NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Talimogene laherparepvec for treating metastatic melanoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using talimogene laherparepvec in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal (see the project documents) and the public. This document should be read along with the evidence base (the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using talimogene laherparepvec in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 13 April 2016

Second appraisal committee meeting: 19 April 2016

Details of membership of the appraisal committee are given in the project documents.

1 Recommendations

1.1 Talimogene laherparepvec is not recommended within its marketing authorisation, that is for treating regionally or distantly metastatic, unresectable melanoma (Stage IIIB, IIIC and IVM1a) that has not spread to bone, brain, lung or other internal organs.

1.2 People whose treatment with talimogene laherparepvec was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Talimogene laherparepvec (Imlygic, Amgen) is derived from the herpes simplex virus type-1. It is a modified form of the virus that kills cancer cells. Talimogene laherparepvec is injected directly into cutaneous, subcutaneous and nodal lesions that are visible on the skin, palpable, or detectable with ultrasound guidance. The company noted that it has 2 complementary mechanisms of action: replication that causes cell rupture/lysis and death (intracellular or direct effect) and post-lysis release of tumour-derived antigens and granulocyte macrophage colony-stimulating factor (GM-CSF), stimulating a systemic immune response from antigen-presenting cells upon distant tumour sites (extracellular or indirect effect). Talimogene laherparepvec has a marketing authorisation in the UK for the treatment of adults with 'unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease'.

2.2 The most common adverse reactions with talimogene laherparepvec in clinical trials of metastatic melanoma were flu-like symptoms (very common), injection-site reactions (very common) and cellulitis (common and potentially serious). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The acquisition cost of talimogene laherparepvec is £1,670 per 1 ml vial of either 1,000,000 plaque forming units (PFU) per ml or 1,000,000 PFU per ml (excluding VAT; company's submission). The company has agreed a patient access scheme with the Department of Health. If talimogene laherparepvec had been recommended, this scheme would provide a simple discount to the list price of talimogene laherparepvec at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee considered evidence submitted by Amgen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company identified 1 randomised clinical trial, OPTiM. OPTiM was a multinational (including UK), open-label randomised clinical trial that compared talimogene laherparepvec injected directly into lesions with granulocyte macrophage colony-stimulating factor (GM-CSF) injected subcutaneously, in people with stage IIIB, IIIC, or IV melanoma that was not considered to be surgically resectable (n=436). Data for the whole population was included in the company's submission, but the submission focused on the subgroup relevant to the marketing authorisation (stages IIIB to IVM1a and non-visceral disease, n=249). People were randomised in a 2:1 ratio to talimogene laherparepvec (n=295) or GM-CSF (n=141). Talimogene laherparepvec was administered by injection into the lesion at an initial dose of 1,000,000 plaque forming units (PFU) per ml. Subsequent doses of 100,000,000 PFU/ml were administered 3 weeks after the initial dose and then once every 2 weeks. The total volume administered was up to 4.0 ml per treatment session. GM-CSF was

administered subcutaneously at a dose of 125 micrograms per m^2 once daily for 14 days of a 28-day cycle, followed by a 14 day rest period. People who completed treatment in the 12 month study duration could enter into a 6 month extension study to assess the long-term safety and efficacy of talimogene laherparepvec.

3.2 The company noted that baseline characteristics for the overall patient population and the stage IIIB–IVM1a population were similar. It also noted that in the stage IIIB–IVM1a population, baseline characteristics were generally balanced between treatment groups except for ECOG status of zero (74% compared with 63% for patients in the talimogene laherparepvec and GM-CSF groups respectively).

3.3 The primary endpoint was durable response rate defined as partial response or complete response that lasted continuously for over 6 months. Response was assessed using the modified World Health Organization (WHO) criteria by blinded central review. Talimogene laherparepvec was associated with a higher durable response rate than GM-CSF based on the final data analysis. The company also presented results for overall survival (defined as the time from the date of randomisation to the date of death from any cause) and time to treatment failure (defined as time from baseline until the first clinically-relevant disease progression, where there is no response after the clinically relevant disease progression).The company highlighted that the results for the stage IIIB–IVM1a population were consistent to those for the intention to treat population in the OPTiM trial.

Table 1 Results in the OPTiM trial

Endpoint	OPTiM	
	talimogene laherparepvec (n=163)	**GM-CSF (n=86)**
Primary data cut off – 31 March 2014		
Durable response rate	25.2%	1.2%
Odds Ratio, p value	28.6, 0.0001	
Median overall survival (months)	41.1	21.5
Hazard Ratio, p value	0.57, 0.0009	
Median time to treatment failure (months)	13.1	3.3
Hazard Ratio, p value	0.27, 0.0001	
Overall response rate (%)	40.5%	2.3%
p value	<0.0001	
Complete response (%)	16.6%	0.0%
Final data cut off – August 2014		
Durable response rate	25.2%	1.2%
Odds Ratio, p value	28.6, 0.0001	
Median overall survival (months)	46.8	21.5
Hazard Ratio, p value	0.56, 0.0008	
Overall response rate (%)	40.5%	2.3%
p value	<0.0001	
Complete response	16.6%	0.0%

3.4 The company also presented results from exploratory analyses investigating the systemic activity of talimogene laherparepvec. Results showed that in analyses of patients with non-injected lesions, 27 out of 79 patients (34.2%) had more than 50% overall decrease in size in non-visceral lesions, and 8 out of 71 patients (11.3%) had more than 50% overall decrease in size in visceral lesions. Out of 2,116 individual lesions directly injected with talimogene laherparepvec 1,361 (64.3%) decreased in size by more than 50% and 995 (47.0%) completely resolved. Out of 981 non-injected non-visceral lesions, 331 (33.7%) decreased in size by more than 50% and 212 (21.6%) completely resolved. Of 177 visceral lesions, 27 (15.3%) decreased in size by more than 50%. In patients with non-visceral disease 1,026 of 1,441 (71.2%) individual lesions directly

injected with talimogene laherparepvec decreased in size by more than 50% and 809 (56.1%) completely resolved. Out of 538 non-injected lesions, 224 (41.6%) decreased in size by more than 50%.

3.5 The company presented results on health-related quality of life using the FACT-BRM questionnaire. Improvements in the total score were defined as increases of more than 5 points from baseline that were sustained for more than 1 treatment cycle. Improvements in individual domains were defined as increases of more than 2 points from baseline that were sustained for more than 1 cycle. Improvements in individual items were defined as increases of more than 1 point from baseline that were sustained for more than 1 cycle. The company stated that these definitions of improvement were regarded as clinically meaningful.

3.6 The company did not do an indirect treatment comparison to compare talimogene laherparepvec with the different comparators in the scope (ipilimumab, dabrafenib and vemurafenib) because none of the trials had a common comparator to form an evidence network with talimogene laherparepvec or GM-CSF. It noted that there were substantial differences between the patient populations included in OPTiM (in which 57% of patients had stage IIIB–IVM1a disease) and the randomised-controlled trials for the comparators (in which only 11-23% of patients had stage IIIB–IVM1a disease). The company concluded that given the challenges of having a disconnected network and different populations, it was not feasible to do a network meta-analysis.

3.7 The company assessed alternative methods to compare talimogene laherparepvec with the comparators in the scope and considered adjustment based on the Korn prediction model to be most appropriate. The Korn model predicts overall survival using pooled data from 2,100 patients from 42 trials of different treatments for metastatic melanoma done between 1975 and 2005 with prognostic factors including gender, ECOG performance status, presence of visceral metastases, and

presence of brain metastases. The company noted that the Korn prediction model could be used to adjust overall and progression-free survival data from each comparator based on the patient characteristics in OPTiM, so that the adjusted comparator's overall and progression-free survival curves would represent the expected survival if the patients in the comparator trial had similar patient characteristics as those in OPTiM. The company used the modified Korn prediction model based on the approach followed in the company's submission for NICE's technology appraisal of ipilimumab for previously untreated advanced melanoma. This modified model included data from OPTiM and from 2 randomised-controlled trials for ipilimumab (MDX010-20 and CA184-024). The model also included the presence of elevated lactate dehydrogenase levels as a prognostic factor. The company considered this method to be appropriate because it included key patient prognostic factors, including a covariate for presence of visceral disease, and had been used in previous NICE appraisals (ipilimumab for previously untreated advanced, unresectable or metastatic, melanoma and pembrolizumab for advanced melanoma not previously treated with ipilimumab).

Table 2 Modified Korn overall survival and progression-free survival model results for ipilimumab and trial results for talimogene laherparepvec in people with stage IIIB–IVM1a disease

	Trial results (months)	Modified Korn (months)
Median overall survival		
T-VEC	46.8	–
Ipilimumab (pooled)	10.9	21.3
Mean overall survival (AUC)[a]		
T-VEC	36.9	–
Ipilimumab (pooled)	19.5	29.2
Median progression-free survival		
T-VEC	13.1	–
Ipilimumab (pooled)	2.8	5.3
Mean progression-free survival (AUC)[b]		
T-VEC	20.6	–
Ipilimumab (pooled)	8.0	15.2

[a] Calculated using the shorter available time period (55 months).
[b] Calculated using the shorter available time period (43 months).
Abbreviations: AUC, area under the curve; T-VEC, talimogene laherparepvec.

3.8 The company also used a 2-step Korn adjustment to account for a potential interaction effect for ipilimumab. The 2-step Korn adjustment accounts for the same prognostic factors as the modified Korn but includes an additional adjustment to capture a possible treatment-subgroup interaction effect between ipilimumab and the disease stage. The company noted that these results were subject to considerable uncertainty because the modified Korn prediction model assumes that differences between studies in all measured and unmeasured confounders are captured by the prediction model, and the adjustment factor is assumed to fully represent the degree of difference in the populations. It also noted that the 2-step adjustment method relies on the magnitude of the treatment effect of ipilimumab in the subgroup with stage IIIB–IVM1a disease which is captured by using an estimate of the interaction effect between ipilimumab and earlier stage disease. The company highlighted that the subgroup of patients with stage IIIB–IVM1a

disease in the ipilimumab trial included less than 10% of the overall population. The company concluded that based on these analyses, talimogene laherparepvec was associated with a benefit in overall survival compared with ipilimumab (modified Korn method) and in the worst possible scenario, with similar overall survival compared with ipilimumab (2-step Korn method).

Table 3 Two-step Korn overall survival and progression-free survival model results for ipilimumab and trial results for talimogene laherparepvec in people with stage IIIB–IVM1a disease

	Trial results (months)	Two-step Korn (months)
Median overall survival		
T-VEC	46.8	–
Ipilimumab (pooled)	10.9	Not reached
Mean overall survival (AUC)[a]		
T-VEC	33.5	–
Ipilimumab (pooled)	18.0	32.3
Median progression-free survival		
T-VEC	13.1	–
Ipilimumab (pooled)	2.8	17.6
Mean progression-free survival (AUC)[b]		
T-VEC	18.2	–
Ipilimumab (pooled)	7.4	18.6

[a] Calculated using the shorter available time period (48 months).
[b] Calculated using the shorter available time period (35 months).
Abbreviations: AUC, area under the curve; T-VEC, talimogene laherparepvec.

3.9 The company noted that the incidence of all treatment-emergent adverse events experienced by patients with stage IIIB–IVM1a melanoma was higher in the talimogene laherparepvec group (99%) compared with the GM-CSF group (93%). The incidence of serious adverse events and treatment-related adverse events were also higher in the talimogene laherparepvec group (serious adverse events 20%, treatment-related adverse events 93%) compared with the GM-CSF group (serious adverse

events 13%, treatment-related adverse events 79%). However, discontinuation rates were comparable between the talimogene laherparepvec group (9%) and the GM-CSF group (7%).

3.10 The company submission included an overview of the adverse events associated with talimogene laherparepvec, ipilimumab, vemurafenib and dabrafenib, including rates of dose discontinuations and/or modifications identified with these agents. These data showed that talimogene laherparepvec compared favourably in terms of safety with other recommended treatments for metastatic melanoma.

ERG comments

3.11 The ERG noted that durable response is not a commonly used endpoint (neither primary nor secondary) in other trials of metastatic melanoma; the draft European Public Assessment Report noted that this is a new clinically relevant endpoint that has not been validated and is potentially prone to bias. The ERG also noted that although people could have a durable response despite disease recurrence, progression after 6 months or developing new lesions, it agreed with the European Medicines Agency's view that durable response rate is an acceptable endpoint because it captures a relevant clinical effect of the treatment.

3.12 The ERG noted that in the intention-to-treat population, 53.4% of patients in the OPTiM trial had prior treatment for metastatic melanoma. However, the ERG highlighted that the type of treatment received in the trial differed from what would be available for patients with metastatic melanoma in clinical practice today. The ERG considered that the patient population in the OPTiM trial is generally similar to the population that is likely to be considered for treatment with talimogene laherparepvec in clinical practice in England although it is unclear if the effectiveness for previously treated melanoma in the OPTiM trial could be replicated in clinical practice in England because of differences in standard treatment of regionally or distantly metastatic unresectable melanoma.

3.13 The ERG noted that the open-label OPTiM trial was prone to bias, because perceived beliefs about the relative efficacy of talimogene laherparepvec may have influenced decisions about whether to stop treatment (particularly in the GM-CSF arm) or having another therapy. The ERG also noted that those in the GM-CSF arm were more likely to withdraw their consent, which was another potential source of bias and favoured talimogene laherparepvec. Additionally, clinical assessments of response were subjective, susceptible to investigator bias, and could have ultimately influenced the determination of stable disease, complete response, and partial response and also durable response rate and overall response rate.

3.14 The ERG noted that in the company submission the results for people with non-visceral metastatic disease were consistent with the results from the intention-to-treat population. However, the ERG noted that the magnitude of difference between arms for all endpoints was much greater in patients with non-visceral metastatic disease than in the intention-to-treat population. The ERG expressed concern that the population under consideration was based on and derived solely from an analysis of an exploratory post-hoc subgroup. The ERG's main concern was that the subgroup was a mixture of people with stage III and stage IVM1a disease, that are likely to have different disease trajectories.

3.15 The ERG noted that the proportion of people with melanoma that is visible on the skin, palpable, or detectable with ultrasound guidance (injectable melanoma) in the studies of the comparator technologies is unknown. Therefore the characteristics of patients with non-visceral metastatic disease in these trials may differ from those in the OPTiM trial.

3.16 The ERG had the following concerns relating to the use of alternative models for estimating relative effectiveness of talimogene laherparepvec and ipilimumab:

- The modified Korn model was used to correct for differences in patient characteristics between 2 ipilimumab trials and the OPTiM trial. The ERG considered that this model was not appropriate because it was developed using data from people with predominantly stage IVM1b and stage IVM1c disease, despite the OPTiM trial containing mostly people with stage IVM1a disease. In addition, the modified Korn model included an adjustment for elevated lactate dehydrogenase, which is not relevant for people with stage IIIB, stage IIIC or stage IVM1a disease, but had the effect of reducing the size of the coefficients associated with other adjustment factors (and improving the relative efficacy of talimogene laherparepvec). Korn data are dominated by the most seriously affected patient groups (stage IVM1b and stage IVM1c) rather than by those with stage IVM1a disease who are the only people with stage IV disease featured in the target subgroup of the OPTiM trial. Furthermore, in the OPTiM trial 57% of people in the talimogene laherparepvec arm of the trial had stage IIIB, stage IIIC or stage IVM1a disease compared with less than 20% in the ipilimumab trials.

- The effectiveness of ipilimumab may vary significantly by stage of disease. The company attempted to correct for this case-mix imbalance by using the two-step Korn model, which is a further application of the modified Korn model. This additional adjustment is likely to mean that the problems previously described are further compounded.

- The original Korn publication specified different models for progression-free survival and overall survival. The ERG suggested that

the company's use of the same modified Korn model for both overall survival and progression-free survival is inappropriate

3.17 Given the lack of clinical-effectiveness evidence available, the ERG considered that the company was correct to attempt to apply alternative approaches for the comparison of talimogene laherparepvec with ipilimumab. However, the ERG did not consider the Korn models (or modifications to them) to be appropriate to estimate the effectiveness of ipilimumab in people with stages IIIB to stage IVM1a of the disease because the prognostic factors were derived from later stage metastatic melanoma which has a different disease trajectory to the patients in the OPTiM trial . The ERG suggested therefore that the relative clinical effectiveness of talimogene laherparepvec compared with ipilimumab was unknown. The ERG highlighted that talimogene laherparepvec does, however, appear to have a better safety profile than ipilimumab or pembrolizumab although there is limited data to support the long-term safety of talimogene laherparepvec

Cost effectiveness

3.18 The company used a de novo partitioned survival model to compare the cost effectiveness of talimogene laherparepvec with ipilimumab in people with unresectable, regionally or distantly metastatic melanoma with no bone, brain, lung or other visceral disease; that is, patients with stage IIIB–IVM1a disease. The perspective was that of the NHS and personal social services. The time horizon was lifetime (30 years), the cycle length was 1 week and a half-cycle correction was applied. Costs and outcomes were discounted at 3.5% per year.

3.19 The model included 3 states: non-progressive disease (including complete response, partial response and stable disease), progressive disease (defined as an increase of more than 25% in the sum of the surface areas of all measurable tumours, or an increase of more than 25% in a single lesion or the appearance of a new lesion) and death. The company

assumed that patients enter the model in the non-progressive disease state and have treatment with talimogene laherparepvec or ipilimumab. Transition to another state depends on response to treatment. After disease progression, patients have best supportive care defined as non-curative health care and palliative care. The company assumed that treatment with talimogene laherparepvec continued for at least 6 months after disease progression. For ipilimumab, the dosing was based on that used in NICE technology appraisal guidance on ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma and was lower than that stated in the summary of product characteristics. The use of subsequent therapies was not included in the model. It was assumed that patients who died had palliative care for up to 3 months before terminal care and death.

3.20 Clinical inputs for talimogene laherparepvec were taken from OPTiM, and from CA184-024 and MDX010-020 for ipilimumab. The company used data from the final data cut off from OPTiM for talimogene laherparepvec, and pooled the published clinical trial data for ipilimumab from CA182-024 and MDX010-020. The company used the progression-free and overall survival results from the modified Korn prediction model and the 2-stage Korn adjustment in the model (see section 3.11). The mean age of patients in the model was 64 years.

3.21 The company applied different parametric curves to extrapolate progression-free survival data in the model and concluded that the generalised gamma distribution provided the best fit to the data for talimogene laherparepvec and ipilimumab. The company stated that because of the lack of data on ipilimumab for people with non-visceral disease, there is uncertainty about the treatment effect of ipilimumab in the population considered in the model.

3.22 The company modelled overall survival using a 3-part curve fit based on changes on the slope of the overall survival Kaplan-Meier curves:

- first part of the 3-part curve fit (until 40.7 months for talimogene laherparepvec and until 29.7 months for ipilimumab): the company used Kaplan-Meier overall survival data from the trials
- second part of the 3-part curve fit from the start of the data cut until the end of observed trial data (62 and 55 months for talimogene laherparepvec and ipilimumab respectively): the company applied different parametric curves to the overall survival Kaplan-Meier data from the modified Korn prediction model and the 2-stage Korn adjustment and concluded that the exponential distribution provided the best fit for talimogene laherparepvec and ipilimumab
- third part of the 3-part curve fit (from 62 and 55 months for talimogene laherparepvec and ipilimumab, respectively, to 10 years): the company used observational disease-specific data from the AJCC registry based on the publication from Balch et al. (2009) and mortality data from life tables published by the Office of National Statistics. Data from life tables alone was used from year 10 onwards.

3.23 The company obtained the utility values from NICE technology appraisal guidance on dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. The company included in the model adverse events of grade 3 or more with an incidence of 2% or more. Utility decrements because of adverse events were obtained from a time-trade-off study done by the company in the general population in the UK, in which respondents were asked to value different states associated with advanced melanoma (n=300). The company also used utility values from this study for the different states in the model and utility values sourced from the literature in sensitivity analyses.

3.24 The company included in the model data on healthcare resource use associated with treatment, disease progression, and palliative care. The company did a survey and a costing study to estimate healthcare resource use associated with adopting talimogene laherparepvec in the NHS. The company estimated the cost of talimogene laherparepvec

based on individual patient-level data from OPTiM, calculating the mean number of vials per injection per day including wastage. Costs associated with adverse events for ipilimumab were taken from NICE technology appraisal guidance on ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma and on ipilimumab for previously treated advanced (unresectable or metastatic) melanoma, and inflated to present year. The company assumed that costs for managing nausea and vomiting were the same as for managing diarrhoea, and that cost for managing anaemia was similar to the cost for managing fatigue. It also assumed that the cost of managing cellulitis was the same as for managing rash, and that the cost for managing headache was the same as for managing pain. The cost of managing constipation and dyspnoea was assumed to be zero. The company stated that these assumptions were consistent with previous appraisals.

3.25 The company submission presented the results from the cost-effectiveness analysis of talimogene laherparepvec compared with ipilimumab for people with advanced melanoma and non-visceral disease (that is, stage IIIB–IVM1a melanoma). The company's base-case used an anticipated list price of £1,445 per vial for talimogene laherparepvec. However, this price was superseded by a price of £1,670 per vial. The list price of £3,750 per vial was used for ipilimumab. The company submission presented analysis using the modified Korn prediction model (the company's preferred method) and the 2-stage Korn adjustment. The results showed that talimogene laherparepvec was associated with 1.34 additional quality-adjusted life years (QALYs) compared with ipilimumab when using the modified Korn prediction model. When using the 2-stage Korn adjustment, talimogene laherparepvec provided 0.35 additional QALYs compared with ipilimumab. Because both talimogene laherparepvec and ipilimumab have confidential patient access schemes, the costs and incremental cost effectiveness ratios cannot be presented.

3.26 The company presented sensitivity analysis varying duration of treatment, response rates, administration costs, discount rates, utility values and cost of terminal care by 20%. The company suggested that the variable that had the highest effect on the incremental cost-effectiveness ratio (ICER) for talimogene laherparepvec compared with ipilimumab was duration of treatment with talimogene laherparepvec and ipilimumab when using the modified Korn prediction model and the 2-stage Korn adjustment.

ERG comments

3.27 The ERG noted that the effectiveness of ipilimumab was synthesised from data from 2 clinical trials. The reliability of this synthesised comparator depends upon several assumptions. The ERG had the following concerns:

- The company's network focussed on ipilimumab as the main comparator whereas pembrolizumab may be a more relevant comparator.
- Pooling ipilimumab data from the arms of 2 published clinical trials assumes that (a) dacarbazine and gp100 are both ineffective, (b) survival patterns are equivalent regardless of whether ipilimumab is administered as a first-line or as a subsequent line of therapy, and (c) censoring occurs at a constant rate within each (arbitrary) time period. The ERG was not convinced that these assumptions can be substantiated.
- The use of either the modified Korn or two-step Korn models as to derive effectiveness estimates for ipilimumab (see section 3.16).

3.28 The ERG suggested that the company's use of the same modified Korn model for both overall survival and progression-free survival is inappropriate (see section 3.16). The ERG suggested that this is likely to lead to misrepresentation of estimated progression-free survival trends for ipilimumab and substantial additional uncertainty in estimated model outcomes, which in turn will affect the balance between survival time spent in the progression-free and progressed health states.

ERG exploratory analyses

3.29 The ERG considered the stepwise way in which overall survival was estimated (see section 3.22). It commented that it is generally appropriate to use Kaplan–Meier analysis results directly in a model before using projection methods. However, in this case, the final analysis of the trial data had not been used in the model. The ERG carried out a curve-fitting exercise to re-analyse the final data cut (requested during the clarification process) and found that a 2-part exponential model closely followed the trial overall survival data from 9 months (about 270 days) until the last recorded death at 47 months (about 1,400 days).

3.30 The ERG highlighted that the company model exponential trend deviated markedly from the final recorded trial data and leads to a clear separation from the exponential trend identified by the ERG. This resulted in a more advantageous overall survival estimate for talimogene laherparepvec compared to the long-term projection resulting from the fitted ERG curve. The ERG's projections suggested that the company estimate for the mean overall survival of those treated with talimogene laherparepvec may have been overstated by 49% to 59%. This could have a substantial effect on the model estimates of QALYs gained from treatment with talimogene laherparepvec compared to any comparator, leading to sizeable increases in the size of estimated ICERs.

3.31 In the second phase of modelling overall survival, the company used the published results of the analyses of patient registry data on which the AJCC staging classification was based, with the addition of UK life table information. The ERG commented that:

- the AJCC trends only provided results for a maximum of 10 years from the date of diagnosis for patients with stage I to stage III disease, and from the recorded time of first distant metastases for patients with stage IV disease. The ERG highlighted that this meant the estimates used in the company model mixed patients at very different times in

their disease progression, starting from 0 to more than 20 years after first diagnosis

- the application of the data on which the AJCC analysis was performed to model the survival data in the OPTiM trial implied that talimogene laherparepvec had little or no continuing benefit after 5 years, because these data were gathered before the current era of novel immunological treatments with longer survival benefit
- there was no clinical justification to support the sudden change in long-term mortality rate at the junction between Phase 1b and Phase 2 in the company model, which increased the mortality rate after exactly 270 weeks (62.1 months)
- for phase 3 of the overall survival projection, the ERG was not aware of any evidence that the remaining cohort of long-term survivors is at the same mortality risk as the general population.

3.32 The ERG identified a number of other issues relating to the model which all increased the ICER by a small amount. Of note, the ERG commented that the health state utility values obtained from the commissioned study had greater face validity than those used in the base case analysis, which were from the NICE technology appraisal of dabrafenib in which there was no difference in utility with complete response, partial response and stable disease. When the ERG applied the commissioned study utility estimates this reduced the number of incremental QALYs gained by a small amount for talimogene laherparepvec compared to ipilimumab.

3.33 Because of the issues highlighted by the ERG, it did not consider that any estimates of the cost effectiveness of talimogene laherparepvec compared with ipilimumab in patients with non-visceral metastatic disease were reliable. The ERG suggested that using different assumptions, widely differing estimated ICERs could be obtained. For example, talimogene laherparepvec appeared to be dominant compared with ipilimumab (better outcomes at lower cost) in the modified Korn

model but dominated by ipilimumab (poorer outcomes at higher cost) in the 2-step Korn model. Therefore, quoting any specific ICERs would be unreliable.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of talimogene laherparepvec, having considered evidence on the nature of metastatic melanoma and the value placed on the benefits of talimogene laherparepvec by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The committee discussed the current management of metastatic melanoma in the NHS, and the potential place of talimogene laherparepvec in the treatment pathway. The committee noted that the marketing authorisation for talimogene laherparepvec was for unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease and that this was based on evidence from a post-hoc subgroup within the OPTiM trial (57% of the overall trial population who had non-visceral metastatic disease). The committee heard from clinical experts that in clinical practice, treatment with talimogene laherparepvec would be suitable for approximately 10 to 15% of people with unresectable metastatic melanoma. The committee noted that the comparators in the final scope were the immunotherapy agent ipilimumab, and the BRAF inhibitors vemurafenib and dabrafenib. Pembrolizumab and nivolumab were not included as comparators in the scope of this appraisal. However, the committee noted the recent positive NICE recommendation for pembrolizumab, and that nivolumab had also been appraised by NICE (although at the time of the committee meeting that recommendation was awaiting final publication). The committee heard from the clinical experts

that these treatments would be considered for the same group of patients as talimogene laherparepvec. The committee also understood that there are two alternative modes of treatment depending on whether people have slowly or rapidly progressing disease; immunotherapies such as ipilimumab and pembrolizumab; and targeted treatment such as BRAF inhibitors. The Committee heard that in the light of emerging evidence of long term benefit experienced by some people taking immunotherapy, this would be used in preference to the BRAF inhibitors where clinically possible. The committee heard from the clinical experts that patients suitable for treatment with talimogene laherparepvec may have multiple small lesions which make surgical resection impractical, and that other localised therapies such as isolated limb perfusion are not widely available. A particular feature of talimogene laherparepvec is the lower toxicity than other available treatments. The committee agreed that pembrolizumab and nivolumab were not included in the scope and therefore could not be considered as comparators. It concluded that the most clinically relevant comparator for this appraisal was ipilimumab.

4.2 The committee discussed the clinical need for talimogene laherparepvec. It noted comments from the patient expert that it might be a particularly valuable option for people with visible skin tumours, which can be a source of great anxiety. The committee also heard that before 2011 treatments for metastatic melanoma were very limited, and having a choice of treatments would be particularly valuable to people with this condition. The committee heard from the patient and clinical experts that ipilimumab can be associated with severe side effects and that an alternative treatment with an improved toxicity profile would be desirable. Clinical experts considered the main benefits of talimogene laherparepvec to be that the method of administration is acceptable to patients, and that it has an improved toxicity profile compared to currently available treatments (particularly ipilimumab) The committee concluded that the availability of a new treatment option with a novel mechanism of action

and improved tolerability would be valuable for people with metastatic melanoma if it was shown to be as clinically effective as other available treatments.

4.3 The committee discussed the clinical effectiveness of talimogene laherparepvec. It noted that the trial evidence which underpins the marketing authorisation comes solely from an exploratory post-hoc subgroup of people in the OPTiM study who had non-visceral metastatic melanoma. The committee was aware that the comparator arm in the trial was granulocyte macrophage colony-stimulating factor (GM-CSF), which in the view of the clinical experts was clinically ineffective, effectively equivalent to placebo, and is not used in clinical practice. The committee noted that, like ipilimumab and pembrolizumab, talimogene laherparepvec is a disease-modifying immunotherapy, and it is hoped that some patients who achieve a complete or sustained response may require no further treatment for melanoma. The committee heard from clinical experts that although durable response rate is a new, non-validated endpoint in clinical trials of advanced melanoma, it is considered to be more clinically meaningful than overall response rate because of its association with a reduced risk of recurrence. The committee recognised that in the OPTiM trial, talimogene laherparepvec showed a statistically significant improvement of 25.3 months in overall survival (p value 0.0008), durable response rate of 25.2% (compared with 1.2% with GM-CSF) and complete response rate of 16.6% (compared with 0% for GM-CSF), based on the final data cut (August 2014). The committee also gave consideration to the systemic activity of talimogene laherparepvec and agreed that there was some evidence of a systemic effect (that is, decrease in size of some non-injected lesions). The committee considered the concerns raised by the evidence review group (ERG) about the potential for bias in the trial because of limited blinding, differences in the withdrawal rates in the 2 arms, and the use of a non-validated primary endpoint, all of which made it difficult to interpret the efficacy results. The

committee concluded that although talimogene laherparepvec was clinically effective compared with an ineffective treatment (GM-CSF), the analysis was based on a post-hoc analysis against a comparator not relevant for decision-making. It was therefore difficult to draw conclusions from these trial data alone on the effectiveness of talimogene laherparepvec compared with immunotherapies in current clinical practice.

4.4 The committee discussed the company's approach to estimating the clinical effectiveness of talimogene laherparepvec compared with ipilimumab. The committee acknowledged that it was not feasible for the company to carry out a network meta-analysis because of the lack of a common comparator in the trial network. It also understood that the population in OPTiM was not directly comparable with the population in other trials because there were substantial differences in the patient characteristics; for example, in OPTiM, 57% of patients had stage IIIB–IVM1a disease compared with only 11–17% in the ipilimumab trials. Furthermore, it was not clear what proportion of the relevant stage IIB–IVM1a population in the ipilimumab trials had injectable lesions that could have been treated with talimogene laherparepvec. The committee heard from the clinical experts that there is a general lack of evidence on the effectiveness of any melanoma treatments for stage IIIB–IVM1a advanced melanoma, and that the OPTiM trial represents the best evidence for this stage of disease. The committee also heard that the disease trajectory of stage III melanoma is likely to differ from that of stage IVM1a, with a different life expectancy, and also noted the clinical expert's comment that as a general rule, earlier-stage disease with a smaller tumour burden is likely to respond better to treatment than later-stage disease. The committee noted that the company had explored ways in which talimogene laherparepvec could be compared with ipilimumab for stage IIB–IVM1a disease using the modified and two-step Korn methods. These adjusted the progression-free and overall survival data from the pooled ipilimumab trials by stage of disease and lactate dehydrogenase

(LDH) level in the modified Korn method and, in addition, adjusted for a better disease response in earlier-stage disease in the two-step Korn method. The committee noted that when the two-step Korn method was used, the overall survival estimates for ipilimumab were close to those for talimogene laherparepvec in the OPTiM trial, and indeed the confidence intervals overlapped. When the modified Korn method was used, the adjusted survival estimates for ipilimumab were lower. These estimates were then used to calculate the relative effectiveness of talimogene laherparepvec compared with ipilimumab. The company considered that the two-step adjustment represented the 'worst case' estimate of the effectiveness of talimogene laherparapvec. The committee noted the ERG's comment that the company should be complimented on their thorough approach to the problem of defining an appropriate comparison with ipilimumab from the available trial data. However, it accepted the underlying concern of the ERG that the Korn method was flawed in this population (stage IIIB–IVM1a disease) because the algorithm was developed using data from people with predominantly stage IVM1b and stage IVM1c disease, which have different disease trajectories. It also questioned the inclusion of an adjustment for LDH level in the modified Korn method, as this is of limited relevance for people with stage IIIB, stage IIIC or stage IVM1a disease. Furthermore, the LDH adjustment had the effect of reducing the influence of other prognostic adjustment factors, leading to an overestimate of the efficacy of talimogene laherparepvec compared with ipilimumab. The committee concluded that the evidence presented was not sufficient to draw any firm conclusions about the clinical effectiveness of talimogene laherparepvec compared with relevant comparators in this patient population. Moreover, on the evidence available, the committee could not be confident that talimogene laherparepvec had been convincingly shown to be at least as effective as ipilimumab in this patient group.

Cost effectiveness

4.5 The committee considered the company's model, which compared talimogene laherparepvec with ipilimumab in people with stage IIIB to stage IVM1a melanoma. The committee considered that the 3-state model structure was similar to models used in other melanoma appraisals and therefore accepted that it was appropriate for decision-making. The committee noted that the company had used a multi-stage approach to modelling overall survival based on different data sources. It noted the ERG's comments that, in principle, the multi-stage approach (using Kaplan-Meier data directly followed by modelled projections of overall survival) was generally appropriate. However, they questioned the sudden change in the shape of the curve at 62.1 months, and also the removal of any melanoma-related mortality after 10 years. The committee accepted the basic structure of the company's model, but gave further consideration to the assumptions used in the modelling of survival.

4.6 The committee noted that in the company's base-case analysis, talimogene laherparepvec was more effective than ipilimumab, with an incremental quality-adjusted life year (QALY) gain of 0.34 and 1.24 depending on whether the two-step or modified Korn method was used. The committee was aware that the company had used Korn methods to correct for differences in patient characteristics between the ipilimumab trials and OPTiM. The committee acknowledged the ERG's concerns that the Korn method was not suitable for modelling progression in stage IIIB to stage IVM1a melanoma (see section 4.4). The committee agreed that the modifications to the Korn method (the modified and two-step Korn) further compounded the underlying issues with the Korn method. The committee concluded that the clinical effectiveness of talimogene laherparepvec compared with ipilimumab was highly uncertain, and the estimates provided by the company could not be considered a reliable estimate of the cost effectiveness of talimogene laherparepvec.

4.7 The committee discussed the exploratory approach taken by the ERG to model overall survival for talimogene laherparepvec. The committee noted that the ERG considered that the company had overestimated the overall survival with talimogene laherparepvec by between 49% and 59%. The ERG identified a 2-part exponential model which they considered closely followed the overall survival data from the latest data cut in the OPTiM trial, whereas they considered that the company's modelled projection deviated markedly from the final recorded trial data, resulting in a much more advantageous estimate of overall survival for talimogene laherparepvec than that calculated by the ERG. The ERG's approach resulted in a reduction in the mean overall survival from 108.5 months, as calculated by the company, to 73 months. This was lower than the overall survival in the ipilimumab trials, indicating that overall survival with talimogene laherparepvec could be less favourable than with ipilimumab. The committee heard from the ERG that the use of this analysis would have a substantial effect on the estimates of QALYs gained from treatment with talimogene laherparepvec compared to any comparator, with the possibility that talimogene laherparepvec was dominated by ipilimumab (was less effective and more costly). The committee expressed concern that it had not seen enough evidence to be confident that talimogene laherparepvec was as clinically effective as ipilimumab or other currently available therapies in this group of patients. The lack of suitable effectiveness inputs in the economic model prevented the committee from calculating a plausible incremental cost effectiveness ratio.

4.8 The committee noted the uncertainties in the clinical and cost-effectiveness evidence but considered whether there may be a subgroup of patients for whom talimogene laherparepvec was more clinically effective. The committee agreed that there may be some people with non-visceral disease who might prefer to be treated with talimogene laherparepvec rather than other more toxic immunotherapies, and others

who may have co-existing conditions which make the existing immunotherapies unsuitable. The committee agreed that talimogene laherparepvec may be a reasonable option for unresectable non-visceral metastatic melanoma that is unsuitable for other immunotherapies, but the committee was not presented with evidence to define this group. The committee concluded that it was not possible to establish that talimogene laherparepvec was a cost-effective use of NHS resources for patients with stage IIIB to IVM1a melanoma given the uncertainty about its effect on overall survival compared with ipilimumab and other immunotherapies.

4.9 The committee noted that the company stated that talimogene laherparepvec was innovative and a step change in the management of advanced melanoma because the mechanism of action was novel in that it produces local tumour control and leads to a systemic anti-tumour immune response. Furthermore, this is the only treatment approved specifically for people with regionally or distantly metastatic melanoma with no visceral disease (stage IIIB to stage IVM1A) and is associated with fewer treatment-related grade 3 and 4 adverse events compared with existing treatments. The committee agreed that this was an innovative approach to the treatment of melanoma. It also noted that talimogene laherparepvec is being investigated as combination therapy with other agents, which the committee considered may be important in the future. However, the committee could not identify any specific health-related benefit that had not already been captured in the QALY calculation.

4.10 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the

PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title: Talimogene laherparepvec for treating metastatic melanoma**	**Section**
Key conclusion		
Talimogene laherparepvec is not recommended within its marketing authorisation for treating regionally or distantly metastatic, unresectable melanoma (Stage IIIB, IIIC and IVM1a) that has not spread to bone, brain, lung or other internal organs. The Committee concluded that it could not be confident in establishing a reliable estimate of the effectiveness of talimogene laherparepvec compared with immunotherapies in current clinical practice. The lack of suitable effectiveness inputs in the economic model prevented the committee from calculating a plausible estimate of cost effectiveness.		1.1, 4.3, 4.7
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee concluded that the availability of a new treatment option with a novel mechanism of action and improved tolerability would be valuable for people with metastatic melanoma.	4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee agreed that this was an innovative approach to the treatment of melanoma. It also noted that talimogene laherparepvec is being investigated as combination therapy with other agents, which the committee considered may be important in the future. However, the committee could not identify any specific health-related benefit that had not already been captured in the QALY calculation	4.10
What is the position of the treatment in the pathway of care for the condition?	Talimogene laherparepvec has a marketing authorisation for unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. This was based on evidence from a post-hoc subgroup within the OPTiM trial (57% of the overall trial population who had non-visceral metastatic disease). The committee heard from clinical experts that in clinical practice, treatment with talimogene laherparepvec would be suitable for approximately 10 to 15% of people with unresectable metastatic melanoma.	4.1

Adverse reactions	The committee heard from the patient and clinical experts that ipilimumab can be associated with severe side effects and that an alternative treatment with an improved toxicity profile would be desirable. Clinical experts considered the main benefits of talimogene laherparepvec to be that the method of administration is acceptable to patients, and that it has an improved toxicity profile compared to currently available treatments (particularly ipilimumab).	4.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The trial evidence which underpins the marketing authorisation came solely from an exploratory post-hoc subgroup of people in the OPTiM study who had non-visceral metastatic melanoma. The committee concluded that talimogene laherparepvec was clinically effective compared with an ineffective treatment (GM-CSF) but it was difficult to draw conclusions from these trial data alone on the effectiveness of talimogene laherparepvec compared with immunotherapies in current clinical practice.	4.3

Relevance to general clinical practice in the NHS	The committee heard from the clinical experts that patients suitable for treatment with talimogene laherparepvec may have multiple small lesions which make surgical resection impractical, and that other localised therapies such as isolated limb perfusion were not widely available. The committee agreed that pembrolizumab and nivolumab were not included in the scope and therefore could not be considered as comparators. It concluded that the most clinically relevant comparator for this appraisal was ipilimumab.	4.1
Uncertainties generated by the evidence	The committee concluded that the evidence presented was not sufficient to draw any firm conclusions about the clinical effectiveness of talimogene laherparepvec compared with relevant comparators in this patient population. Moreover, on the evidence available, the committee could not be confident that talimogene laherparepvec had been convincingly shown to be at least as effective as ipilimumab in this patient group.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee agreed that talimogene laherparepvec may be a reasonable option for unresectable non-visceral metastatic melanoma that is unsuitable for other immunotherapies, but the committee was not presented with evidence to define this group.	4.8

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The evidence for effectiveness was based on a post-hoc analysis against a comparator (GM-CSF) which was not relevant for decision-making, and it was therefore difficult to draw conclusions from these trial data alone on the effectiveness of talimogene laherparepvec compared with immunotherapies in current clinical practice.	4.3
Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that the company had used a multi-stage approach to modelling overall survival based on different data sources to compare talimogene laherparepvec with ipilimumab in people with stage IIIB to stage IVM1a melanoma. The committee accepted the basic structure of the company's model but questioned some of the model inputs.	4.6

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee acknowledged the ERG's concerns that the Korn method was not suitable for modelling progression in stage IIIB to stage IVM1a melanoma. It agreed that the modifications to the Korn method (the modified and two-step Korn) further compounded the underlying issues with the Korn method. The Committee concluded that the clinical effectiveness of talimogene laherparepvec compared with ipilimumab was so uncertain that despite attempts by the company to calculate an incremental cost-effectiveness ratio.	4.7
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee could not identify any specific health-related benefit that had not already been captured in the QALY calculation.	4.9

Are there specific groups of people for whom the technology is particularly cost effective?		
What are the key drivers of cost effectiveness?	The company suggested that the variable that had the highest effect on the l cost-effectiveness of talimogene laherparepvec compared with ipilimumab was duration of treatment with talimogene laherparepvec and ipilimumab when using the modified Korn prediction model and the 2-stage Korn adjustment.	3.26
Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that it was not possible to establish whether talimogene laherparepvec was a cost-effective use of NHS resources given the uncertainty about its effect on overall survival compared with ipilimumab and other immunotherapies.	4.9
Additional factors taken into account		
Patient access schemes (PPRS)	The committee concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.	4.11
End-of-life considerations	The case for end-of-life considerations was not made during this appraisal.	-

Equalities considerations and social value judgements	No equalities issues were raised in the evidence submissions or at the Committee meeting.	-

5 Related NICE guidance

Further information is available on the NICE website.

Published

- Nivolumab for treating advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 384 (2016).
- Pembrolizumab for advanced melanoma not previously treated with ipilimumab. NICE technology appraisal guidance 366 (2015).
- Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab. NICE technology appraisal guidance 357 (2015).
- Melanoma: assessment and management. NICE guideline 14 (2015).
- Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. NICE technology appraisal guidance 321 (2014).
- Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 319 (2014).
- Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma. NICE interventional procedure guidance 446 (2013).
- Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. NICE technology appraisal guidance 269 (2012).
- Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 268 (2012).
- Skin cancer prevention: information, resources and environmental changes. NICE public health guidance 32 (2011).
- Improving outcomes for people with skin tumours including melanoma. NICE guidance on cancer services (2010)

Under development

- Cobimetinib with vemurafenib for treating advanced, unresectable or metastatic BRAF V600 mutation-positive melanoma. NICE technology appraisal guidance, publication expected June 2016.
- Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma. NICE technology appraisal guidance, publication expected August 2016.
- Skin cancer. NICE quality standard, publication expected August 2016

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam
Chair, Appraisal Committee
March 2016

7 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month,

except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Justin Daniels
Consultant Paediatrician, North Middlesex University Hospital

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Ms Sarah Parry
Clinical Nurse Specialist - Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

Dr Nerys Woolacott

Senior Research Fellow, Centre for Reviews and Dissemination, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Christian Griffiths

Technical Lead

Eleanor Donegan

Technical Adviser

Bijal Joshi
Project Manager

8 Sources of evidence considered by the committee

A. The evidence review group (ERG) report for this appraisal was prepared by Liverpool Reviews & Implementation Group (LR*i*G):

- Fleeman N, Bagust A, Boland A, Beale S, et al. Talimogene laherparepvec for treating metastatic melanoma [ID508]: A Single Technology Appraisal, January 2016

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Amgen (talimogene laherparepvec)

II. Professional/specialist and patient/carer groups:

- British Association of Skin Cancer Specialist Nurses (BASCSN)
- Cancer Research UK
- Melanoma Focus
- Melanoma UK
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Bristol-Myers Squibb (ipilimumab)
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Roche Products (vemurafenib)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on talimogene laherparepvec by attending the initial committee discussion and providing a written statement to the committee. They are invited to comment on the ACD.

- Professor Christian Ottensmeier, Professor of Experimental Cancer medicine, and Consultant Medical Oncologist representing Royal College of Physicians - clinical expert
- Professor Kevin Harrington, Professor of biological cancer therapies, representing Amgen and Melanoma UK- clinical expert
- Mrs Jackie Hodgetts, Nurse clinician ,representing British Association of Skin Cancer Specialist Nurses - clinical expert
- Mrs Gillian Nuttall, representing Melanoma UK - patient expert

D. Representatives from the following company attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- Amgen (talimogene laherparepvec)

ISBN: [to be added at publication]