ipilimumab (Yervoy®) 5mg/mL concentrate for solution for infusion

SMC No. (779/12)

Bristol-Myers Squibb

06 April 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

*ipilimumab (Yervoy®)* is not recommended for use within NHS Scotland.

**Indication under review:** Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

Ipilimumab demonstrated a survival benefit over an investigational gp100 peptide vaccine in previously treated patients with advanced melanoma.

The submitting company’s justification of the treatment’s cost in relation to its health benefits was not sufficient and, in addition, the submitting company did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
**Indication**

Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

**Dosing Information**

The recommended induction regimen of ipilimumab is 3mg/kg administered intravenously over a 90-minute period every three 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. Assessments of tumour response should be conducted only after completion of induction therapy.

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

**Product availability date**

10 August 2011

**Summary of evidence on comparative efficacy**

Ipilimumab is a T-cell potentiator 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 cell death. It has a novel mechanism of action, stimulating the body’s immune system to target and destroy the tumour. Ipilimumab is the first medicine to be licensed in the UK for the treatment of advanced melanoma in adults who have received prior therapy. It is given by intravenous infusion every three weeks for a total of four doses.

MDX010-20 was a phase III, randomised, multi-centre, double-blind study to evaluate the efficacy and safety of ipilimumab, with or without glycoprotein100 (gp100) vaccine, in patients with advanced melanoma who had failed previous therapy. Patients were recruited if they had an Eastern Cooperative Oncology Group performance status of 0 or 1, positive HLA-A*0201 status, normal haematologic, hepatic and renal function, and had received previous treatment with a chemotherapy regimen that included at least one of the following: dacarbazine, temozolomide, fotemustine, carboplatin or interleukin-2.

gp100 vaccine is an investigational cancer vaccine comprising HLA-A*0201-restricted peptides derived from the melanosomal protein, gp100. As there was no accepted standard of care for advanced melanoma, gp100 vaccine was chosen as an active control in this study. gp100 vaccine is not a licensed product and has not demonstrated any benefit in advanced melanoma.

Patients were randomised in a 3:1:1 ratio, with stratification according to baseline metastasis stage and receipt or non-receipt of previous interleukin-2 therapy, to receive: ipilimumab 3mg/kg plus gp100 peptide vaccine (n=403), ipilimumab 3mg/kg (n=137) or gp100 vaccine (n=136). Placebo injections were given to maintain double blinding.
All treatments were administered once every three weeks for four cycles. Ipilimumab was administered as a 90-minute intravenous infusion and gp100 vaccine as two subcutaneous injections into the anterior thigh. For patients who developed new lesions or if the existing baseline lesions grew, additional treatments could be administered. Patients with stable disease for three months’ duration after week 12, or a confirmed partial or complete response, were offered additional courses of therapy with their assigned treatment regimen if they had disease progression (re-induction).

The primary outcome was overall survival, measured in the intention to treat population. The median overall survival was 10.0 months (95% confidence interval [CI] 8.5 to 11.5) and 6.4 months (95% CI 5.5 to 8.7) in the ipilimumab plus gp100 and gp100 group respectively: hazard ratio (HR) for death 0.68 (95% CI 0.55 to 0.85), p<0.001. The median overall survival was 10.1 months (95% CI 8.0 to 11.8) in the ipilimumab group: HR for death compared with gp100 group 0.66 (95% CI 0.51 to 0.87), p=0.003. There was no difference in survival between the ipilimumab plus gp100 group and the ipilimumab group: HR 1.04 (95% CI 0.83 to 1.30), p=0.76.

Survival rates for ipilimumab plus gp100, ipilimumab and gp100 treated patients were 44%, 46% and 25% at 12 months, 30%, 33% and 16% at 18 months and 22%, 24% and 14% at 24 months.

Re-induction therapy was given to 40 patients but only 32 were included in the efficacy analysis because of major protocol violations. There were 23 patients in the ipilimumab plus gp100 group, eight patients in the ipilimumab group and one patient in the gp100 group. Overall 68% (21/31) of all ipilimumab-treated patients achieved a partial or complete response or stable disease; the patient in the gp100 vaccine group had progressive disease.

**Summary of evidence on comparative safety**

An adverse event was experienced by most patients in the study, including diarrhoea (38%, 33% and 20% in the ipilimumab plus gp100, ipilimumab and gp100 groups respectively), nausea (34%, 35% and 39%), fatigue (36%, 42% and 31%), decreased appetite (23%, 27% and 22%), pyrexia (20%, 12% and 17%) and immune-related dermatological events (40% 44% and 17%). Grade 4 adverse events were experienced by 6.8%, 8.4% and 6.1% of patients respectively. These were gastrointestinal, respiratory and dermatological events.

The most common adverse events were immune related, mainly affecting the skin and gastrointestinal tract which occurred in approximately 60% of patients treated with ipilimumab and 32% of patients treated with gp100 alone. The grade 3 or 4 immune-related adverse event rate was 10 to 15% in the ipilimumab groups and 3% in the gp100 group. The most common immune-related adverse event was diarrhoea, occurring in 27 to 31% of patients treated with ipilimumab. Four patients treated with ipilimumab received infliximab for diarrhoea of grade 3 or higher, or colitis.

There were 14 deaths (2.1%) related to the study drugs, seven were associated with immune-related adverse events (five in the ipilimumab plus gp100 group and two in the ipilimumab group).

**Summary of clinical effectiveness issues**

Patients with advanced melanoma have a poor prognosis, with a median survival of approximately seven months. They tend to be relatively young, with a median age of diagnosis of 57 years, and are often fit enough to receive further treatment. Ipilimumab is the first treatment to demonstrate a survival benefit in patients with advanced melanoma who have received previous therapy. There are currently
no licensed treatment options for these patients. Dacarbazine is the only chemotherapy recommended as a first-line treatment option for patients with advanced melanoma. SMC clinical experts suggest that there is no consensus about treatment in patients who have received prior therapy; patients may be entered into a clinical study, receive off-label chemotherapy or best supportive care (BSC). SMC clinical experts have confirmed that there is an unmet need in this patient population.

The pivotal study did not have a placebo control group so assumptions must be made regarding efficacy compared with BSC. However, the European Medicines Agency (EMA) noted that no clinical benefit has yet been demonstrated for gp100 vaccine monotherapy. All patients in the pivotal study had HLA-A*0201 positive advanced melanoma (required because of the inclusion of gp100 vaccine in this study); this represents approximately 40% of patients with advanced melanoma. Phase II studies have demonstrated efficacy of ipilimumab in patients who are HLA-A*0201 negative.

The dose of ipilimumab chosen for the pivotal phase III study was 3mg/kg which is the licensed dose in the marketing authorisation. Phase II studies have demonstrated a dose-response effect up to 10mg/kg, so the optimum dosing of ipilimumab is currently uncertain. The EMA has requested further efficacy and safety data in a randomised study comparing 3mg/kg versus 10mg/kg ipilimumab in advanced melanoma as a condition of the marketing authorisation. A small proportion of patients who had achieved a response to induction therapy received re-induction therapy on disease progression; overall survival of these patients is not reported separately so it is unknown if this further treatment improved survival.

The pivotal phase III study identified a grade 3 or 4 immune-related adverse event rate of 10 to 15%. Patients who receive ipilimumab need to be monitored closely. In the study, most immune-related adverse events occurred in the gastrointestinal tract or skin; however, the ipilimumab summary of product characteristics states that the liver, nervous, endocrine and other organ systems can also be affected. These events will require prompt medical attention and the administration of corticosteroids. Staff and patients will require education on the potentially severe and life-threatening nature of these events. Most adverse events present during treatment but they may occur months after the administration of ipilimumab. This adverse event profile may have service implications. The sponsor company has implemented a Risk Management Plan that includes the use of educational materials targeted at both the healthcare team and the patient.

The marketing authorisation permits the use of ipilimumab in patients with untreated brain metastases or ocular melanoma. These patients were excluded from the pivotal study therefore efficacy data in these patient groups are limited.

**Summary of comparative health economic evidence**

The company submitted a cost-utility analysis comparing ipilimumab to best supportive care (BSC) in adult patients with advanced melanoma who have received prior therapy. A partitioned Markov model was used, with three key health states: disease before progression, disease after progression and death. The main data source was the pivotal clinical study, on the assumption that gp100 peptide vaccine had no efficacy or adverse events. The ipilimumab arm of the economics model was thus based on the combined ‘ipilimumab only’ and ‘ipilimumab plus gp100 vaccine’ arms of the clinical study, and BSC in the economic model used the data from the ‘gp100 vaccine only’ arm.

Data on disease progression and survival from the clinical study were used in the economic model but a key issue was the length of survival beyond the end of the clinical trial follow-up period. Three methods were considered for extrapolating the observed data:
(i) Fit a single curve to data from each arm of the trial, as would be normal practice – the company argued that this was not valid because of a ‘significant change in hazards at around 18 months (steep rate of mortality followed by flat survival curve).’

(ii) Fit curves in two stages, one up to 18 months and one for the remaining period. While this was reported to offer a good fit to observed data, as would be expected, the second curve predicted very few further deaths from melanoma among survivors at 18 months, which was judged implausible.

(iii) As for (ii) above but using registry data to predict survival beyond 18 months.

In the base case, strategy (iii) was used for overall survival and strategy (ii) for progression-free survival.

Quality of life was measured in the pivotal trial using the EORTC QLQ-C30 and the SF-36. Both measures were mapped to utility values and the submitting company plotted these in terms of the number of days before the patient’s death (where applicable) and an average for patients who did not die in the course of the clinical trial. Comparisons were available with a published research study that had used the standard gamble technique in British and Australian members of the public to value health states relevant to advanced melanoma. It was argued that the analysis based on EORTC QLQ-C30 was more relevant because it had been measured in the patients in the clinical trial, the utility values had greater face validity, and it is a cancer-specific scale. Values included 0.81 when the patient was more than 120 days from death, 0.61 in the last 30 days of life and 0.86 if the patient did not die in the course of the clinical trial.

Resource use included the cost of general management of advanced melanoma but the main cost related to the ipilimumab used. While the aim was to give patients 4 doses of treatment, the average from the clinical trial was 3.69 doses and this was the basis of the costing used. It was assumed that 30% of the excess medicine in a vial would be wasted, the remainder being re-used through vial sharing between patients.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS offered a discount on the price of the medicine. As SMC has not recommended use of the medicine, however, the PAS cannot be implemented in NHS Scotland. The result with the PAS was a cost per quality adjusted life year (QALY) of £45,470 based on an added lifetime cost of £60,501, and a QALY gain of 1.32.

There were two main issues:
(i) the estimation of the long-term effects of the medicine
(ii) the utility values used

Extrapolation of clinical trial data is common in economic modelling and the principle is accepted, but the method selected in this submission resulted in a very large predicted QALY gain for this therapy area and stage of disease, and was based on a modelling approach not generally used in submissions for medicines for advanced cancer. In the base case analysis (time horizon 40 years), the QALY gain was estimated at 1.32. However, the sensitivity analyses reveal that when the time horizon was 15 years the QALY gain was 1.03, a reduction of 0.29 on the base case (cost per QALY of £71k with PAS). This suggests a substantial proportion of the QALY estimate derives from patients living far beyond the projected mean survival of 14 months with BSC; indeed, the submission shows that a small number of patients are assumed to still be alive 40 years after treatment.
Similarly, if the approach to extrapolation followed normal practice using goodness-of-fit measures to select a method for extrapolating from the observed clinical trial data, the QALY gain would have been 0.59, a reduction of 0.73 on the base case (£103k per QALY with PAS). This means that of the base case QALY gain, 0.73 of 1.32, or 55%, derives from the unusual approach to extrapolation.

Long-term survival with this medicine does not seem to be consistent with the fact that in the clinical study only around 2% of patients experienced a complete response; this suggests the survival benefit is being overstated by the model developed by the submitting company.

In response to questions, the company provided further information on the extrapolation, but there remains considerable doubt: for example, it is unclear at what point the change in hazards starts. SMC clinical experts confirmed that in previous trials of other therapies for advanced melanoma there was some evidence to support long-term survival. However, in the company’s model, the magnitude of the gain is considerable: the average patient’s life expectancy on BSC was 1.2 years but with ipilimumab it was modelled as being 3.7 years, a three-fold increase. With so few patients having been followed up beyond 2 years, such conclusions may not be robust.

These extrapolations were combined with utility values which seemed high for patients with advanced cancer, especially after progression, and which seem to ignore the impact of adverse events. For example, the submission stated the normal utility value for a 56-year old is 0.84 but even when the patient is within 4 months of death their utility was 0.81 according to the company’s modelling estimates; in the last month of life the patient’s quality-of-life was 0.61. The utility values seemed at odds with testimony from patient groups about the impact of the disease and of the adverse events associated with ipilimumab. It was assumed that any adverse events were captured by the EORTC QLQ-C30 but it is possible patients do not complete this when they feel ill.

There are other issues that could also impact. For example, the submission used registry data as the basis for the long-term extrapolation of survival but this was based on American practice in the 1990s and its relevance to Scotland 20 years later is unclear. In addition, the base case analysis assumed a degree of vial sharing, which may not be practicable given the small predicted patient numbers. One further issue was the choice of comparator; while SMC clinical experts indicate that BSC is an option for older, less fit patients who could not withstand further chemotherapy (and thus a relevant comparator), there may be some use of other off-label treatments.

SMC considered the likely range of cost-effectiveness ratios for ipilimumab with the application of the PAS and the remaining uncertainties in the economic case. The committee considered the benefits of ipilimumab in the context of the SMC decision modifiers and agreed that the criteria for a substantial improvement in life expectancy and the absence of other options of proven benefit for the disease in question were satisfied. Despite this, however, the committee was unable to accept ipilimumab due to the additional upwards uncertainty around the cost per QALY relating to the survival extrapolation and the reliability of the utility values in the economic case.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

A Patient Interest Group was received from: Melanoma Action and Support Scotland.
Additional information: guidelines and protocols

The British Association of Dermatology issued revised UK consensus guidelines for the management of cutaneous melanoma in 2010. No chemotherapy has been shown to provide a survival benefit in patients with advanced melanoma. Dacarbazine is recommended as the standard treatment option outside of clinical studies, although it is acknowledged that the benefits are limited.

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN guidance 72: Cutaneous Melanoma in July 2003 and updated in February 2004. The standard chemotherapy of choice for stage IV melanoma is dacarbazine, multiple drug regimens have not been shown to provide a benefit over dacarbazine.

Both guidelines predate the licensing of ipilimumab.

Additional information: comparators

There are no licensed treatment options for patients with advanced melanoma who have received prior therapy. Patients may receive BSC, second line chemotherapy or referral for clinical studies.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>3mg/kg by intravenous infusion every three weeks for four doses</td>
<td>£18,750</td>
<td>£75,000</td>
</tr>
</tbody>
</table>

Costs from eVadis on 21 November 2011 and do not include the cost of re-treatment. Doses based on body weight of 70kg. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 35 patients in year 1 and 40 patients in year 5. Based on an estimated uptake of 5% in year 1 and 26% in year 5, the net impact on the medicines budget, as there are no displaced medicines, was estimated at £132K in year 1 and £758K in year 5 without the PAS. These estimates do not assume any vial sharing of ipilimumab.

The market share assumptions seem low and clinical experts in Scotland have warned that the incidence of melanoma is increasing. Given the interest in the medicine among patients and clinicians, the estimated budget impact may have been underestimated.
References

The undernoted reference was supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 16 March 2012.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.