#### 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 ondemand treatment of asthma are based on the results of many clinical trials involving sev-

eral 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.

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# 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

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

## Selected references from Prescrire's literature search.

- **1-** Prescrire Rédaction "Traitement de l'asthme l'e 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
- **5-** Prescrire Rédaction "Crise d'asthme grave 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
- **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)
- 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): 876
- scrire 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.

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