דצמבר 2019

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

פרסום עדכון בעלוני התכשיר :
Symbicort Turbuhaler 80/4.5 micrograms/dose

הרכב:

Each delivered dose (the dose that leaves the mouthpiece) contains: budesonide 80 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.

התוויה:

Symbicort Turbuhaler is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists.

Note: Symbicort Turbuhaler (80/4.5 micrograms/inhalation) is not appropriate in patients with severe asthma.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **נובמבר 2019.**

העדכונים העיקריים בעלון לרופא הם:

4.4 Special warnings and precautions for use

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchospasm Symbicort ~~Turbuhaler~~ should ~~then~~ be discontinued~~; treatment~~ immediately, the patient should be ~~re-~~ assessed and an alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway (see section 4.8).

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma~~.~~, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see section 4.8).

The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. ~~Patients who have required high dose emergency corticosteroid therapy in the past or prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may also be at risk. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.~~ Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic

corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia.

Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.

During transfer from oral therapy to Symbicort Turbuhaler, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR), which have been reported after use of systemic and topical corticosteroids.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

~~The metabolic conversion of budesonide is impeded by substances metabolized by CYP P450 3A4 (e.g. itraconazole, ritonavir). The concomitant administration of these~~ Potent inhibitors of ~~CYP P450 3A4 may~~CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide~~. The~~ and concomitant use ~~of these drugs~~ should be avoided ~~unless~~. If this is not possible the ~~benefit outweighs~~ time interval between administration of the ~~increased risk of systemic side-effects.~~inhibitor and budesonide should be as long as possible (section 4.4). In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increase in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

4.6 Fertility, pregnancy and lactation

Fertility

There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure (see section 5.3).

4.8 Undesirable effects

Endocrine disorders	Very rare	~~Signs or symptoms of systemic glucocorticosteroid effects eg~~ Cushing's syndrome. adrenal suppression, growth retardation, decrease in bone mineral density,
Psychiatric disorders	Uncommon	~~Agitation, restlessness, nervousness, sleep disturbances~~Aggression, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural ~~disturbances (mainly~~changes (predominantly in~~ children)~~
Eye disorders	Uncommon	Vision blurred (see also section 4.4)
Cardiac disorders	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each maintenance dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid. If oropharyngeal thrush occurs, patients should also rinse their mouth out with water after the as-needed inhalations.

As with other inhalation therapy, paradoxical bronchospasm may occur ~~in very rare cases (see section 4.4 Special warnings and precautions for use).~~ very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Symbicort should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section 4.4).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. ~~These may include~~These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's Syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma ~~(see section 4.4 Special warning and precautions for use).~~. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,
קארין קנבל דובסון

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