HAUTE AUTORITÉ DE SANTÉ

PULMONOLOGY
New medicinal product
March 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

BRIMICA GENUAIR and DUAKLIR GENUAIR

(aclidinium/formoterol), adrenergic / anticholinergic

Insufficient clinical benefit in chronic obstructive pulmonary disease

Main points

- BRETARIS GENUAIR and DUAKLIR GENUAIR have marketing authorisation as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
- The efficacy data do not show clinical benefit provided by the aclidinium/formoterol combination versus each component as a monotherapy.
- They have no impact on the long-term decline in pulmonary function.

Therapeutic use

- The first measure to take with COPD is to reduce risk factors, in particular tobacco use. Reconditioning and chest physiotherapy help to improve the symptoms and quality of life.
- Medicinal treatment of stable COPD seeks to reduce clinical symptoms and reduce the frequency and severity of complications related to exacerbations.
  Short-acting inhaled bronchodilators (beta-2 agonists or anticholinergics) taken on demand are first-line symptomatic treatments.
  Long-acting inhaled bronchodilators, beta-2 agonists (formoterol, salmeterol, indacaterol) and anticholinergics (tiotropium, glycopyrronium), are recommended when dyspnea persists despite the use of a short-acting bronchodilator several times a day.
  The fixed combination of a long-acting (LA) beta-2 agonist (indacaterol) and an LA anticholinergic (glycopyrronium) must be restricted to patients with moderate to very severe COPD whose symptoms are already controlled by the free indacaterol and glycopyrronium combination.
  Inhaled corticosteroids can only be used together with a long-acting bronchodilator in patients with severe COPD defined by an FEV1 of < 50% of the theoretical value and repeated exacerbations. They do not reduce overall mortality and increase the risk of lower respiratory infections, in particular pneumonia, for which severity of the disease, age and comorbidities already increase the risk.
  Systemic corticosteroids are not recommended.
  The use of long-acting theophylline is limited due to a narrow therapeutic margin.
- Oxygen therapy is reserved for patients with daytime hypoxemia ($PaO_2 \leq 55$mmHg).
- **Role of the medicinal product in the therapeutic strategy**
  BRIMICA GENUAIR and DUAKLIR GENUAIR do not have a role in the therapeutic strategy for COPD.

Clinical data

- Two randomised studies evaluated the efficacy of BRIMICA GENUAIR/DUAKLIR GENUAIR versus aclidinium, formoterol and a placebo, over a 24-week period, in adults with moderate to severe COPD (post-bronchodilator FEV between 30 and 80% of predicted value, FEV/FVC <70%). Each study enrolled and randomised around 1,700 patients. In the pooled population of both studies, FEV1 before bronchodilator administration was 1.368 L, or 47.7% of the predicted value, values consistent with those of a population with moderate to severe COPD.
- The results on the co-primary endpoints (FEV1 at 1 hour post-dose and pre-dose morning FEV) at 24 weeks showed a statistically significant and clinically relevant difference versus placebo. The change in FEV1 post-dose was significantly greater and clinically relevant with BRIMICA GENUAIR/DUAKLIR GENUAIR relative to the

aclidinium 400 µg alone group (mean adjusted difference pooled population: 0.118 L, p<0.0001), reflecting the efficacy of formoterol. The change from pre-dose FEV1 was significantly higher in the BRIMICA GENUAIR/DUAKLIR GENUAIR group compared to the formoterol 12 µg monotherapy group, but not clinically relevant (mean adjusted difference in each of the studies: +0.085 L, p<0.0001 and: +0.045 L p=0.010; pooled population: +0.068 L; p<0.0001, clinical relevance threshold ≥0.100 L). This study shows that aclidinium does not provide additional clinically-relevant efficacy with formoterol on the primary endpoint of pre-dose FEV.

- The most commonly-reported adverse events on BRIMICA GENUAIR/DUAKLIR GENUAIR versus placebo were exacerbations of COPD (17.1%), nasopharyngitis (6.3%) and headaches (6.8%). The proportion of patients who had a severe COPD exacerbation (requiring hospitalisation) was 4.0% in the BRIMICA GENUAIR/DUAKLIR GENUAIR group and 4.6% in the placebo group. The most commonly-reported serious AE was exacerbation of COPD (2.1% in the BRIMICA GENUAIR/DUAKLIR GENUAIR group, 2.7% in the placebo group). In a study versus formoterol, the most commonly-reported AEs that appeared during treatment (≥ 5%) were urinary infections (6.6% of patients of the BRIMICA GENUAIR/DUAKLIR GENUAIR group and 5.6% of patients of the formoterol group), sinusitis (5.1% of patients of the BRIMICA GENUAIR/DUAKLIR GENUAIR group versus 5.6% of patients of the formoterol group) and nasopharyngitis (6.4% of patients of the BRIMICA GENUAIR/DUAKLIR GENUAIR group versus 4.5% of patients of the formoterol group).

Benefit of the medicinal product

- The actual benefit* of BRIMICA GENUAIR and DUAKLIR GENUAIR is insufficient to justify reimbursement by National Health Insurance.
- Does not recommend inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 16 March 2016 (CT-14614 and CT-14796) available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".