HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
10 MARCH 2021
The legally binding text is the original French opinion version

Indacaterol acetate / glycopyrronium bromide/ mometasone furoate
ENERZAIR BREEZHALER 114 µg / 46 µg / 136 µg, inhalation powder, hard capsules

Re-evaluation

Key points

Favourable opinion for reimbursement in the maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The main objective of pharmacological treatment of asthma in adults and adolescents is to ensure durable maintenance of asthma control, including the reduction of symptoms, the prevention of asthma attacks and exacerbations, the reduction of the impact of the condition on everyday activities, at the same time limiting adverse reactions related to pharmacological treatments.

Treatment is primarily based on two types of medicinal products that aim to act, firstly, on the bronchospasm and, secondly, on the underlying inflammation. Traditionally, a distinction is made between:
- reliever therapy for attacks: inhaled short-acting beta2-agonist (SABA) bronchodilators. These treatments were initially used alone; however, a strategy combining an inhaled long-acting beta2-agonist (LABA) but with a short action onset (formoterol) with an inhaled corticosteroid is now also recommended;
- maintenance therapy: inhaled corticosteroids (ICS) as monotherapy or in combination with a long-acting beta2-agonist (LABA) bronchodilator. Other medicinal products have a limited role, either due to their modest effect size (leukotriene receptor antagonists (montelukast), or their narrow therapeutic window (prolonged-release theophylline). The most severe forms of asthma may require biologic therapy (depending on the disease phenotype) and/or oral corticosteroid therapy.

This therapeutic dichotomy is currently in the process of disappearing, insofar as it has been demonstrated that reliever therapy using a combination of formoterol (LABA) and an inhaled corticosteroid leads to a reduction in severe exacerbations.
The therapeutic management is adapted to the severity of the disease. International consensus has identified 5 severity steps with treatment escalation in the event of non-control or partial control of asthma. The treatment adjustment strategy is defined by the GINA (Global Strategy for Asthma Management and Prevention).

Severe asthma corresponds to steps 4 and 5:
- step 4: asthma requiring the use of maintenance therapy combining a moderate-dose ICS and LABA (preferential maintenance therapy);
- step 5: uncontrolled step 4 asthma requiring recourse to maintenance therapy with a high-dose ICS and LABA, with a LAMA (tiotropium) or a biologic therapy as add-on therapy if necessary, depending on the asthma phenotype.

In all cases the reliever therapy to be favoured in the event of an attack is formoterol/low-dose inhaled corticosteroid.
Before reaching a conclusion of uncontrolled asthma implying a potential treatment escalation, it is necessary to eliminate a differential diagnosis, to assess compliance with treatment and to correct the inhalation technique if necessary, to identify and treat any exacerbating factors (smoking, allergens in the home, occupational environment, etc.) and concomitant diseases or conditions.

Patients who are inadequately controlled with high-dose ICS/LABA combination therapy at GINA step 5 have the following treatment options, in addition to optimising compliance with treatment and modifying risk factors:
- increase in ICS dose;
- addition of a LAMA;
- oral corticosteroid therapy;
- addition of a biologic therapy depending on the phenotype.

At step 5, it is important to be able to adjust the ICS doses based on the patient's needs.
In this case, different strengths of the CSI/LABA combinations are used.

Role of the medicinal product in the care pathway
ENERZAIR BREEZHALER is a triple fixed combination of:
- an inhaled corticosteroid (ICS): mometasone furoate,
- a long-acting beta2-agonist (LABA): indacaterol acetate,
- a long-acting muscarinic receptor antagonist (LAMA): glycopyrronium bromide.

This medicinal product is a therapeutic alternative in adults with severe asthma, at step 5 according to the GINA classification, not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.
The Committee points out that ENERZAIR BREEZHALER contains **a high fixed dose** of corticosteroid (160 µg), which has several consequences:
- **ENERZAIR BREEZHALER does not enable the patient's treatment to be adjusted in order to find the minimum effective ICS dose.** If a reduction in the ICS dose is to be envisaged, a free combination of ICS/LABA/LAMA must be used.
- to treat symptoms in patients taking this medicinal product, it will only be possible to use a short-acting beta2-agonist, which is not the preferential option in step 5. As a reminder, the preferential

option for the treatment of patients in step 5 is based on the “SMART” (Single Maintenance And Reliever Therapy) strategy, which enables maintenance therapy and symptomatic treatment using the same combination (low-dose ICS + formoterol), the efficacy of which has been demonstrated on exacerbations.

Special recommendations

The provisions of article L. 162-17 of the French Social Security Code concerning the retail formulary list of reimbursed medicinal products and the provisions of article L. 5123-2 of the French Public Health code concerning the hospital formulary list of medicinal products approved for use indicate that the Committee may, in view of quality and safety of care requirements relative to the medicinal product that it is assessing, issue recommendations that may, in particular, concern the qualification or expertise of prescribers.

In application of these provisions, the proper use of a medicinal product in patients at an advanced stage of the disease, whose management is difficult, may require special supervision of the prescription of the medicinal product.

The Committee points out that the patients eligible for ENERZAIR BREEZHALER have severe asthma (step 5), which is not adequately controlled, with highly incapacitating, permanent respiratory symptoms sometimes requiring emergency care. Firstly, the repeated occurrence of exacerbations can be life-threatening. Secondly, the persistence of bronchial obstruction (FEV1/FVC < 70%) can cause airway remodelling and lead to a progressive deterioration in respiratory function. Reducing the number of exacerbations is therefore a major objective in both the short and long term in order to preserve respiratory function as far as possible.

In addition, these patients require optimised management implying:
- confirmation of the diagnosis of severe asthma and elimination of a differential diagnosis via an exhaustive exploration;
- assessment of compliance with treatment, which is one of the pillars of asthma control and, in particular, control of exacerbations; compliance with long-term asthma control therapy is low in real-world conditions (less than 60%);
- verification and correction of the inhalation technique if it is not correct, adequate patient education being an essential component of management;
- identification and treatment of aggravating factors (smoking, allergens or toxins in the home, occupational environment, etc.) and concomitant diseases/conditions;
- and adaptation of the choice of medicinal product in a context in which ENERZAIR BREEZHALER presents specificities, notably due to its high fixed corticosteroid dose (see care pathway).

Finally, the management of these severe patients sometimes requires the use of systemic corticosteroids for a significant period of time, and it is necessary to regularly and accurately assess their benefit in view of the adverse effects of these long-term treatments, at the same time seeking the minimum effective dose.

Considering these elements, the Committee recommends that the initial prescription of ENERZAIR BREEZHALER be made in consultation with a respiratory medicine specialist.

COMMITTEE'S CONCLUSIONS

Clinical benefit

- Asthma leads to disability and a marked deterioration in quality of life and may be life-threatening.
- ENERZAIR BREEZHALER is a symptomatic treatment for asthma.
- Considering:
  - efficacy results having demonstrated the superiority of ENERZAIR BREEZHALER on FEV1 at 26 weeks, with a modest effect size compared to the comparator, ATECTURA BREEZHALER (indacaterol/mometasone), indicated in patients not adequately controlled by an ICS and a SABA, i.e. at a treatment step below that of ENERZAIR BREEZHALER, but the absence of demonstrated superiority on asthma control,
  - the demonstrated non-inferiority compared to the salmeterol/fluticasone + tiotropium free triple combination, in terms of variation in AQLQ quality of life score after 24 weeks of treatment, although these results are of limited relevance since the study was an open-label one,
  - the absence of robust data on the reduction of exacerbations,
  - and in view of its known safety profile,

  the efficacy/adverse effects ratio is moderate.
- The therapeutic alternatives are free and fixed combinations of high-dose ICS/LABA + LAMA used as a free triple combination.
- ENERZAIR BREEZHALER is a fixed combination of an inhaled corticosteroid (ICS), mometasone furoate, a long-acting beta2-agonist (LABA), indacaterol acetate, and a long-acting muscarinic antagonist (LAMA), glycopyrronium bromide. This medicinal product is a therapeutic alternative in adults with severe asthma, at step 5 according to the GINA classification, not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.
- **Public health impact:**

  Considering:
  - the seriousness of severe asthma and its prevalence,
  - the medical need partially met by other ICS/LABA + LAMA combinations,
  - the lack of response to the identified need:
    - the absence of any expected additional impact on morbidity and mortality and/or the quality of life of patients (in view of the methodological limitations of the superiority study versus a non-relevant comparator and the non-inferiority demonstrated versus the free triple combination on quality of life in an open-label study),
    - the absence of an additional impact on the organisation of care,

  ENERZAIR BREEZHALER is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ENERZAIR BREEZHALER is moderate in the MA indication.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

Recommended reimbursement rate: 30%

Clinical Added Value

Considering:

- **demonstration of the superiority of the indacaterol/glycopyrronium/mometasone (150/50/160 µg) fixed triple combination, in comparison with high-dose ICS/LABA (mometasone/indacaterol) dual therapy on lung function assessed by residual FEV1 after 26 weeks, but taking into account:**
  - **the choice of a comparator of little relevance in the study, approved for less advanced stages than those targeted by this triple therapy,**
  - **the low clinical relevance of the effect size on FEV1 after 26 weeks (observed difference of +65 mL), and the absence of a significant difference on asthma control (assessed on ACQ-7 after 26 weeks) compared to indacaterol/mometasone (150/320 µg) dual therapy,**
  - **the absence of robust demonstration of efficacy on exacerbations, this endpoint having been assessed for exploratory purposes (unranked secondary endpoint) in the superiority study;**
- **the demonstration of non-inferiority compared to the free triple combination of salmeterol/fluticasone (50 / 500 µg), twice daily, + tiotropium (5 µg), once daily, in terms of variation in AQLQ quality of life score after 24 weeks of treatment, in an open-label study, which limits relevance;**
- **the medical need partially met by existing alternatives;**

the Transparency Committee considers that ENERZAIR BREEZHALER provides no clinical added value (CAV V) in the maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.