HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 February 2008

ATIMOS 12 micrograms/actuation, solution for inhalation in pressurised container
Pressurised container providing 100 actuations (CIP: 369 512-6)

Applicant: CHIESI SA

formoterol fumarate dihydrate

ATC code : R03AC13

List I

Marketing authorisation (MA) date: 26 August 2005
MA Variation: 1 October 2007 (Extension of indication to COPD)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication "**relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease**".

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

formoterol fumarate dihydrate

1.2. Indication

- "For the long-term symptomatic treatment of persistent, moderate to severe asthma in patients requiring regular bronchodilator therapy in combination with long-term anti-inflammatory therapy (inhaled and/or oral glucocorticoids).

  Glucocorticoid therapy should be continued on a regular basis."
- **"Relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease."**

1.3. Dosage

The dosage depends on the severity of the disease.

Asthma:
Adults (including the elderly) and adolescents aged 12 years and above:
Usual dose: one actuation morning and evening (24 micrograms of formoterol fumarate dihydrate per day). In severe cases, up to a maximum of two actuations in the morning and two in the evening (48 micrograms of formoterol fumarate dihydrate per day). The maximum daily dose is four actuations (48 micrograms of formoterol fumarate dihydrate).

Chronic obstructive pulmonary disease:
Adults (aged 18 years and above):
The usual dose is 1 actuation twice daily (one in the morning and one in the evening, *i.e.* 24 micrograms of formoterol fumarate per day). The daily dose for regular use should not exceed two inhalations. If required, additional inhalations above those prescribed for regular therapy may be used for relief of symptoms, up to a maximum total daily dose of four inhalations (regular plus required). More than two inhalations should not be taken on any single occasion.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

R	:	Respiratory system
R03	:	Drugs for obstructive airway diseases
R03A	:	Adrenergics agents for inhalation
R03AC	:	Selective beta-2 adrenoreceptor agonists
R03AC13	:	Formoterol

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines

Long-acting beta-2 agonist bronchodilators for inhalation with the following indications:
- long-term symptomatic treatment of asthma;
- long-term symptomatic treatment of COPD.

formoterol: FORADIL 12 µg
OXIS TURBUHALER 12 µg per actuation (not marketed)
salmeterol : SEREVENT 25 µg per actuation
SEREVENT DISKUS 50 µg per actuation, powder for inhalation
SISEROL 25 µg per actuation (not marketed)
SISEROL DISKUS 50 µg per actuation (not marketed)

Within the scope of obstructive lung diseases other than asthma, the wording of the indication for FORADIL does not fully overlap that for the other proprietary products: “regular relief of symptoms in patients with asthma and other reversible obstructive lung diseases”.

2.2.2. Not strictly comparable medicinal products

Long-acting bronchodilators in combination with a corticosteroid:

formoterol + budesonide: SYMBICORT TURBUHALER 200 and 400 µg per actuation
salmeterol + fluticasone: SERETIDE DISKUS 500/50 µg per actuation

Within the scope of the indication in COPD:

- the indication for SYMBICORT TURBUHALER 200 and 400 µg per actuation in COPD is restricted to the symptomatic treatment of severe COPD (FEV_1 < 50% predicted normal value) in patients having a history of repeated exacerbations and significant symptoms despite regular therapy with a long-acting bronchodilator.
- The indication for SERETIDE DISKUS 500/50 µg/actuation in COPD is restricted to symptomatic treatment of patients whose FEV_1 (measured before bronchodilator use) is lower than 60% of predicted normal value and who have a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy.

2.3. Medicines with a similar therapeutic aim

These are proprietary medicines containing short-acting bronchodilators (beta-2 agonists and anticholinergics alone or in combination), non-inhaled proprietary products containing long-acting beta-2 agonists, and products containing methylxanthines (theophyllines).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

In a 12-week, randomised, double-blind study in 457 stable COPD patients (40% ≤ pre-bronchodilator FEV_1 ≤ 70% of predicted normal value and ≥ 900 ml and FEV_1 reversibility ≤ 12 %), formoterol pressurised inhalation solution (ATIMOS) was non-inferior to formoterol dry powder inhaler (FORADIL) on FEV_1 measured 12 hours post dose (AUC).

3.2. Adverse events

The tolerance profile of ATIMOS was similar to that of FORADIL. No specific mention of patients treated for COPD was made in the “adverse events” section of the SPC.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

COPD causes disability, a marked deterioration in quality of life and may be life-threatening.

This proprietary medicine may be used for regular symptomatic treatment of COPD and has no impact on the long-term decline in lung function.

Public health benefit:

In terms of public health, COPD represents a major burden. The subpopulation of patients who may benefit from treatment with ATIMOS represents a considerable burden.

Improved management of COPD is a public health need within the scope of identified priorities (GTNDO[1] priorities). However, the therapeutic need for symptomatic management of COPD is covered by existing symptomatic treatments.

In light of the clinical trial data and given the alternatives available, this proprietary product is not expected to have an impact in terms of morbidity and mortality or quality of life.

Consequently ATIMOS is not expected to benefit public health.

The efficacy/adverse effects ratio is moderate.

This proprietary medicine provides first-line therapy for patients in constant respiratory discomfort despite the use of short-acting bronchodilators several times daily.
Regular symptomatic treatment with formoterol should only be continued if symptoms improve. There are no guidelines for the use of formoterol to treat acute symptoms.

There are alternative drugs available.

The actual benefit of ATIMOS 12 micrograms/actuation, pressurised solution for inhalation is substantial.

4.2. Improvement in actual benefit

ATIMOS 12 micrograms/actuation, pressurised solution for inhalation provides no improvement in actual benefit (IAB V) compared to the other long-acting bronchodilators available in this indication.

4.3. Therapeutic use

No drug is capable of preventing the long-term progression of COPD to chronic respiratory failure. Outside exacerbations, drug therapy aims to reduce symptoms and the incidence and severity of complications.

Bronchodilators, taken on demand or on a regular basis, provide the main symptomatic treatment for COPD. These are mainly beta-2 agonists and anticholinergics, available as inhaled formulations. Theophyllines may be used if the patient finds it hard to use inhaled bronchodilators or if the latter do not improve the dyspnoea sufficiently. However, their use is limited by the narrowness of their therapeutic window.

[1] National Technical Group for Definition of Public Health Goals (DGS-2003)

Inhaled short-acting bronchodilators (beta-2 agonists or anticholinergics) taken on demand are recommended as first-line treatment.

Long-acting (LA) bronchodilators are recommended when regular symptomatic treatment is necessary, i.e. when dyspnoea persists despite the use of a short-acting bronchodilator several times a day.

Two LA beta-2 agonists are available, formoterol and salmeterol. They have shown a benefit over placebo.

Tiotropium (a long-acting anticholinergic) showed a benefit over placebo and ipratropium (a short-acting anticholinergic) but, compared with LA beta-2 agonists, the observed differences were not clinically relevant.

These three drugs may be used for regular first-line symptomatic treatment of COPD.

Inhaled corticosteroids may only be used jointly with an LA bronchodilator. The formoterol /budesonide combination is indicated only in the symptomatic treatment of patients with severe COPD, i.e. those with FEV_1 < 50% of predicted normal value and repeated exacerbations despite regular bronchodilator treatment.

The salmeterol /fluticasone combination is indicated only for patients whose FEV_1 (measured before bronchodilator use) is less than 60% of predicted normal value) with a history of recurrent exacerbations and significant symptoms despite regular bronchodilator treatment.

Treatment with an LA bronchodilator or the combination of an LA bronchodilator and an inhaled corticosteroid is purely symptomatic. It should therefore only be continued if it is seen to reduce symptoms.

Systemic corticosteroids are not recommended.

Oxygen therapy is reserved for patients with diurnal hypoxaemia (PaO_2 < 55 mm Hg) some time after an acute episode and despite optimal treatment.

4.4. Target population

According to available French epidemiological data, approximately 3.5 million people have chronic bronchitis, with progression to COPD in one third of cases. Consequently the target population in this indication may be estimated to be approximately 1,150,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for this extension of indication.

4.5.1. Packaging : Appropriate to prescription requirements.

4.5.2. Reimbursement rate: 65%.