaction should not be replaced.
- **YERVOY** must be permanently discontinued in patients with a very severe (Grade 4) rash or severe (Grade 3) pruritus and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled, corticosteroid taper should occur over a period of at least 1 month.
  Caution should be used when considering the use of **YERVOY** in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior cancer immune stimulatory therapy.

See **DOSAGE AND DIRECTIONS FOR USE – Recommended dose modifications**.

Immune-related neurological adverse reactions
YERVOY is associated with serious immune-related neurological adverse reactions. Fatal Guillain-Barré syndrome has been reported (see **SIDE EFFECTS**).
Myasthenia gravis-like symptoms have also been reported. Patients may present with muscle weakness. Sensory neuropathy may also occur.
Panhypopituitarism has been reported (see "*Immune-related endocrinopathy*" below).
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 omitted. If neurologic symptoms resolve to baseline, the patient may resume **YERVOY** at the next scheduled dose. Doses omitted due to an adverse reaction should not be replaced.
- **YERVOY** must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to **YERVOY** and intravenous corticosteroid therapy (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 **DOSAGE AND DIRECTIONS FOR USE – Recommended dose modifications**.

Immune-related endocrinopathy
YERVOY can cause inflammation of the endocrine system organs, manifesting as hypophysitis, hypopituitarism, adrenal insufficiency and hypothyroidism (see **SIDE EFFECTS**) 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.
Immune-related endocrinopathy observed in clinical trials was generally controlled with immunosuppressive therapy and hormone replacement therapy.
If there are any signs of adrenal insufficiency 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 omitted. It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.
Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with **YERVOY** may be resumed, and corticosteroid taper should occur over a period of at least 1 month.
See **DOSAGE AND DIRECTIONS FOR USE – Recommended dose modifications**.

Other immune-related adverse reactions
The following additional adverse reactions suspected to be immune-related have been reported: uveitis, eosinophilia, including DRESS Syndrome, lipase elevation, glomerulonephritis, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, pericarditis and pneumonitis (see **SIDE EFFECTS**).
If severe (Grade 3 or 4), these reactions may require immediate high-dose corticosteroid therapy and discontinuation of **YERVOY**.
For **YERVOY**-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.
See **DOSAGE AND DIRECTIONS FOR USE – Recommended dose modifications**.

Infusion reaction
In case of a severe infusion reaction, **YERVOY** infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive **YERVOY** with close monitoring.

Patients with autoimmune disease
YERVOY should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening.

Concurrent administration with vemurafenib
The concurrent administration of **YERVOY** and vemurafenib is not recommended due to increased toxicity.

Effects on ability to drive and to use machines
Because of potential adverse reactions such as fatigue, patients should be advised to use caution when driving or operating machinery until they are certain that **YERVOY** does not adversely affect them.

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

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.

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

PREGNANCY AND LACTATION
Safety and efficacy in pregnancy and lactation have not been established.

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

Lactation:
It is not known whether ipilimumab is secreted in human milk. Because of the potential for adverse reactions in nursing infants, **YERVOY** should not be used in women breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE
YERVOY should be administered under the supervision of healthcare professionals experienced in the treatment of cancer.
YERVOY should not be administered as an intravenous push or bolus injection.

Recommended dosing:
The recommended induction regimen of **YERVOY** is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses.
Patients should receive the entire induction regimen (four 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-induction 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-induction 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**.

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. In some cases, addition of other immunosuppressive therapy may be considered. Dose reduction is not recommended. Doses that are omitted due to an adverse reaction should 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 **WARNINGS AND SPECIAL PRECAUTIONS**.

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 WARNINGS AND SPECIAL PRECAUTIONS 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, pericarditis, pancreatitis, non-infectious myocarditis)	• ≥ Grade 3 immune-related reaction[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. The decision whether to discontinue **YERVOY** should be based on severity.
[c] Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.
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 WARNINGS AND SPECIAL PRECAUTIONS 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 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	
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 should 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. The decision whether to omit a scheduled dose should be based on severity.
ULN = upper limit of normal

Preparation for administration
PREPARE INFUSION USING ASEPTIC TECHNIQUE.
YERVOY injection should be visually inspected for particulate matter and discolouration prior to administration. The vial should be discarded if solution is cloudy, there is pronounced discolouration (solution may have pale yellow colour), or there is foreign particulate matter other than translucent-to-white particulates.
YERVOY injection (5 mg/ml) may be used for intravenous administration without dilution after transferring to an infusion container using an appropriate sterile syringe, or after diluting with sterile sodium chloride 9 mg/ml (0,9 % solution) or sterile 5 % dextrose injection solution to a concentration ranging from 1 mg/ml to 4 mg/ml. Diluted solution should be mixed by gentle inversion. An in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 0,2 µm or 1,2 µm) should be used for intravenous infusion.
Determine the number of vials of **YERVOY** (5 mg/ml) needed (see **Recommended dosing**).
Allow the vials to stand at room temperature for approximately 5 minutes.
Withdraw the required volume of **YERVOY** solution (5 mg/ml) using an appropriate sterile syringe and transfer into a sterile, evacuated glass bottle or intravenous bag (PVC or non-PVC).

Compatibility
YERVOY 5 mg/ml is compatible with:
- Glass, polyvinyl chloride (PVC) and non-PVC intravenous bags
- PVC intravenous extension/administration sets
- Polyethersulfone (0,2 µm and 1,2 µm) and nylon (0,2 µm) in-line filters

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

Administration
The entire solution of the **YERVOY** dose should be infused through a low-protein-binding in-line filter (pore size of 0,2 µm to 1,2 µm) over a 90-minute period. A separate infusion line should be used for the infusion, and the line should be flushed with sterile sodium chloride 9 mg/ml (0,9 %) solution for injection or sterile 5 % dextrose injection at the end of infusion.

SIDE EFFECTS
YERVOY is most commonly associated with adverse reactions resulting from increased or excessive immune activity.
Very commonly reported adverse reactions (occurring at ≥ 10 %) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority of adverse reactions were mild to moderate (Grade 1 or 2). **YERVOY** therapy was discontinued for adverse reactions in 10 % of patients.
Side effects are presented by system organ class and frequency in patients with advanced melanoma who were treated with **YERVOY** 3 mg/kg in clinical trials (n = 767). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies are defined as:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100).

Adverse reactions in patients with advanced melanoma treated with YERVOY 3 mg/kg:

Infections and infestations
Uncommon sepsis[a], septic shock[a], 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, thrombocytopenia, eosinophilia, neutropenia

Immune system disorders
Uncommon hypersensitivity
Very rare anaphylactic reaction (shock)

Endocrine disorders
Common hypopituitarism (including hypophysitis), hypothyroidism
Uncommon adrenal insufficiency, hyperthyroidism, hypogonadism, hyperpituitarism

Metabolism and nutrition disorders
Very common decreased appetite
Common dehydration, hypokalaemia
Uncommon hyponatremia, alkalosis, hypophosphataemia, 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[a], meningitis, syncope, cranial neuropathy, brain oedema, peripheral neuropathy, ataxia, tremor, myoclonus, dysarthria

Eye disorders
Common blurred vision, eye pain
Uncommon uveitis, vitreous haemorrhage, iritis, reduced visual acuity, foreign body sensation in eyes, conjunctivitis

Cardiac disorders
Uncommon dysrhythmia, atrial fibrillation

Vascular disorders
Common hypotension, flushing, hot flush
Uncommon vasculitis, angiopathy[a], peripheral ischaemia, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common dyspnoea, cough
Uncommon respiratory failure, acute respiratory distress syndrome[a], lung infiltration, pulmonary oedema, pneumonitis, allergic rhinitis

Gastrointestinal disorders
Very common diarrhoea, vomiting, nausea
Common gastrointestinal haemorrhage, colitis[a], constipation, gastroesophageal reflux disease, abdominal pain
Uncommon gastrointestinal perforation[a], large intestine perforation[a], intestinal perforation[a], peritonitis[a], gastroenteritis, diverticulitis, pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus, mucosal inflammation

Hepatobiliary disorders
Common abnormal hepatic function
Uncommon hepatic failure[a], hepatitis, hepatomegaly, jaundice

Skin and subcutaneous tissue disorders
Very common rash, pruritus
Common dermatitis, erythema, vitiligo, urticaria, alopecia, night sweats, dry skin
Uncommon toxic epidermal necrolysis[a,b], leukocytoclastic vasculitis, skin exfoliation, eczema, hair colour changes, Stevens-Johnson Syndrome

Musculoskeletal and connective tissue disorders
Common arthralgia, myalgia, musculoskeletal pain, muscle spasms
Uncommon polymyalgia rheumatica, arthritis

Renal and urinary disorders
Uncommon renal failure[a], glomerulonephritis, renal tubular acidosis

Reproductive system and breast disorders
Uncommon amenorrhoea

General disorders and administration site conditions
Very common fatigue, injection site reaction, pyrexia
Common chills, asthenia, oedema, pain, influenza-like illness (symptoms)
Uncommon multi-organ failure[a], infusion related reaction
Rare systemic inflammatory response syndrome

Investigations
Common increased alanine aminotransferase (AST), increased aspartate aminotransferase (ALT), increased blood bilirubin, increased blood alkaline phosphatase, weight decrease
Uncommon abnormal liver function test, increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotropin, increased lipase, increased blood amylase, decreased blood testosterone
Rare abnormal blood prolactin

[a] Including fatal outcome.
[b] Patients developed Stevens-Johnson syndrome which evolved into toxic epidermal necrolysis.

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 all occurred at a frequency of < 1 %: meningism, myocarditis, pericardial effusion (pericarditis), cardiomyopathy, autoimmune hepatitis, erythema multiforme, autoimmune nephritis, autoimmune thyroiditis, hyperpituitarism, secondary adrenocortical insufficiency, hypoparathyroidism, thyroiditis, episcleritis, blepharitis, eye oedema, scleritis, temporal arteritis, Raynaud's phenomenon, proctitis, palmar-plantar erythrodysesthesia syndrome, psoriasis, haematuria, proteinuria, decreased blood thyroid stimulating hormone, decreased blood gonadotrophin, decreased thyroxine, leucopenia, polycythemia, myasthenia gravis-like symptoms, cytokine release syndrome, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis and ocular myositis.

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).
Additional information and the management guidelines for these adverse reactions are described in **WARNINGS AND SPECIAL PRECAUTIONS**.

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

Immune-related hepatotoxicity
In the **YERVOY** 3 mg/kg monotherapy group, 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.
Fatal hepatic failure has been reported in < 1 % of patients.

Immune-related skin adverse reactions
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 or moderate (Grade 1 or 2).
Fatal toxic epidermal necrolysis has been reported in < 1 % of patients who received **YERVOY** in combination with gp100.
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been very rarely reported with **YERVOY** in post-marketing use.

Immune-related neurological reactions
There were no reports of immune-related neurological reactions in the **YERVOY** 3 mg/kg monotherapy group.
Severe (Grade 3) meningitis and fatal Guillain-Barré syndrome were each 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.

Other immune-related adverse reactions
The following additional adverse reactions suspected to be immune-related have been reported in < 2 % of patients treated with **YERVOY** 3 mg/kg monotherapy: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in < 1 % of patients treated with **YERVOY** 3 mg/kg in combination with gp100 peptide vaccine.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted. See **SIDE EFFECTS**.

IDENTIFICATION
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, amorphous ipilimumab particulates.

PRESENTATION
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.

STORAGE INSTRUCTIONS
Store under refrigeration at 2 °C to 8 °C.
Store in the original package in order to protect from light.
Do not freeze.
For single use only. Discard any unused portion.
Once opened, the product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/ml and 4 mg/ml) has been demonstrated for 24 hours at 25 °C and 2 °C to 8 °C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours either under refrigeration (2 °C to 8 °C) or at room temperature (25 °C).
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
47/30.1/0522

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Equity Pharmaceuticals (Pty) Ltd.
100 Sovereign Drive
Route 21 Corporate Park
Nellmapius Drive
Irene Pretoria

DATE OF PUBLICATION OF THE PACKAGE INSERT
02 October 2014
30 September 2016
YERVOY is a trademark of Bristol-Myers Squibb Company, used under license by Equity Pharmaceuticals (Pty) Ltd.

SCHEDULING STATUS:
Schedule S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:
YERVOY® 5 mg/ml solution for infusion

Read all of this leaflet carefully before receiving YERVOY
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- **YERVOY** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT YERVOY CONTAINS:
Each vial contains 5 mg/ml ipilimumab.
Inactive ingredients:
Tris-hydrochloride, sodium chloride, mannitol, pentetic acid, polysorbate 80 and water for injection.

2. WHAT YERVOY 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.
YERVOY is used to treat advanced melanoma (a type of skin cancer) in adults.

3. BEFORE YOU RECEIVE YERVOY:
You should not receive YERVOY:
- if you are allergic (hypersensitive) to ipilimumab or any of the other ingredients of **YERVOY** (see **WHAT YERVOY CONTAINS**).

Children
YERVOY should not be used in children below 18 years of age.

Take special care with YERVOY:
- if you have, or develop, any of the conditions listed below:
  - **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 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, behavioural changes, dizziness or lightheadedness, sweating, rapid heart rate, weight loss or weight gain.
  - **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 if 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 healthcare professional 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).

Pregnancy and breastfeeding:
Do not use **YERVOY** if you are pregnant. 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 highly 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 the active substance, ipilimumab, gets into breast milk.
You should not breastfeed your baby when receiving **YERVOY**.

Important information about some of the ingredients of YERVOY:
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.

Effects on ability to drive and to use 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.

Using other medicines with YERVOY:
Always tell your healthcare professional if you are taking any other medicine.
(This includes complementary or traditional medicines.)
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**.

Do not take any other medicines during your treatment without talking to your doctor first.
The combination of **YERVOY** and vemurafenib (another medicine used for the treatment of melanoma) is not recommended.

4. 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.
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 receive more YERVOY than you should
Since a healthcare professional will administer **YERVOY,** he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

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 **YERVOY**. 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 **YERVOY**, ask your doctor.

5. POSSIBLE SIDE EFFECTS:
YERVOY can have side effects.
Not all side effects reported for YERVOY are included in this leaflet.
Should your general health worsen or if you experience any untoward effects while receiving YERVOY, please consult your doctor, pharmacist or other healthcare professional for advice.
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.
YERVOY can also cause hypersensitivity (allergic) reactions.
Tell your doctor immediately if you get any of the following side effects:
Do not try to treat your symptoms with other medicines.

The following side effects have been reported in clinical trials:
Frequent
- diarrhoea, vomiting or feeling sick (nausea)
- bleeding in the stomach or intestine, inflammation of the intestines (colitis), constipation, heartburn, stomach pain
- underactive function of the thyroid gland which can cause tiredness or weight gain, underactive function of the pituitary gland which can cause low blood pressure, dizziness, tiredness
- skin rash, itching
- 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
- abnormal function of the liver which can be associated with eye or skin yellowing (jaundice), pain on the right side of your stomach area, tiredness, itching (pruritus)
- 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
- pain in muscles and joints, muscle spasms
- feeling tired or weak, reaction at site of injection, fever
- loss of appetite
- weight loss
- shivering, lack of energy, swelling, pain
- tumour pain

Less frequent
- bowel perforation, inflammation 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
- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)
- 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, hyperpituitarism which can cause: rapid heart rate, sweating, weight loss or could also cause: high blood pressure, high blood glucose, weight gain, fragile skin, easy bruising, weakness
- allergic reaction, serious, potential life-threatening allergic reaction (hives (red itchy welts), rash, itching, or swelling of your lips, tongue, throat, or face; shortness of breath or wheezing or sudden cough; dizziness or feeling faint or palpitations (feel like your heart is racing or fluttering)
- 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
- 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
- liver failure, inflammation of the liver, enlarged liver, yellowing of the skin or eyes (jaundice)
- kidney function failure, kidney disease
- irregular or abnormal heart beat
- extreme difficulty in breathing, fluid accumulation in the lungs, inflammation of the lungs, hay fever
- changes in mental health, depression, lowered sex drive
- 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, eye muscle inflammation
- inflammation of the blood vessels, disease of the blood vessels, restriction in the blood supply to the extremities, low blood pressure when standing up
- inflammation of the muscles causing pain or stiffness in the hip and shoulder, painful joints
- absence of menstrual periods
- multi organ dysfunction, reaction related to infusion of the medicine
- 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)
- 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)
- inflammation of the chest or abdomen that can lead to fluid collection around the lungs or intestines
- change in hair colour
- flu-like discomfort
- multi-organ inflammation
- inflammation of the heart that can lead to weakness of the heart muscle or fluid around the heart
- decreased hearing
- inflammation that can lead to decreased function of several organs of your body including; the liver, the thyroid gland, the kidney, the pancreas, the brain or the lymph glands

Changes in test results
YERVOY may cause changes in the results of tests carried out by your doctor. These include:
- 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
- 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)

6. STORING AND DISPOSING OF YERVOY:
Store all medicines out of reach of children.
Store under refrigeration at 2 °C to 8 °C.
Store in the original package in order to protect from light.
Do not freeze.
For single use only. Discard any unused portion.
Once opened, the product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/ml and 4 mg/ml) has been demonstrated for 24 hours at 25 °C and 2 °C to 8 °C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours either under refrigeration (2 °C to 8 °C) or at room temperature (25 °C).
Do not use **YERVOY** 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.

7. PRESENTATION OF YERVOY:
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.

8. IDENTIFICATION OF YERVOY:
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, amorphous ipilimumab particulates.

9. REGISTRATION NUMBER:
47/30.1/0522

10. NAME AND ADDRESS OF REGISTRATION HOLDER:
Equity Pharmaceuticals (Pty) Ltd.
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Route 21 Corporate Park
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Irene Pretoria
Tel: 012 3451747

APPROVED
By Petra van Rooyen at 2:50 pm, May 17, 2019

11. DATE OF PUBLICATION:
02 October 2014
30 September 2016
YERVOY is a trademark of Bristol-Myers Squibb Company, used under license by Equity Pharmaceuticals (Pty) Ltd.

Bristol-Myers Squibb

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Live Text:	☒ Yes / ☐ No	Production Site:	Anagni
Country:	ZA	CTM:	Emiliano Parisi
Product Name:	INS YERVOY FCT	Printing Colours:	Black
Product Code:	1336887A1		
Barcode Type:	2/5 (6509)		
Format/Dimension:	860 x 300 (90 x 45) mm		
Font Size Text:	7 pt	Technical Colours:	Diecut
Min. Font Size Text:	7 pt		
Line Space:	7,5 pt (2,6 mm)		
Proof No.: 3	16.05.2019 Manconi		
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SKEDULERINGSTATUS:
Skedule S4

HANDELSNAAM, STERKTE EN DOSERINGSVORM:
YERVOY® 5 mg/ml oplossing vir infusie

Lees die hele pamflet deeglik deur voordat jy YERVOY ontvang
- Hou hierdie pamflet. Dit is moontlik dat jy dit weer sal wil deurlees.
- Indien jy nog vrae het, vra asseblief jou dokter of apteker.
- **YERVOY** is vir jou persoonlik voorgeskryf en jy moet nie jou medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al is hulle simptome dieselfde as joune.

1. WAT YERVOY BEVAT:
Elke flessie bevat 5 mg/ml ipilimumab.
Onaktiewe bestanddele:
Tris-hidrochloried, natriumchloried, mannitol, penteensuur, polisorbaat 80 en water vir inspuiting.

2. WAARVOOR YERVOY GEBRUIK WORD
YERVOY bevat die aktiewe bestanddeel ipilimumab, 'n proteïen wat jou immuunstelsel help om kankerselle deur jou immuunselle te val en te vernietig.
YERVOY word gebruik om gevorderde melanoom ('n tipe velkanker) by volwassenes te behandel.

3. VOORDAT JY YERVOY ONTVANG:
Jy moet nie YERVOY ontvang nie:
- indien jy allergies (hipersensitief) is vir ipilimumab of vir enige van die ander bestanddele van **YERVOY** (kyk **WAT YERVOY BEVAT**).

Kinders
YERVOY moet nie gebruik word by kinders onder 18 jaar oud nie.

Wees ekstra versigtig met YERVOY:
- as jy enige van die onderstaande siektetoestande het, of dit ontwikkel:
  - **ontsteking van die derms (kolitis)** wat kan vererger of oorgaan in bloedings of dermperforasie. Tekens en simptome van kolitis kan bestaan uit diarree (waterige, los of sagte ontlasting), 'n ongewone toename in die aantal ontlastings, bloed in jou ontlasting of donkerkleurige ontlasting, pyn of teerheid in jou maagstreek.
  - **ontsteking van die lewer (hepatitis)** wat kan lei tot lewerversaking. Tekens en simptome van hepatitis kan bestaan uit geelwordende oë of vel (geelsug), pyn aan die regterkant van jou maagstreek, moegheid.
  - **ontsteking van die vel** wat kan lei tot ernstige velreaksie (toksiese epidermale nekrolise). Tekens en simptome van ernstige velreaksie kan bestaan uit veluitslag, met of sonder jeuk, afskilferende vel**,** droë vel.
  - **ontsteking van die senuwees** wat kan lei tot verlamming. Simptome van senuweeprobleme kan bestaan uit spierswakte, gevoelloosheid of 'n tintelende gevoel in jou hande of voete, verlies aan bewussyn of moeilik wakker word.
  - **ontsteking van die hormoonproduserende kliere** (veral die hipofise, bynier en skildklier) wat die werking van hierdie kliere kan beïnvloed. Tekens en simptome dat jou kliere nie behoorlik werk nie kan bestaan uit hoofpyne, dowwe sig of dubbelvisie, moegheid, afname in seksuele dryfkrag, gedragsveranderinge, duiseligheid of lighoofdigheid, sweet, vinnige hartslag, gewigsverlies of gewigstoename.
  - **inflammasie van die oë**. Tekens en simptome kan bestaan uit rooiheid van die oë, pyn in die oë, probleme met visie of dowwe visie.

Vertel jou dokter dadelik as jy hierdie tekens of simptome het, of as dit erger word. **Moenie probeer om jou simptome met ander medisyne te behandel nie.** Jou dokter kan jou voorsien van ander medisyne om meer ernstige komplikasies te voorkom en om jou simptome te verminder, of hy/sy kan die volgende dosis **YERVOY** uitstel, of jou behandeling met **YERVOY** heeltemal stopsit.
Let asseblief daarop dat hierdie tekens en simptome soms later na vore kan kom en dat dit weke of maande na jou laaste dosis kan ontstaan. Voordat jy behandeling kry, sal jou dokter jou algemene gesondheid kontroleer. Jy sal ook bloedtoetse tydens die behandeling ondergaan.

Raadpleeg eers jou dokter of professionele gesondheidsorgkundige voordat YERVOY aan jou gegee word:
- indien jy 'n **outo-immuunsiekte** het ('n siektetoestand waarby die liggaam sy eie selle aanval);
- indien jy tans **chroniese virusinfeksie van die lewer** het, waaronder hepatitis B (HBV) of hepatitis C (HCV), of as jy dit voorheen gehad het;
- as jy 'n infeksie met **mens-immuungebreksvirus** (MIV) het, of verworwe immuungebreksindroom (VIGS).

Swangerskap en borsvoeding:
Moenie **YERVOY** gebruik as jy swanger is nie. Die uitwerkings van **YERVOY** by swanger vroue is onbekend, maar dit is moontlik dat die aktiewe bestanddeel, ipilimumab, 'n ongebore baba kan beskadig.
- As jy 'n vrou is wat swanger kan raak, moet jy doeltreffende voorbehoeding gebruik terwyl jy met **YERVOY** behandel word.
- Indien jy swanger raak terwyl jy **YERVOY** gebruik, vertel jou dokter.

Dit is nie bekend of die aktiewe bestanddeel, ipilimumab, in borsmelk voorkom nie.
Jy moet nie jou baba borsvoed terwyl jy **YERVOY** ontvang nie.

Belangrike inligting oor sommige van die bestanddele van YERVOY:
Vertel jou dokter as jy op 'n lae-natrium (lae-sout) dieet is, voordat **YERVOY** aan jou toegedien word. Dit bevat 2,3 mg natrium per ml konsentraat.

Effek op die vermoë om te bestuur en masjinerie te gebruik:
Moenie bestuur of masjinerie gebruik nadat **YERVOY** aan jou toegedien is nie, tensy jy seker is dat jy goed voel. 'n Moeë of swak gevoel is 'n baie algemene newe-effek van **YERVOY**. Dit kan jou vermoë om te bestuur of masjinerie te gebruik aantas.

Die gebruik van ander medisyne met YERVOY:
Lig altyd jou professionele gesondheidsorgkundige in as jy enige ander medisyne neem.
(Dit sluit komplementêre of tradisionele medisyne in.)
Voordat **YERVOY** aan jou toegedien word, lig jou dokter in:
- as jy tans enige medisyne neem wat jou immuunstelsel onderdruk, soos kortikosteroïede. Hierdie medisyne kan die effek van **YERVOY** beïnvloed. As jy egter reeds met **YERVOY** behandel word, kan jou dokter kortikosteroïede aan jou toedien om die newe-effekte te verminder wat jy met **YERVOY** kan hê.
- indien jy enige medisyne neem wat bloedklonting voorkom (antistolmiddels). Hierdie medisyne kan die kans op 'n bloeding in die maag of derms verhoog, wat 'n newe-effek is van **YERVOY**.

Moenie enige ander medisynes tydens jou behandeling gebruik sonder dat jy eers met jou dokter gepraat het nie.
Die kombinasie van **YERVOY** en vemurafenib ('n ander medisyne wat gebruik word vir die behandeling van melanoom) word nie aanbeveel nie.

4. HOE YERVOY GEGEE WORD:
YERVOY sal in die hospitaal of kliniek aan jou gegee word onder die toesig van 'n ervare dokter.
Dit sal aan jou toegedien word as 'n infusie ('n indruppeling) in die aar (binneaars) vir die duur van 90 minute.
Die hoeveelheid **YERVOY** wat aan jou gegee word sal uitgewerk word volgens jou liggaamsgewig.
Jy sal eenmaal elke 3 weke met **YERVOY** behandel word, vir altesaam 4 dosisse.
Na verwagting kan jy met die behandeling met **YERVOY** opmerk dat daar nuwe letsels op jou vel ontstaan, of dat bestaande letsels verder groei.
Jou dokter sal aanhou om **YERVOY** aan jou te gee vir altesaam 4 dosisse, afhangende van hoe jy die behandeling verdra.

Indien jy meer YERVOY ontvang as wat jy moet
Aangesien **YERVOY** deur 'n gesondheidsorgkundige toegedien word, sal hy/sy die dosering kontroleer. In geval van 'n oordosering, sal jou dokter die oordosering hanteer.

Indien jy 'n dosis van YERVOY oorslaan
Dit is baie belangrik dat jy hou by al jou afsprake om **YERVOY** te ontvang. Indien jy nie 'n afspraak nagekom het nie, vra jou dokter wanneer jou volgende dosis beplan kan word.

Indien jy ophou om YERVOY te gebruik
Staking van jou behandeling kan die effek van **YERVOY** stop. Moenie behandeling met **YERVOY** staak nie, tensy jy dit met jou dokter bespreek het.
Indien jy nog vrae het oor jou behandeling of die gebruik van **YERVOY**, vra jou dokter.

5. MOONTLIKE NEWE-EFFEKTE:
YERVOY kan newe-effekte hê.
Nie alle newe-effekte wat vir YERVOY aangemeld is, is by hierdie inligtingsblad ingesluit nie.
Indien jou algemene gesondheid agteruitgaan of jy enige ongunstige effekte ervaar terwyl jy YERVOY ontvang, raadpleeg asseblief jou dokter, apteker of ander professionele gesondheidsorgkundige.
Let op vir belangrike simptome van ontsteking.
YERVOY werk op jou immuunstelsel en kan **ontsteking** veroorsaak in dele van jou liggaam.
Ontsteking kan ernstige skade aan jou liggaam veroorsaak en sommige siektetoestande weens ontsteking kan lewensbedreigend wees. **YERVOY** kan ook hipersensitiwiteitsreaksies (allergie) veroorsaak.

Lig jou dokter dadelik in as jy enige van die volgende newe-effekte kry:
Moenie probeer om jou simptome met ander medisynes te behandel nie.
Die volgende newe-effekte is met kliniese proewe aangemeld:
Dikwels
- diarree, braking of naarheid (siek gevoel)
- bloeding in die maag of derms, ontsteking van die derms (kolitis), hardlywigheid, sooibrand, maagpyn
- onderaktiewe skildklierwerking, wat moegheid en gewigstoename kan veroorsaak, onderaktiewe hipofisewerking wat lae bloeddruk, duiseligheid en moegheid kan veroorsaak
- veluitslag, jeuk
- ontsteking en rooiheid van die vel, velverkleuring in vlekke (vitiligo), galbulte (jeukende knopperige uitslag), haarverlies of hare word dunner, uitermatige nagsweet, droë vel
- abnormale lewerfunksie wat gekenmerk word deur geel oë of vel (geelsug), pyn aan die regterkant van die maagstreek, moegheid, jeuk (pruritus)
- dehidrasie
- verwarring
- skade aan die senuwees (met gevolglike pyn, swakheid en krampe), duiseligheid, hoofpyn
- dowwe visie, pyn in die oë
- lae bloeddruk, tydelike rooiheid van die gesig en nek, gevoel van hewige warmte met sweet en versnelde hartslag
- kortasemigheid, hoes
- pyn in die spiere en gewrigte, spierspasmas
- voel moeg of swak, reaksie by die plek van inspuiting, koors
- verlies aan eetlus
- gewigsverlies
- koue rillings, gebrek aan energie, swelling, pyn
- pyn in die gewas

Minder dikwels
- deurbraak van die derm, ontsteking van die maagwand, ontsteking van die dunderm, ontsteking van die dikderm of die pankreas, maagsweer, ontsteking van die slukderm, verstopping van die derms
- ernstige en moontlike noodlottige afskilfering van die vel (toksiese epidermale nekrolise)
- onderaktiewe bynierwerking, ooraktiewe skildklierwerking, wat kan lei tot: vinnige hartklop, sweet en gewigsverlies, probleem met die kliere wat sekshormone vervaardig, hiperhipofisisme wat: vinnige hartklop, sweet, gewigsverlies, of ook: hoë bloeddruk, hoë bloedglukose, gewigstoename, brose vel, maklike kneusplekke en swakheid kan veroorsaak.
- allergiese reaksie, ernstige, moontlike lewensbedreigende allergiese reaksie (galbulte (rooi, jeukerige uitslag), uitslag, jeukerige of geswelde lippe, tong, keel of gesig; kortasemigheid, asemfluit of skielike hoes; duiseligheid of 'n flou gevoel of hartkloppings (voel asof jou hart versnel of fladder)).
- ernstige en moontlik lewensbedreigende senuwee-ontsteking wat lei tot pyn, swakheid of verlamming in die ledemate (Guillain-Barré-sindroom), floute, senuwee-ontsteking in die brein, oormatige ophoping van vog in die brein, moeilike koördinering van bewegings (ataksie), bewe, kort onwillekeurige spiersametrekkings, spraakprobleme
- ernstige bakteriële infeksie van die bloed (sepsis, septiese skok), ontsteking om die brein en rugmurg, ontsteking van die maag en derms, ontsteking van die maagwandmembraan (dit veroorsaak koors, braking en maagpyn), urienweginfeksie, infeksie van die asemhalingsweg
- lewerversaking, ontsteking van die lewer, vergrote lewer, vergeling van die vel of oë (geelsug)
- nierversaking, niersiekte
- ongereelde of abnormale hartslag
- uiterste asemhalingsprobleme, ophoping van vog in die longe, longontsteking, hooikoors
- veranderinge in geestelike gesondheid, depressie, verminderde seksdryfkrag
- oogontsteking, wat lei tot rooiheid of pyn, bloeding in die oog, ontsteking van die gekleurde deel van die oog, verswakte visie, 'n gevoel dat daar iets in die oog sit, geswelde waterige oë, ontsteking van die oogspier
- ontsteking van die bloedvate, bloedvatsiekte, beperkte bloedtoevoer na die ledemate, lae bloeddruk met regop staan
- ontsteking van die spiere, wat pyn of styfheid in die heup en skouer veroorsaak, pynlike gewrigte
- maandstondes bly weg
- versteurde funksie van meervoudige organe, 'n reaksie op die infusie van die geneesmiddel
- 'n aantal simptome veroorsaak deur kanker in die liggaam, soos hoë konsentrasies kalsium en cholesterol in die bloed en lae konsentrasies suiker in die bloed (paraneoplastiese sindroom)
- 'n aantal metaboliese komplikasies wat na kankerbehandeling na vore tree, gekenmerk deur hoë konsentrasies kalium en fosfaat in die bloed en lae konsentrasies kalsium in die bloed (tumorlisesindroom).
- ontsteking van die longe of buikholte wat kan lei tot vloeistofversameling rondom die longe en ingewande
- verandering in haarkleur
- griepagtige ongemak
- ontsteking in vele organe
- ontsteking van die hartspier wat kan lei tot swakheid van die hartspier of vloeistof om die hart
- gehoor verswak
- ontsteking wat kan lei tot verminderde aktiwiteit in verskeie van jou liggaamsorgane, waaronder: die lewer, die skildklier, die nier, die pankreas, die brein of limfkliere

Veranderinge in toetsresultate
YERVOY kan veranderinge veroorsaak in die resultate van toetse wat deur jou dokter uitgevoer word. Dit sluit in:
- 'n abnormale variasie in die hormone en lewerensieme in die bloed
- abnormale lewerfunksiewaardes
- abnormale konsentrasies kalsium, natrium, fosfaat of kalium in die bloed
- aanwesigheid van bloed of proteïene in die urien
- 'n abnormale hoë alkaliniteit van die bloed en ander liggaamsweefsels
- niere wat nie sure op 'n normale manier uit die bloed kan verwyder nie
- 'n variasie in die aantal rooibloedselle (wat suurstof vervoer), witbloedselle (wat 'n belangrike rol speel by infeksiebestryding) of plaatjies (selle wat die bloed help stol)

6. BERGING EN WEGDOENING VAN YERVOY:
Hou alle medisyne buite bereik van kinders.
Bewaar in 'n yskas by 2 °C tot 8 °C.
Bewaar in die oorspronklike verpakking om die inhoud teen lig te beskerm.
Moenie vries nie.
Slegs vir eenmalige gebruik. Gooi die ongebruikte gedeelte weg.
Sodra dit oopgemaak is, moet die produk, of die verdunde produk, dadelik ingedrup word. Die chemiese en fisiese in-gebruik stabiliteit van die onverdunde of verdunde konsentraat (tussen 1 mg/ml en 4 mg/ml) is vir 24 uur by 25 °C en by 2 °C tot 8 °C aangetoon. Indien dit nie dadelik gebruik word nie, kan die infusie oplossing (onverdun of verdun) tot en met 24 uur, óf in 'n yskas (2 °C tot 8 °C) óf by kamertemperatuur (25 °C), bewaar word.
Moenie **YERVOY** gebruik na die vervaldatum wat op die kartonhouer en die flessie se etiket na "EXP." aangedui word nie. Die vervaldatum dui op die laaste dag van daardie maand.

7. AANBIEDING VAN YERVOY:
10 ml van 'n 5 mg/ml steriele konsentraat in 'n helder, kleurlose flessie (tipe I glas) met 'n grys prop (bedekte butielrubber) en 'n ligblou afwip-deksel (aluminium). Verpakkingsgrootte van 1.
OF
40 ml van 'n 5 mg/ml steriele konsentraat in 'n helder, kleurlose flessie (tipe I glas) met 'n grys prop (bedekte butielrubber) en 'n pers afwip-deksel (aluminium). Verpakkingsgrootte van 1.

8. IDENTIFIKASIE VAN YERVOY:
YERVOY is 'n steriele, preserveermiddelvrye, helder tot effens opaalagtige, kleurlose tot liggeel oplossing vir binneaarse infusie, wat 'n klein hoeveelheid sigbare, deursigtige-tot-wit, amorfe, ipilimumab-deeltjies kan bevat.

9. REGISTRASIENOMMER:
47/30.1/0522

10. NAAM EN ADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:
Equity Pharmaceuticals (Edms) Bpk.
Sovereignrylaan 100
Route 21 Corporate Park
Nellmapiusrylaan
Irene Pretoria
Tel: 012 3451747

11. DATUM VAN PUBLIKASIE:
02 Oktober 2014
30 September 2016
YERVOY is 'n handelsmerk van Bristol-Myers Squibb Company; gebruik onder lisensie deur Equity Pharmaceuticals (Edms) Bpk.

SKEDULERINGSTATUS: S4

HANDELSNAAM EN DOSEERVORM
YERVOY® 5 mg/ml oplossing vir infusie

SAMESTELLING
Elke flessie bevat 5 mg/ml ipilimumab.
Onaktiewe bestanddele:
Tris-hidrochloried, natriumchloried, mannitol, penteensuur, polisorbaat 80, natriumhidroksied (pH-instelling), soutsuur (pH-instelling) en water vir inspuiting.

FARMAKOLOGIESE KLASSIFIKASIE
A 30.1 Antiliggame

FARMAKOLOGIESE WERKING
Farmakodinamiese eienskappe
Ipilimumab is 'n rekombinante mens-monoklonale antiliggaam wat aan die sitotoksiese T-limfosietverwante antigeen 4 (CTLA-4) bind. Ipilimumab is 'n IgG1-kappa immunoglobulien met 'n benaderde molekulêre gewig van 148 kDa. Ipilimumab word in soogdierselkultuur (Chinese hamsterovarium) deur rekombinante DNS-tegnologie vervaardig. CTLA-4 is 'n negatiewe reguleerder van T-selaktivering. Ipilimumab is 'n T-sel-stimulator wat spesifiek die remmende sein van CTLA-4 blokkeer, wat lei tot gevolglike T-selaktivering, proliferasie en limfosietinfiltrasie in gewasse, met gevolglike tumorseldood. Die werkingsmeganisme van ipilimumab geskied indirek, deur die versterking van die T-selbemiddelde immuunrespons.
By pasiënte met melanoom wat ipilimumab ontvang het, het die gemiddelde absolute aantal limfosiete (ALC) in perifere bloed tydens die hele dosisinduksieperiode toegeneem.
In die perifere bloed van pasiënte met melanoom is 'n gemiddelde styging in die persentasie geaktiveerde HLA-DR$^+$ CD4$^+$ en CD8$^+$ T-selle na behandeling met ipilimumab waargeneem, wat strook met die werkingsmeganisme. Daar is ook 'n gemiddelde styging in die persentasie sentrale geheue (CCR7$^+$ CD45RA$^-$) CD4$^+$ en CD8$^+$ T-selle en 'n kleiner, maar beduidende, gemiddelde styging in die persentasie effektor geheue (CCR7$^-$ CD45RA$^-$) CD8$^+$ T-selle na behandeling met ipilimumab waargeneem.

Farmakokinetiese eienskappe
Die farmakokinetika van ipilimumab is bestudeer by 498 pasiënte met melanoom in 'n gevorderde stadium wat induksiedosisse gekry het wat gewissel het van 0,3 tot 10 mg/kg, elke drie weke toegedien, gedurende 4 dosisse. Die K_{maks}, K_{min} en AOK van ipilimumab het geblyk proporsioneel te wees met die dosis binne die bestek van die doserings wat ondersoek is. Na herhaalde toediening van ipilimumab wat elke 3 weke toegedien is, blyk dit dat die opruiming nie wissel met die tyd nie en is 'n minimale sistemiese ophoping waargeneem aan die hand van 'n ophopingsindeks van 1,5 of laer vir K_{maks}, K_{min} en AOK. Ipilimumab ewewigstoestand is bereik met die derde dosis, wat eenmaal elke 3 weke toegedien was. Gebaseer op die populasie- farmakokinetiese analise, is die volgende farmakokinetiese parameters van ipilimumab verkry: 'n mediane terminale halfleeftyd van 15 dae (standaardafwyking (SA) 4,62 dae); 'n meetkundige gemiddelde sistemiese opruiming van 15,3 ml/h met 'n variasiekoëffisiënt persentasie (VK %) van 38,5 %; en 'n meetkundige gemiddelde verspreidingsvolume by ewewigstoestand van 7,22 l met 'n VK % van 10,5 %. By ewewigstoestand, wat met 'n 3 mg/kg induksieregimen bereik was, was die gemiddelde (± SA) ipilimumab serumtrogkonsentrasies 21,8 µg/ml (± 11,2).

Spesiale populasies:
Die opruiming van ipilimumab het met 'n hoër liggaamsmassa en met hoër basislynwaarde van laktaatdehidrogenase (LDH) toegeneem. Daar is egter geen dosisaanpassing nodig nie vir verhoogde LDH of liggaamsmassa, na toediening wat op mg/kg gebaseer is. Die opruiming van ipilimumab is nie deur ouderdom (reikwydte 26 tot 86 jaar), geslag, lewerfunksie (bepaal aan die hand van albumien en alkaliese fosfatase), gelyktydige gebruik van mondelike budesonied, nierfunksie (geskatte GFT 22 ml/min of meer), prestasiestatus, HLA-A2*0201-status en voorafgaande sistemiese kankerbehandeling geraak nie.

Pediatriese pasiënte:
Die veiligheid en doeltreffendheid van **YERVOY** by pediatriese pasiënte is nie bepaal nie.

Bejaarde pasiënte:
Oor die algemeen is daar nie verskille in veiligheid of doeltreffendheid tussen die bejaardes (65 jaar en ouer) en jonger pasiënte (onder 65 jaar) gerapporteer nie.

Nierontoereikendheid:
Die veiligheid en doeltreffendheid van **YERVOY** is nie by pasiënte met nierontoereikendheid ondersoek nie.

Lewerontoereikendheid:
Die veiligheid en doeltreffendheid van **YERVOY** is nie by pasiënte met lewerontoereikendheid ondersoek nie.

INDIKASIES
YERVOY word aangedui vir die behandeling van voorheen-behandelde onopereerbare of metastatiese melanoom.

KONTRA-INDIKASIES
Hipersensitiwiteit vir ipilimumab of vir enige van die ander bestanddele in die formulering (kyk **SAMESTELLING**).

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS
YERVOY word geassosieer met inflammatoriese newe-effekte wat die gevolg is van verhoogde of buitensporige immuunwerking (immuunverwante newe-effekte), wat waarskynlik in verband staan met die werkingsmeganisme. Immuunverwante newe-effekte, wat ernstig of lewensbedreigend kan wees, kan die maagdermkanaal, die lewer, die vel, die senuweestelsel, die endokrienstelsel of ander orgaansisteme betrek. Alhoewel die meeste immuunverwante newe-effekte tydens die induksieperiode voorgekom het, is aanvang daarvan ook maande na die laaste dosis van YERVOY gerapporteer. Tensy daar 'n alternatiewe etiologie bepaal is, moet diarree, verhoogde frekwensie van stoelgange, bloed in die ontlasting, verhoogde lewerfunksiewaardes (LFT), huiduitslag en endokrinopatie as inflammatories en YERVOY-verwant beskou word. Vroeë diagnose en voldoende behandeling van die newe-effekte is noodsaaklik om lewensbedreigende komplikasies te beperk.
Sistemiese behandeling met 'n hoë-dosis kortikosteroïed, met of sonder toegevoegde immuunonderdrukkende terapie, kan nodig wees vir die beheer van ernstige immuunverwante newe-effekte.

Immuunverwante gastro-intestinale reaksies
YERVOY is geassosieer met ernstige immuunverwante gastro-intestinale reaksies. Sterftes te wyte aan gastro-intestinale perforasie is gerapporteer (kyk **NEWE-EFFEKTE).**
Pasiënte moet gemoniteer word vir gastro-intestinale tekens en simptome wat aanduidend kan wees van immuunverwante kolitis of gastro-intestinale perforasie. Dit kan klinies voordoen as diarree, verhoogde frekwensie van stoelgange, buikpyn, of hematochesie, met of sonder koors. Diarree of kolitis wat voorkom na aanvang van **YERVOY** moet sonder versuim geëvalueer word om infeksie of ander oorsake van siekte uit te skakel. In kliniese proewe is immuunverwante kolitis geassosieer met bewyse van slymvliesinflammasie, met of sonder swere, en limfosiet- en neutrofiel-infiltrasie.

Aanbevelings vir die beheer van diarree of kolitis is gebaseer op die erns van die simptome:
- Pasiënte met 'n ligte tot matige (graad 1 of 2) diarree ('n toename tot en met 6 stoelgange per dag), of vermeende ligte tot matige kolitis (bv. buikpyn of bloed in die stoelgang) kan op **YERVOY** bly. Simptomatiese behandeling (bv. loperamied, vloeistofvervanging) en deeglike monitering word aangeraai. Indien ligte tot matige simptome terugkeer of vir 5 - 7 dae aanhou, moet die beplande dosis van **YERVOY** uitgestel word en moet behandeling met 'n kortikosteroïed (bv. prednisoon 1 mg/kg mondelik een keer per dag, of ekwivalent) begin word. Indien daar 'n vermindering is in die graad van erns tot graad 0 - 1, of teruggekeer word tot basislyn, kan **YERVOY** hervat word met die volgende beplande dosis. Dosisse wat uitgestel is as gevolg van 'n newe-effek moet nie vervang word nie.
- **YERVOY** moet permanent gestaak word by pasiënte met ernstige (graad 3 of 4) diarree of kolitis en behandeling met 'n hoë-dosis binneaarse kortikosteroïed (bv. metielprednisoloon 2 mg/kg/dag) moet dadelik begin word. Sodra diarree en ander simptome onder beheer is, moet vermindering van die kortikosteroïed oor 'n tydperk van ten minste 1 maand geskied.
  In kliniese proewe het vinnige vermindering (oor periodes < 1 maand) gelei tot die terugkeer van diarree of kolitis by sommige pasiënte. Pasiënte moet geëvalueer word vir tekens van gastro-intestinale perforasie of peritonitis.
  Vir die beheer van diarree of kolitis wat nie reageer op kortikosteroïede nie, kan die toevoeging van 'n alternatiewe immuunonderdrukkende middel tot die behandeling met die kortikosteroïed oorweeg word. In kliniese proewe is 'n enkele dosis van infliksimab 5 mg/kg bygevoeg, tensy teenaangedui. Infliksimab moet nie gebruik word indien gastro-intestinale perforasie of sepsis vermoed word nie. Verwys na die voorskrifinligting vir infliksimab.

Kyk **DOSIS EN GEBRUIKSAANWYSINGS – Aanbevole dosisaanpassings**.

Immuunverwante hepatotoksisiteit
YERVOY word geassosieer met ernstige immuunverwante hepatotoksisiteit. Noodlottige lewerversaking is gerapporteer (kyk **NEWE-EFFEKTE**).
By pasiënte wat **YERVOY** 3 mg/kg monoterapie in MDX010-20 ontvang het, was die aanvangstyd vir matig-tot-ernstige of noodlottige (graad 2 – 5) immuunverwante hepatotoksisiteit vanaf 3 tot 9 weke nadat die behandeling begin is. Met die protokol-gespesifiseerde behandelingsriglyne het die tyd tot opklaring gestrek vanaf 0,7 tot 2 weke.
Die hepatiese transaminase en bilirubien moet voor elke dosis van **YERVOY** getoets word, omdat vroeë veranderings in laboratoriumtoetse aanduidend kan wees van 'n ontluikende immuunverwante hepatitis. Stygings in LFT (lewerfunksietoetse) kan ontwikkel sonder dat kliniese simptome teenwoordig is.
Stygings in aspartaat-transaminase (AST) en alanien-transaminase (ALT) of totale bilirubien moet ondersoek word om ander oorsake van lewerbeskadiging, waaronder infeksies, tumorgroei, of gelyktydige medikasie, uit te sluit en dit moet gemoniteer word totdat dit opgeklaar het. Biopsies van die lewer van pasiënte wat immuunverwante hepatotoksisiteit gehad het, het tekens van akute inflammasie (neutrofiele, limfosiete en makrofage) getoon.
YERVOY moet met versigtigheid toegedien word aan pasiënte met transaminasevlakke van 5 keer die bogrens van normaal (BGN) of meer, of bilirubienvlakke van meer as 3 keer die BGN by basislyn.
- By pasiënte met verhoogde AST of ALT binne die bestek van > 5 – ≤ 8 x die BGN of totale bilirubien binne die bestek van > 3 – ≤ 5 x die BGN wat vermoedelik in verband staan met **YERVOY**, moet die beplande dosis van **YERVOY** uitgestel word en LFT gemoniteer word totdat dit genormaliseer het. Nadat LFT-vlakke verbeter (AST en ALT ≤ 5 x BGN en totale bilirubien ≤ 3 x BGN), kan **YERVOY** met die volgende beplande dosis hervat word. Dosisse wat uitgestel is as gevolg van 'n newe-effek moet nie vervang word nie.
- By pasiënte met verhoogde AST of ALT > 8 x BGN of bilirubien > 5 x BGN wat vermoedelik in verband staan met **YERVOY**, moet die behandeling finaal gestaak word en moet behandeling met sistemiese hoë-dosis binneaarse kortikosteroïed behandeling (bv. metielprednisoloon 2 mg/kg daagliks of ekwivalent) dadelik begin word. By hierdie pasiënte moet LFT gemoniteer word totdat dit genormaliseer het. Wanneer simptome opgeklaar het en LFT volgehoue verbetering toon of tot basislyn terugkeer, moet vermindering van die kortikosteroïed oor 'n tydperk van ten minste 1 maand geskied. Verhoogde LFT tydens die verminderingsproses kan beheer word met 'n hoër dosis van die kortikosteroïed en deur 'n stadiger verminderingsproses.
- By pasiënte met beduidende stygings in LFT wat onvatbaar is vir kortikosteroïed behandeling, kan toevoeging van 'n alternatiewe immuunonderdrukkende middel tot die kortikosteroïed behandeling oorweeg word.

Kyk **DOSIS EN GEBRUIKSAANWYSINGS – Aanbevole dosisaanpassings**.

Immuunverwante newe-effekte van die vel
YERVOY is geassosieer met ernstige newe-effekte van die vel, wat immuunverwant kan wees. Noodlottige toksiese epidermale nekrolise is gerapporteer (kyk **NEWE-EFFEKTE**).
By pasiënte wat **YERVOY** 3 mg/kg as monoterapie in MDX010-20 ontvang het, was die mediane aanvangstyd van matig-tot-ernstige of noodlottige (graad 2 - 5) newe-effekte van die vel 3 weke (binne die bestek van 0,9 – 16 weke), vanaf aanvang van behandeling. Met die protokol-gespesifiseerde behandelingsriglyne, het opklaring by die meeste gevalle (87 %) voorgekom, met 'n mediane tyd vanaf die eerste simptome tot opklaring van 5 weke (binne die bestek van 0,6 tot 29 weke).

Veluitslag en pruritus wat deur YERVOY veroorsaak is, moet volgens graad van erns behandel word:
- Pasiënte met 'n ligte tot matige (graad 1 of 2) newe-effekte van die vel kan behandeling met **YERVOY** voortsit met simptomatiese behandeling (bv. antihistaminika). Vir ligte tot matige veluitslag of pruritus wat vir 1 tot 2 weke voortduur en nie verbeter met plaaslike kortikosteroïede nie, moet behandeling met mondelike kortikosteroïede begin word (bv. prednisoon 1 mg/kg eenmaal per dag of ekwivalent).
- Vir pasiënte met 'n ernstige (graad 3) newe-effek van die vel, moet die beplande dosis van **YERVOY** uitgestel word. Indien die aanvanklike simptome verbeter tot lig (graad 1) of opklaar, kan die behandeling met **YERVOY** met die volgende beplande dosis hervat word. Dosisse wat uitgestel is as gevolg van 'n newe-effek moet nie vervang word nie.
- **YERVOY** moet permanent gestaak word by pasiënte met ernstige (graad 4) uitslag of ernstige (graad 3) pruritus en behandeling met 'n hoë-dosis binneaarse kortikosteroïed (bv. metielprednisoloon 2 mg/kg/dag) moet dadelik begin word. Sodra die uitslag of pruritus onder beheer is, moet vermindering van die kortikosteroïed oor 'n tydperk van ten minste 1 maand geskied.
  Versigtigheid moet aan die dag gelê word wanneer daar oorweeg word om **YERVOY** te gebruik by 'n pasiënt wat voorheen 'n ernstige of lewensbedreigende ongunstige velreaksie op 'n vorige immuun-stimulerende kankerbehandeling gehad het.

Kyk **DOSIS EN GEBRUIKSAANWYSINGS – Aanbevole dosisaanpassings**.

Immuunverwante neurologiese newe-effekte
YERVOY is geassosieer met ernstige immuunverwante neurologiese newe-effekte. Noodlottige Guillain-Barré-sindroom is gerapporteer (kyk **NEWE-EFFEKTE**).
Miastenie gravis-agtige simptome is ook gerapporteer. Pasiënte kan ook spierswakte vertoon. Sensoriese neuropatie kan ook voorkom.
Panhipopituïtarisme is ook gerapporteer (kyk *"Immuunverwante endokrinopatie"* hieronder).
Onverklaarbare motoriese neuropatie, spierswakheid of sensoriese neuropatie wat > 4 dae voortduur, moet geëvalueer word en nie-inflammatoriese oorsake soos verslegtende siekte, infeksies, metaboliese sindroom en gepaardgaande medikasie, moet uitgesluit word.
- By pasiënte met matige (graad 2) neuropatie (motoriese, met of sonder sensoriese) wat waarskynlik in verband staan met **YERVOY**, moet die beplande dosis uitgestel word. Wanneer die neurologiese simptome weer opgeklaar het tot basislyn, kan die pasiënt **YERVOY** met die volgende beplande dosis hervat. Dosisse wat uitgestel is as gevolg van 'n newe-effek moet nie vervang word nie.
- **YERVOY** moet permanent gestaak word by pasiënte met ernstige (graad 3 of 4) sensoriese neuropatie wat vermoedelik verband hou met **YERVOY** en behandeling met 'n binneaarse kortikosteroïed (bv. metielprednisoloon 2 mg/kg/dag) moet dadelik begin word.
- Progressiewe tekens van motoriese neuropatie moet as immuunverwant beskou word en dienooreenkomstig behandel word. **YERVOY** moet permanent gestaak word by pasiënte met ernstige (graad 3 of 4) motoriese neuropatie, ongeag die oorsaak.

Kyk **DOSIS EN GEBRUIKSAANWYSINGS – Aanbevole dosisaanpassings**.

Immuunverwante endokrinopatie
YERVOY kan ontsteking van die organe van die endokriene stelsel veroorsaak, wat tot uiting kom as hipofisitis, hipopituïtarisme, bynierontoereikendheid en hipotiroïdisme (kyk **NEWE-EFFEKTE**) en pasiënte kan voordoen met nie-spesifieke simptome wat kan ooreenkom met ander oorsake soos breinmetastase of onderliggende siekte. Die mees algemene kliniese beeld behels hoofpyn en moegheid. Die simptome kan ook defekte in die gesigsveld, gedragsveranderings, elektrolietversteurings en hipotensie behels.
Bynierkrisis as 'n oorsaak van die pasiënt se simptome moet uitgesluit word.
Immuunverwante endokrinopatie wat met kliniese proewe waargeneem is kon oor die algemeen onder beheer gekry word met immuunonderdrukkende terapie en hormoonvervangingsterapie.
Indien daar tekens van 'n bynierkrisis is, soos ernstige dehidrasie, hipotensie, of skok, word onmiddellike toediening van binneaarse kortikosteroïede met mineralokortikoïede werking aanbeveel; die pasiënt moet ook geëvalueer word vir die teenwoordigheid van sepsis of infeksies.
By tekens van bynierontoereikendheid, sonder dat die pasiënt 'n bynierkrisis het, moet verdere ondersoeke gedoen word, waaronder laboratoriumtoetse en afbeeldings. Evaluering van die laboratoriumresultate vir beoordeling van die endokriene funksie kan uitgevoer word voordat die behandeling met kortikosteroïede begin word. As die beeldvorming van die bynier of die laboratoriumtoetse van die endokriene funksie abnormaal is, word 'n kortstondige kursus met hoë-dosis kortikosteroïede (bv. deksametasoon 4 mg elke 6 uur of ekwivalent) aanbeveel as behandeling vir die ontsteking van die aangetaste klier en moet die beplande dosis **YERVOY** uitgestel word. Dit is tans nie bekend of die behandeling met kortikosteroïede die klierfunksie herstel nie. Daar moet ook met 'n geskikte hormoonvervanging begin word. Langtermyn hormoonvervangingsterapie kan nodig wees.
Sodra die simptome of die laboratoriumafwykings onder beheer is en 'n algemene verbetering by die pasiënt merkbaar is, kan die behandeling met **YERVOY** hervat word en moet uitfasering van die kortikosteroïed oor 'n tydperk van ten minste 1 maand geskied.
Kyk **DOSIS EN GEBRUIKSAANWYSINGS – Aanbevole dosisaanpassings**.

Ander immuunverwante newe-effekte
Die volgende addisionele newe-effekte wat vermoedelik immuunverwant is, is gerapporteer: uveïtis, eosinofilie insluitend "DRESS"-sindroom, verhoogde lipase, glomerulonefritis, iritis, hemolitiese anemie, verhoogde amilase, multi-orgaanversaking, hartsakontsteking en pneumonitis (kyk **NEWE-EFFEKTE**).
Indien hierdie reaksies ernstig is (graad 3 of 4), kan onmiddellike behandeling met sistemiese hoë-dosis kortikosteroïede en beëindiging van **YERVOY** nodig wees.
Vir **YERVOY** verwante uveïtis, iritis of episkleritis, moet plaaslike kortikosteroïed-oogdruppels oorweeg word, indien medies aangedui.
Kyk **DOSIS EN GEBRUIKSAANWYSINGS – Aanbevole dosisaanpassings**.

Infusiereaksie
In die geval van 'n ernstige infusiereaksie moet **YERVOY** infusie gestaak word en geskikte mediese behandeling toegepas word. Pasiënte met 'n ligte of matige infusiereaksie kan **YERVOY** met deeglike monitering ontvang.

Pasiënte met outo-immuunsiekte
YERVOY moet vermy word by pasiënte met ernstige aktiewe outo-immuunsiekte waar verdere immuunaktivering potensieel dringend lewensbedreigend is.

Gelyktydige toediening met vemurafenib
Die gelyktydige toediening van **YERVOY** en vemurafenib word nie aanbeveel nie as gevolg van verhoogde toksisiteit.

Effek op die vermoë om te bestuur en masjinerie te gebruik
As gevolg van moontlike newe-effekte soos moegheid, moet pasiënte aangeraai word om versigtig te wees as hulle bestuur of masjinerie hanteer, totdat hulle seker is dat **YERVOY** hulle nie nadelig aantas nie.

INTERAKSIES
YERVOY (ipilimumab) is 'n mens-monoklonale antiliggaam wat nie deur sitochroom-P450-ensieme (CYPs) of ander metaboliserende ensieme gemetaboliseer word nie en sal na verwagting nie 'n effek op CYPs of ander metaboliserende ensieme in terme van inhibisie of induksie hê nie. Daar word dus nie verwag dat **YERVOY** farmakokineties-gebaseerde interaksies sal hê nie.

Ander vorms van interaksies
Kortikosteroïede
Die gebruik van sistemiese kortikosteroïede by basislyn, voordat daar met **YERVOY** begin word, moet vermy word want hulle kan die farmakodinamiese aktiwiteit en doeltreffendheid van **YERVOY** ontwrig. Sistemiese kortikosteroïede of ander immuunonderdrukkers kan egter nadat daar begin is met **YERVOY** gebruik word om immuunverwante newe-effekte te behandel.
Teenstolmiddels
Dit is bekend dat die gebruik van antistolmiddels die risiko vir gastro-intestinale bloeding verhoog. Aangesien gastro-intestinale bloeding 'n newe-effek van **YERVOY** is (kyk **NEWE-EFFEKTE**), moet pasiënte wat aanvullende antistolterapie nodig het akkuraat gemoniteer word.

SWANGERSKAP EN LAKTASIE
Die veiligheid en doeltreffendheid met swangerskap en laktasie is nie vasgestel nie.

Swangerskap:
YERVOY word nie aanbeveel tydens swangerskap nie. Vrugbare vroue moet hoogs doeltreffende voorbehoeding toepas.

Laktasie:
Dit is nie bekend of ipilimumab in borsmelk uitgeskei word nie. As gevolg van die moontlikheid van newe-effekte by borsgevoede babas, moet **YERVOY** nie toegedien word aan vrouens wat hul babas borsvoed nie.

DOSIS EN GEBRUIKSAANWYSINGS
YERVOY moet onder die toesig van professionele gesondheidsorgkundiges, wat ervaring met die behandeling van kanker het, toegedien word.
YERVOY moet nie as 'n binneaarse stoot- of bolusinspuiting toegedien word nie.

Aanbevole dosering:
Die aanbevole induksieregimen van **YERVOY** is 3 mg/kg, elke 3 weke binneaars vir 90 minute lank toegedien; altesaam vier dosisse word toegedien.
Pasiënte moet die volle induksieregimen (vier dosisse) kry, afhangende van hoe dit verdra word, ongeag die verskyning van nuwe letsels of groei van bestaande letsels.
Beoordeling van die tumor-respons op **YERVOY** moet eers na voltooiing van die induksieterapie uitgevoer word.
Bykomende behandeling met **YERVOY** (herinstelling met vier dosisse) kan oorweeg word vir pasiënte wat progressiewe siekte ("PD") ontwikkel na 'n vorige volledige of gedeeltelike reaksie ("CR" of "PR"), of na 'n stabiele siekte ("SD"), wat langer as 3 maande vanaf die eerste beoordeling van die gewas geduur het.
Die aanbevole herinstellingsregimen van **YERVOY** is 3 mg/kg, elke 3 weke, vir 90 minute lank binneaars toegedien; altesaam vier dosisse word toegedien afhangende van hoe dit verdra word, ongeag die verskyning van nuwe letsels of die groei van bestaande letsels.
Lewerfunksiewaardes (LFT) en tiroïedfunksiewaardes moet by basislyn ondersoek word en ook voor elke dosis van **YERVOY**.

Permanente beëindiging van behandeling of uitstelling van dosisse:
Vir die behandeling van immuunverwante newe-effekte kan dit nodig wees om 'n dosis uit te stel of die behandeling met **YERVOY** permanent te staak en te begin met sistemiese hoë-dosis kortikosteroïede. In sommige gevalle kan die toevoeging van 'n ander immuunonderdrukkende terapie oorweeg word. Dosisverlaging word nie aanbeveel nie. Dosisse wat uitgestel is as gevolg van 'n newe-effek moet nie vervang word nie.
Die riglyne vir permanente staking of uitstel van beplande dosisse word beskryf in **Tabelle 1A** en **1B**. Gedetailleerde riglyne vir die hantering van immuunverwante newe-effekte word beskryf by **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**.

Tabel 1A: Wanneer moet gebruik van YERVOY permanent gestaak word

Staak YERVOY permanent by pasiënte met die volgende newe-effekte. Behandeling van hierdie newe-effekte, waarvan daar aangetoon is, of vermoed word, dat hulle immuunverwant is mag ook hoë dosis kortikosteroïedbehandeling benodig (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS vir gedetailleerde behandelingsriglyne).	
Ernstige of lewensbedreigende newe-effekte	**NCI-CTCAE v3 graad[a]**
Gastro-intestinaal: Ernstige simptome (buikpyn, ernstige diarree of 'n beduidende verandering in die aantal stoelgange, bloed in die ontlasting, gastro-intestinale bloeding, gastro-intestinale perforasie)	• Diarree of kolitis graad 3 of 4
Lewer: Ernstige stygings in aspartaat-aminotransferase (AST), alanien-aminotransferase (ALT) of totale bilirubien, of simptome van lewertoksisiteit	• AST of ALT > 8 x BGN of • Totale bilirubien > 5 x BGN
Vel: Lewensbedreigende veluitslag (waaronder die sindroom van Stevens-Johnson of giftige epidermale nekrolise) of ernstige algemeen verspreide pruritus wat die aktiwiteite van die daaglikse lewe ontwrig of wat 'n mediese ingryping vereis	• Veluitslag graad 4 of pruritus graad 3
Neurologies: Nuwe simptome van, of agteruitgang van reeds bestaande, ernstige motoriese of sensoriese neuropatie	• Motoriese of sensoriese neuropatie graad 3 of 4
Ander orgaansisteme[b]: (bv. nefritis, pneumonitis, hartsakontsteking, pankreatitis, nie-aansteeklike miokarditis)	• Immuunverwante reaksies ≥ graad 3[c] • Immuunverwante oogversteurings ≥ graad 2 wat NIE op plaaslike immuunonderdrukkende terapie reageer nie

[a] Toksisiteitsgrade ooreenkomstig die kriteria van die "National Cancer Institute Common Terminology Criteria for Adverse Events". Weergawe 3.0 (NCI-CTCAE v3).
[b] Vir elke ander newe-effek waarvoor aangetoon is of vermoed word dat dit immuunverwant is, moet die graad volgens die CTCAE bepaal word. Die besluit om die gebruik van **YERVOY** te staak, moet gebaseer wees op die graad van erns.
[c] Pasiënte met ernstige (graad 3 of 4) endokrinopatie wat onder beheer gehou word met hormoonvervangingsterapie kan bly op die behandeling.
BGN = bogrens van normaal

Tabel 1B: Wanneer moet 'n beplande dosis van YERVOY uitgestel word

Stel die YERVOY dosis[a] uit by pasiënte met die volgende immuunverwante newe-effekte. Kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS vir gedetailleerde behandelingsriglyne.	
Ligte tot matige newe-effekte	**Aksie**
Gastro-intestinaal: Matige diarree of kolitis, wat óf nie onder beheer met mediese behandeling is nie óf wat aanhou (5 – 7 dae) of terugkeer	1. Stel die dosis uit tot die newe-effek verminder tot graad 1 of graad 0 (of terugkeer na basislyn). 2. Indien vermindering van die newe-effek voor die volgende beplande dosis plaasvind, hervat die behandeling by die volgende beplande dosis. 3. Indien vermindering van die newe-effek nie voor die volgende beplande dosis plaasvind nie, hou aan om dosisse uit te stel totdat die newe-effek verminder en hervat dan die behandeling. 4. Indien vermindering van die newe-effek tot graad 1 of graad 0 nie plaasvind nie, of dit nie na die basislyn terugkeer nie, moet die gebruik van **YERVOY** gestaak word.
Lewer: Matige stygings in transaminase (AST of ALT > 5 tot ≤ 8 x BGN) of totale bilirubien (> 3 tot ≤ 5 x BGN)	
Vel: Matige tot ernstige (graad 3)[b] veluitslag of algemeen verspreide/intense pruritus, ongeag die etiologie	
Endokrien: Ernstige newe-effekte in die endokriene kliere, soos hipofisitis en tiroïditis wat nie voldoende onder beheer is met hormoonvervangende terapie of met hoë-dosis immuunonderdrukkende terapie nie	
Neurologies: Matige (graad 2)[b] onverklaarbare motoriese neuropatie, spierswakheid of sensoriese neuropatie (wat langer as 4 dae voortduur)	
Ander matige newe-effekte[c]	

[a] Dosisverlaging van **YERVOY** word nie aanbeveel nie. Dosisse wat uitgestel is as gevolg van 'n newe-effek moet nie vervang word nie.
[b] Grade van toksisiteit is ooreenkomstig die kriteria van die "National Cancer Institute Common Terminology Criteria for Adverse Events". Weergawe 3.0 (NCI-CTCAE v3).
[c] Vir elke newe-effek van ander orgaansisteme wat as immuunverwant geag word, moet die graad volgens die CTCAE bepaal word. Die besluit om 'n beplande dosis uit te stel, moet gebaseer word op die graad van die erns.
BGN = bogrens van normaal

Voorbereiding vir toediening
WERK ASEPTIES BY DIE BEREIDING VAN DIE INFUSIE.
Voor toediening moet **YERVOY** inspuiting visueel geïnspekteer word vir enige deeltjies en verkleuring. Die flessie moet weggegooi word as die oplossing troebel is, as daar duidelike verkleuring is (die oplossing kan 'n liggeel kleur hê), of as daar enige vreemde deeltjies buiten deursigtige-tot-wit deeltjies is.
YERVOY inspuiting (5 mg/ml) kan gebruik word vir binneaarse toediening sonder verdunning na oordrag na 'n infusiehouer met behulp van 'n toepaslike steriele spuit, of na verdunning met steriele natriumchloried 9 mg/ml (0,9 % oplossing) of steriele 5 % dekstrose-inspuiting oplossing tot 'n konsentrasie wat wissel van 1 mg/ml tot 4 mg/ml.
Die verdunde oplossing moet liggies rondgeswaai word om te meng. Vir binneaarse infusie gebruik 'n in-lyn, steriele, nie-pirogene filter met lae proteïnbinding (poriegrootte van 0,2 µm tot 1,2 µm).
Bepaal die aantal flessies **YERVOY** (5 mg/ml) wat benodig word (kyk **Aanbevole dosering**).
Laat die flessies vir ongeveer 5 minute by kamertemperatuur staan.
Onttrek die vereiste volume **YERVOY** oplossing (5 mg/ml) met behulp van 'n geskikte steriele inspuiting en plaas dit oor na 'n steriele vakuumglasfles of binneaarse sak (PVC of nie-PVC).

Verenigbaarheid
YERVOY 5 mg/ml is verenigbaar met:
- Glas, polivinielchloried (PVC) en nie-PVC binneaarse sakke
- PVC binneaarse verlenging/toedieningstelle
- Poliëtersulfoon (0,2 µm tot 1,2 µm) en nylon (0,2 µm) in-lyn filters

Alle gedeeltelik gebruikte of leë flessies **YERVOY** moet vernietig word ooreenkomstig plaaslike regulasies.

Toediening
Die hele oplossing van die **YERVOY** dosis moet deur 'n lae-proteïen-bindende filter (poriegrootte van 0,2 µm tot 1,2 µm) oor 'n 90-minute tydperk ingedrup word. 'n Aparte infusielyn moet gebruik word vir die infusie en die lyn moet gespoel word met steriele natriumchloried 9 mg/ml (0,9 %) oplossing vir inspuiting of steriele 5 % dekstrose-inspuiting aan die einde van die infusie.

NEWE-EFFEKTE
YERVOY word mees algemeen geassosieer met newe-effekte as gevolg van verhoogde of buitensporige immuunwerking.
Die mees dikwels gerapporteerde newe-effekte (by ≥ 10 %) was diarree, uitslag, pruritus, moegheid, naarheid, braking, verminderde eetlus en buikpyn. Die meerderheid newe-effekte was lig tot matig van aard (graad 1 of 2). **YERVOY** behandeling is weens newe-effekte by 10 % van die pasiënte gestaak.
Newe-effekte word weergegee volgens sisteem/orgaanklasse en frekwensie by pasiënte met gevorderde melanoom wat behandel is met **YERVOY** 3 mg/kg in kliniese proewe (n = 767). Binne elke frekwensiekategorie word die newe-effekte weergegee in afnemende mate van erns. Frekwensies word gedefinieer as:
Baie algemeen (≥ 1/10), algemeen (≥ 1/100 tot < 1/10); ongewoon (≥ 1/1 000 tot < 1/100)

Newe-effekte by pasiënte met melanoom in 'n gevorderde stadium wat behandel was met YERVOY 3 mg/kg:

Infeksies en besmettings
Ongewoon sepsis[a], septiese skok[a], urienweginfeksie, boonste lugweginfeksie, onderste lugweginfeksie

Neoplasmas goedaardig, kwaadaardig en nie gespesifiseer nie (insluitende siste en poliepe)
Algemeen tumorpyn
Ongewoon paraneoplastiese sindroom

Bloed- en limfstelselversteurings
Algemeen anemie, limfopenie
Ongewoon hemolitiese anemie, trombositopenie, eosinofilie, neutropenie

Immuunstelselversteurings
Ongewoon hipersensitiwiteit
Baie skaars anafilaktiese reaksie (skok)

Endokriene versteurings
Algemeen hipopituïtarisme (waaronder hipofisitis), hipotiroïdisme
Ongewoon bynierontoereikendheid, hipertiroïdisme, hipogonadisme, hiperpituïtarisme

Metabolisme en voedingsversteurings
Baie algemeen verminderde eetlus
Algemeen dehidrasie, hipokalemie
Ongewoon hiponatremie, alkalose, hipofosfatemie, tumorlise-sindroom

Psigiatriese versteurings
Algemeen verwarde toestand
Ongewoon psigiese toestandveranderinge, depressie, verminderde libido

Senuweestelselversteurings
Algemeen perifere sensoriese neuropatie, duiseligheid, hoofpyn, letargie
Ongewoon Guillain-Barré-sindroom[a], meningitis, sinkopee, kraniale neuropatie, breinedeem, perifere neuropatie, ataksie, tremor, mioklonus, disartrie

Oogversteurings
Algemeen dowwe visie, oogpyn
Ongewoon uveïtis, glasvogbloeding, iritis, gesigskerpte neem af, vreemde liggaamgevoel in oë, konjunktivitis

Hartversteurings
Ongewoon disritmie, atriale fibrillasie

Bloedvatversteurings
Algemeen hipotensie, blosing, warmgloede
Ongewoon vaskulitis, angiopatie[a], perifere iskemie, ortostatiese hipotensie

Respiratoriese, bors en mediastinale versteurings
Algemeen dispnee, hoes
Ongewoon respiratoriese versaking, akute asemhalingsnood-sindroom[a], longinfiltraat, pulmonêre edeem, pneumonitis, allergiese rinitis

Gastro-intestinale versteurings
Baie algemeen diarree, naarheid, braking
Algemeen gastro-intestinale bloeding, kolitis[a], hardlywigheid, gastro-esofageale refluksiekte, buikpyn
Ongewoon gastro-intestinale perforasie[a], dikderm perforasie[a], intestinale perforasie[a], peritonitis[a], gastro-enteritis, divertikulitis, pankreatitis, enterokolitis, maagsweer, dikdermsweer, esofagitis, ileus, slymvliesontsteking

Hepatobiliêre versteurings
Algemeen abnormale lewerfunksie
Ongewoon lewerversaking[a], hepatitis, hepatomegalie, geelsug

Vel- en onderhuidse weefselversteurings
Baie algemeen uitslag, pruritus
Algemeen dermatitis, eriteem, vitiligo, urtikarie, alopesie, nagsweet, droë vel
Ongewoon toksiese epidermale nekrolise[a,b], leukositoklastiese vaskulitis, velafskilfering, ekseem, haarkleurveranderinge, Stevens-Johnson-Sindroom

Skeletspierstelsel- en bindweefselversteurings
Algemeen artralgie, mialgie, skeletspierstelselpyn, spierspasmas
Ongewoon polymyalgia rheumatica, artritis

Nier- en urienwegversteurings
Ongewoon nierversaking[a], glomerulonefritis, renale tubulêre asidose

Voortplantingstelsel- en borsversteurings
Ongewoon amenorree

Algemene versteurings en toestande by die plek van toediening
Baie algemeen moegheid, reaksie by die plek van inspuiting, pireksie
Algemeen koue rillings, astenie, edeem, pyn, griepagtige sieke (simptome)
Ongewoon multi-orgaanversaking[a], infusieverwante reaksie
Skaars sistemiese inflammatoriese sindroom

Ondersoeke
Algemeen verhoogde alanien-aminotransferase, verhoogde aspartaat-aminotransferase, verhoogde bloedbilirubien, verhoogde bloedalkalifosfatase, gewigsvermindering
Ongewoon abnormale lewerfunksiewaardes, verhoogde bloedkreatinien, verhoogde bloedtiroïedstimulerende hormoon, verlaagde bloedkortisol, verlaagde bloedkortikotrofien, verhoogde lipase, verhoogde bloedamilase, verlaagde bloedtestosteroon
Skaars abnormale bloedprolaktien

[a] Insluitende noodlottige uitkoms.
[b] Pasiënte het Stevens-Johnson-Sindroom ontwikkel en dit het oorgegaan in toksiese epidermale nekrolise.

Addisionele newe-effekte wat nie hierbo vermeld word nie, is gerapporteer by pasiënte wat ander dosisse (laer of hoër as 3 mg/kg) **YERVOY** in melanoom-kliniese proewe ontvang het. Hierdie addisionele newe-effekte het met 'n frekwensie van < 1 % voorgekom: meningisme, miokarditis, perikardiale effusie (hartsakontsteking), kardiomiopatie, outo-immuun hepatitis, veelvuldige eriteem, outo-immuun nefritis, outo-immuun tiroïditis, hiperpituïtarisme, sekondêre bynierskorsontoereikendheid, hipoparatiroïdisme, tiroïditis, episkleritis, blefaritis, oog edeem, skleritis, temporale arteritis, verskynsel van Raynaud, proktitis, palmoplantêre eritrodisestesie-sindroom, psoriase, hematurie, proteïnurie, verminderde bloedtiroïedstimulerende hormoon, verlaagde bloedgonadotropien, verlaagde tiroksien, leukopenie, polisitemie, miastenie gravis- tipe simptome, sitokienvrystellingsindroom, sarkoïdose, neurosensoriese hipo-akoesie, outo-immuun sentrale neuropatie (enkefalitis), miositis, polimiositis en okulêre miositis.

Beskrywing van bepaalde newe-effekte
Behalwe waar aangedui, is die data vir die volgende bepaalde newe-effekte gebaseer op pasiënte wat óf **YERVOY** 3 mg/kg monoterapie (n = 131) óf **YERVOY** 3 mg/kg in kombinasie met gp100 (n = 380) ontvang het in 'n fase 3 studie oor gevorderde (onopereerbare of metastatiese) melanoom (MDX010-20).
Bykomende inligting en die behandelingsriglyne vir hierdie newe-effekte word beskryf onder **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**.

Immuunverwante gastro-intestinale reaksies
In die **YERVOY** 3 mg/kg monoterapiegroep is diarree en kolitis, ongeag die graad van erns, onderskeidelik by 27 % en 8 %, gerapporteer.
Die frekwensie van ernstige (graad 3 of 4) diarree en ernstige (graad 3 of 4) kolitis was elk 5 %.
Stertes te wyte aan gastro-intestinale perforasie is by < 1 % pasiënte gerapporteer wat **YERVOY** 3 mg/kg in kombinasie met gp100 ontvang het.

Immuunverwante hepatotoksisiteit
In die **YERVOY** 3 mg/kg monoterapiegroep is stygings in AST en ALT, ongeag die graad van erns, onderskeidelik by 1 % en 2 % van die pasiënte gerapporteer.
Daar was geen verslae oor ernstige (graad 3 of 4) styging in AST of ALT nie.
Noodlottige lewerversaking is by < 1 % van die pasiënte gerapporteer.

Immuunverwante newe-effekte van die vel
In die **YERVOY** 3 mg/kg monoterapiegroep was uitslag en pruritus, ongeag die graad van erns, elk by 26 % van die pasiënte gerapporteer.
Veluitslag en pruritus veroorsaak deur **YERVOY** was oorwegend lig tot matig (graad 1 of 2).
Noodlottige toksiese epidermale nekrolise is gerapporteer by < 1 % van die pasiënte wat **YERVOY** in kombinasie met gp100 ontvang het.
'n Geneesmiddelreaksie met eosinofilie en sistemiese simptome ("DRESS") is baie seldsaam aangemeld met **YERVOY** met gebruik na bemarking.

Immuunverwante neurologiese reaksies
Daar was geen berigte van immuunverwante neurologiese reaksies by die **YERVOY** 3 mg/kg monoterapiegroep nie.
By < 1 % van die pasiënte wat **YERVOY** 3 mg/kg in kombinasie met gp100 gekry het, is ernstige (graad 3) meningitis en noodlottige Guillain-Barré-sindroom elk gerapporteer.
Simptome wat lyk soos miastenie gravis is ook gerapporteer by < 1 % van die pasiënte wat in kliniese proewe hoër dosisse van **YERVOY** gekry het.

Immuunverwante endokrinopatie
In die groep met **YERVOY** 3 mg/kg as monoterapie, is hipopituïtarisme, ongeag die graad van erns, by 4 % van die pasiënte gerapporteer. Bynierontoereikendheid, hipertiroïdisme en hipotiroïdisme, ongeag die graad van erns, is elk by 2 % van die pasiënte gerapporteer.
Die voorkoms van ernstige (graad 3 of 4) hipopituïtarisme was by 3 % van die pasiënte gerapporteer. Daar was geen berigte van ernstige (graad 3 of 4) bynierontoereikendheid, hipertiroïdisme of hipotiroïdisme nie.

Ander immuunverwante newe-effekte
Die volgende bykomende newe-effekte wat vermoedelik immuunverwant is, is gerapporteer by < 2 % van die pasiënte wat met **YERVOY** 3 mg/kg monoterapie behandel is: uveïtis, eosinofilie, verhoogde lipase en glomerulonefritis. Daarbenewens is iritis, hemolitiese anemie, verhoogde amilase, multi-orgaanversaking en pneumonitis gerapporteer by < 1 % van die pasiënte wat met **YERVOY** 3 mg/kg in kombinasie met gp100 peptiedvaksien behandel is.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
In geval van oordosering moet pasiënte deeglik gemoniteer word vir tekens of simptome van newe-effekte, en moet geskikte simptomatiese behandeling begin word. Kyk **NEWE-EFFEKTE**.

IDENTIFIKASIE
YERVOY is 'n steriele, preserveermiddelvrye, helder tot effens opaalagtige, kleurlose tot liggeel oplossing vir binneaarse infusie, wat 'n klein hoeveelheid sigbare, deursigtige-tot-wit, amorfe, ipilimumab-deeltjies kan bevat.

AANBIEDING
10 ml met 5 mg/ml steriele konsentraat in 'n helder, kleurlose flessie (tipe I glas) met 'n grys prop (bedekte butielrubber) en 'n ligblou afwip-deksel (aluminium). Verpakkingsgrootte van 1.
OF
40 ml met 5 mg/ml steriele konsentraat in 'n helder, kleurlose flessie (tipe I glas) met 'n grys prop (bedekte butielrubber) en 'n pers afwip-deksel (aluminium). Verpakkingsgrootte van 1.

BERGINGSINSTRUKSIES
Bewaar in 'n yskas by 2 °C tot 8 °C.
Bewaar in die oorspronklike verpakking om die inhoud teen lig te beskerm.
Moenie vries nie.
Slegs vir eenmalige gebruik. Gooi die ongebruikte gedeelte weg.
Sodra dit oopgemaak is, moet die produk, of die verdunde produk, dadelik ingedrup word. Die chemiese en fisiese in-gebruik stabiliteit van die onverdunde of verdunde konsentraat (tussen 1 mg/ml en 4 mg/ml) is vir 24 uur by 25 °C en by 2 °C tot 8 °C aangetoon. Indien dit nie dadelik gebruik word nie, kan die infusie oplossing (onverdun of verdun) tot en met 24 uur, óf in 'n yskas (2 °C tot 8 °C) óf by kamertemperatuur (25 °C), bewaar word.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER
47/30.1/0522

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT
Equity Pharmaceuticals (Edms) Bpk.
Sovereignrylaan 100
Route 21 Corporate Park
Nellmapiusrylaan
Irene Pretoria

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET
02 Oktober 2014
30 September 2016
YERVOY is 'n handelsmerk van Bristol-Myers Squibb Company; gebruik onder lisensie deur Equity Pharmaceuticals (Edms) Bpk.

APPROVED
By Petra van Rooyen at 2:51 pm, May 17, 2019

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Live Text: ☒ Yes / ☐ No
Country: ZA
Product Name: INS YERVOY FCT
Product Code: 1336887A1
Barcode Type: 2/5 (6509)
Format/Dimension: 860 x 300 (90 x 45) mm
Font Size Text: 7 pt
Min. Font Size Text: 7 pt
Line Space: 7,5 pt (2,6 mm)
Proof No.: 3 16.05.2019 Manconi
Pag. 2/2
Production Site: Anagni
CTM: Emiliano Parisi
Printing Colours: Black
Technical Colours: Diecut