# Lilly response to factual accuracy check of ERG Report on pemetrexed in maintenance treatment of NSCLC, 23th October 2009

*This document contains commercial-in-confidence data, marked in red and underlined.*

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| Summary 1.4.2 clinical, page 10 | The primary endpoint of the key trial was changed by the manufacturer from OS to PFS during the course of the trial. No information was provided that fully justified the change of clinical endpoint and *it is not clear at what time point the decision was made.* | Amendment timeline was provided. | This text "*it is not clear at what time point the decision was made"* should be removed. | Clinical Study Report Section 9.7.1<br><br>The decision to change was discussed with the FDA 11 January 2007, the protocol amendment for primary outcome was made 21 February 2007 (JMEN CSR pg 650), and the final analysis plan was amended on 14th June 2007. The primary (first) datalock (PFS) was 21 November 2007. The final datalock (OS) was 18 December 2008. |
| Summary 1.4.2 clinical, page 10 | The trial was not powered to perform the subgroup analysis, thus the reliance on the results should be treated with due caution. | The statistical power of the trial was sufficient to analyse the non-squamous sub-group separately | This text should be removed or corrected. | Clinical Study Report Section 8.2 states that histology subgroup analysis was added as an objective in the final Statistical Analysis Plan prior to datalock. Previous pemetrexed studies demonstrated differential efficacy by histology. It was expected that the treatment effect in the non-squamous subgroup would be |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| | | | | greater than in the overall population on which sample size was calculated. Power for the subgroup would be increased. Retrospective power calculations for hazard ratios of 0.7 yield ≥90% power for both PFS and OS (364 and 332 events, respectively) and the observed hazard ratio of 0.44 for PFS has 100% power. |
| Summary 1.4.2 clinical, page 10 | The restriction of the licensed population to only the non-squamous sub-group effectively reduces the statistical power of the trial, with consequences of increased uncertainty in the cost-effectiveness analysis. | The statistical power of the trial was sufficient to analyse the non-squamous sub-group separately. | This text should be corrected to: "although the trial was originally powered for the ITT population, information regarding the benefits to the non-squamous population led to subsequent analysis of this population with retention of sufficient power. | Clinical Study Report Section 8.2 states that histology subgroup analysis was added as an objective in the final Statistical Analysis Plan prior to datalock. Previous pemetrexed studies demonstrated differential efficacy by histology. It was expected that the treatment effect in the non-squamous subgroup would be greater than in the overall population on which sample size was calculated. Power for the subgroup would be increased. Retrospective power calculations for hazard ratios of 0.7 yield ≥90% power for both PFS and OS (364 and 332 events, respectively) and the observed hazard ratio of 0.44 for PFS has |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| | | | | 100% power. |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Summary, Section 1.5.1 page 11 | The trial excluded patients who had received pemetrexed or vinorelbine as a first-line treatment; hence there is no information on how patients treated with first-line vinorelbine or pemetrexed will respond to pemetrexed administered as maintenance therapy. These patients will therefore not be eligible for pemetrexed maintenance therapy. | Patients who receive pemetrexed or vinorelbine as first-line therapy are not able to receive pemetrexed maintenance therapy within the licensed marketing authorisation. Therefore these patients are out of scope of this NICE Technology Appraisal. | This text should be removed or changed to state the licence only relates to patients who have received gemcitabine, paclitaxel or docetaxel platinum doublets as first-line therapy. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| | | | | |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| Section 3.1 Population, page 16 | In the MS, the manufacturer's clinical evidence is only applicable to those patients who have received a first-line platinum doublet containing gemcitabine, paclitaxel or docetaxel (as reflected by the licensed indication); this means that no inference about the clinical effectiveness of pemetrexed maintenance in patients who received first-line pemetrexed or vinorelbine can be made. | No inference should be made or required regarding use in patients outside the licensed indication. | The text "no inference …can be made" should be removed as it refers to unlicensed use of pemetrexed therapy. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.<br><br>The submission only relates to patients who have received a platinum doublet containing gemcitabine, docetaxel or paclitaxel in accordance with the NICE scope and the licensed indication. |
| Section 4.1.4 Description and critique of manufacturer's approach to validity assessment Page 23 | In addition, the ERG is aware that patients in clinical practice in England and Wales will also be treated with vinorelbine or pemetrexed as a first-line therapy. None of the patients in the JMEN trial[2] received these treatments (pemetrexed was not licensed for first-line therapy at the start of the JMEN trial[2]) and therefore no inference can be made regarding the efficacy or safety of pemetrexed as a maintenance therapy for patients receiving these first-line treatments. | No inference should be made or required regarding use in patients outside the licensed indication. This is also outside the NICE scope for this appraisal. | The text "no inference …can be made" should be removed as it refers to unlicensed use of pemetrexed therapy. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel<br><br>The submission only relates to patients who have received a platinum doublet containing gemcitabine, docetaxel or paclitaxel in accordance with the NICE scope and the licensed |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| | | | | indication |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Table 4-4 Adverse events, page 25 | ***Timing of assessment***<br>On study: repeated every 2 cycles of therapy. Assessment within 7 days prior to day 1 of each cycle | Assessment of adverse events occurred at every cycle and for 30 days after last dose of drug | This text should be revised to "repeated prior to every cycle of therapy and for 30 days after the last dose of drug" | Section 6.3 of study protocol |
| Section 4.1.6 page 26 | The point at which the primary outcome was changed appears to be after an interim analysis even though the protocol states that an interim analysis was not planned. | No interim analysis was conducted prior to the change in primary outcome, or at any point. The first analysis was the primary analysis. | This text should be removed as factually incorrect. | No interim analysis was conducted prior to the change in primary outcome. The first analysis was the primary analysis.<br><br>The decision to change was discussed with the FDA 11 January 2007, the protocol amendment for primary outcome was made 21 February 2007 (JMEN CSR pg 650), and the final analysis plan was amended on 14th June 2007. The primary (first) datalock (PFS) was 21 November 2007. The final datalock (OS) was 18 December 2008. |
| Section 4.1.6, page 27 | The trial was not powered to perform the treatment-by- | Although the power of the treatment-by-histology | This text should be removed or corrected. | Submission Section 6.4 |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| | histology interaction. | interaction was not pre-calculated in the Statistical analysis Plan, the results of the test were highly statistically significant which demonstrate that the JMEN trial was adequately powered to assess this interaction. | | |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Summary statement, Section 4.1.7, page 27. | the decision to change the primary endpoint of the JMEN trial[2] from OS to PFS. This decision had the effect of truncating the data available for analysis for OS, which is of critical importance to the economic evaluation. | Final OS analysis was conducted as originally planned. | This text should be removed as it is incorrect. | MS Section 6.3.3<br><br>Final datalock for OS was on 18 Dec 2008 as planned initially. |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Section 4.2.2 Table 4-6, page 29 | Median PFS upper limit of CI 0.39 | The upper limit is 0.59 | Median PFS upper limit of CI 0.59 | Submission page 47<br><br>CSR addendum |
| Section 4.2.2 page 30 | For OS, the unadjusted HRs indicate a statistically significant effect of pemetrexed only for patients with stable disease | Stage IIIB and IV subgroups are also statistically significant | Stage IIIB and IV should be added to this sentence | Appendix 3, Table 10-4 |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| | following induction therapy, patients treated with paclitaxel or a taxane-based CTX, patients who received carboplatin as induction therapy and patients with PS 0. | | | |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Section 4.3.2, page 34. | the trial was not powered to perform this subgroup analysis. | There was sufficient power for this subgroup analysis | This text should be removed. | Clinical Study Report Section 8.2 states that histology subgroup analysis was added as an objective in the final Statistical Analysis Plan prior to datalock. Previous pemetrexed studies demonstrated differential efficacy by histology. It was expected that the treatment effect in the non-squamous subgroup would be greater than in the overall population on which sample size was calculated. Power for the subgroup would be increased. Retrospective power calculations for hazard ratios of 0.7 yield ≥90% power for both PFS and OS (364 and 332 events, respectively) and the observed hazard ratio of 0.44 for PFS has 100% power. |
| | | | | |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| Section 4.3.2, page 34. | having a high proportion of second-line treatments than are not commonly prescribed in the UK, which may affect OS and PFS | Second-line therapies were given post progression and do not impact PFS | Remove “and PFS” from this text | |
| Section 4.3.2, page 34. | excluding patients treated with first-line vinorelbine or pemetrexed, both of which are available in the UK | The submission only relates to patients who have received a platinum doublet containing gemcitabine, docetaxel or paclitaxel in accordance with the NICE scope and the licensed indication. | This text should be removed as it refers to unlicensed use of pemetrexed and is out of the scope of this appraisal. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. |
| Description of manufacturer’s economic model. Section 5.3.1, page 38 | It is worth noting that AEs are not captured in the model, but are explored in the sensitivity analysis (SA) | The model assessed the impact of AEs both from the cost and outcomes perspective. The model applied the percentage of AEs observed in each arm of the trial to an average cost per AE obtained from Duran et al (2008). In addition, the model takes into consideration the associated disutility from AEs as reported in Nafees (2008). | This text should be amended to appropriately reflect the methods of the model or removed | Submission pages 89, 97 and 98<br><br>Excel Model Worksheets: ‘Inputs’ ‘PemAEs’ ‘PlaceboAEs’ ‘Pem utility’ and ‘Placebo utility’<br><br>Nafees 2008 was provided as a reference |
| Description of | Second-line CTX is composed of | The model has applied | This text should be amended to | Submission Tables 26, 29 and 30 |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| manufacturer's economic model. Section 5.3.1, page 38 | either docetaxel or erlotinib monotherapy which are assumed to have the same unit costs. | different drug unit costs and also different drug administration costs to docetaxel and erlotinib. | appropriately reflect the methods of the model or removed | Excel Model Worksheets: 'Inputs' 'Pem PDT costs' and 'Placebo PDT |
| Table 5-7, Source of preference data, page 48 | It is not clear how representative this sample is of the UK adult population. | The sample, as described in Nafees 2008, differed in percentages of females, ethnic minorities and university education | This text needs to be amended to reflect Nafees 2008. | Nafees 2008 was provided as a reference. |
| Assessment of the manufacturer's economic model. Table 5-8 Critical appraisal checklist, Page 49 | Q: Was the effectiveness of the programme or services established?<br>A: The effectiveness of maintenance therapy…<br>Furthermore, the trial did not allow patients to receive first-line vinorelbine or pemetrexed – both of which are licensed for use in the UK. | The submission only relates to patients who have received a platinum doublet containing gemcitabine, docetaxel or paclitaxel in accordance with the NICE scope and the licensed indication | This text should be removed as it refers to unlicensed use of pemetrexed and is out of the scope of this appraisal. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Section 7.2.2, page 69 | The JMEN trial[2] showed a mean OS benefit of 5.3 months in the pemetrexed maintenance arm compared with the placebo arm for the licensed non-squamous population | The reported value of a mean overall survival of 5.3 months was derived from the economic model. The reference provided here is for the median overall survival which was 5.2 months, within the Lancet publication. | Amended text should state "The JMEN trial[2] showed a median OS benefit of 5.2 months in the pemetrexed maintenance arm compared with the placebo arm for the licensed non-squamous population. The mean estimate derived from the economic model was 5.3 months". | Mean overall survival 5.3 months, page 48 of MS.<br><br>Median overall survival 5.2 months, Ciuleanu T, et al, Lancet 2009. |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Section 7.2.3, page 71 | NICE approval of pemetrexed for first-line CTX {NICE, 2009 #44} | This TA has now been issued, TA 181 | Text should be amended to state TA181. | www.nice.org.uk |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Section 8.1, page 74 | The trial excluded patients treated with first-line vinorelbine or pemetrexed, both of which are available in the UK | The submission only relates to patients who have received a platinum doublet containing gemcitabine, docetaxel or paclitaxel in | This text should be removed as it refers to unlicensed use of pemetrexed and is out of the scope of this appraisal. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| | | accordance with the NICE scope and the licensed indication. | | platinum doublet with gemcitabine, paclitaxel or docetaxel. |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed<br><br>The use of first-line vinorelbine and pemetrexed is outside the licensed indication for pemetrexed maintenance and therefore not within the NICE scope for this appraisal. | CiC information removed | CiC information removed |
| CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Section 10, Appendix 1. Table 10-1, page 81 | Q - Were there any confounding factors that may attenuate the interpretation of the results of the RCT.<br><br>A - Patients in the JMEN trial[2] received either docetaxel, gemcitabine or paclitaxel as induction therapy. In England and Wales, patients may also receive vinorelbine or pemetrexed. | The submission only relates to patients who have received a platinum doublet containing gemcitabine, docetaxel or paclitaxel in accordance with the NICE scope and the licensed indication. | This text should be removed as it refers to unlicensed use of pemetrexed and is out of the scope of this appraisal. | Summary of Product Characteristics. Section 4.1 Therapeutic Indication states:<br><br>First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. |
| CiC information | CiC information removed | CiC information removed | CiC information removed | CiC information removed |

| Section, page | Current text | Description of erratum | Amendment required | Justification for amendment |
|---|---|---|---|---|
| removed | | | | |