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Review

The European Medicines Agency review of ipilimumab (Yervoy) for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy: Summary of the scientific assessment of the Committee for Medicinal Products for Human Use

Zahra Hanaizi [a,*], *Barbara van Zwieten-Boot* [b], *Gonzalo Calvo* [c], *Arantxa Sancho Lopez* [c], *Maaike van Dartel* [b], *Jorge Camarero* [c], *Eric Abadie* [d], *Francesco Pignatti* [a]

[a] *European Medicines Agency, London, United Kingdom*
[b] *Medicines Evaluation Board, Den Haag, The Netherlands*
[c] *Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain*
[d] *Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis, France*

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ABSTRACT

On 13 July 2011 the European Commission issued a marketing authorisation valid throughout the European Union (EU) for ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

Ipilimumab is a monoclonal antibody that specifically blocks the inhibitory signal of cytotoxic T lymphocyte antigen 4 (CTLA-4), resulting in T cell activation, proliferation and lymphocyte infiltration into tumours, leading to tumour cell death. The recommended induction regimen of ipilimumab is 3 mg/kg administered intravenously over a 90 min period every 3 weeks for a total of four doses.

In a phase 3 trial in patients with advanced melanoma, median overall survival for ipilimumab was 10 months versus 6 months for gp100, an experimental melanoma vaccine (Hazard ratio (HR) 0.66; 95% confidence interval (CI): 0.51, 0.87; $p = 0.0026$).

Ipilimumab was most commonly associated with adverse reactions resulting from increased or excessive immune activity. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of ipilimumab. The most common side-effects (affecting more than 10% of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain. The objective of this paper is to summarise the scientific review of the application leading to approval in the EU. The detailed scientific assessment report and product information, including the summary of product characteristics (SmPC), are available on the European Medicines Agency (EMA) website (www.ema.europa.eu).

* *Corresponding author:* Address: European Medicines Agency, 7 Westferry Circus, London E14 4HB, United Kingdom.
E-mail address: zahra.hanaizi@ema.europa.eu (Z. Hanaizi).
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1. Background

About 20% of patients diagnosed with melanoma develop metastatic disease which is associated with a median survival of about 6–9 months.[1–3] Available treatments have included systemic therapy, surgery and radiotherapy. Systemic therapy includes chemotherapy and immunotherapy. Palliative radiotherapy is indicated for symptomatic relief of metastases to brain, bones and viscera. Complete resection of isolated metastases may occasionally achieve long term survival. Chemotherapy with dacarbazine (DTIC) may achieve objective response rates of about 20%, of which less than 5% is complete remission. Higher response rates have been seen using combination chemotherapy; however, no increase in survival has been demonstrated with combination regimens when compared to DTIC alone.[4] Immunotherapy for metastatic melanoma includes interferon-alfa (IFNa) and interleukin 2 (IL-2). The observed response rates for both IFNa and IL-2 are comparable to the responses achieved with DTIC.[5,6] Until recently, no one drug or combination of drugs demonstrated any impact on survival in metastatic melanoma.[7] Recurrent melanoma is resistant to most standard systemic therapy and no effective second line treatments have been available.

On 5 May 2010, the applicant Bristol-Myers Squibb Pharma EEIG submitted an application for marketing authorisation for ipilimumab to the European Medicines Agency (EMA). Ipilimumab is a fully human anti-human cytotoxic T lymphocyte antigen 4 (CTLA-4) (CD152) monoclonal antibody of the IgG1-κ isotype. Ipilimumab binds to human and cynomolgus CTLA-4.

The scientific review was conducted by the Committee for Medicinal Products for Human Use (CHMP). The CHMP recommended the granting of a marketing authorisation for ipilimumab based on a positive benefit-risk balance. Following this review the European Commission issued a marketing authorisation on 13 July 2011 for ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

The detailed scientific assessment report and the most current product information are available on the EMA website (www.ema.europa.eu).

2. Non-clinical aspects and clinical pharmacology

Ipilimumab showed specific binding to activated, but not resting, T cells from the cynomolgus monkey and from humans.

The anti-tumour activity of ipilimumab was tested in a human CTLA-4 transgenic, mouse CTLA-4 knock out mouse. Anti-tumour activity was only seen when ipilimumab was administered at or near the time of the expected peak of the primary (anti-tumour) immune response. The relevance of this study, and other anti-tumour studies conducted using homologous mouse tumour models was considered limited because in all these studies the (blocking) CTLA-4 antibody was administered at the time or shortly after tumour inoculation i.e. at the time of a (primary) immune response against the tumour.

In cynomolgus monkeys, ipilimumab (10 mg/kg) administered concurrently with T cell antigens enhanced the antigen-specific antibody response.

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently and included colitis (which resulted in a single fatality), dermatitis and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate).

Reproductive and developmental toxicology studies were not performed with ipilimumab. Results of further embryofoetal, pre/post-natal development studies were requested to be submitted post-approval. The effect of ipilimumab on male and female fertility is unknown.

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In phase 2 studies, this increase was dose-dependent. In the pivotal study MDX010-20, increased ALC throughout the induction dosing period was observed for ipilimumab at 3 mg/kg with or without gp100 but not for gp100 peptide vaccine alone.

The pharmacokinetic profile 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. Cmax, Cmin and AUC of ipilimumab were found to be dose proportional within the dose range examined. Ipilimumab steady state was reached by the third dose administered once every 3 weeks. 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 an mg/kg basis. No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

The use of systemic corticosteroids at baseline, before starting ipilimumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab to treat immune-related adverse reactions.

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

3. Clinical efficacy

The clinical aspects of the application were supported by one phase 3 pivotal study MDX010-20 and seven supportive phase 1/2 studies, as well as high-level data from a phase 3 study CA184024. Three of the clinical studies (including the pivotal study) evaluated the recommended dose of 3 mg/kg administered once every 3 weeks (q3w) for four doses whereas other studies evaluated ipilimumab at 10 mg/kg.

3.1. *Pivotal study MDX010-20*

Study MDX010-20 was a randomised, double-blind, multicentre study comparing ipilimumab (MDX-010) monotherapy, ipilimumab in combination with an experimental melanoma peptide vaccine (gp100), and gp100 monotherapy in HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma.[8]

The study enrolled HLA-A*0201-positive males and females above 18 years of age with a histologic diagnosis of unresectable Stage III or IV melanoma who had relapsed, failed, or were not able to tolerate at least one or more prior treatment regimens. Patients with primary ocular melanoma, primary central nervous system (CNS) melanoma or active, untreated CNS metastasis were excluded from the study.

Subjects were randomised in a 3:1:1 ratio to receive ipilimumab (3 mg/kg) in combination with gp100 q3w up to four doses; ipilimumab (3 mg/kg) plus vaccine placebo q3w up to four doses; or ipilimumab placebo plus gp100 q3w up to four doses.

The rationale for using the 3 mg/kg dose in the pivotal study MDX010-20 was based on early clinical studies, which provided evidence of clinical activity of ipilimumab at doses of 1 and 3 mg/kg in patients with metastatic melanoma.

The primary end-point was overall survival (OS), and the primary efficacy analysis compared the difference in OS between ipilimumab plus gp100 versus gp100 monotherapy using stratified log-rank test. The two stratification factors were baseline TNM status (M0, M1a, or M1b versus M1c) and prior treatment with IL-2. Secondary end-points included Best Overall Responses Rate (BORR) determined from week 12 to 24 and confirmed at least 4 weeks later, disease control rate (DCR), duration of response, time to response, progression-free survival (PFS), PFS rate (PFSR) at week 12, time-to-progression, delayed response, Health-related Quality of Life (HRQoL) and safety. Tumour response status was assessed by the investigator.

A total of 676 patients were randomised: 137 to the ipilimumab monotherapy group, 403 to the ipilimumab + gp100 group and 136 to the gp100 alone group. The majority had received all four doses during induction. Baseline characteristics were well balanced across groups. The median age was 57 years. The majority (71–73%) of patients had M1c stage disease and 37–40% of patients had an elevated LDH at baseline. A total of 77 patients had a history of previously treated brain metastases.

Almost all patients included in the MDX010-20 study had had prior surgery related to cancer, and all patients had received prior systemic therapies (IL-2, DTIC, temozolomide, fotemustine and/or carboplatin); 91.9% of the patients received prior chemotherapy, 40.1% and 47.9% of patients received prior immunotherapy (IFNa, IL-2 or 7 or PEG-IFNa) and 43.8% and 38.2% had prior radiotherapy, in the ipilimumab monotherapy and ipilimumab + gp100 groups, respectively.

The primary efficacy results are presented in Table 1 and Fig. 1.

The treatment effect on OS was consistent within most of the subgroups explored (M-stage, prior IL-2, baseline LDH, age and sex). However, for women aged 50 years and above ($n = 79$), the HR was close to 1.

The HRQoL for patients with cancer may be negatively impacted by both disease progression and treatment toxicities. In this study, most changes from baseline in HRQoL domains were 'no change' to 'moderate' across the three treatment groups.

3.2. *Other supportive studies*

Seven supportive studies were submitted in the application. The primary end-point for most studies was BORR. In general the response rates to ipilimumab monotherapy, obtained in the supportive studies were comparable to the BORR reported for the pivotal MDX010-20 study. Study CA1840042 was an open label multicentre phase 2 study with a two-stage design. The study is still ongoing, and only results from an interim analysis of the first stage were submitted. The primary objective of the study was to assess the DCR determined after week 12, after ipilimumab monotherapy. For the first stage of the study, 28 patients with stage IV melanoma with brain metastases, were enrolled (Arm A). During induction phase patients were treated with 10 mg/kg ipilimumab every 3 weeks for four doses. Confirmed objective response rate for brain metastases was 5/28 (17.9%).

High-level results from a recently finalised study CA184024, a randomised, placebo-controlled phase 3 study evaluating OS in patients with previously untreated, advanced melanoma[9] were also provided. The two treatment arms were ipilimumab plus DTIC (ipilimumab + DTIC; $N = 250$) and placebo plus DTIC (DTIC; $N = 252$). Ipilimumab was administered at a dose of 10 mg/kg every 3 weeks for four doses, followed by maintenance therapy with 10 mg/kg ipilimumab for eligible patients. A 2.1 month improvement in median overall survival was observed for ipilimumab + DTIC arm compared to DTIC (HR of 0.72, $P < 0.001$).

4. Clinical safety

The safety database included results for patients treated with ipilimumab at 3 mg/kg ($n = 622$) and at 10 mg/kg ($n = 353$) treated in phase 2 and 3 melanoma trials.

Throughout the clinical programme in advanced melanoma, the vast majority (>96%) of patients with metastatic melanoma experienced adverse events (AEs) of any grade during the induction phase, including the gp100 monotherapy group as well as all ipilimumab treatment groups.

The most frequently reported adverse reactions ($\geqslant$10% of patients) observed in MDX010-20 were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain. The majority were Grade 1–2. In patients receiving ipilimumab 3 mg/kg monotherapy, the frequency of treatment-related Grade 3–4 AEs was 20.6% in the main study MDX010-20 and 14.4% in the pooled 3 mg/kg group. Grade 4 events were 3.8% and 1.8%, respectively. The most common treatment-related Grade 3–4 AEs were colitis and diarrhoea.

Immune-related AEs (irAEs) primarily involved the gastrointestinal (GI) tract and skin, and less frequently, the liver, endocrine glands and nervous system. While most immune-related adverse reactions occurred during the induction period, onset has also been reported months after the last dose of ipilimumab. The early diagnosis of irAEs was important to

Table 1 – Overall survival by treatment (MDX010-20 study – ITT population).

	Ipi + gp100 (n = 403)	Ipi (n = 137)	gp100 (n = 136)	Total (n = 676)
Number of events	306	100	119	525
Median (months)	9.95	10.12	6.44	9.10
95% CI for median	(8.48, 11.50)	(8.02, 13.80)	(5.49, 8.71)	(8.31, 10.12)
HR versus gp100 with 95% CI	0.68 (0.55, 0.85)	0.66 (0 51, 0.87)		
Log-rank p value versus gp100	0.0004	0.0026		
HR versus ipilimumab with 95% CI	1.04 (0.83, 1.30)			
Log-rank p value versus ipilimumab	0.7575			

Cox model for Hazard ratios (HR) and log-rank test p-values were stratified by baseline M-stage at randomisation (M0, M1a, M1b versus M1c) and prior treatment with IL-2 (yes versus no).
95% Confidence intervals (CIs) for median were computed using Brookmeyer and Crowley method. 95% confidence intervals (CIs) for HR were computed using Cox model.

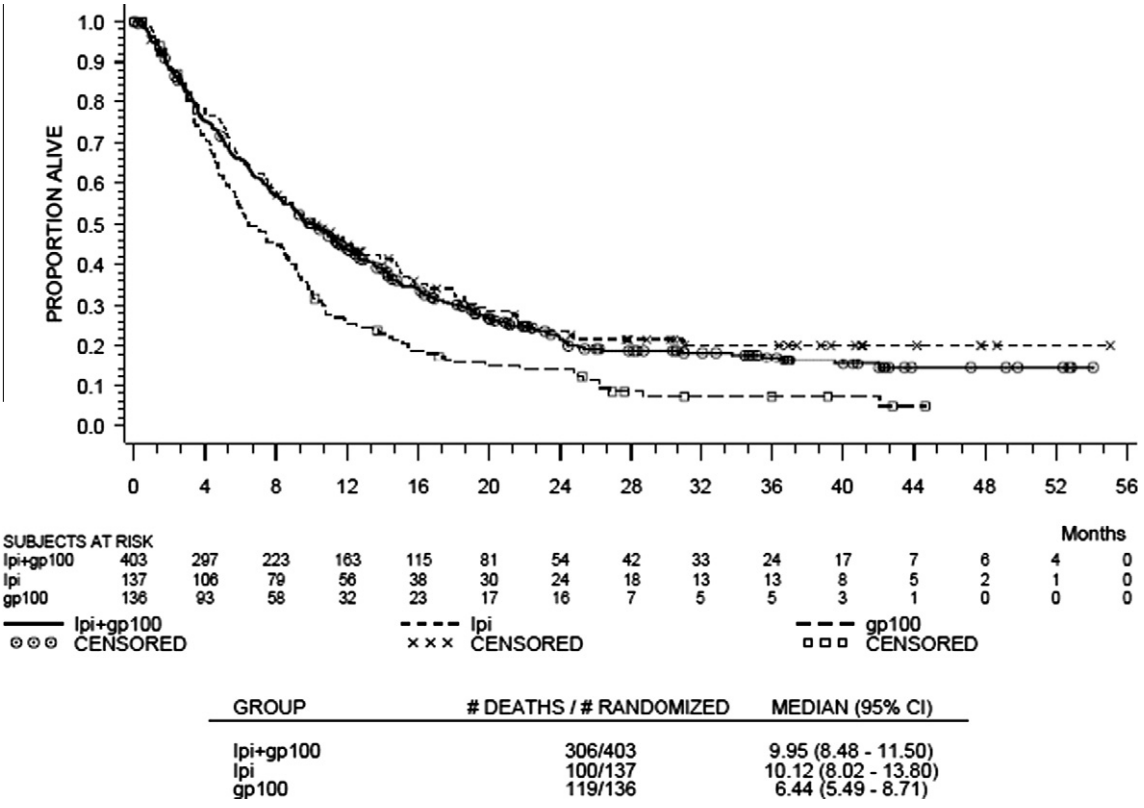

Fig. 1 – Overall survival by treatment (MDX010-20 study – ITT population).

initiate therapy and minimise complications. Immune-related AEs were generally managed with either symptomatic therapy for Grade 1–2 events, systemic corticosteroids for Grade 3–4 events, or other immunosuppressants (e.g. infliximab, mycophenolate mofetil) for steroid-unresponsive GI or hepatic irAEs. Management of irAEs was usually paired with omission of dosing for mild or moderate events and permanent discontinuation for severe irAEs.

In the ipilimumab 3 mg/kg monotherapy group, diarrhoea and colitis of any severity were reported in 27% and 8%, respectively. The frequency of Grade 3–4 diarrhoea or colitis was 5% each. The median time to onset of Grade 3–4 or fatal immune-related gastrointestinal reactions was 8 weeks (range 5–13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution occurred in most cases (90%). Immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations and lymphocytic and neutrophilic infiltration.

Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of any severity were reported in 1% and 2% of patients, respectively. There were no reports of Grade 3–4 AST or ALT elevation. Time to onset of Grade 2–4 or fatal immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes and macrophages).

Rash and pruritus of any severity were each reported in 27% of patients. Ipilimumab-induced rash and pruritus were predominantly Grade 1–2 and responsive to symptomatic

therapy. The median time to onset of moderate to Grade 2–4 or fatal skin adverse reactions was 3 weeks from start of treatment (range 0.9–16 weeks). With protocol-specified management guidelines, resolution occurred in most cases (87%).

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. Grade 3–4 hypopituitarism was reported in 3% of patients. Time to onset of Grade 2–4 immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with hormone replacement therapy.

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

In patients receiving ipilimumab 3 mg/kg monotherapy, the frequency of treatment-related serious adverse events (SAEs) was 16.8% in MDX010-20 and 17.1% in the pooled 3 mg/kg group. In the MDX010-20 study, treatment-related SAEs were reported in 16.8%, 12.6% and 3.8% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100 and gp100 monotherapy groups, respectively. The most common treatment-related SAEs reported in the ipilimumab monotherapy and ipilimumab plus gp100 groups were primarily irAEs, most commonly colitis (5.3% and 3.4%, respectively) and diarrhoea (3.8% and 3.4%, respectively).

In MDX010-20, treatment-related deaths were reported in 3.1%, 2.1% and 1.5% of patients in the ipilimumab monotherapy, ipilimumab + gp100 and gp100 monotherapy groups, respectively. In the ipilimumab groups, 1.5% and 1.3% of patients experienced a treatment-related death in association with irAEs. The rate of deaths during the induction phase as well as treatment-related deaths for the entire study duration was similar between the 3 mg/kg and 10 mg/kg groups. Fatalities due to gastrointestinal perforation, hepatic failure, toxic epidermal necrolysis, or Guillain-Barré syndrome have each been reported in <1% of patients who received ipilimumab 3 mg/kg in combination with gp100. Myasthenia gravis-like symptoms have also been reported in <1% of patients who received higher doses of ipilimumab in clinical trials.

5. Risk management plan

Important identified risks are irAEs and severe infusion reactions. Enhanced monitoring in a post-marketing prospective observational cohort study will be implemented. Educational materials will be distributed to healthcare professionals and patients to ensure their awareness of signs, symptoms and management of the risks associated with irAEs.

Information was missing with regard to reproductive and lactation data, which will be addressed post-approval as part of the routine pharmacovigilance and a non-clinical embryo-foetal development and pre- and post-natal development study. Other missing information included paediatric data, data in different ethnic groups, potential pharmacodynamic interaction with systemic immunosuppressants, patients with severe renal and hepatic impairment, patients with autoimmune disease and the long-term safety of ipilimumab. These will be addressed as part of the routine pharmacovigilance activities as well as the post-marketing prospective observational cohort study which will follow patients for a minimum of 3 years.

6. Discussion and benefit-risk assessment

An improvement of overall survival was observed in the pivotal study in adult patients with advanced previously treated melanoma receiving ipilimumab monotherapy. Overall survival is an important objective in this population because of the very short prognosis in the long-term. The OS benefit observed in the pivotal study was consistent within most of the subgroups analyses. However, for women above 50 years of age, a HR close to 1 was observed in Study MDX010-20 and just above 1 in study CA184024. As the subgroups analysis included only small numbers of patients, no definitive conclusions can be drawn from these data.

Patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the pivotal clinical trial. Results of the supportive study CA1840042 suggest that ipilimumab might be effective against brain metastases. However, the effect may require prior radiotherapy and disruption of the blood–brain barrier. No data regarding the use in patients with ocular melanoma were provided. It is uncertain whether the immunogenicity of ocular and skin melanoma are comparable and, therefore, whether a similar effect of ipilimumab is to be expected. As no additional safety concerns are expected, the CHMP considered that these should not be an absolute contra-indication for ipilimumab treatment.

Results of non-clinical pharmacodynamic studies and phase 2 studies suggest that higher efficacy might be expected for the 10 mg/kg dose, but also increased toxicity. No direct comparison between the two doses is available. The applicant committed to conduct a randomised comparison of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival end-point in order to further optimise the dose of ipilimumab.

Ipilimumab was associated with inflammatory adverse reactions resulting from increased or excessive immune activity, likely to be related to its mechanism of action. Immune-related adverse reactions, which could be severe or life-threatening, might involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, liver function tests elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for the management of severe irAEs. Ipilimumab must be permanently discontinued in patients with Grade 3–4 diarrhoea or

colitis, and high-dose intravenous corticosteroid therapy should be initiated immediately. Ipilimumab-specific management guidelines for immune-related adverse reactions are described in the product information.

The severity and the number of reported AEs constitute a need for an ongoing (post approval) search for sub-groups of patients for whom ipilimumab treatment will appear to work out more favourably, and for those in which it is less beneficial (possibly women above 50 years of age, patients with primary CNS or ocular melanoma or patients at risk to experience severe AEs, e.g. patients with autoimmune disease).

As no safety and efficacy data are available, ipilimumab should not be used in children below 18 years of age. Ipilimumab is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. Because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue ipilimumab therapy taking into account the benefit for the child and for the woman.

In conclusion, the CHMP considered that the risk/benefit balance of ipilimumab was positive for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy and recommended the granting of a marketing authorisation valid throughout the European Union for ipilimumab. The EMA will review new information about ipilimumab on a regular basis. The most current information on this medicinal product is available on the EMA website (http://www.ema.europa.eu).

Conflict of interest statement

None declared.

Disclaimer

This publication is a summary of the European Public Assessment Report, the summary of product characteristics (SmPC), and other product information available on the EMA website. Healthcare professionals and interested readers are referred to the EMA website for up-to-date information on this marketing authorisation (www.ema.europa.eu). The authors remain solely responsible for the opinions expressed in this publication.

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