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**HTA and Health Outcomes**

Medical and Product Information: [redacted]

11th September 2009

Meindert Boysen
Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
Level 1A, City Tower
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Manchester
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Dear Meindert,

**Re: STA on Pemetrexed for the maintenance treatment of non small cell lung cancer – clarification regarding clinical and cost-effectiveness data**

Please find attached part 2 of our response to the clarification questions. Part 1 of our response (individual patient data from the JMEN trial) has already been couriered to you on disc.

The response document (file "PemetrexedSTA_clarificationresponse_11thsept09.doc") in itself does not contain any confidential information. The following attachments related to the data presented in the response are commercial in confidence:

[redacted]

I have also enclosed the Appendix E confidentiality form to document the confidential data in both Part 1 and Part 2 of our response.

If you have any further questions or need further clarifications, please do not hesitate to contact me.

Kind regards

Yours sincerely

[redacted]

Encl:

Lilly response to NICE clarification questions
(file “PemetrexedSTA_clarificationresponse_11thsept09.doc”)
File “DOF_JMEN_grade3&4AEs_ITT.rtf”
File “nsqgr34_epri.rtf”
[redacted]
File “fqdisa17.rtf”
[redacted]

# STA on pemetrexed in maintenance treatment of NSCLC

## Lilly response to clarification questions

## 11th September 2009

## Section A: General

### A1 Adverse events

a) Please provide the file“DOF_JMEN_grade3/4AEs_ITT_non-squamous”. Table 12 (in the manufacturer submission,pp. 52) references this file but the file is missing from the documentation provided.

Attached with this letter is the file “DOF_JMEN_grade3&4AEs_ITT.rtf” for all randomised patients, in support of Table 12 in the manufacturer’s submission and the file “nsqgr34rel_epi.rtf”, which summarises the incidence of grade 3/4 toxicities for the licensed non-squamous population, in support of Table 13 in the manufacturer’s submission.

## Section B: Clarifications of the effectiveness data

### B1 Subgroups

a) Please provide overall survival (OS) and progression free survival (PFS) hazard ratios together with confidence intervals and the actual OS and PFS figures for the licensed non-squamous population for each of the following subgroups by trial arm:

- Disease stage (presenting outcomes for stage IIIb separately from stage IV)
- Response status prior to maintenance therapy (presenting outcomes for patients assessed as complete response at the start of maintenance, separately from partial response patients and again separately for stable disease patients)
- First-line treatment (presenting outcomes according to the first line regimen – so gemcitabine/cisplatin, docetaxel/cisplatin, paclitaxel/cisplatin gemcitabine/carboplatin, docetaxel/carboplatin and paclitaxel/carboplatin patients analysed separately)
- First-platinum treatment (cisplatin separately from carboplatin)
- ECOG performance status (PS0 separately from PS1)

As specified in the original statistical analysis plan for the JMEN trial, Lilly conducted a pre-specified covariate-adjusted analysis using the Cox proportional hazards model stratified by non-platinum component of the induction therapy (section 6.3.5 of manufacturer’s submission). Additional data from these analyses are summarised in Table 1 and Table 2 below. The hazard ratios in these tables demonstrate the effect of each variable (eg, the risk of death is 31% lower for East Asians as compared to all other ethnicities within the trial).

**Table 1. Covariate-adjusted final overall survival for non-squamous patients**

| Variable (N=474[a,b], 328 events) | HR (95% CI) | p-value[c] |
|---|---|---|
| Study treatment arm (pemetrexed versus placebo) | 0.70 (0.56–0.88) | 0.0021 |
| ECOG performance status (0 versus 1) | 1.23 (0.98–1.54) | 0.0792 |
| Cisplatin[d] (yes versus no) | 1.04 (0.81–1.33) | 0.7816 |
| Induction response (PR/CR versus SD) | 0.97 (0.77–1.22) | 0.7721 |
| East Asian (yes versus no) | 0.69 (0.53–0.90) | 0.0066 |
| Nonsmoker (yes versus no) | 0.90 (0.67–1.20) | 0.4741 |
| Gender (female versus male) | 0.66 (0.50–0.87) | 0.0035 |
| Age (<65 years versus ≥65 years) | 0.87 (0.69–1.10) | 0.2537 |
| Stage (IIIB versus IV) | 1.12 (0.84–1.49) | 0.4587 |

[a]Stratified by non-platinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel)
[b]Seven patients were excluded due to missing values for one or more cofactors
[c]p-value is from chi-square test
[d]Description of platinum agent in induction regimen: all patients were treated with a platinum-based regimen, either with cisplatin (yes) or carboplatin (no)
CI = confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PR, partial response; SD, stable disease
Note: Analysis of overall survival was performed following final datalock in December 2008, subsequent to the histological reclassification of a total of three patients, including one patient who was initially classified as having adenocarcinoma, which was subsequently reclassified as squamous cell carcinoma

**Table 2. Covariate-adjusted analysis for progression-free survival for non-squamous patients**

| | Non-squamous (N=475[a,b], 359 events) | |
|---|---|---|
| Variable | HR (95% CI) | p-value[c] |
| Study treatment arm (pemetrexed versus placebo) | 0.45 (0.36–0.56) | <0.0001 |
| ECOG PS (1 versus 0) | 1.04 (0.84–1.29) | 0.725 |
| Induction response (PR/CR versus SD) | 1.04 (0.83–1.30) | 0.739 |
| East Asian (yes versus no) | 1.12 (0.87–1.42) | 0.383 |
| Nonsmoker (yes versus no) | 1.02 (0.78–1.34) | 0.861 |
| Gender (female versus male) | 0.77 (0.59–0.99) | 0.040 |
| Age (<65 versus ≥65 years) | 1.19 (0.94–1.50) | 0.153 |

[a]Stratified by non-platinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel); nine patients were excluded due to missing values for one or more cofactors.
[b]Stratified by non-platinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel); eight patients were excluded due to missing values for one or more cofactors (seven non-squamous patients and one squamous patient)
[c]p-value is from the Mantel Haenszel chi-square test
CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PR, partial response; PS, performance status; SD, stable disease
Note: Data analysis for progression-free survival was performed following the primary datalock in November 2007. Analysis of final overall survival was performed following final datalock in December 2008, subsequent to the histological classification of a total of three patients. However, the reclassification of these patients is not expected to impact the conclusions drawn from the primary analysis of progression-free survival.

Only ethnicity and gender were found to be statistically significant for overall survival, with females and East Asians (ie, Asian descent, but not from Indian subcontinent) deriving

better survival outcomes (Table 1). For progression-free survival, only gender was statistically significant, with females deriving better outcomes (Table 2). These factors have been previously shown to have favourable prognosis in advanced NSCLC, irrespective of treatment. On this basis, further exploration of subgroups within the economic modelling was not conducted as it was not likely to produce any significant further information or clarity in regards to the decision problem.

As can be seen in Table 3 below, the sample sizes of some of the requested subgroups are too small to provide robust analyses. For example, there were only 5 patients with complete response, all in the pemetrexed arm, and less than 20 patients in each arm for docetaxel/cisplatin, docetaxel/carboplatin or paclitaxel/cisplatin. Therefore, some subgroups have been merged, e.g. taxanes/platinum, to enable more meaningful analyses.

The requested subgroup analyses are provided in Table 4.

**Table 3. Summary of select baseline characteristics and demographics for the non-squamous population in the JMEN study**

| | Non-squamous population (N=481) | | |
|---|---|---|---|
| | **Pemetrexed N=325** | **Placebo N=156** | **Total N=481** |
| Disease stage prior to induction therapy[a], n (%) | | | |
| Unknown | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Stage IIIB | 55 (16.9) | 30 (19.2) | 85 (17.7) |
| Stage IV | 269 (82.8) | 126 (80.8) | 395 (82.1) |
| ECOG PS at randomisation[b], n (%) | | | |
| Unknown | 2 (0.6) | 0 (0.0) | 2 (0.4) |
| 0 | 133 (40.9) | 60 (38.5) | 193 (40.1) |
| 1 | 190 (58.5) | 96 (61.5) | 286 (59.4) |
| Best tumour response to induction therapy, n (%) | | | |
| Unknown | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Complete response | 5 (1.5) | 0 (0.0) | 5 (1.0) |
| Partial response | 143 (44.0) | 78 (50.0) | 221 (45.9) |
| Stable disease | 174 (53.5) | 78 (50.0) | 252 (52.4) |
| Progressive disease[c] | 2 (0.6) | 0 (0.0) | 2 (0.4) |
| Specific induction regimen, n (%) | | | |
| Unknown | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Docetaxel + carboplatin | 14 (4.3) | 6 (3.8) | 20 (4.2) |
| Docetaxel + cisplatin | 5 (1.5) | 3 (1.9) | 8 (1.7) |
| Gemcitabine + carboplatin | 90 (27.7) | 37 (23.7) | 127 (26.4) |
| Gemcitabine + cisplatin | 107 (32.9) | 61 (39.1) | 168 (34.9) |
| Paclitaxel +carboplatin | 89 (27.4) | 36 (23.1) | 125 (26.0) |
| Paclitaxel +cisplatin | 19 (5.8) | 13 (8.3) | 32 (6.7) |

ECOG, Eastern Cooperative Oncology Group; PS, performance status
[a]One patient was missing disease stage status
[b]Two patients were missing performance status information
[c]Two patients were randomised but not treated due to progressive disease at the time of study entry
**Note:** Baseline characteristics presented here represent the baseline characteristics of the histological subgroups subsequent to the histological reclassification of a total of three patients following the initial datalock in November 2007 (including the reclassification of one patient in the pemetrexed-treated from adenocarcinoma to squamous cell carcinoma)

**Table 4. Summary of efficacy parameters by subgroups, pemetrexed vs placebo for the non squamous population in the JMEN study**

| Subgroup | N | Overall survival | | Progression-free survival | |
|---|---|---|---|---|---|
| | | Unadjusted hazard ratio (95%CI) | Median (months) | Unadjusted hazard ratio (95%CI) | Median (months) |
| Stage IIIB | 85 | 0.52 (0.31-0.87) | 17.5 vs 8.7 | 0.56 (0.33-0.94) | 4.3 vs 1.6 |
| Stage IV | 395 | 0.75 (0.58-0.97) | 15.0 vs 10.6 | 0.43 (0.33-0.55) | 4.8 vs 2.7 |
| | | | | | |
| Partial response to induction therapy | 221 | 0.83 (0.59-1.15) | 14.4 vs 11.7 | 0.45 (0.32-0.61) | 4.6 vs 1.7 |
| Partial or complete response* to induction therapy | 226 | 0.81 (0.58-1.12) | 14.4 vs 11.7 | 0.45 (0.33-0.61) | 4.5 vs 1.7 |
| Stable disease with induction therapy | 252 | 0.61 (0.45-0.83) | 16.6 vs 8.6 | 0.44 (0.32-0.61) | 4.5 vs 2.8 |
| | | | | | |
| Gemcitabine/cisplatin induction therapy | 168 | 0.84 (0.57-1.24) | 13.8 vs 11.0 | 0.48 (0.33-0.70) | 4.2 vs 2.8 |
| Gemcitabine/carboplatin induction therapy | 127 | 0.75 (0.48-1.17) | 14.0 vs 9.1 | 0.55 (0.36-0.84) | 4.6 vs 1.6 |
| Paclitaxel/carboplatin induction therapy | 125 | 0.60 (0.39-0.94) | 16.5 vs 9.1 | 0.41 (0.26-0.64) | 4.7 vs 2.8 |
| Paclitaxel/platinum* induction therapy | 157 | 0.65 (0.44-0.96) | 16.5 vs 10.3 | 0.43 (0.29-0.65) | 4.6 vs 2.8 |
| Taxane*/platinum* induction therapy | 185 | 0.57 (0.40-0.82) | 16.6 vs 9.1 | 0.36 (0.25-0.53) | 4.8 vs 2.6 |
| | | | | | |
| Cisplatin induction therapy | 208 | 0.80 (0.56-1.12) | 14.0 vs 11.5 | 0.48 (0.35-0.68) | 4.1 vs 2.8 |
| Carboplatin induction therapy | 272 | 0.62 (0.46-0.83) | 15.9 vs 8.8 | 0.42 (0.31-0.57) | 5.0 vs 2.3 |
| | | | | | |
| Performance status 0 | 193 | 0.57 (0.39-0.82) | 17.7 vs 10.3 | 0.33 (0.23-0.48) | 5.5 vs 1.6 |
| Performance status 1 | 286 | 0.80 (0.60-1.06) | 14.1 vs 10.6 | 0.53 (0.40-0.70) | 4.3 vs 2.8 |

*Combination of requested subgroups due to small sample size of individual subgroups

The Kaplan-Meier curves for these subgroups are in the attached files (CiC information removed)

The results in Table 4 suggest consistent benefit for pemetrexed across all subgroups, with hazard ratios ranging from 0.52 to 0.84, all <1. This range of point estimates is consistent with the assumption of a uniform effect of pemetrexed, but manifesting with statistical variation (as is typical of subgroup results in a clinical trial).

The following limitations should be considered when evaluating any one subgroup:

- this trial was not powered to demonstrate statistically significant benefit in these subgroups
- these analyses are not adjusted for potentially prognostic factors (e.g., gender) or other confounding factors

## B2 Second-line therapy

a) Please provide a breakdown of second-line therapy (for the licensed non-squamous population) by trial arm, explaining the reasons for second-line therapy (whether progression or adverse events or other reasons).

b) Please provide further clarification and justification of the 18.5% cross over 0reported in the submission (did cross-over always occur after unblinding, and did it always count as second line treatment?).

c) Please provide a breakdown of second-line therapy by stage of disease for the licensed non-squamous population.

d) Please also provide the mean and maximum number of second line chemotherapy cycles for each trial arm for the licensed non-squamous population.

a). Please refer to the first table in the attached file (CiC information removed) for a breakdown of subsequent therapies for the licensed population. Some of the agents may have been used as combination regimens or as third-line or later. However, the percentages of patients would still be representative of those who received second-line therapy. Commonly used agents are erlotinib, gefitinib, docetaxel and pemetrexed which have regulatory approvals as second-line agents in various geographies.

The reasons for initiating second-line therapy were not recorded in the clinical trial. However, the reasons for discontinuation of study therapy for the licensed population who received subsequent therapy are summarised in Table 5. The majority of patients discontinued study therapy due to progression.

**Table 5. Summary of Reasons for Discontinuation for Patients Who Received Post-Discontinuation Therapy**
**Histology Subgroup: Adenocarcinoma, Large Cell Lung Cancer & Other or Indeterminate Histology**

All Randomized Patients
H3E-MC-JMEN Final Overall Survival Analysis

| Reasons for Discontinuation | Pemetrexed (N = 173) n | (%) | Placebo (N = 105) n | (%) | Total (N = 278) n | (%) |
|---|---|---|---|---|---|---|
| Progressive Disease | 133 | (76.9) | 100 | (95.2) | 233 | (83.8) |
| Subject Decision | 14 | (8.1) | 2 | (1.9) | 16 | (5.8) |
| Adverse Event | 13 | (7.5) | 1 | (1.0) | 14 | (5.0) |
| Physician Decision | 8 | (4.6) | 2 | (1.9) | 10 | (3.6) |
| Entry Criteria Not Met | 3 | (1.7) | 0 | (0.0) | 3 | (1.1) |
| Protocol Violation | 1 | (0.6) | 0 | (0.0) | 1 | (0.4) |

b). Following discontinuation of therapy, the investigator was unblinded to treatment assignment. Subsequent therapies were initiated at the investigator's discretion and therefore cross-over in the placebo arm to pemetrexed was an option.

c). Please refer to the second and third tables in the attached file (CiC information removed) for a breakdown of subsequent therapies for Stage IIIB and IV, respectively, for the licensed population. The percentage of patients who received subsequent therapies in the licensed population is consistent with the overall population.

The fourth and fifth tables summarise subsequent therapies for performance status 0 and 1, respectively, for the licensed population.

d). Duration of second-line therapy was not recorded in the clinical trial.

## B3 Analysis by geographic region

a) Please provide the results of any analyses undertaken by geographical region or centre for the licensed non-squamous population.

Table 6 summarises efficacy endpoints that have been analysed by geographic regions. As with Question B1, results are consistent among these regions, although the absolute values for overall survival are longer for the Asian region (consistent with the results presented in Table 1 for East Asian ethnicity). Again, these are the results for unadjusted analyses which did not account for potential differences in other baseline prognostic factors.

**Table 6. Summary of Efficacy of Nonsquamous Population by Geographic Regions**

| | N | Unadjusted hazard ratio (95% CI) | Log-rank p-value | Pemetrexed | Placebo |
|---|---|---|---|---|---|
| **EU region** | 230 | | | | |
| Overall survival | | 0.67 (0.49-0.92) | 0.014 | | |
| Median (months) | | | | 13.8 | 8.1 |
| One-year rate | | | | 55% | 36% |
| Progression-free survival | 231 | 0.48 (0.35-0.66) | <0.00001 | | |
| Median (months) | | | | 4.6 | 2.7 |
| **Non-Asian region** | 310 | | | | |
| Overall survival | | 0.67 (0.51-0.88) | 0.004 | | |
| Median (months) | | | | 13.0 | 8.5 |
| One-year rate | | | | 54% | 36% |
| Overall survival from start of induction | | 0.68 (0.51-0.89) | 0.006 | | |
| Median (months) | | | | 16.2 | 12.0 |
| One-year rate | | | | 67% | 49% |
| **Asian region** | 171 | | | | |
| Overall survival | | 0.75 (0.51-1.10) | 0.139 | | |
| Median (months) | | | | 18.9 | 13.8 |
| One-year rate | | | | 71% | 54% |
| Overall survival from start of induction | | 0.75 (0.51-1.10) | 0.138 | | |
| Median (months) | | | | 21.9 | 17.1 |
| One-year rate | | | | 81% | 67% |

EU region = Austria, Bulgaria, Croatia, Czech Republic, Germany, Greece, Hungary, Italy, Netherlands, Poland, Romania, Spain
Non-Asian region = EU region, Australia, Brazil, Turkey, US
Asian region = China, India, Korea, Taiwan

## B4 Reasons for discontinuation

a) Please provide information on reasons for discontinuation for the licensed non-squamous population for each trial arm

Please refer to the attached file “fqdisa17” for a summary of reasons for discontinuation for the licensed population. The results are similar to those for the overall population.

## Section C: Clarifications of the economic data

### C1 Individual patient data

a) To allow for a probabilistic sensitivity analysis to be undertaken, please provide a limited anonymised extract of the individual patient data from the JMEN trial for each non-squamous patient as follows:

- unique anonymised patient identifier
- trial arm (pemetrexed or placebo)
- days from randomisation to disease progression/withdrawal or censoring re-progression/withdrawal
- censoring for progression/withdrawal (yes/no)
- days from randomisation to death or censoring re-death
- censoring for death (yes/no)
- cycles of trial medication administered
- cycles of second-line chemotherapy administered
- type of second-line chemotherapy administered (list agent(s) or state “none”)
- days from randomisation to start of second-line chemotherapy
- disease stage at baseline (IIIB/IV)
- performance status at baseline (PS0/1)
- histological sub-type (adeno/large cell/other)
- response status prior to maintenance (complete response/partial response/stable disease)

The requested dataset has been sent separately (as part 1 of our response) on disc. The dataset is to be treated as “commercial in confidence” and to be destroyed following use. All requested variables have been included, except number of cycles of second-line therapy which were not recorded.

### C2 Anti-emetic therapy

a) Please provide the following for the licensed non-squamous population and for each trial arm:

- medications prescribed
- duration of treatment for each episode
- number of patients given anti-emetic therapy at any time
- total number of anti-emetic treatment episodes (or the total number of patient cycles in which treatment was given)

The antiemetic medications reported for the licensed population are summarised in Table 7. With the exception of prochlorperazine, these agents are 5HT3 antagonists which are typically prescribed around the time of chemotherapy dosing and would thus be accounted for in the HRG for chemotherapy administration. The similar percentage of patients receiving anti-emetics in both study arms suggests that usage was part of an investigator's usual practice of prophylaxis.

**Table 7. Summary of Antiemetic Drugs Taken On Study or Within 30 days of Discontinuation All Randomised non-squamous Patients**

**H3E-MC-JMEN**

| | Pemetrexed (N=325) | | Placebo (N=156) | |
|---|---|---|---|---|
| **Drug Name** | **n** | **%** | **n** | **%** |
| **Any** | **103** | **31.7** | **49** | **31.4** |
| **DOLASETRON** | **3** | **0.9** | **3** | **1.9** |
| **DOLASETRON MESILATE** | **4** | **1.2** | **2** | **1.3** |
| **GRANISETRON** | **26** | **8.0** | **21** | **13.5** |
| **ONDANSETRON** | **62** | **19.1** | **17** | **10.9** |
| **ONDANSETRON HYDROCHLORIDE** | | | **1** | **0.6** |
| **PALONOSETRON** | **1** | **0.3** | | |
| **PROCHLORPERAZINE** | **9** | **2.8** | **1** | **0.6** |
| **RAMOSETRON** | **1** | **0.3** | **3** | **1.9** |
| **RAMOSETRON HYDROCHLORIDE** | | | **1** | **0.6** |
| **TROPISETRON** | **15** | **4.6** | **10** | **6.4** |

Duration of antiemetic therapy and number of unique episodes are not available due to inconsistent reporting of start and stop dates and intermittent use of these agents. For example, the start date may correspond to the first cycle of therapy and the stop date with the last cycle.

Costs of these antiemetic agents are summarised in Table 8. The 5HT3 antagonists are recommended to be administered prior to chemotherapy as a single prophylactic dose. Pemetrexed is classified as having low emetic risk.

**Table 8. Cost of antiemetic agents administered in JMEN (Source: BNF, March 2009, pp 224-227)**

| Drug | Presentation | Price | Standard dose* | Cost per daily dose |
|---|---|---|---|---|
| **Dolasetron 20mg/ml** | 0.625ml (12.5mg) amp | £4.00 | n/a (for post-operative N/V) | - |
| | 5ml (100mg) | £13.00 | 100 mg | £13.00 |
| **Granisetron** | | | | |
| Tablets | 1mg x 10 tablets | £65.49 | 2 mg | £13.10 |
| | 2mg x 5 tablets | £65.49 | 2 mg | £13.10 |
| 1mg/ml injection | 1ml amp | £8.60 | 1 mg | £8.60 |
| | 3ml amp | £25.79 | 1 mg | £8.60 |
| **Ondansetron** | | | | |
| Tablets | 4mg x 30 tabs | £107.91 | 16 mg | £14.39 |
| | 8mg x 10 tabs | £71.94 | 16 mg | £14.39 |
| Oral lyophilisates | 4mg x 10 tabs | £35.97 | 16 mg | £14.39 |

| | | | | |
|---|---|---|---|---|
| | 8mg x 10 tabs | £71.94 | 16 mg | £14.39 |
| Syrup | 4mg/5ml x 50 ml | £35.97 | 16 mg | £14.39 |
| Injection 2mg/ml | 2ml amp | £5.99 | 8 mg | £11.98 |
| | 4 ml amp | £11.99 | 8 mg | £11.99 |
| Suppositories | 16mg x 1 supp | £14.39 | 16 mg | £14.39 |
| **Palonosetron** 50mcg/ml | 5ml amp | £55.89 | 0.25 mg | £55.89 |
| **Prochlorperazine**** | | | | |
| Generic | 5mg tabs x 28 tabs | £2.09 | Maximum 40 mg/day | £0.60 |
| | 5mg x 84 tabs | £4.14 | Maximum 40 mg/day | £0.39 |
| Stemetil | 5mg x 84 tabs | £6.18 | Maximum 40 mg/day | £0.59 |
| | Syrup 5mg/5ml x 100ml | £3.48 | Maximum 40 mg/day | £1.39 |
| Injection 12.5mg/ml | 1 ml amp | £0.54 | Maximum 40 mg/day | £2.16 |
| **Tropisetron** | Discontinued | | | |
| **Ramosetron** | Not in BNF | | | |

*Recommended doses as prophylaxis (Multinational Association of Supportive Care in Cancer, March 2008) http://data.memberclicks.com/site/mascc/MASCC_Guidelines_Update.pdf

** Prochlorperazine is not discussed in MASCC Guidelines. Doses are based on Stemetil product information http://emc.medicines.org.uk/medicine/16491. Doses may be repeated on consecutive days.

## C3 Dose reduction

a) Please provide the following for the licensed non-squamous population and for each trial arm:

- total number of planned cycles of trial medication
- total number of planned cycles where 100% of the planned dose was given
- total number of planned cycles where 75% of the planned dose was given
- total number of planned cycles where 50% of the planned dose was given
- total number of planned cycles where none of the planned dose was given (i.e. missed cycles)

There was no planned number of cycles; all patients were to be treated until progression. No doses were omitted. If the patient could not receive a dose within 42 days of the previous dose, the patient was discontinued from therapy. Table 9 summarises the intensity of each dose/cycle.

**Table 9. Summary of dose intensity for all cycles of therapy**

| | Pemetrexed | placebo |
|---|---|---|
| 100% | 2527 | 707 |
| 90% | 2 | 0 |
| 75% | 21 | 2 |
| 50% | 3 | 0 |
| Total number of cycles | 2553 | 709 |

## C4 Hospitalisations

a) Please provide the summary information given in Table JMEN.12.10 of the Clinical Study Report (CSR_main, pp. 143) for the licensed non-squamous population.

b) Please provide further details of the hospitalisations the licensed non-squamous population as follows:

- time/cycle in which episode occurred
- length of stay
- description and HRG/DRG code for the episode
- any AEs related to the episode

Within the submitted economic analyses, HRG episodes were associated with grade 3/4 adverse events. There is significant variation in practice within the countries from which patients were included in the trial and therefore it is not considered appropriate to extrapolate hospital data to the UK population. For example one patient in China was hospitalised for 64 nights for chest pain.

In the clinical trial, some discharge dates were missing leading to extreme outliers by imputing the latest date that the patient was known not to be hospitalised (e.g., one patient with a missing discharge date was conservatively calculated to have a length of stay of 97 nights). When the hospitalisations with missing discharge dates are excluded (n=8), the average length of stay is reduced to a mean of 9.0 nights with a standard deviation of 8.9 nights and the median remains 7 nights. There were no missing dates for the drug-related AE hospitalisations.

a). Table 10 summarises AE-related hospitalisations for the licensed population. The number of percentage of patients hospitalised is low for both arms and the difference between arms is not significant for all or non-drug-related hospitalisations. These hospitalisations are attributable to co-morbidities and disease symptoms which occur regardless of treatment approach. Drug-related hospitalisations represent the minority of admissions.

**Table 10. Summary of All Hospitalisations due to Adverse Events (on Study or Within 30 Days of Last Study Drug Dose)**

All Nonsquamous Patients

| | Pemetrexed (n=325) | Placebo (n=156) | P-value |
|---|---|---|---|
| Patients with at least 1 hospitalisation n (%) | 51 (15.7) | 20 (12.8) | 0.493 |
| All hospitalisations | 73 | 22 | |
| Mean (SD) length of stay (nights) | 10.3 (14.0) | 9.8 (5.4) | |
| Median (range) length of stay (nights) | 7 (1-97) | 9 (1-21) | |
| **Patients hospitalised due to drug-related AEs n (%)** | **13 (4.0)** | **0** | **0.012** |
| Hospitalisations involving drug-related events | 15 | 0 | |
| Mean (SD) length of stay (nights) | 8.5 (5.9) | 0 | |
| Median (range) length of stay (nights) | 6 (2-20) | 0 | |
| Patients hospitalised due to non-drug-related AEs n (%) | 44 (13.5) | 19 (12.2) | 0.773 |
| Hospitalisations not involving drug-related events | 58 | 20 | |
| Mean (SD) length of stay (nights) | 10.7 (15.5) | 10.1 (5.6) | |
| Median (range) length of stay (nights) | 7 (1-97) | 10 (1-21) | |

Abbreviations: AE = adverse event; N = number of randomised patients; n = number of patients with event; SD = standard deviation

Notes: p-value from Fisher exact test. One placebo patient was hospitalised twice, but causality was not assessed; this patient's data are not included in results for drug-related and nondrug-related.

The mean and standard deviation values in Table 10 demonstrate the variation in practice and the difficulty in applying these data in a meaningful way to UK clinical practice within the economic model.

b. The types of adverse events causing hospitalisations are highly varied. For the drug-related hospitalisations, the most common adverse events were febrile neutropenia, followed by anaemia, mucositis and pneumonia. Other drug-related adverse events were neutropenia, urosepsis, venous thrombosis, renal failure and asthenia. For all hospitalisations, the most common adverse events were pneumonia+bronchitis+respiratory tract infections and dyspnea+respiratory failure.

## C5 Adverse events

a) Please provide the number of episodes of toxicity as well as the number of patients suffering at least one episode (or the number of patient cycles involving an episode) for the licensed non-squamous population.

b) Table 12 of the Manufacturer's submission (MS, page 52) references the file "DOF_JMEN_grade3/4AEs_ITT_non-squamous" but this file is missing from the documentation provided. Please provide this table.

a). The percentage of patients experiencing grade 3/4 toxicity and the number of episodes are summarised in the attached file "nsqgr34rel_epi". For most toxicities, patients rarely experienced more than one episode.

b). Please see response for Section A1.

## C6 Transfusions

a) Please provide information for the licensed non-squamous population together with the total number of each type of transfusion given (i.e where a patient receives multiple transfusions).

Twenty-nine pemetrexed patients and three placebo patients in the licensed population received transfusions. A summary of transfusions is provided in Table 11. The majority of transfusions were delivered in the outpatient setting.

**Table 11. Summary of Transfusions On Study or Within 30 Days of Discontinuation All Randomized Nonsquamous Patients**

H3E-MC-JMEN

| Type of Transfusion | Pemetrexed (N=325) Number of Patients | Pemetrexed (N=325) Number of Transfusions | Placebo (N=156) Number of Patients | Placebo (N=156) Number of Transfusions |
|---|---|---|---|---|
| Fresh Frozen Plasma (FFP) | 1 | 1 | | |
| Packed Red Blood Cells (PRBC) | 25 | 51 | 2 | 5 |
| Platelets | 2 | 2 | 1 | 1 |
| Whole Blood | 3 | 3 | | |

## C7 Type of scan patients received in the trial

a) Please provide information on the proportion of patients receiving chest-x ray, MRI and CT scan for the licensed non-squamous population and for each trial arm.

Table 12 summarises the methods of assessing lesions at baseline. Patients may have been monitored by multiple methods, but same methods were to be used throughout study. The vast majority of the patients were assessed with CT scans, the most common method being 'Spiral CT' (which compares well with UK practice) as it enables more effective examination of the lesions. Of the six patients without baseline methods, four were complete responders following induction therapy so therefore had no baseline lesions to assess and the other two did not receive study treatment (censored in PFS analysis).

**Table 12. Summary of Baseline Lesion Methods of Measurement**

All Randomized Nonsquamous Patients

H3E-MC-JMEN

| Baseline Lesion Method of Measurement | Pemetrexed (N=325) n | Pemetrexed (N=325) % | Placebo (N=156) n | Placebo (N=156) % |
|---|---|---|---|---|
| *** | 6 | 1.8 | | |
| BONE SCAN/CHSTXR/CT | | | 1 | 0.6 |
| BONE SCAN/MRI/SPIRAL CT | 1 | 0.3 | 1 | 0.6 |
| BONE SCAN/SPIRAL CT | 26 | 8.0 | 9 | 5.8 |
| CHSTXR/CT/SPIRAL CT | | | 1 | 0.6 |
| CHSTXR/PHYS/SPIRAL CT | | | 1 | 0.6 |
| CHSTXR/SPIRAL CT | 1 | 0.3 | 1 | 0.6 |
| CT | 27 | 8.3 | 13 | 8.3 |
| CT/MRI | 1 | 0.3 | | |
| MRI | 1 | 0.3 | 1 | 0.6 |
| MRI/SPIRAL CT | 6 | 1.8 | 3 | 1.9 |
| PHYS/SPIRAL CT | 3 | 0.9 | 3 | 1.9 |
| SPIRAL CT | 253 | 77.8 | 122 | 78.2 |

*** 6 patients had no baseline lesion measurements

Summary of Reasons for Discontinuation
Histology Subgroup: Adenocarcinoma, Large Cell Lung Cancer & Other or Indeterminate Histology
All Randomized Patients
H3E-MC-JMEN Final Overall Survival Analysis

| Reasons for Discontinuation | Pemetrexed (N = 325) n | (%) | Placebo (N = 156) n | (%) | Total (N = 481) n | (%) |
|---|---|---|---|---|---|---|
| Progressive Disease | 225 | (69.2) | 135 | (86.5) | 360 | (74.8) |
| Subject Decision | 37 | (11.4) | 6 | (3.8) | 43 | (8.9) |
| Adverse Event | 28 | (8.6) | 3 | (1.9) | 31 | (6.4) |
| Physician Decision | 17 | (5.2) | 4 | (2.6) | 21 | (4.4) |
| Death | 1 | (0.3) | 4 | (2.6) | 5 | (1.0) |
| Due to Study Disease | 1 | (0.3) | 3 | (1.9) | 4 | (0.8) |
| Due to Adverse Event | 0 | (0.0) | 1 | (0.6) | 1 | (0.2) |
| Entry Criteria Not Met | 5 | (1.5) | 0 | (0.0) | 5 | (1.0) |
| Lost to follow up | 2 | (0.6) | 1 | (0.6) | 3 | (0.6) |
| Protocol Violation | 2 | (0.6) | 1 | (0.6) | 3 | (0.6) |
| Satisfactory Response | 2 | (0.6) | 0 | (0.0) | 2 | (0.4) |

Abbreviations: N = total number of randomized patients; n = number of patients in each category.

Program Location: home/lillyce/prd/ly231514/h3e_mc_jmen/final/programs_stat/fqdisa1
Output Location: home/lillyce/prd/ly231514/h3e_mc_jmen/final/programs_stat/tfl_output/fqdisa17.rtf
Data Location: home/lillyce/prd/ly231514/h3e_mc_jmen/final/data/shared/ads

PRODUCTION DATA - PRODUCTION MODE 16APR2008 02:17
Summary of Adverse Events Possibly Related to Study Drug (Grade 3 or 4 only)
By CTCAE Term and Maximum Grade, On Study or Within 30 Days of Discontinuation
All Randomized Patients
H3E-MC-JMEN

| CTCAE Term | Pemetrexed (N = 441) n | (%) | Placebo (N = 222) n | (%) | p-Value |
|---|---|---|---|---|---|
| Patients with >=1 Adverse Event | 70 | (15.9) | 9 | (4.1) | <.001 |
| Patients with >=1 Laboratory Adverse Event | 28 | (6.3) | 5 | (2.3) | 0.023 |
| ALT, SGPT (serum glutamic pyruvic transaminase) | 1 | (0.2) | 0 | (0.0) | >.999 |
| GGT (g-Glutamyl transpeptidase) | 0 | (0.0) | 1 | (0.5) | 0.335 |
| Hemoglobin | 12 | (2.7) | 1 | (0.5) | 0.070 |
| Leukocytes (total WBC) | 7 | (1.6) | 1 | (0.5) | 0.279 |
| Lymphopenia | 1 | (0.2) | 1 | (0.5) | >.999 |
| Neutrophils/granulocytes (ANC/AGC) | 13 | (2.9) | 0 | (0.0) | 0.006 |
| Platelets | 9 | (2.0) | 1 | (0.5) | 0.177 |
| Patients with >=1 Non-Laboratory Adverse Event | 54 | (12.2) | 4 | (1.8) | <.001 |
| Anorexia | 8 | (1.8) | 0 | (0.0) | 0.057 |
| Constipation | 3 | (0.7) | 1 | (0.5) | >.999 |
| Constitutional Symptoms - Other | 1 | (0.2) | 0 | (0.0) | >.999 |
| Cough | 2 | (0.5) | 0 | (0.0) | 0.554 |
| Cystitis | 1 | (0.2) | 0 | (0.0) | >.999 |
| Dehydration | 1 | (0.2) | 0 | (0.0) | >.999 |
| Dermatology/Skin - Other | 2 | (0.5) | 0 | (0.0) | 0.554 |
| Diarrhea | 2 | (0.5) | 0 | (0.0) | 0.554 |
| Distention/bloating,abdominal | 1 | (0.2) | 1 | (0.5) | >.999 |
| Dyspnea (shortness of breath) | 2 | (0.5) | 0 | (0.0) | 0.554 |

Abbreviations: CTCAE = common terminology criteria for adverse events; N = total number of randomized patients;
n = number of patients in each category.

Note: Patients may be counted in more than one category.

CTCAE Version 3.0

p-Values from Fisher's Exact Test.

Program Location : CABINETS¥SPREE¥RMP¥Clinical¥Oncology¥Alimta¥NSCLC¥H3E-MC-JMEN¥CSR¥PROGRAMS¥FQCTCAC.sas
Output Location : CABINETS¥SPREE¥RMP¥Clinical¥Oncology¥Alimta¥NSCLC¥H3E-MC-JMEN¥CSR¥OUTPUTS¥FQCTCAC1
Data Set Location : RMP.SAS.H3ES.L.MCJMEN.ADS.INTRM2

PRODUCTION DATA - PRODUCTION MODE 16APR2008 02:17
Summary of Adverse Events Possibly Related to Study Drug (Grade 3 or 4 only)
By CTCAE Term and Maximum Grade, On Study or Within 30 Days of Discontinuation
All Randomized Patients
H3E-MC-JMEN

| CTCAE Term | Pemetrexed (N = 441) n | (%) | Placebo (N = 222) n | (%) | p-Value |
|---|---|---|---|---|---|
| Fatigue (asthenia, lethargy, malaise) | 22 | (5.0) | 1 | (0.5) | 0.001 |
| Febrile neutropenia | 3 | (0.7) | 0 | (0.0) | 0.555 |
| Glomerular filtration rate | 3 | (0.7) | 0 | (0.0) | 0.555 |
| Hemorrhage, pulmonary/upper respiratory Nose | 1 | (0.2) | 0 | (0.0) | >.999 |
| Hot flashes/flushes | 1 | (0.2) | 0 | (0.0) | >.999 |
| Infection (clinical/microbio) - Gr 3/4 neutrophils-Pulmonary/Upper respiratory - Lung (pneumonia) | 2 | (0.5) | 0 | (0.0) | 0.554 |
| Infection (clinical/microbio) - Gr 3/4 neutrophils-Renal/Genitourinary - Urinary tract NOS | 1 | (0.2) | 0 | (0.0) | >.999 |
| Infection with normal ANC/Gr 1/2 neutrophils-Pulmonary/Upper respiratory - Lung (pneumonia) | 1 | (0.2) | 0 | (0.0) | >.999 |
| Mucositis/stomatitis (clinical exam) Anus | 1 | (0.2) | 0 | (0.0) | >.999 |
| Mucositis/stomatitis (clinical exam) Oral cavity | 2 | (0.5) | 0 | (0.0) | 0.554 |
| Nausea | 4 | (0.9) | 1 | (0.5) | 0.669 |
| Neuropathy: sensory | 3 | (0.7) | 0 | (0.0) | 0.555 |
| Pain Musculoskeletal - Bone | 1 | (0.2) | 0 | (0.0) | >.999 |
| Pain Musculoskeletal - Joint | 1 | (0.2) | 0 | (0.0) | >.999 |
| Pain Pulmonary/Upper Respiratory - Chest/thorax NOS | 1 | (0.2) | 0 | (0.0) | >.999 |
| Pneumonitis/pulmonary infiltrates | 1 | (0.2) | 0 | (0.0) | >.999 |
| Pruritus/itching | 3 | (0.7) | 0 | (0.0) | 0.555 |
| Rash; acne/acneiform | 1 | (0.2) | 0 | (0.0) | >.999 |
| Renal failure | 2 | (0.5) | 0 | (0.0) | 0.554 |

Abbreviations: CTCAE = common terminology criteria for adverse events; N = total number of randomized patients;
n = number of patients in each category.

Note: Patients may be counted in more than one category.

CTCAE Version 3.0

p-Values from Fisher's Exact Test.

Program Location : CABINETS¥SPREE¥RMP¥Clinical¥Oncology¥Alimta¥NSCLC¥H3E-MC-JMEN¥CSR¥PROGRAMS¥FQCTCAC.sas
Output Location : CABINETS¥SPREE¥RMP¥Clinical¥Oncology¥Alimta¥NSCLC¥H3E-MC-JMEN¥CSR¥OUTPUTS¥FQCTCAC1
Data Set Location : RMP.SAS.H3ES.L.MCJMEN.ADS.INTRM2

Summary of Adverse Events Possibly Related to Study Drug (Grade 3 or 4 only)
By CTCAE Term and Maximum Grade, On Study or Within 30 Days of Discontinuation
All Randomized Patients
H3E-MC-JMEN

| CTCAE Term | Pemetrexed (N = 441) n | (%) | Placebo (N = 222) n | (%) | p-Value |
|---|---|---|---|---|---|
| Renal/Genitourinary - Other | 1 | (0.2) | 0 | (0.0) | >.999 |
| Rigors/chills | 1 | (0.2) | 0 | (0.0) | >.999 |
| Thrombosis/embolism (vascular access-related) | 1 | (0.2) | 0 | (0.0) | >.999 |
| Vomiting | 1 | (0.2) | 0 | (0.0) | >.999 |

Abbreviations: CTCAE = common terminology criteria for adverse events; N = total number of randomized patients;
n = number of patients in each category.

Note: Patients may be counted in more than one category.

CTCAE Version 3.0

p-Values from Fisher's Exact Test.

Program Location : CABINETS¥SPREE¥RMP¥Clinical¥Oncology¥Alimta¥NSCLC¥H3E-MC-JMEN¥CSR¥PROGRAMS¥FQCTCAC.sas
Output Location : CABINETS¥SPREE¥RMP¥Clinical¥Oncology¥Alimta¥NSCLC¥H3E-MC-JMEN¥CSR¥OUTPUTS¥FQCTCAC1
Data Set Location : RMP.SAS.H3ES.L.MCJMEN.ADS.INTRM2

Summary of Grade 3 or 4 Drug-Related Episodes
All Randomized Nonsquamous Patients
H3E-MC-JMEN

| AECTC Term | Pemetrexed (N=325) Patients n(%) | Pemetrexed (N=325) Episodes | Placebo (N=156) Patients n(%) | Placebo (N=156) Episodes |
|---|---|---|---|---|
| **Laboratory Events** | | | | |
| GGT (g-Glutamyl transpeptidase) | | | 1 ( 0.6) | 1 |
| Hemoglobin | 8 ( 2.5) | 9 | | |
| Leukocytes (total WBC) | 4 ( 1.2) | 5 | 1 ( 0.6) | 1 |
| Neutrophils/granulocytes (ANC/AGC) | 9 ( 2.8) | 14 | | |
| Platelets | 6 ( 1.8) | 6 | 1 ( 0.6) | 1 |
| **Non-Laboratory Events** | | | | |
| Anorexia | 3 ( 0.9) | 3 | | |
| Constipation | 1 ( 0.3) | 1 | 1 ( 0.6) | 1 |
| Cough | 1 ( 0.3) | 1 | | |
| Cystitis | 1 ( 0.3) | 1 | | |
| Dermatology/Skin - Other | 2 ( 0.6) | 2 | | |
| Diarrhea | 1 ( 0.3) | 1 | | |
| Distention/bloating,abdominal | 1 ( 0.3) | 1 | 1 ( 0.6) | 1 |
| Fatigue (asthenia, lethargy, malaise) | 12 ( 3.7) | 12 | 1 ( 0.6) | 1 |
| Febrile neutropenia | 3 ( 0.9) | 3 | | |
| Glomerular filtration rate | 2 ( 0.6) | 2 | | |
| Hemorrhage, pulmonary/upper respiratory Nose | 1 ( 0.3) | 1 | | |
| Hot flashes/flushes | 1 ( 0.3) | 1 | | |
| Infection (clinical/microbio) - Gr 3/4 neutrophils-Pulmonary/Upper respiratory - Lung (pneumonia) | 1 ( 0.3) | 1 | | |
| Infection (clinical/microbio) - Gr 3/4 neutrophils-Renal/Genitourinary - Urinary tract NOS | 1 ( 0.3) | 1 | | |
| Infection with normal ANC/Gr 1/2 neutrophils-Pulmonary/Upper respiratory - Lung (pneumonia) | 1 ( 0.3) | 1 | | |

Program Location : Home/lillyce/prd/ly231514/h3e_mc_jmen/intrm2/programs_stat/nsqgr34rel_epi.sas
Output Location : Home/lillyce/prd/ly231514/h3e_mc_jmen/intrm2/programs_stat/tfl_output/nsqgr34rel_epi.rtf
Data Set Location : Home/lillyce/prd/ly231514/h3e_mc_jmen/intrm2/data/shared/legacy_ads

Summary of Grade 3 or 4 Drug-Related Episodes
All Randomized Nonsquamous Patients
H3E-MC-JMEN

| AECTC Term | Pemetrexed (N=325) Patients n(%) | Pemetrexed (N=325) Episodes | Placebo (N=156) Patients n(%) | Placebo (N=156) Episodes |
|---|---|---|---|---|
| Mucositis/stomatitis (clinical exam) Anus | 1 ( 0.3) | 1 | | |
| Mucositis/stomatitis (clinical exam) Oral cavity | 2 ( 0.6) | 2 | | |
| Nausea | 2 ( 0.6) | 2 | 1 ( 0.6) | 1 |
| Neuropathy: sensory | 3 ( 0.9) | 3 | | |
| Pain Musculoskeletal - Bone | 1 ( 0.3) | 1 | | |
| Pain Musculoskeletal - Joint | 1 ( 0.3) | 1 | | |
| Pain Pulmonary/Upper Respiratory - Chest/thorax NOS | 1 ( 0.3) | 1 | | |
| Pneumonitis/pulmonary infiltrates | 1 ( 0.3) | 1 | | |
| Pruritus/itching | 2 ( 0.6) | 2 | | |
| Rash; acne/acneiform | 1 ( 0.3) | 1 | | |
| Renal failure | 1 ( 0.3) | 1 | | |
| Renal/Genitourinary - Other | 1 ( 0.3) | 2 | | |
| Rigors/chills | 1 ( 0.3) | 1 | | |
| Thrombosis/embolism (vascular access-related) | 1 ( 0.3) | 1 | | |
| Vomiting | 1 ( 0.3) | 1 | | |

Program Location : Home/lillyce/prd/ly231514/h3e_mc_jmen/intrm2/programs_stat/nsqgr34rel_epi.sas
Output Location : Home/lillyce/prd/ly231514/h3e_mc_jmen/intrm2/programs_stat/tfl_output/nsqgr34rel_epi.rtf
Data Set Location : Home/lillyce/prd/ly231514/h3e_mc_jmen/intrm2/data/shared/legacy_ads