HAUTE AUTORITÉ DE SANTÉ

RESPIRATORY MEDICINE
Update
November 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ULTIBRO BREEZHALER (indacaterol, glycopyrronium) long-acting bronchodilator

Moderate clinical benefit in continuous bronchodilator treatment of chronic obstructive pulmonary disease

Main points

- ULTIBRO BREEZHALER has Marketing Authorisation in continuous bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
- The results of new data have led to the conclusion that this fixed combination of two long-acting bronchodilators has a moderate clinical benefit in this indication (and no longer substantial) in a population restricted to patients with moderate to very severe COPD whose symptoms are already controlled by the combination of indacaterol and glycopyrronium separately administered.
- ULTIBRO BREEZHALER is more specifically for patients with moderate to very severe COPD who have associated persistent dyspnoea despite use of a long-acting bronchodilator in monotherapy.

Therapeutic use

- Any diagnosis of COPD, based on lung function tests, leads to recommendations of smoking cessation, vaccinations, physical activity, pulmonary rehabilitation in case of limitation of activities and short-acting bronchodilators. The symptoms (dyspnoea, exacerbations) determine the therapeutic choices.
  In case of daily dyspnoea and/or exacerbations, a long-acting beta-2 agonist (LABA) or muscarinic antagonist (LAMA) bronchodilator is recommended.
  A clinical and functional reassessment is proposed 1 to 3 months after the change, then every 3 to 12 months depending on the severity of the COPD. If the dyspnoea persists, a dual bronchodilation (LABA + LAMA) improves respiratory function (FEV1), quality of life and dyspnoea and reduces exacerbations without increasing adverse effects.
  In case of frequent exacerbations despite optimal bronchodilator treatment, a combination of LABA + inhaled corticosteroids (ICS) is proposed, respecting the FEV1 thresholds of the Marketing Authorisation, or in case of associated dyspnoea (mMRC ≥ 2), a LABA + LAMA combination is particularly suitable.
  Triple therapy (LABA + LAMA + ICS) is indicated if exacerbations persist despite one of these options. The persistence of dyspnoea despite a dual bronchodilation or of exacerbations despite a triple therapy leads to the discussion of other treatments (theophylline if dyspnoea, macrolides if exacerbations, low-dose opioids if refractory dyspnoea).
- **Role of the proprietary medicinal product in the therapeutic strategy**
  ULTIBRO BREEZHALER is a second-line medicinal product in patients with moderate to very severe stage COPD who have associated persistent dyspnoea in the event of insufficient response to a long-acting bronchodilator used as a monotherapy.
  Continuation of treatment with a combination of LABA + LAMA bronchodilators is not recommended in case of lack of benefit for the patient.

Clinical data

- The results of studies in patients with moderate to severe COPD evaluating the indacaterol/glycopyrronium (IND/GLY) combination compared with long-acting bronchodilators in monotherapy (glycopyrronium, tiotropium) or in free combination (indacaterol + glycopyrronium and tiotropium + formoterol) have already been analysed (see the Transparency Committee Opinion on 7 May 2014). These studies demonstrated the superiority of the IND/GLY combination compared to monotherapies in terms of pre-dose FEV1 and frequency of exacerbations all severities combined (but not on severe exacerbations); however, the improvements observed were of low magnitude, of little or no clinical relevance. Moreover, the non-inferiority of the fixed-dose IND/GLY combination compared with the free combination of its substances was demonstrated in terms of the pre-dose FEV1, and compared with the free combination tiotropium + formoterol in terms of quality of life.
- A new randomised, double-blind, non-inferiority study compared the fixed-dose IND/GLY combination at 1 administration/day to the fixed-dose fluticasone/salmeterol (FC/SAL) combination 500/50 µg at 2 administrations/day in 3362 patients with a moderate to severe COPD with an FEV1 ≥ 25% and < 60% of the theoretical value and a history of at least 1 moderate to severe exacerbation the year prior to inclusion.
  The annual frequency of exacerbations of all severities combined was lower with the IND/GLY combination than with the FC/SAL combination after 52 weeks of treatment: 3.59 exacerbations/year in the IND/GLY group versus 4.03 in the FC/SAL group, $p < 0.001$. No significant difference was observed between the groups on the annual frequency of severe exacerbations.
  The time to occurrence of first exacerbation was longer with the IND/GLY combination than with the FC/SAL combination for moderate to severe exacerbations ($p < 0.001$) and severe exacerbations (19% extension, $p = 0.046$).
  In this study, the most common adverse events were upper respiratory tract infections (outside of adverse events noted as exacerbation of COPD), which is consistent with the known safety profile for this product. In a safety study versus tiotropium and versus placebo, the IND/GLY combination was non-inferior to each of its comparators in terms of serious adverse events after 52 weeks of treatment (primary endpoint). On a composite endpoint including all deaths and all cardiovascular and cerebrovascular serious adverse events, the score obtained in the IND/GLY group was higher than that obtained in the placebo group, but it was not different from that obtained in the tiotropium group.
  Pharmacovigilance data detected new safety signals, dysphonia and angioedema in connection with a hypersensitivity to glycopyrronium.

Benefit of the medicinal product

- The actual benefit* of ULTIBRO BREEZHALER is moderate.
- Recommends 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 22 November 2017 (CT-16132) and is 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.