NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Talimogene laherparepvec for treating unresectable metastatic melanoma

1 Recommendations

1.1 Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IIIB, IIIC or IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if:

- treatment with systemically administered immunotherapies is not suitable and
- the company provides talimogene laherparepvec with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with talimogene laherparepvec was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	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. It is injected directly into cutaneous, subcutaneous and nodal lesions that are visible on the skin, palpable, or detectable with ultrasound guidance. The company states that talimogene laherparepvec 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).
Marketing authorisation	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'.
Adverse reactions	The most common adverse reactions 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.
Recommended dose and schedule	Administered by intralesional injection at an initial dose of 1,000,000 plaque forming units (PFU) per ml, followed by doses of 100,000,000 PFU per ml at 3 weeks and then every 2 weeks.
Price	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 100,000,000 PFU per ml (excluding VAT; company's submission). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of talimogene laherparepvec, with the discount applied 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 does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Amgen and a review of this submission by the evidence review group (ERG). It also considered evidence received from patient and professional groups. See the committee papers for full details of the evidence.

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 considered the clinical-effectiveness evidence presented by the company and its critique by the evidence review group (ERG). The clinical-effectiveness evidence for talimogene laherparepvec is in the company's submission (pages 42–114) and in the evidence review group (ERG's) report (pages 33–62). The committee also considered additional evidence submitted in response to consultation and a critique by the ERG.

Current clinical management of unresectable, metastatic melanoma

4.2 The marketing authorisation for talimogene laherparepvec is for unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. The committee noted that this is based on evidence from a post-hoc subgroup within the OPTiM trial (57% of the overall trial population with no visceral metastatic disease). The clinical experts stated that in clinical practice, treatment with talimogene laherparepvec would be

suitable for approximately 10 to 15% of people with unresectable metastatic melanoma.

4.3 The patient expert stated that talimogene laherparepvec might be a particularly valuable option for people with visible skin tumours, which can be a source of great anxiety. The 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 systemic treatments (particularly ipilimumab). They stated that patients with melanoma that is 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. Having a choice of effective treatments would be particularly valuable to people with this condition. 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.

Comparators

4.4 The comparators in the final scope were the immunotherapy agent ipilimumab, and the BRAF inhibitors vemurafenib and dabrafenib. The newer systemic immunotherapy agents, pembrolizumab and nivolumab, were not included as comparators in the scope of this appraisal. However, the committee noted the recent NICE recommendations for pembrolizumab for melanoma that has or has not been treated with ipilimumab and also for nivolumab, which had been published by the time of the final meeting of the committee. The clinical experts noted that these treatments would be considered for the same group of patients as talimogene laherparepvec. For patients with BRAF negative or wild type disease the only alternative therapy in routine clinical practice would be systemically administered immunotherapy agents. However, for people

with the BRAF-V600 mutation, the disease can be treated either with immunotherapy or BRAF-specific agents. This choice would be influenced by the overall burden of disease, and whether it is slowly or rapidly progressing. A BRAF inhibitor, such as vemurafenib or dabrafenib, is likely to be the preferred treatment for people with BRAF-V600 mutations whose disease is progressing rapidly, while immunotherapies such as ipilimumab, pembrolizumab and nivolumab will be used for people with BRAF-V600 mutations with more slowly progressive disease or a lower tumour burden. The committee heard that in the light of emerging evidence of long-term benefit experienced by some people having immunotherapy, this would generally be used in preference to the BRAF inhibitors whenever clinically possible. For practical purposes, the group of patients considered for immunotherapy, and in particular talimogene laherparepvec (who have earlier stage disease and no visceral metastases) would not correspond with those for whom a BRAF inhibitor would be the first choice of treatment. The committee concluded that the most clinically relevant comparator within the scope for this appraisal was ipilimumab. The committee noted that the newer immunotherapies, pembrolizumab and nivolumab, were not included in the scope and therefore could not be considered as direct comparators as part of the appraisal process. However it was reasonable for the committee to acknowledge their increasing use in clinical practice, particularly since they had shown superior short-term outcomes to ipilimumab in clinical trials and had lower toxicity than ipilimumab.

Results of the OPTiM trial

4.5 The evidence underpinning the marketing authorisation for talimogene laherparepvec came solely from an exploratory post-hoc subgroup analysis of people in the OPTiM trial who had melanoma with no visceral metastases. 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 is clinically ineffective, effectively

equivalent to placebo, and is not used in clinical practice. The committee noted that, in common with ipilimumab, pembrolizumab and nivolumab, talimogene laherparepvec is a disease-modifying immunotherapy and some patients who have a complete or sustained response may require no further treatment for melanoma. The clinical experts stated 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. In the OPTiM trial, talimogene laherparepvec showed a statistically significant improvement of 25.3 months in overall survival (p value 0.0008), a durable response rate of 25.2% (compared with 1.2% for GM-CSF) and a complete response rate of 16.6% (compared with 0% for GM-CSF). The ERG raised concerns 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 accepted that talimogene laherparepvec was clinically effective when compared with GM-CSF, although it also acknowledged that this was based on a post-hoc analysis of a subgroup in the trial, using a comparator that was considered ineffective and is not in clinical use in the NHS.

Comparison with ipilimumab

4.6 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 the subgroup in OPTiM for which the licence was granted (stage IIIB to IVM1a disease) was not directly comparable with the population in the ipilimumab trials, because there were substantial differences in the patient characteristics. In particular, only 11–17% of patients in the ipilimumab trials had stage IIIB-IVM1a disease; the others had more advanced melanoma. Also, it was not clear what proportion of the small number of

patients with stage IIIB–IVM1a disease in the ipilimumab trials had injectable lesions that could have been treated with talimogene laherparepvec.

4.7 The clinical experts stated that there is a 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.

4.8 The committee noted that the company had explored ways in which talimogene laherparepvec could be compared with ipilimumab for stage IIIB–IVM1a disease using the modified and 2-step Korn methods to correct for differences in patient characteristics between the ipilimumab trials and OPTiM. 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 also adjusted for a better disease response in earlier-stage disease in the 2-step Korn method. The 2 different estimates of ipilimumab efficacy were then used to calculate the relative effectiveness of talimogene laherparepvec compared with ipilimumab. When the modified Korn method was used (the best case), the adjusted survival estimates for ipilimumab were lower than for talimogene laherparepvec. However, the committee noted that the confidence intervals around the adjusted ipilimumab data overlapped with the talimogene laherparepvec trial results. The committee noted that when the 2-step Korn method was used, which the company considered to be the 'worst case', the overall survival estimates for ipilimumab were very similar to those for talimogene laherparepvec in the OPTiM trial. The committee acknowledged that the company had made efforts to make a comparison with ipilimumab but

noted the uncertainty of that comparison, largely because of the lack of efficacy data for ipilimumab in the relevant population.

4.9 Of the 2 methods used by the company, the committee considered that the modified Korn (best case) was the less reliable because it had heard from the clinical expert that treatment response was likely to be better in early-stage than in later-stage disease, and the method did not take this into account. In the 2- step Korn method talimogene laherparepvec had not been shown to be superior to ipilimumab. 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 for modelling progression in 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, because this is of limited relevance for people with stage IIIB, stage IIIC or stage IVM1a disease. Also, the LDH adjustment had the effect of reducing the influence of other prognostic adjustment factors, leading to a potential overestimate of the efficacy of talimogene laherparepvec compared with ipilimumab. The committee agreed that the modifications to the Korn method (the modified and 2-step Korn) further compounded the underlying issues with the Korn method. The committee concluded that the evidence presented was not sufficient to draw any firm conclusions about the relative clinical effectiveness of talimogene laherparepvec compared with ipilimumab in this patient population.

Cost effectiveness

4.10 The committee considered the cost-effectiveness evidence presented by the company and its critique by the ERG. The cost-effectiveness evidence is in the company's submission (pages 115–208), in the appendices to the

company's submission and in the ERG report (pages 63–105). The committee also considered additional evidence submitted by the company in response to consultation and a critique by the ERG.

The company's model

4.11 The company's model 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 company had used a multi-stage approach to modelling overall survival based on different data sources. The committee 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, the ERG 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.

4.12 The committee discussed the extrapolation of overall survival data in the talimogene laherparepvec arm of the company's model (based on the entire Kaplan-Meier curve to 60 months) and the ERG's exploratory analysis (which used a 2-part exponential model from 9 to 47 months, when the last death was recorded). These different approaches led to 2 divergent survival trends resulting in very different estimates of long-term survival for patients who had talimogene laherparepvec. The committee heard from the company's representative that it considered the entire Kaplan-Meier curve to be most relevant for the purposes of extrapolation because it uses the full extent of the trial follow-up data, noting that 24% of patients in the talimogene laherparepvec arm were alive at 47 months and remained so at 60 months. The ERG stated that the Kaplan-Meier method estimates survival only for those time points

when a death occurred, and therefore only the survival estimates at the time of these events can be legitimately used for fitting projective trends to trial data. Extending the data used for survival estimation beyond the last recorded death, as the company had done, involves assuming that, across an extended time period in which no deaths occur and beyond, any patient still alive can be expected to remain indefinitely free of the risk of death from any cause (not just melanoma). The ERG did not consider this method of extrapolating survival beyond 47 months to be plausible. The ERG also referred to the results of the Kaplan-Meier analysis from OPTiM, which indicated that, following the last recorded death at 47 months, 39 patients remained alive and at risk. These were all censored due to the termination of the trial on a particular date, even though the patients were recruited at different times. This means that the true time of death of these patients cannot be determined. The ERG's approach resulted in a reduction in 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 noted the ERG's comment that the company had overestimated overall survival with talimogene laherparepvec by between 49% and 59%. 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 people with stage IIIB to stage IVM1a melanoma. The committee concluded that, because of the lack of suitable effectiveness inputs in the economic model, it had not been presented with a plausible incremental cost-effectiveness ratio (ICER) for talimogene laherparepvec compared with ipilimumab.

4.13 The company submitted additional analyses in response to the appraisal consultation document, intended to address uncertainty in the relative clinical effectiveness of talimogene laherparepvec compared with

ipilimumab. This included the use of the Korn method for adjusting the effectiveness of ipilimumab data in the intention to treat population from the OPTiM trial (stage IIIB to IVM1c). The committee reconsidered the use of Korn methodology for adjusting the baseline characteristics of the ipilimumab trial, including the results of the Korn adjustment in the intention to treat population (stage IIIB to IVM1c), which was a broader population than the marketing authorisation of talimogene laherparepvec. These results suggested that talimogene laherparepvec was at least as effective as ipilimumab. The committee noted that these analyses did not address the underlying methodological concern that the Korn algorithm (which was based predominantly on patients with later-stage disease) was not valid because it had not been calibrated against patient-level data from ipilimumab trials in a similar population to the OPTIM trial (see section 4.9).

4.14 In response to consultation the company also submitted a 'naïve' indirect comparison of talimogene laherparepvec with ipilimumab in which GM-CSF, dacarbazine and gp100 were assumed to be equally ineffective in the treatment of metastatic melanoma. But the committee did not consider it to be a reliable method of establishing the relative effectiveness of these agents. The committee appreciated that the company had made every reasonable effort to adjust the ipilimumab data, but there is no methodologically valid way of comparing talimogene laherparepvec with ipilimumab in stage IIIB to IVM1a melanoma. The committee noted the proven long-term survival benefit in a proportion of patients who had ipilimumab (based on 5-year overall survival data) and concluded that it is not possible to resolve the uncertainty about the relative effectiveness of talimogene laherparepvec compared with ipilimumab (and other newer systemically administered therapies). The committee considered that it needed to be very confident that talimogene laherparepvec is at least as effective as ipilimumab before recommending it as an option for all patients in the licensed population, given that

ipilimumab monotherapy has been increasingly replaced by newer therapies that have shown better short-term effectiveness in clinical trials, with lower toxicity.

4.15 The committee considered additional analyses on the cost effectiveness of talimogene laherparepvec compared with dacarbazine (which has not been shown to prolong overall survival), and best supportive care that were submitted as part of the company's response to consultation. The committee noted that the ICERs for talimogene laherparepvec compared with dacarbazine and best supportive care were approximately £23,900 and £24,100 per QALY gained, and were substantially lower than the corresponding ICERs for ipilimumab compared with dacarbazine and best supportive care (approximately £47,900 and £42,200 per QALY gained, respectively, in technology appraisal guidance on ipilimumab for melanoma that has not been treated before and on ipilimumab for melanoma that has been treated before). The committee noted that these figures applied to patients at different stages of disease and were not directly comparable, and so could not be used to draw conclusions about the relative cost effectiveness of these agents.

4.16 The committee considered whether there may be a subgroup of patients for whom talimogene laherparepvec would be particularly beneficial, in particular whether there was a group of patients for whom talimogene laherparepvec might be the only effective option, such as those for whom systemic immunotherapy was contraindicated. The clinical expert, in response to consultation, had highlighted that there were people with BRAF-negative disease for whom systemically administered immunotherapy is not suitable and who currently had no other effective treatment options. The committee noted the cost-effectiveness analyses presented comparing talimogene laherparepvec with dacarbazine and best supportive care. While these analyses did not specifically relate to a population with melanoma for whom systemically administered immunotherapies were not suitable, the committee was satisfied that they

gave an indication of the cost effectiveness of talimogene laherparepvec in this situation. It concluded that talimogene laherparepvec is a clinically and cost-effective option for people with unresectable non-visceral metastatic melanoma for whom systemically administered immunotherapies are not suitable.

4.17 The company stated that talimogene laherparepvec is innovative and a step change in the management of advanced melanoma because it has a novel mechanism of action, in that it produces local tumour control and leads to a systemic anti-tumour immune response. Also, it 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 intra-lesion injections are an innovative approach to the treatment of melanoma, although the marketing authorisation did not support the systemic action of talimogene laherparepvec. The committee also noted that talimogene laherparepvec is being investigated as a combination therapy with other agents, which it 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.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.18 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 unresectable, metastatic melanoma	Section
Key conclusion		
Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if: • treatment with systemically administered immunotherapies is not suitable and • the company provides talimogene laherparepvec with the discount agreed in the patient access scheme. The committee concluded that although it could not be confident in establishing a reliable estimate of the effectiveness of talimogene laherparepvec compared with immunotherapies currently used in clinical practice, it is clinically and cost effective in people for whom treatment with systemically administered immunotherapies is not suitable. The cost effectiveness of talimogene laherparepvec compared with best supportive care in people for whom systemically administered immunotherapy not suitable is approximately £24,000 per QALY gained.		1.1, 4.9, 4.16

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.	4.3
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 talimogene laherparepvec is an innovative approach to the treatment of melanoma. It also noted that talimogene laherparepvec is being investigated as combination therapy with other agents, which it 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.	4.17

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 is 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.	4.2
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).	4.3
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The evidence underpinning the marketing authorisation came solely from an exploratory post-hoc subgroup analysis of people in the OPTiM trial who had non-visceral metastatic	4.3, 4.5

	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 systemically administered immunotherapies used in current clinical practice.	
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 are not widely available.	4.4
Uncertainties generated by the evidence	The committee concluded that the evidence presented was not sufficient to draw any firm conclusions about the relative clinical effectiveness of talimogene laherparepvec compared with ipilimumab in this patient population.	4.9

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee agreed that talimogene laherparepvec is a reasonable option for people with unresectable non-visceral metastatic melanoma for whom systemically administered immunotherapies are not suitable, and that it is clinically effective compared with best supportive care.	4.16
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. The committee noted 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). The committee concluded that talimogene laherparepvec is clinically effective in people for whom treatment with systemically administered immunotherapies is not suitable.	4.5

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.	4.11
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 2-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 uncertain, largely because of the lack of efficacy data for ipilimumab in the relevant population.	4.13

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.	4.17
Are there specific groups of people for whom the technology is particularly cost effective?	The committee concluded that talimogene laherparepvec is cost effective in people for whom treatment with systemically administered immunotherapies is not suitable.	4.16
What are the key drivers of cost effectiveness?	The Committee concluded that the clinical effectiveness of talimogene laherparepvec compared with ipilimumab was uncertain, largely because of the lack of efficacy data for ipilimumab in the relevant population.	4.13, 4.15

Most likely cost-effectiveness estimate (given as an ICER)	The committee was not able to determine the ICER for talimogene laherparepvec compared with ipilimumab because of uncertainties in the relative clinical effectiveness of these agents. The committee considered talimogene laherparepvec to be cost effective compared with dacarbazine (£23,900 per QALY gained) and best supportive care (£24,100 per QALY gained) in people whose disease was not suitable for treatment with systemically administered immunotherapies.	4.13, 4.15 4.16
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.	4.20
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 Implementation

5.1 Section 7of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions,

local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable, regionally or distantly metastatic (Stage IIIB, IIIC or IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs and the doctor responsible for their care thinks that talimogene laherparepvec is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Amgen have agreed that talimogene laherparepvec will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

6 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
July 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

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.

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 and Irina Voicechovskaja
Technical Leads

Eleanor Donegan
Technical Adviser

Marcia Miller and Liv Gualda
Project Managers

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