Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission

pembrolizumab 50mg powder for concentrate for solution for infusion (Keytruda®) SMC No. (1087/15)

Merck Sharp and Dohme Ltd

4 November 2016

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 resubmission assessed under the end of life and orphan process

pembrolizumab (Keytruda®) is not recommended for use within NHS Scotland.

Indication under review: as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. This submission relates to use in adults previously treated with ipilimumab.

In a phase II randomised study, pembrolizumab improved progression free survival compared with chemotherapy in patients with advanced melanoma previously treated with ipilimumab and, if BRAF V600 mutant-positive, a BRAF or MEK inhibitor.

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

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. This submission relates to use in adults previously treated with ipilimumab.

Dosing Information

The recommended dose is pembrolizumab 2mg/kg administered intravenously over 30 minutes every three weeks. Patients should be treated until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

Product availability date

July 2015
Pembrolizumab meets SMC end of life and orphan equivalent criteria.
Pembrolizumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 11 March 2015.

Summary of evidence on comparative efficacy

Pembrolizumab is a monoclonal antibody which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity which is involved in the control of T-cell immune responses. Pembrolizumab therefore potentiates T-cell responses, including anti-tumour responses, by blocking PD-1 binding to PD-L1 and PD-L2 in antigen presenting cells, tumours or other cells in the tumour microenvironment.[1] Pembrolizumab has received marketing authorisation as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. In this submission, the submitting company has requested that SMC considers the use of pembrolizumab for patients with unresectable or metastatic melanoma who have been previously treated with ipilimumab. Vemurafenib and dabrafenib are licensed as monotherapy for the treatment of adult patients with BRAF V600 mutant-positive unresectable or metastatic melanoma. SMC accepted vemurafenib and dabrafenib for restricted use as first line therapy. SMC has also previously accepted ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in patients who have received prior therapy and for first-line use.

The evidence to support the use of pembrolizumab in advanced melanoma in patients who have received previous ipilimumab therapy comes from one pivotal study (KEYNOTE-002).[2,3] This is a randomised multi-centre phase II study comparing pembrolizumab at two dosing levels with investigator's choice of chemotherapy in 540 adults with advanced (unresectable stage III or stage IV) melanoma. The randomisation to pembrolizumab or investigator's choice of chemotherapy was open-label; however, the allocation of the pembrolizumab dose was double-blind. Patients were included if they had a European Cooperative Oncology Group performance

status (ECOG PS) of 0 or 1 and advanced melanoma with progressive disease within 24 weeks after at least two doses of ipilimumab and had received a BRAF or MEK inhibitor (or both) if their tumour was BRAF V600 mutant-positive. Patients were also required to have resolution or improvement of any ipilimumab-related adverse events to grade 0 or 1 and prednisolone dose ≤10mg/day for at least two weeks before the first dose of study drug.[2] All efficacy and safety results cited below are from the second interim analysis, except for the overall survival (OS) results which are from the final OS analysis after 368 deaths.[3]

Patients were stratified according to ECOG PS (0 versus 1), lactate dehydrogenase (LDH) concentration (normal versus elevated) and BRAF status (V600 mutant versus wild type) then randomised equally to receive pembrolizumab intravenous (IV) 2mg/kg (licensed dose) (n=180) or 10mg/kg (n=181) every three weeks or investigator's choice of chemotherapy (n=179) from the following: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel alone or carboplatin alone. Patients received treatment until disease progression or unacceptable toxicity.[2] Table 1 lists the number of patients who received each chemotherapy treatment.[2]

Table 1: Chemotherapy received in the control group[2]

Chemotherapy	**Proportion of patients (n=179)**
Dacarbazine	25%
Oral temozolomide	24%
Paclitaxel plus carboplatin	23%
Paclitaxel	16%
Carboplatin	7%
No chemotherapy	5%

Patients randomised to investigator's choice of chemotherapy could cross over to receive pembrolizumab 2mg/kg or 10mg/kg every three weeks in a double-blind fashion after independently verified disease progression and a washout period of at least 28 days; 48% had crossed over at the second interim analysis.[1]

The co-primary outcomes of the study were progression-free survival (PFS), defined as the time from randomisation until documented disease progression according to Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1, or death from any cause, and OS, defined as the time from randomisation until death from any cause. The primary outcome at the second interim analysis was PFS and the primary outcome at the final analysis was OS.[2,3]

At the second interim analysis (12 May 2014, median follow-up of 10 months), 72% (129/180), and 87% (155/179) had experienced an event in the pembrolizumab 2mg/kg and chemotherapy groups respectively. The median PFS was 2.9 months in the pembrolizumab 2mg/kg group and 2.7 months in the chemotherapy group, hazard ratio (HR) 0.57 (95% confidence interval [CI] 0.45 to 0.73), $p<0.0001$.[2] The median PFS for all patients was around the time of the first scan (performed at 12 weeks). PFS rates are presented in table 2 below.

Table 2: Progression free survival rate from KEYNOTE-002[2]

PFS rate	Pembrolizumab 2mg/kg	Chemotherapy
PFS rate at six months	34%	16%
PFS rate at nine months	24%	8%

The pre-specified subgroup analyses and sensitivity analyses of the primary endpoint supported the overall results.[2] Subgroup analysis of patients who were PD-L1 positive and PD-L1 negative also favoured pembrolizumab.[1]

At the final (primary) OS analysis (November 2015, median follow-up of 28 months in the full study population), 68.3% (123/180) and 71.5% (128/179) of patients had died in the pembrolizumab 2mg/kg and chemotherapy groups, respectively. There was no significant difference between the treatment groups. Median OS was 13.4 months and 11.0 months in the respective groups; HR 0.86 (95% CI 0.67 to 1.10), p=0.117. The 24-month OS rates were 36% and 30%, respectively. A total of 55% (98/179) of patients in the chemotherapy group had crossed over to receive pembrolizumab.[3]

The secondary outcome of objective response rate (defined as the percentage of patients with complete or partial responses according to RECIST) was achieved by 21% (38/180) and 4.5% (8/179) in the pembrolizumab 2mg/kg and chemotherapy groups respectively (p<0.001). The median duration of response had not been reached in the pembrolizumab group 2mg/kg group; in the chemotherapy group, median duration of response was 37 weeks.[2]

Health-related quality of life was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). Baseline scores were similar among the treatment groups. Pembrolizumab was associated with a smaller deterioration in health status compared with chemotherapy. The least squares mean change from baseline to week 12 was -2.6 in the pembrolizumab 2mg/kg group (n=176) and -9.1 in the chemotherapy group (n=167); difference = 6.5, (p=0.011).[2]

Summary of evidence on comparative safety

In KEYNOTE-002, a treatment-related adverse event was reported in 67% (120/178) of patients in the pembrolizumab 2mg/kg group compared with 81% (138/171) of patients in the chemotherapy group. Grade 3 or 4 treatment-related adverse events were reported in 11% and 26% of patients respectively; the most common in the pembrolizumab 2mg/kg group were fatigue, generalised oedema and myalgia.[2]

Serious treatment-related adverse events were reported in 7.3% and 10% of patients in the pembrolizumab 2mg/kg group and chemotherapy group respectively. The most common serious treatment-related adverse events in the pembrolizumab group were diarrhoea and pneumonitis. The proportions of patients discontinuing treatment due to a treatment-related adverse event were 2.2% and 5.8% respectively.[2]

Adverse events that were potentially immune-mediated were reported regardless of whether they were considered to be treatment-related. These were hypothyroidism (6.2% and 0.6%),

hyperthyroidism (3.9% and nil), hepatitis (1.1% and 0.6%), colitis (1.1% and 0.6%), pneumonitis (1.7% and nil), hypophysitis (0.6% and nil), hypersensitivity (0.6% and 1.8%), infusion-related reaction (nil and 0.6%) and nephritis (0.6% and nil) reported in the pembrolizumab 2mg/kg group and the chemotherapy group respectively.[2]

Summary of clinical effectiveness issues

In patients who have previously received ipilimumab, current treatment options are limited to best supportive care, which may include palliative chemotherapy such as dacarbazine. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area as current treatment options are limited, overall prognosis remains poor and further new treatments are still urgently needed. Pembrolizumab meets SMC end of life and orphan equivalent criteria.

Pembrolizumab has received marketing authorisation as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. The submitting company has requested that SMC considers the use of pembrolizumab for patients with unresectable or metastatic melanoma who have been previously treated with ipilimumab. The company submitted to SMC separately for patients with advanced (unresectable or metastatic) melanoma previously untreated with ipilimumab, and SMC has advised that pembrolizumab is accepted for use in this setting.

The co-primary outcomes of KEYNOTE-002 were the clinically relevant outcomes of PFS and OS. At the second interim analysis, a statistically significant PFS benefit associated with pembrolizumab was demonstrated over chemotherapy. At the final OS analysis, the pembrolizumab group had a numerical but not significant improvement in median OS compared with the chemotherapy group: 13.4 months versus 11.0 months.[3] There was less deterioration in health-related quality of life in the pembrolizumab-treated patients compared with those receiving chemotherapy,[2] although this subjective outcome may have been biased by the open-label design of the study.

In KEYNOTE-002 the difference in median PFS was statistically significant but very small (0.2 months). The median PFS for all treatment groups is around the time of the 12 week scan, as more than half of the patients in the study had progressive disease at this time.[2] The submitting company suggested that the six month PFS rate is more clinically relevant: this was 34% in the pembrolizumab 2mg/kg group (licensed dosing schedule) and 16% in the chemotherapy group. Crossover from the chemotherapy group to receive pembrolizumab was permitted upon disease progression.[2] The final OS analysis is confounded as 55% of patients had crossed over from the chemotherapy group to receive treatment with pembrolizumab.[3] The submitting company conducted a *post hoc* analysis of OS results from the second interim analysis but the results of this analysis have been deemed to be confidential by the submitting company.

Subgroup analysis of patients who were PD-L1 positive and PD-L1 negative was consistent with results in the full study population, favouring pembrolizumab over chemotherapy. PD-L1 expression was tested retrospectively and the study groups were not stratified for this.[1]

Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to its novel mechanism of action and objective and progression free response rates.

Immune-related adverse events have been reported in patients taking pembrolizumab, including pneumonitis, colitis, hepatitis, nephritis and endocrinopathies. These are mostly reversible and can be managed with dose interruptions, corticosteroids and supportive care. Patients treated with pembrolizumab must be given a Patient Alert Card and be informed about the risks associated with treatment; refer to the summary of product characteristics for further information.[1]

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of pembrolizumab, as an end of life and orphan medicine, in the context of treatments currently available in NHS Scotland, specifically as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults (previously treated with ipilimumab).

The key points expressed by the group were:

- Metastatic melanoma is an incurable cancer that affects a disproportionate number of young adults and often leads to complex and severe symptoms. Consequently it has a particularly severe impact on patients/families/carers' daily life.
- Despite recent advances in systemic therapy, overall prognosis remains poor. There are no other options to increase progression free survival for patients where ipilimumab has failed or is not tolerated.
- The clinicians emphasised that the clinical trials required to satisfy the regulatory authorities are often still at a relatively early stage of follow up and therefore do not fully capture the long term benefits of immunotherapy treatment options. The full impact on disease control (or possibly cure) may not become apparent until long after the course is finished.
- The clinicians experience has been that even as a second line option after ipilimumab, pembrolizumab is better than first line ipilimumab. This is unlike any other treatment for cancer where subsequent treatments generally perform less well than the first line treatment option.
- Ipilimumab and pembrolizumab have a different adverse effect (AE) profile. While both have similar rates of Grade 3 and 4 AEs the clinicians noted that AEs associated with pembrolizumab are mainly thyroid and skin related which can be detected early and managed relatively easily.
- SMC has accepted pembrolizumab for use in patients not yet treated with ipilimumab. The option to use it in the post-ipilimumab setting will only impact on the cohort of patients currently on ipilimumab and there will be no such patient cohort within a few years.

Additional Patient and Carer Involvement

We received a patient group submission from Melanoma Action and Support Scotland (MASScot). MASScot has not received any pharmaceutical company funding in the last two years. Representatives from MASScot also participated in the PACE meeting. Many of the key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing pembrolizumab to best supportive care (BSC) in adults with advanced melanoma who had received prior therapy with ipilimumab. BSC is comprised of no treatment and some systemic therapies which are not expected to improve survival but only to treat symptoms. This included dacarbazine, paclitaxel, carboplatin, interferon alfa-2b, vindesine and temozolomide.

A partitioned Markov model was used, with three key health states: pre-progression, post-progression and death. In the model, time-to-death sub-health states were used to capture patients' quality of life as a function of time until death. These sub-health states are <30 days to death, 30-90 days to death, 90-180 days to death and >180 days to death. The analysis was conducted over a 40-year time horizon, with patients assumed to enter the model at the age of 60 years. The main data source was the KEYNOTE-002 pivotal clinical study described above. To estimate PFS, the company used the Kaplan-Meier (KM) data until 13 weeks then fitted a Gompertz parametric function to extrapolate the data over the model time horizon. To estimate OS in the pembrolizumab arm, the company used KM data from the pivotal study for the first year, data from a published ipilimumab study assuming the same relative rates of survival for both patient cohorts for years one to ten, and then registry data plus general population mortality data from year 10 onwards.

Utility values were estimated from EQ-5D data collected in the pivotal study and were included in the model based on time to death. The utility values were 0.77 for patients with estimated survival of >180 days, 0.62 for estimated survival of 90-180 days, 0.52 for estimated survival of 30-90 days and 0.42 for estimated survival of <30 days. Medicines cost and resource use covered medicine acquisition and administration costs plus on-going care costs for advanced melanoma.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS is a complex scheme.

With the PAS, the company estimated a cost per QALY of £35,161 based on an incremental cost of £41,974 and a QALY gain of 1.19.

The company presented a variety of deterministic and scenario analyses. The model is most sensitive to the following;

- Varying the HR from the 2 stage crossover adjustment increased the with-PAS ICER to £105k.
- PFS of pembrolizumab from 13 weeks and applying the upper bound of the Gompertz scale increased the with-PAS ICER to £103k.
- PFS of pembrolizumab from 13 weeks and applying the lower bound of the Gompertz treatment effect increased the with-PAS ICER to £55k.
- Using a 10 year time horizon increased the with-PAS ICER to £47k and reduced the QALY gain to 0.79.
- Modelling the utilities based upon disease progression (applying a utility for pre- and post-progression) increased the with-PAS ICER to £39k.
- Adjusting for crossover using the inverse probability of censoring weights (IPCW) approach increased the with-PAS ICER to £39k.

- Modelling OS based upon the HR from the KEYNOTE-002 study and using an alternative data source to extrapolate the data beyond year 1 increased the with-PAS ICER to £55k and reduced the QALY gain to 0.73.

The main weaknesses with the analysis are:

- There is some uncertainty in the approach used as the method of extrapolation resulted in a relatively large QALY gain for this stage of disease. The majority of the QALY gain is accrued in the post-progression state which highlights that a substantial proportion of the estimated gain is coming from the extrapolation phase of the model. In addition, there is some question about the face validity of the QALY gain as the long-term survival estimated by the model may not be consistent with the clinical study which showed that only around 2% of patients experienced a complete response. Furthermore, the method used to extrapolate OS involved a number of steps and assumptions which increased uncertainty in the model. To support the model predictions, the company provided a comparison of the final median OS analysis from the study with the median OS estimates predicted by the model. While the model appears a reasonable fit to the study data (prior to crossover adjustment) and registry information, the gain in OS in the study was not statistically significant and the assumption that the benefit from pembrolizumab treatment is maintained over the 40 year time horizon is uncertain and difficult to validate. Sensitivity analyses suggested that other plausible approaches would increase the cost per QALY. For example, when the hazard ratio from the two-stage full covariate analysis was applied to an alternative data set to extrapolate the data beyond year 1, the with-PAS ICER increased to £55k and the QALY gain reduced to 0.73, which indicated that the QALY gain is sensitive to the choice of extrapolation method.
- The OS data were confounded by 48% of the control arm patients crossing over to receive pembrolizumab at the interim analysis. The SMC statistician advised that crossover of this scale makes adjustment challenging and this is highlighted by the fact that different crossover methods produced quite different results, with the OS hazard ratios varying between 0.63 in the base case analysis to 0.85 when no adjustment was made. Using the IPCW and rank preserving structural failure time (RPSFT) methods increased the with-PAS ICERs to £39k and £64k respectively. Given the uncertainty associated with crossover adjustment, the company also provided the results using the unadjusted hazard ratio, which increased the ICER to £80k. However, this analysis is likely to be particularly conservative.
- The model structure further impacts the utility value elicitation as it is based upon time to death and not disease progression. While this is not the conventional approach, it has been used in previous submissions for advanced melanoma. The company also provided the results of the analysis using the more conventional approach (utility values attached to pre- and post-progression health states) which increased the with-PAS ICER to £39k and reduced the QALY gain to 1.07.

The Committee considered the benefits of pembrolizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was met. In addition, as pembrolizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept pembrolizumab for use in NHS Scotland.

Additional information: guidelines and protocols

A collaboration of multi-disciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer published; Diagnosis and treatment of melanoma, European consensus-based interdisciplinary guideline - update 2016.[5] It states that the two main goals of systemic therapy of metastatic disease are prolongation of survival and reduction of tumour size or load with a resultant increase in symptom-free course or a decrease in symptoms. Treatments in the guidance include targeted therapy (vemurafenib and dabrafenib), immunotherapy (the CTLA-4 inhibitor ipilimumab and the PD-1 antibodies nivolumab and pembrolizumab) and chemotherapy (dacarbazine). The guidance notes there are insufficient data to establish a treatment algorithm for stage IV melanoma. However general principles include:

- Mutation testing of tumour tissue (at least BRAF; NRAS CKIT in subtypes) is a prerequisite for treatment decisions, and should be performed preferentially in metastatic tumour tissue from AJCC stage IIIB onwards
- PD-1 checkpoint blockade either as monotherapy or in combination with CTLA-4 blockade should be considered as a good option for first-line treatment for all patients with unresectable metastatic melanoma, independently from BRAF status.
- When BRAF-inhibitors are considered for BRAF mutated patients, they must be given in combination with MEK inhibitors.
- In BRAF mutated patients there are presently no data whether BRAF/MEK inhibition should be given in the first or second line, and trials on the best sequencing of targeted therapy and immunotherapy are ongoing.
- Chemotherapy may be considered in patients in good performance status with resistance to kinase inhibitors and checkpoint blockade.
- C-KIT inhibitors may have a role in the small proportion of c-KIT mutant melanomas

The National Institute for Health and Care Excellence (NICE) published a guideline on Melanoma: assessment and management of melanoma on 29 July 2015.[6] For systemic anticancer treatment this recommends targeted treatment with dabrafenib and vemurafenib as options for treating unresectable or metastatic BRAF V600 mutation positive melanoma and immunotherapy with ipilimumab as an option for treating unresectable or metastatic melanoma that has been previously treated or not. These agents are recommended only if manufacturers provide them with discounts agreed in patient access schemes. Cytotoxic chemotherapy with dacarbazine can be considered for patients with stage IV metastatic melanoma if neither immunotherapy nor targeted therapy are suitable. Further chemotherapy should not be routinely offered to patients with stage IV metastatic melanoma who have been previously treated with dacarbazine, except in the context of a clinical trial.

The European Society for Medical Oncology (ESMO) published Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, in 2015.[7] These guidelines note that patients with metastatic melanoma should have metastasis (preferably) or the primary tumour screened for detection of BRAFV600- mutation. Treatment options for the first- and second-line setting include anti-PD1 antibodies (pembrolizumab, nivolumab), ipilimumab, an anti-CTLA4 antibody, for all patients, and BRAF/MEK inhibitor combinations for patients with BRAF-mutant melanoma. If clinical trials or the approved new targeted compounds are not available, cytotoxic drugs such as dacarbazine (DTIC) or temozolomide may be administered, with modest activity shown.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 72; Cutaneous Melanoma in July 2003 (and updated in February 2004).[8] This guideline was withdrawn in February 2015 and is currently in progress.

Additional information: comparators

Nivolumab, best supportive care, including palliative chemotherapy may be offered.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Pembrolizumab	**2mg/kg by intravenous infusion every 3 weeks**	**19,725**

Cost from dm&d on 24 August 2016. Cost per course based on body weight of 70kg and an estimated five cycles of treatment (median time on treatment in the pembrolizumab 2mg/kg subgroup of KEYNOTE-002 was 113 days). The cost does not take a patient access scheme into consideration.

Additional information: budget impact

The submitting company estimated there would be 126 patients eligible for treatment with pembrolizumab in all years.

Without the PAS, the gross and net impact on the medicines budget was estimated to be £1.1m in year 1 and £59k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Pembrolizumab powder for concentrate for solution for infusion (Keytruda®) summary of product characteristics. Merck Sharp & Dohme Limited. https://www.medicines.org.uk/emc/medicine/30602 Last updated 03 August 2016

2. Ribas A, Puzanov I, Drummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015 16, 8, 908-18 plus supplementary appendix

3. *Commercial in Confidence**

4. *Commercial in Confidence**

5. Garbe C, Peris K, Hauschild A et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2016. European Journal of Cancer 2016; 63:201-17

6. National Institute for Health and Care Excellence (NICE) guideline on Melanoma: assessment and management of melanoma on 29 July 2015.

7. Dummer R, Hauschild A, Lindenblatt N et al. on behalf of the ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26 (Supplement 5): v126–v132, 2015

8. Scottish Intercollegiate Guidelines Network. Guideline number 72; Cutaneous Melanoma. July 2003.

This assessment is based on data submitted by the applicant company up to and including 14 October 2016.

**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. 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.