

# budesonide + formoterol

New dose regimen

## Asthma attacks: a step backwards

● **Using the budesonide + formoterol combination for both maintenance treatment of asthma and on-demand control of asthma attacks amounts to intensifying maintenance treatment. It is not a valid treatment objective, and is likely to confuse asthma patients.**



NOT ACCEPTABLE

Maintenance and on-demand treatment of asthma are based on the results of many clinical trials involving several hundred thousand patients (1-3). Maintenance treatment depends on asthma severity and is based on inhaled steroid monotherapy at the minimal effective dose. Adding an inhaled long-acting beta-2 agonist does not seem to provide a tangible clinical benefit for patients (1,2).

Treatment of asthma attacks is based on short-acting high-dose beta-2 agonists, which are rapidly effective and have few adverse effects (4,5).

The fixed-dose combination of budesonide and formoterol (Symbicort<sup>o</sup>, AstraZeneca) was first marketed for maintenance treatment of asthma. The SPC now also mentions, in the posology section, the possible use of this product to treat asthma attacks.

**A two-phase licence extension process.** The company first submitted, through the European mutual recognition procedure, an application including data from three trials. These trials compared budesonide + formoterol, for both maintenance and on-demand treatment, versus budesonide, alone or with formoterol, for maintenance treatment, and terbutaline for attacks (6-10). The application was rejected in 2004 (9). The company then submitted new data, and the new marketing terms were finally granted in late 2006 (10).

**Intensified maintenance treatment.** The new data are mainly based on two double-blind randomised trials including 3394 and 3335 patients (11,12). The first trial, in patients who were all receiving maintenance treatment with budesonide + formoterol, compared treatment of asthma attacks with budesonide + formoterol, or formoterol, or terbutaline (11). The second trial also included

three groups: two groups received maintenance treatment with budesonide + formoterol, and used budesonide + formoterol or terbutaline for asthma attacks; the third group received maintenance treatment with fluticasone + salmeterol and used terbutaline for attacks (12).

In these trials the patients used their "attack" treatments once or twice a day on average, which, in the groups only treated with budesonide + formoterol, represented an intensification of the maintenance treatment. It is therefore hardly surprising that patients in these groups showed more improvement in some criteria for asthma control (11,12).

### Increased risk of adverse effects.

There were no major differences in adverse effects between the different treatments tested in these trials (6-8,11,12). However, the use of the budesonide + formoterol combination for both maintenance and on-demand treatment leads to an increase in drug exposure, and a higher risk of adverse effects (a).

Long-acting beta-2 agonists accumulation may carry an added risk of cardiac disorders, tremor, hypokalaemia and hyperglycaemia (13).

Unless combined with an inhaled steroid, long-acting beta-2 agonists can increase the risk of hospitalisation and life-threatening asthma attacks. There are reports of asthma aggravation associated with the use of a long-acting beta-2 agonist (salmeterol), even when combined with a steroid (2,14).

In addition, the risk of adrenal failure increases with the dose of inhaled steroid (including budesonide) (15).

The budesonide + formoterol combination should not be recommended for 'on demand' use to control asthma attacks (b). It exposes patients to an added risk of adverse effects, and undermines the clear-cut message that has been found to help patients manage their asthma: the clear distinction between maintenance treatment, with an inhaled steroid at the minimal required dose, and control of attacks with a short-acting beta-2 agonist.

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a- A risk management plan has been launched (ref 16).  
b- The French Transparency Committee concluded that,

## budesonide + formoterol (Symbicort<sup>o</sup>)

Powder for inhalation

■ **New posology:** "Adults (18 years and older) (...): Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. (...) a total daily dose of up to 12 inhalations could be used for a limited period (...)"

[French marketing authorisation through the mutual recognition procedure after initial Swedish authorisation]

**Steroid + long-acting beta-2 agonist**

in this setting, Symbicort<sup>o</sup> did not represent an improvement over existing treatments (ref 17).

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