HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

10 MARCH 2021

The legally binding text is the original French opinion version

formoterol/glycopyrronium/budesonide

TRIXEO AEROSPHERE 5 µg/7.2 µg/160 µg, pressurised inhalation, suspension

First assessment

Key points

Favourable opinion for reimbursement as maintenance treatment in adult patients with severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.

Unfavourable opinion for reimbursement as maintenance treatment in moderate COPD.

What therapeutic improvement?

No clinical added value in the management of severe COPD.

◗ Role in the care pathway?

The Committee reiterates:
- **the importance of supporting patients in the overall management of their COPD, including smoking cessation, physical activity and therapeutic education,**
- **that compliance with treatment, the inhaler technique, comorbidities and the evolution of respiratory function should be systematically assessed before any adjustment of treatment;**
- **that in the event of insufficient efficacy or adverse effects, a decrease of treatment, in particular discontinuation of inhaled corticosteroids, should be considered.**

The therapeutic strategy, recommended by the SPLF since 2016, is as follows:

In all patients, as soon as COPD has been diagnosed by a pulmonary function test (FEV_1/CV <0.70), physical activity is recommended, as well as smoking cessation aid;

When symptoms (dyspnoea) are episodic and not very intense, pharmacological treatment is limited to short-acting inhaled bronchodilators on demand;

In the case of daily dyspnoea and/or exacerbations, the first-line treatment is long-acting beta2-agonist (LABA) or long-acting muscarinic antagonist (LAMA) bronchodilator monotherapy.

If symptoms persist, despite well managed treatment, dual therapy may be proposed after having:
- eliminated any other cause of treatment lack of efficacy (differential or associated diagnosis, poor compliance, incorrect inhaler technique),
- verified the implementation of help to quit smoking,
- performed a respiratory function assessment.

This dual therapy is based on a combination of two long-acting bronchodilators (LABA + LAMA) for patients whose primary symptom is dyspnoea, or exacerbations associated with dyspnoea (mMRC ≥2). For patients with exacerbations, but with no associated significant dyspnoea, the combination of an inhaled corticosteroid (ICS) with a LABA may be considered.

Triple therapy (LABA + LAMA + ICS) is indicated if exacerbations persist despite dual therapy. In addition, recent international guidelines mention that a modulation of efficacy according to blood eosinophil count should be considered.

In all cases, a clinical and functional assessment is offered 1 to 3 months after changing the treatment, then every 3 to 12 months, depending on the severity of the COPD.

Role of the medicinal product in the care pathway

TRIXEO AEROSPHERE is a triple fixed-dose combination containing a LABA, a LAMA and a high-dose ICS, respectively formoterol, glycopyrronium and budesonide.

Considering the available data, in particular having demonstrated a modest efficacy on the reduction of exacerbations compared to LABA/ICS or LABA/LAMA dual therapy, and the characteristics of this medicinal product containing a high-dose ICS preventing any adjustment, TRIXEO AEROSPHERE represents a therapeutic alternative for patients with severe COPD, who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA, and who continue to have persistent exacerbations.

In addition, in view of the accumulation of exploratory data on the efficacy of triple fixed-dose combinations evaluated by eosinophil count, including for this combination, and in accordance with the recent GOLD 2021 and ERS 2020 guidelines, the prescription of TRIXEO AEROSPHERE should be preferred for patients with an eosinophil count ≥ 150 cells/µL, considering that the addition of ICS treatment would have little or no effect for patients with an eosinophil count < 150 cells/µL.

Finally, it should be noted that only the TRIXEO AEROSPHERE triple fixed-dose combination containing a high-dose ICS has been granted an MA, despite the development of a triple fixed-dose combination containing a moderate-dose ICS. In view of the data provided, which does not demonstrate any difference of efficacy between the moderate and high doses, the Committee regrets that this triple fixed-dose combination including a moderate-dose ICS is not available in order to enable the adjustment of treatment by looking for the minimum effective dose of inhaled corticosteroid.

Reassessment of treatment will make it possible to consider discontinuation of TRIXEO AEROSPHERE in the event of inadequate efficacy or adverse effects.

In view of the data, the available alternatives and the characteristics of this medicinal product, TRIXEO AEROSPHERE has no role in the management of moderate COPD.

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 the requirements of quality and safety of care 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 for patients at an advanced stage of the disease, whose management is difficult, may require a special supervision of the prescription of the medicinal product.

For the advanced stage of the disease, the Committee reiterates that patients eligible for treatment with TRIXEO AEROSPHERE have:
- severe COPD, with persistent exacerbations,
- despite dual therapy with ICS+LABA or LABA+LAMA, for which the prescription has been optimised based on the recommended indications and dosage,
- and taking into account the complementary non-pharmacological approach (smoking cessation, physical activity, differential diagnosis).

Furthermore, recent guidelines favour the addition of an ICS in the context of a triple combination, such as TRIXEO AEROSPHERE, for patients with an eosinophil count ≥ 150 cells/µL.
At this advanced stage, the repeated occurrence of exacerbations can be life-threatening. Reducing the number of exacerbations is therefore a major objective in both the short and long term.

The Committee's recommendations concerning the proper use of this medicinal product are made in a context of known misuse of triple free combinations, and of dual fixed-dose inhaled combinations containing corticosteroids, at stages in which monotherapy or dual therapy with long-acting bronchodilators would be more appropriate. Firstly, there is no need to prescribe a triple combination when monotherapy is adequate and relevant and, secondly, the guidelines recommend the combination of a LABA/LAMA or an ICS/LABA combination depending on the dyspnoeic or exacerbating profile of patients requiring dual therapy.
The Committee highlights the fact that the prescription of TRIXEO AEROSPHERE at this stage of the disease involves a clinical and functional respiratory assessment in order to target the recommended patient population (definite diagnosis) in view of the study data available. In addition, this prescription should take into account the fact that this medicinal product provides a high dose of ICS from the outset and does not allow dose adjustment.

Consequently, the Transparency Committee recommends that initial prescription of TRIXEO AEROSPHERE should be reserved for pulmonology specialists only.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ COPD leads to disability and a marked deterioration in quality of life and may be life-threatening.

◗ TRIXEO AEROSPHERE is a symptomatic medicinal product.

◗ TRIXEO AEROSPHERE combines two long-acting bronchodilators - formoterol (LABA) and glycopyrronium (LAMA) - as well as an inhaled corticosteroid, budesonide (ICS), recommended in combination in the management of severe COPD.
This triple fixed-dose combination has demonstrated its superiority, primarily for patients with severe COPD, compared to a LAMA and LABA combination and an ICS and LABA combination, on the occurrence of exacerbations, which is the most relevant clinical endpoint; the effect size concerning the improvement in respiratory function (FEV_1 evolution) is modest, and the improvement related to quality of life is below the minimal clinical important difference.
The difference observed for exacerbations was also modest. Hence, in view of the safety profile of this medicinal product, the efficacy/adverse effects ratio is moderate in severe COPD.
It is poorly established in moderate COPD, in the absence of guidelines for this product at this stage of the disease.

◗ The therapeutic alternatives represented by the ICS, LABA and LAMA used in triple fixed-dose or free combinations are numerous.

◗ Considering the available data, in particular having demonstrated a modest efficacy on the reduction of exacerbations compared to LABA/ICS or LABA/LAMA dual therapy, and the characteristics of this medicinal product containing a high-dose ICS preventing any adjustment, TRIXEO AEROSPHERE represents a therapeutic alternative for patients with severe COPD, who are not adequately treated by an ICS and LABA combination or a LABA and LAMA combination, and who continue to have persistent exacerbations.
In addition, in view of the accumulation of exploratory data on the efficacy of triple fixed-dose combinations evaluated by eosinophil count (including this combination), and in accordance with the recent GOLD 2021 and ERS 2020 guidelines, the prescription of TRIXEO AEROSPHERE should be preferred for patients with an eosinophil count ≥ 150 cells/µL, considering that the addition of an ICS treatment would have little or no effect for patients with an eosinophil count < 150 cells/µL.
In view of the data, the available alternatives and the characteristics of this medicinal product, TRIXEO AEROSPHERE has no role in the management of moderate COPD.

◗ <u>Public health impact:</u>
Considering:
- the seriousness of the disease
- its high prevalence
- the medical need partially met by the inhaled corticosteroids and bronchodilators currently available,
- the lack of additional response provided by TRIXEO AEROSPHERE to the identified need in the absence of any expected additional impact on morbidity and mortality and/or the patients quality of life, and the absence of any expected impact on the organisation of care,

TRIXEO AEROSPHERE is unlikely to have an additional impact on public health.

Considering these elements, the Committee deems that the clinical benefit of TRIXEO AEROSPHERE is moderate as maintenance treatment for patients with severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.

The clinical benefit of TRIXEO AEROSPHERE is insufficient to justify its public funding cover in the treatment of moderate COPD, in view of the available alternatives.

The Committee issues a favourable opinion for inclusion of TRIXEO AEROSPHERE in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use as maintenance treatment in adult patients with severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.

The Committee issues an unfavourable opinion for inclusion of TRIXEO AEROSPHERE in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication "maintenance treatment of moderate chronic obstructive pulmonary disease (COPD)".

- **Recommended reimbursement rate: 30%**

Clinical Added Value

Considering:

- **demonstration of the superiority of the triple fixed-dose formoterol/glycopyrronium/high-dose budesonide combination compared to LAMA/LABA (formoterol/glycopyrronium) or high-dose ICS/LABA (budesonide/ glycopyrronium) dual therapy, on the rate of moderate to severe exacerbations at 52 weeks (primary endpoint), and on quality of life and FEV_1 at 24 weeks (ranked secondary endpoints), although with differences that are modest or of small clinical relevance,**
- **the absence of a robust comparison with a triple fixed-dose or free combination,**
- **the medical need partially met by existing alternatives,**

the Committee considers that TRIXEO AEROSPHERE provides no clinical added value (CAV V) as maintenance treatment in adult patients with severe COPD who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA.