

Harmonised wording for single-constituent and fixed-dose combination long-acting beta₂ agonist products, agreed by PhVWP 29th May 2006

The following text is proposed for section 4.4 of the SPC for single-constituent salmeterol and formoterol products:

Although [product] may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on [product] during an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with [product]. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on [product].

The following additional wording is to be included in the SPC immediately before reference to the use of inhaled steroids with LABA:

[product] should not be used (and is not sufficient) as the first treatment for asthma.

The following additional wording is proposed, to be included in the SPC after reference to persistence of symptoms with a LABA:

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of [PRODUCT]. Regular review of patients as treatment is stepped down is important. The lowest effective dose of [PRODUCT] should be used.

For fixed-dose combination products containing formoterol or salmeterol with an inhaled steroid, some wording similar to the above agreed wording is already included in the SPCs. To avoid repetition or any confusion regarding steroid use, the following wording is suggested:

Patients should not be initiated on [product] during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with [product]. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on [product].

[To be inserted following existing wording regarding deterioration of control with the product]

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of [product]. Regular review of patients as treatment is stepped down is important. The lowest effective dose of [product] should be used (see section 4.2).

For Symbicort, the following is also agreed (this wording does not apply to Seretide, which has an indication for trial use in the initial management of asthma):

Symbicort should not be used as the first treatment for asthma.

A warning to review patients regularly as treatment is stepped down should also be added to the agreed Article 6 wording for trial use in the initial management of asthma, in section 4.2 of the SPC for Seretide:

Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

The following text is proposed for section 4.4 of the SPC for salmeterol-containing products:

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using [PRODUCT].

The following wording is proposed for inclusion of section 5.1 of the SPC for salmeterol-containing products, to give details of the outcomes from the SMART study:

Safety

The Salmeterol Multi-center Asthma Research Trial (SMART)

SMART was a multi-centre, randomised, double-blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50µg twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥12 years of age, with asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

| <u>Patient group</u> | <u>Number of primary endpoint events /number of patients</u> | | <u>Relative Risk (95% confidence intervals)</u> |
|--|--|------------------|---|
| | <u>salmeterol</u> | <u>placebo</u> | |
| <u>All patients</u> | 50/13,176 | 36/13,179 | 1.40 (0.91, 2.14) |
| <u>Patients using inhaled steroids</u> | 23/6,127 | 19/6,138 | 1.21 (0.66, 2.23) |
| <u>Patients not using inhaled steroids</u> | 27/7,049 | 17/7,041 | 1.60 (0.87, 2.93) |
| <u>African-American patients</u> | 20/2,366 | 5/2,319 | 4.10 (1.54, 10.90) |

(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

| | <u>Number of secondary endpoint events /number of patients</u> | | <u>Relative Risk (95% confidence intervals)</u> |
|---|--|----------------|---|
| | <u>salmeterol</u> | <u>placebo</u> | |
| Respiratory -related death | | | |
| <u>Patients using inhaled steroids</u> | 10/6127 | 5/6138 | 2.01 (0.69, 5.86) |
| <u>Patients not using inhaled steroids</u> | 14/7049 | 6/7041 | 2.28 (0.88, 5.94) |
| Combined asthma-related death or life-threatening experience | | | |
| <u>Patients using inhaled steroids</u> | 16/6127 | 13/6138 | 1.24 (0.60, 2.58) |
| <u>Patients not using inhaled steroids</u> | 21/7049 | 9/7041 | 2.39 (1.10, 5.22) |
| Asthma-related death | | | |
| <u>Patients using inhaled steroids</u> | 4/6127 | 3/6138 | 1.35 (0.30, 6.04) |
| <u>Patients not using inhaled steroids</u> | 9/7049 | 0/7041 | * |

(* = could not be calculated because of no events in placebo group. Bold figures are statistically significant at the 95% level. The secondary

endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all-cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

To reflect these SPC changes in the Patient Information Leaflet (PIL) for salmeterol- and formoterol-containing products, we suggest inclusion of the following:

If you are using [PRODUCT] for asthma, your doctor will want to regularly check your symptoms. If you feel you are getting breathless or wheezy while using [PRODUCT], you should continue to use [PRODUCT] but go to see your doctor as soon as possible, as you may need additional treatment.

PIL wording should also be revised and strengthened where necessary to inform patients clearly that LABA should not be used without inhaled steroids when used for the treatment of asthma.