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Številka: 1382-2/2011
Datum : 2.2.2011

VSEM IMETNIKOM DOVOLJENJ ZA PROMET Z ZDRAVILI, KI SPADAJO V SKUPINO DOLGO DELUJOČIH BETA AGONISTOV

Zahteva za predložitev spremembe tipa IB – dopolnitev povzetka glavnih značilnosti zdravila in navodila za uporabo za zdravila, ki spadajo v skupino dolgo delujočih beta agonistov

Spoštovani,

V oktobru 2010 je delovna skupina za farmakovigilanco (PhVWP) pregledala in ocenila podatke o povečanem tveganju za poslabšanje simptomov astme pri uporabi zdravil iz skupine dolgo delujočih beta agonistov. Na osnovi ocene podatkov je zaključila, da je treba informacije v povzetku glavnih značilnosti zdravila in v navodilih za uporabo zadevnih zdravil ustrezno dopolniti.

Imetnike dovoljenj za promet z zadevnimi zdravili, ki še niso predložili vloge za spremembo prosimo, da Javni agenciji RS za zdravila in medicinske pripomočke v skladu s Pravilnikom o dovoljenju za promet z zdravilom za uporabo v humani medicini (Uradni list RS, št. 59/2006) in obvestilom JAZMP glede nove Uredbe Komisije (ES) št.1234/2008 z dne 24.11.2008 o pregledu sprememb pogojev dovoljenj za promet z zdravili za uporabo v humani medicini in zdravili za uporabo v veterinarski medicini predložijo spremembo tipa IB najkasneje v 30 dneh od objave obvestila. Dodatne informacije in podporna dokumentacija v vlogi niso potrebne.
Rok za implementacijo spremembe je 31. marec 2011. Zdravila, izdelana po 1. avgustu 2011, morajo biti opremljena z novim navodilom za uporabo.

V nadaljevanju vam podajamo odobreno originalno besedilo spremembe, objavljeno je tudi na spletni strani Vodij agencij za zdravila http://www.hma.eu/222.html.

S spoštovanjem,

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Specific wording which should be included in the SmPC

1) Single-constituent salmeterol and formoterol products

- The following text was agreed by PhVWP for inclusion in section 4.4 of the SmPC 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 should be included in the SmPC 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 SmPC 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."

2) Fixed-dose combination products containing formoterol or salmeterol with an inhaled steroid

- For these products, 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 was agreed:

  "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)."

- A warning to review patients regularly as treatment is stepped down should also be

included 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."

For Symbicort:

- The following was 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."

3) Salmeterol-containing products

- The following text was agreed for section 4.4:

"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 was agreed for inclusion of section 5.1, 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

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

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

Specific wording which should be included in the PIL

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 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.
Once you asthma is well controlled your doctor may consider it appropriate to gradually reduce the dose of [PRODUCT]"