Translated from ***Rev Prescrire*** **December 2007; 27 (290): 901**

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.**

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°, 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.

a- A risk management plan has been launched (ref 16).

b- The French Transparency Committee concluded that, in this setting, Symbicort° did not represent an improvement over existing treatments (ref 17).

budesonide + formoterol
(Symbicort°)

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

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "Traitement de l'asthme - 1re partie" *Rev Prescrire* 2007; **27** (284): 436-441.
2- Prescrire Editorial Staff "Long-term asthma therapy" *Prescrire Int* 2007; **16** (91): 522-526.
3- British Thoracic Society and Scottish Intercollegiate Guidelines Network "British Guideline on the management of asthma. A national Clinical Guideline" Revised ed., November 2005: 94 pages.
4- Prescrire Editorial Staff "How to treat asthma attacks" *Prescrire Int* 1996; **5** (25): 154-158.
5- Prescrire Rédaction "Crise d'asthme grave à domicile" *Rev Prescrire* 2007; **27** (284): 441-444.
6- Rabe KF et al. "budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double blind trial" *Chest* 2006; **129**: 246-256.
7- Scicchitano R et al. "Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma" *Curr Med Res Opin* 2004; **20** (9): 1403-1418.
8- Byrne P "budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma" *Am J Respir Crit Care Med* 2005; **171**: 129-136.
9- "AstraZeneca hit by EU delay for Symbicort single inhaler therapy" *Scrip* 2004; (3002): 22.
10- "Symbicort Smart finally gets the nod in Europe" *Scrip* 2006; (3200): 19.
11- Rabe KF et al. "Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study" *Lancet* 2006; **368**: 744-753.
12- Kuna P et al. "Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations" *Int J Clin Pract* 2007; **61** (5): 725-736.
13- Prescrire Rédaction "18-1-2. Patients sous bêta-2 stimulant" *Rev Prescrire* 2007; **27** (290 suppl. interactions médicamenteuses).
14- Prescrire Editorial Staff "Asthma: fatal exacerbation with long-acting beta 2 agonist therapy without concomitant steroid therapy" *Prescrire Int* 2007; **16** (88): 69-70.
15- Prescrire Rédaction "Insuffisance surrénale aiguë: avec les corticoïdes inhalés aussi" *Rev Prescrire* 2007; **27** (289): 826.
16- AFSSAPS "PGR-Symbicort" July 2007: 2 pages.
17- HAS - Commission de la transparence "Avis-Symbicort" 4 July 2007: 14 pages.