National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report

Amgen Response: Factual inaccuracies

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Contains confidential information: AIC: Highlighted in yellow and underlined, CIC: Highlighted in turquoise and underlined

Issue 1 European Commission marketing authorisation status for talimogene laherparepvec

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1 page 9; Section 3.1 page 27. The report states that the a positive opinion for the granting of a marketing authorisation has been issued by the Committee for Medicinal Products for Human Use (CHMP) and is awaiting approval by the European Commission ([redacted])	Text should be updated to state that European Commission marketing authorisation for talimogene laherparepvec was granted on 16 December 2015	This update will remove any doubt regarding the final licensed population for talimogene laherparepvec. It should be noted that the final licensed population is the same as that recommended by the CHMP.	The ERG has made changes where appropriate to the report
Section 2.1, page 19; Section 8, page 100. The report states that T-VEC is 'expected to be licensed' and refers to the 'expected licensed population'.	Text should be updated to state that 'T-VEC is licensed' and to refer to 'the licensed population'	This update will remove any doubt regarding the final licensed population for talimogene laherparepvec. It should be noted that the final licensed population is the same as that recommended by the CHMP.	The ERG has made changes where appropriate to the report

Issue 2 OPTiM clinical data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.5, page 44, Table 9 The % of patients discontinuing from treatment in OPTiM is incorrectly reported as 54.9 for T-VEC and 53.9 for GM-CSF in the ITT population	This should be corrected to 98.6% for T-VEC and 90.1% for GM-CSF as per Table 4-7 of the company submission	Data incorrect. If not amended, treatment discontinuation rates will appear too high and data will not be internally consistent within Table 9.	The ERG agrees the data it entered was incorrect. The ERG has amended data in table
Section 4.2.6, page 46, Table 10 Table 10 title refers to 'final data cut', however DRR and ORR (per EAC) are presented from the primary data cut. These endpoints (per EAC) were only assessed at the primary data cut as specified in Table 6 of the report. Data could not subsequently change for these endpoints.	Remove 'final data cut' from the title of Table 10. Clarify within the table that DRR and ORR are presented at the primary data cut and that OS and TTF are presented at the final data cut.	For clarification purposes. There may be confusion when comparing Table 10 with Table 6 if not amended. Table 6 shows that DRR and ORR (per EAC) are only assessed at the primary data cut.	The ERG has amended table by amending the title and adding relevant footnotes The ERG has also amended the related text in the summary of the ERG report (page 10)
Section 4.2.6, page 46, Table 10 Table 10 has a column title of 'Patients with each type of AE (%)'.	Remove this column title	For clarification purposes. Column header is misleading as this table does not summarise AEs.	This column title was entered in error. The ERG has now removed this
Section 4.3.3, page 55 The report states that mean TTF is 'not reached'	The mean TTF should be corrected to 20.6 months as per Table 43 in the ERG report.	Data incorrect. If not amended, data will be inconsistent within the report.	The ERG agrees the mean value it cited in the text was incorrect. The ERG has amended text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4, page 56, Table 13 The incidence of all-cause treatment-emergent Grade 3 to 5 SAEs is reported as 'NR' in patients with non-visceral metastatic disease	This data can be derived (approximately) from company submission Table 4-32 by summing the percentages for Grade 3 to 5 AEs. 'NR' should be changed to '18%' for T-VEC and '10%' for GM-CSF.	Correction of data. Other data in Table 13 have been calculated by summing percentages from Table 4-32 in the company submission.	The ERG agrees the data it entered was incorrect. The ERG has amended data in table
Section 4.4, page 56, Table 13 The following percentages that are quoted from the OPTiM CSR in the ITT population are incorrect - All cause treatment emergent Grade 3 to 5 AEs: [redacted]% T-VEC, [redacted] % GM-CSF - All cause treatment emergent Grade 3 to 5 SAEs: [redacted] % T-VEC	These percentages should be corrected as per Table 12-2 of the OPTiM CSR (14 April 2014): - All cause treatment emergent Grade 3 to 5 AEs: [redacted] % T-VEC, [redacted] % GM-CSF - All cause treatment emergent Grade 3 to 5 SAEs: [redacted] % T-VEC	Correction of data. Note that this has been marked up as AIC rather than CIC.	The ERG agrees the data it entered was incorrect. The ERG has amended data in table
Section 4.4, page 58, Table 15 Table 15 states that 9% of patients had 'treatment-related AEs leading to discontinuation'	This should be corrected to 'AEs leading to discontinuation'	Correction of data description as these are not specifically treatment-related AEs (see ERG report Table 13).	The ERG agrees the text it entered was incorrect. The ERG has amended text in table
Section 4.7, page 61 The report states the wrong number of patients in the OPTiM trial: 'a relatively large (n=463), open-label, multi-centre, international Phase III trial'.	The number of patients in the OPTiM trial should be corrected from n=463 to n=436	The number of patients is incorrectly stated for the pivotal registration trial. If not amended, patient numbers will be inconsistent within the report.	This was typographical error. The ERG has amended the text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.7, page 61 The report states the wrong number of patients in the OPTiM licensed population: 'These findings were derived from an exploratory post-hoc analysis of 279 patients'	The number of patients in the OPTiM licensed population should be corrected from n=279 to n=249	The number of patients is incorrectly stated for the pivotal registration trial licensed population. If not amended, patient numbers will be inconsistent within the report.	This was typographical error. The ERG has amended the text

Issue 3 Talimogene laherparepvec license based on a post-hoc analysis of a subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 10; Section 1.3, page 12; Section 1.6.2, page 16; Section 4.2.6, page 47; Section 4.7, page 61; Section 8, page 100. The efficacy data in the licensed population (stage IIIB - IVM1a) is described as coming from a post-hoc subgroup analysis of OPTiM (where post-hoc analysis refers to those in which the hypotheses being tested are not specified before any examination of the data).	We propose that the wording 'post-hoc' should be clarified by noting that subgroup analysis by disease stage (IIIB/C, IVM1a, IVM1b, IVM1c) was not post-hoc. It is the specific grouping of stage IIIB-IVM1a disease that was not prespecified.	The wording 'post hoc' is somewhat misleading since subgroup analysis by disease stage was prespecified in the OPTiM statistical analysis plan (as acknowledged in Table 7 of the ERG report). Disease stage was also a randomisation stratification factor (IIIB/C vs IVM1a vs IVM1b vs IVM1c). The credibility of the disease stage subgroup analyses was fully discussed with the EMA and the draft EPAR acknowledges that these analyses adhered to the EMA guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013). The draft EPAR confirms that 'robust statistical analyses based on pre-specification of covariate, replication across studies (study 005/05 and 002/03), consistency across endpoints, statistical significance of treatment-by-covariate interaction and biological plausibility of the observed effect' were performed. These subgroup analyses showed that efficacy was most pronounced in stage IIIB-IVM1a patients which led to the licensed indication.	The ERG agrees that the following subgroups were pre-specified by disease stage: • IIIB/C • IV M1a • IV M1b • IV M1c However the subgroup of patients with stage IIIB to stage IV M1a disease were not a pre-defined subgroup and therefore analysis of this subgroup of patients constitutes a post-hoc analysis. The text has been altered for greater clarity in 2 places: • Section 1.2, page 10 • Section 4.2.6, page 47

Issue 4 OS data used in the OPTiM economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, page 15; Section 5.5.2, page 90 The report incorrectly states that OS data from the earlier, less mature data cut of OPTiM were used in the company model, as opposed to data from the final data cut.	The report should make clear that OS data from the OPTiM final data cut were used in the company model.	Correction of stated data used in the model.	The ERG has deleted reference to the OS being from an earlier data cut

Issue 5 Generalisability of OPTiM licensed population to clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, page 12 The report refers to stage IIIC-IVM1a rather than stage IIIB-IVM1a as the expected patient population for T-VEC in clinical practice: 'Overall, the ERG considers that patients with non-visceral metastatic disease in the OPTiM trial are generally similar to the patients with stage IIIC to stage IV M1a disease likely to be considered for treatment with T-VEC in clinical practice in England'	Sentence should be amended to 'Overall, the ERG considers that patients with non-visceral metastatic disease in the OPTiM trial are generally similar to the patients with stage IIIB to stage IV M1a disease likely to be considered for treatment with T-VEC in clinical practice in England'	Correction of expected patient population.	This was typographical error. The ERG has amended the text