**Reviewer’s report**

**Title:** Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions.

**Version:** 1  **Date:** 24 November 2009

**Reviewer:** Martine Hoogendoorn

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**Major revisions:**

1. One of the major assumptions made: “that the relative treatment effect is independent from the baseline risk” is questionable. A recent subgroup analysis of the UPLIFT trial showed that the RR for tiotropium to reduce exacerbations seems to be highest in patients with moderate COPD according to the GOLD classification and less established in very severe COPD. Although I recognize that this information is only recently available this is a major issue for the validity of the study.

2. In addition to point one, there is no information on the disease severity of the tiotropium users in the database. In the trials only patients with at least moderate COPD are included. Table 2 shows that the cost-effectiveness ratio is strongly depended on the baseline exacerbation risk for hospitalization. If in the database also patients with mild COPD, thus patients with a low baseline risk, are included, the average baseline exacerbation risk for the total group is low. As a result the absolute gain due to treatment is low.

3. The treatment effect was based on one clinical trial, the uplift trial, which was designed and powered to detect a difference in lung function decline and not in exacerbations. As a result, exacerbations leading to hospitalisations did not differ between treatment groups, because they were very infrequent. The Cochrane review on tiotropium of Barr et al, 2005 showed more favourable results for tiotropium. In this review the RR for exacerbations was 0.74 (0.66-0.83) and for hospitalizations 0.64 (0.51-0.83), while in the uplift trial this was 0.86 (0.81-0.91) and 0.94 (0.82-1.07), respectively. The authors did not mention this review or performed a sensitivity analysis with the RR’s of the review.

4. Physicians should choose whether they treat their patients with either a LABA or tiotropium. In the database this does not seem to be done and tiotropium was given in addition to a LABA. The additional effect of tiotropium was therefore small, but this would also have been the case if LABA was given in addition to tiotropium. The right comparison would be tiotropium + usual care versus LABA + usual care, but this question can not be answered with this real life data.

5. The incremental cost-effectiveness ratio (ICER) is not calculated right. The mean incremental cost is 373 euro per patient, while the mean incremental benefit is 0.00048 QALYs. This results in an ICER of (373/0.00048) = 777083 euro/QALY. An ICER is defined as the difference in mean costs between to
treatment options divided by the difference in mean effect and not as the authors probably did, the mean ICER of the 1000 estimates of the difference in cost divided by the effect.

6. Several other studies assessed the cost-effectiveness of tiotropium and all found relatively low ICERS and thus a favourable cost-effectiveness. Results of these trials are not at all mentioned in the discussion. Outcomes of the current trial need to placed in the context of all available information and possible explanations for the differences in outcomes need to give.

Minor revisions:
1. Does tiotropium only affects quality of life by avoiding exacerbations or does it also influence quality of life during the stable phase?
2. The duration of a COPD exacerbation resulting in hospitalizations and therefore the impact on quality of life was too short, 14 days. The impact of a severe exacerbations studied by Seemungal et al was over 30 days.
3. The calculation of the QALYs for a moderate exacerbation was unclear. What is the duration of a moderate exacerbation used? Did I understand it right that the reduction in quality of life was on average 4 times lower than for an exacerbation resulting in hospitalization?
4. The annual rate for moderate exacerbations is strongly dependant on the figure of 23% for prescriptions of both antibiotics and steroids used. This percentage comes from a Dutch study, but prescription behaviour may differ between practices and especially between countries. If this percentage is for example 20%, the exacerbation rate is 0.92 instead of 0.8.
5. Two scenarios are specified, one with tiotropium used additional and one with tiotropium used instead of other LABA. In the result sections it needs to be specified better which results are for which scenario. Scenario 1 and scenario II?

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

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