Cost Effectiveness of Roflumilast (Daxas®) for the maintenance treatment of severe Chronic Obstructive Pulmonary Disease associated with chronic bronchitis in patients with a history of frequent exacerbations

National Centre for Pharmacoeconomics

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Summary

1. In June 2010, Nycomed GmbH submitted an evaluation on the cost-effectiveness of Roflumilast (Daxas®) to the National Centre for Pharmacoeconomics (NCPE). Roflumilast is licensed for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. A revised submission was received on 6th September 2010 following initial discussions. The evaluation was conducted from the perspective of the Health Service Executive.

2. The submission included three treatment options, considered to represent the potential place of roflumilast in the context of its licensed indication and current best practice guidelines:

    1) Roflumilast+ long-acting beta-agonist (LABA) vs LABA
    2) Roflumilast+ LABA+inhaled corticosteroid (ICS) vs LABA+ICS
    3) Roflumilast+LABA vs ICS+LABA

3. The NCPE Review Group had concerns in relation to the clinical effectiveness data used to populate the cost-effectiveness models, as such data was derived from unpublished, subgroup analyses of placebo-controlled trials in which the use of standard treatments (LABA, ICS or both) were restricted.

4. Roflumilast is licensed as an add-on therapy, however there is no direct or indirect evidence to support its use in addition to current standard of care LABA+ICS (comparison 2). The cost-effectiveness model for this comparison incorporates clinical effectiveness data in which heavy use of short-acting beta-agonist (SABA) is taken as a substitute for LABA. Interpretation of the benefits and risks of roflumilast in clinical practice is problematic based on these results.

5. The economic benefits of Roflumilast are modelled by incorporating reduction of exacerbations that require medical intervention and improvement in lung function that delays progression to more severe disease states. The improvement in lung function as shown by differences in post-bronchodilator

FEV_1 increase was modest. Although no significant reduction in severe exacerbation rates was shown in the pivotal roflumilast studies, a relative risk reduction is nonetheless applied to all exacerbations in the cost-effectiveness model, including both moderate and severe exacerbations.

6. The efficacy of roflumilast in reducing exacerbation rates is applied for the lifetime of patients in the model. Pivotal trials provide data for 52 weeks of treatment. The assumption of continuing unabated benefit in reducing exacerbation rate is questionable, given the nature of COPD as a chronic, progressive disease. The uncertainty in this assumption has not been tested in the model.

7. Roflumilast studies failed to show any clinically significant improvement in health-related quality of life, or any reduction in mortality rates. In the model, lower utility values are attached to more severe COPD states and quality adjusted life years (QALYs) are lost in the form of utility decrements associated with COPD exacerbations.

8. The incremental cost-effectiveness ratio for roflumilast under the GMS scheme in the base case is €6,897, €1,541, and €12,350 per QALY for comparisons 1, 2 and 3 respectively. The review group considered roflumilast in addition to ICS+LABA the most likely place of roflumilast in clinical practice (comparison 2). This recognises safety concerns about the use of LABA alone, together with guidelines recommending ICS+LABA in the patient group in question.

9. Scenario analyses, one-way and probabilistic sensitivity analyses were conducted for each of the three comparisons. The key driver of cost per QALY is the relative risk (RR) of exacerbations when treated with Roflumilast. Review group concerns associated with the RR estimates include the application of this benefit for the lifetime of patients in the model, the lack of a significant reduction in severe exacerbations in the pivotal studies, and the lack of any direct or indirect data in which roflumilast+LABA+ICS is compared with LABA+ICS.
10. At a cost-effectiveness threshold of €20,000 per QALY, probabilistic sensitivity analysis indicated the probability of roflumilast in addition to bronchodilator treatment being cost-effective to be 95%, 100% and 60% for

comparisons 1, 2 and 3 respectively. Although the cost-effectiveness ratio provided for comparison 2 is low, considerable uncertainty surrounds the clinical-effectiveness of roflumilast as maintenance therapy for COPD. This uncertainty is not captured in the probabilistic sensitivity analysis.

11. Gross expenditure on roflumilast in year 1 was estimated in a Budget Impact Analysis at €99,228, rising to €3,421,490 in year 5. Although its use will be as an add-on-therapy, Nycomed predict that roflumilast will replace a certain proportion of other COPD therapies resulting in cost offsets which reduce incremental expenditure to €2,432,794 in year 5. Further reductions in healthcare costs are suggested if the reduction in exacerbations rates included in the cost-effectiveness model is realised in practice.

12. Further studies in line with European Medicines Agency recommendations are required to establish the efficacy of roflumilast in addition to LABA+ICS, or as an alternative to ICS in this group of patients. Based on currently available data we do not consider the efficacy data to be sufficiently robust to recommend roflumilast as a cost-effective addition to bronchodilator therapy within its licensed indication.