in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ERRATUM TO

Naloxegol for treating opioid-induced constipation

Erratum by the ERG in response to revised table 45

Erratum (09/02/2015)

The original version of this ERG report was completed and submitted on 21 January 2015.

The ERG received the company's proforma for comments of factual errors on the ERG report on 02 February 2015. In issue 9 (Clarification of KODIAC data used in MTC/indirect comparisons), the company stated that "the The ERG correctly identifies an inconsistency between the data provided and the data used in the MTC analysis and indirect comparisons". Therefore, the company provided a revised table 45 with the correct data. This leads to the following changes in the ERG report:

- a revised first paragraph of section 1.7 of the ERG report,
- a revised paragraph in section 4.3 of the ERG report,
- a revised paragraph in section 4.4 of the ERG report,
- a revised paragraph in section 4.5 of the ERG report.

In preparation of the pre-meeting briefing on 10 February 2015, the ERG prepared table A1 comparing results for naloxegol and placebo from table 45 of the original company's submission (ITT population) with the results presented in the revised table 45 (LIR population). This shows more favourable results for naloxegol in the LIR subpopulation compared with the ITT population.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG was able to replicate and check the results of the indirect and MTC analyses. Results of the ERG were consistent with the results reported in the CS. However, the MTC compares the LIR population for naloxegol with the general population for the comparators. Effectiveness of naloxegol vs. placebo is more favourable in the LIR population than in the ITT population. Therefore, the results of naloxegol in the MTC are overestimated.

(…)

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

(...)

ERG Comment (similarity of population): The population of each included trial was outlined in Tables 43 and 47 of the CS. Overall the studies were similar; the studies were of non-malignant pain largely due to back pain. It would have been advantageous to further analyse population on the basis of baseline characteristics (for pain intensity, opioid dose, duration of opioid use, duration of OIC, previous laxative use). The ERG checked the study reports for this data but no characteristics were consistently reported between trials to make this useful. Further scrutiny of the trials indicated that Meissner et al[43] reported results from cancer pain in approximately 3% of patients. It is unclear why this trial has been included since malignant pain was used as an exclusion criterion for feasible studies. The percentage of patients is probably low enough for this to not be a concern to the overall results. In KODIAC 4 and 5 the population

of patients is clearly stated as '*data for the LIR and LIR+3 step opioid subgroup is [sic!] included in the MTC' (Table 43).* In the revised table 45, the company presents data for the LIR population in the naloxegol trials and the data for the ITT population in the comparator trials. Therefore, the populations in the MTC are not similar which leads to an unfair comparison.

(…)

4.4 Critique of the indirect comparison and/or multiple treatment comparison

(…)

ERG Comment (indirect and MTC analyses): The ERG was able to replicate and check the results of the indirect and MTC analyses. Results of the ERG were consistent with the results reported in the CS. However, the MTC compares the LIR population for naloxegol with the general population for the comparators. Effectiveness of naloxegol vs. placebo is more favourable in the LIR population than in the ITT population. Therefore, the results of naloxegol in the MTC are overestimated.

(…)

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG replicated and checked the results of the indirect and MTC analyses. Results of the ERG were consistent with the results reported in the CS. However, the MTC compares the LIR population for naloxegol with the general population for the comparators. Effectiveness of naloxegol vs. placebo is more favourable in the LIR population than in the ITT population. Therefore, the results of naloxegol in the MTC are overestimated.

Table A1: Summary of results from studies used to conduct the comparisons

(Modified from table 45 to compare ITT population with LIR population in naloxegol)

Outcome	Naloxegol (ITT population, from table 45 of the CS)		Naloxegol (LIR population, from revised table 45)	
	KODIAC 4	**KODIAC 5**	**KODIAC 4**	**KODIAC 5**
Mean change from baseline in SBMs/week (4–12 weeks) *Higher values favourable*	Naloxegol 12.5 mg, OD, n=213: 2.5 Naloxegol 25 mg OD, n=214: 3.3 Placebo, n=214: 1.8	Naloxegol 12.5 mg, OD, n=232: 2.5 Naloxegol 25 mg OD, n=232: 3.2 Placebo, n=232: 1.8	Naloxegol 12.5 mg, OD, n=114: 2.6 Naloxegol 25 mg OD, n=117: 3.5 Placebo, n=118: 2.0	Naloxegol 12.5 mg, OD, n=122: 2.7 Naloxegol 25 mg OD, n=121: 3.6 Placebo, n=120: 2.2
SBM response† over 4 weeks (%) *Higher values favourable*	Naloxegol 12.5 mg, OD, n=213: 39.44% Naloxegol 25 mg OD, n=214,: 43.46% Placebo, n=214: 26.64%	Naloxegol 12.5 mg, OD, n=232: 33.19% Naloxegol 25 mg OD, n=232: 33.62% Placebo, n=232: 25.43%	Naloxegol 12.5 mg, OD, n=114: 45.22% Naloxegol 25 mg OD, n=117,: 45.30% Placebo, n=118: 27.97%	Naloxegol 12.5 mg, OD, n=122: 37.60% Naloxegol 25 mg OD, n=121: 34.68% Placebo, n=120: 24.79%
CSBM response‡ at 4 weeks (%) *Higher values favourable*	Naloxegol 12.5 mg, OD, n=213: 26.1% Naloxegol 25 mg OD, n=214,: 32% Placebo, n=214: 21.3%	Naloxegol 12.5 mg, OD, n=232: 27.7% Naloxegol 25 mg OD, n=232: 25.1% Placebo, n=232: 19.7%	Naloxegol 25 mg OD, n=117,: 35.04% Placebo, n=118: 22.03%	Naloxegol 25 mg OD, n=121: 41.32% Placebo, n=120: 18.33%
DAEs, 4-12 weeks (%) *Lower values favourable*	Naloxegol 12.5 mg, OD, n=211: 4.3% Naloxegol 25 mg OD, n=214,: 10.3% Placebo, n=213: 4.7%	Naloxegol 12.5 mg, OD, n=230: 4.8% Naloxegol 25 mg OD, n=232: 10.3% Placebo, n=231: 4.8%	Naloxegol 12.5 mg, OD, n=114: 4.4% Naloxegol 25 mg OD, n=117,: 9.4% Placebo, n=118: 4.2%	Naloxegol 12.5 mg, OD, n=123: 2.4% Naloxegol 25 mg OD, n=124: 10.5% Placebo, n=120: 5.8%
TEAEs, 4 weeks (%) *Lower values favourable*	Naloxegol 25 mg, OD, n=204: 48% Placebo, n=195: 35%	Naloxegol 25 mg, OD, n=213: 58% Placebo, n=203: 36%	Naloxegol 12.5 mg, OD, n=114: 30.7% Naloxegol 25 mg, OD, n=117: 47% Placebo, n=118: 32.2%	Naloxegol 12.5 mg, OD, n=123: 40.7% Naloxegol 25 mg, OD, n=124: 54% Placebo, n=120: 36.7%

Abbreviations: BD, twice daily; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; FRC, fixed ratio combination; MNTX, methylnaltrexone; OD, once daily; PR, prolonged release; QAD, every other day; SBM, spontaneous bowel movement;

† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period. ‡ Defined as the proportion of patients with ≥3 CSBMs/week at four weeks