הודעה על החמרה (מידע בטיחות)

תאריך: 02-01-2012

שם תכשיר באנגלית:

Budicort® Respules® 0.5 mg/2ml, nebuliser suspension.
Budicort® Respules® 1 mg/2ml, nebuliser suspension.

מספר רישום:

בודיקורט רספיולרס 0.5 מ"ג /2 מ"ל : 113132957500
בודיקורט רספיולרס 1.0 מ"ג /2 מ"ל : 113142957600

שם בעל הרישום: אסטרהזניקה ישראל בע"מ
השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
4.2 Posology and method of administration		*Patients dependent on oral steroids:* When transfer from oral steroids is initiated the patient must be in a relatively stable condition. A high dose of Budicort is given in combination with the previously used oral steroid dose for 10 days. After that, the oral dose should be gradually reduced by e.g. 2.5 mg prednisolone or equivalent per month to the lowest possible level. The oral steroid can often be discontinued entirely. Since budesonide given as Budicort suspension for nebuliser is deposited in the lungs with the aid of inspiration, it is important that the patient inhales calmly and with even breaths through the mouthpiece of the nebuliser. There is no experience of treatment of patients with impaired hepatic or renal function. Since budesonide is eliminated predominantly through metabolism in the liver, increased exposure may be expected in patients with severe cirrhosis of the liver.

A face-mask can be used for children who cannot breathe in through the mouthpiece.

Budicort nebuliser suspension is inhaled with the aid of a jet nebuliser fitted with a mouthpiece or suitable face-mask.

Ultrasonic nebulisers must not be used, as they deliver too low a dose of budesonide to the patient.
The nebuliser and compressor (propeller unit) must be adjusted so that the majority of the delivered drops of liquid are in the range of 3 to 5 micrometres.
An *in-vitro* study has shown that nebulisers of the types Pari Inhalierboy, Pari Master and Aiolos deliver comparable doses of budesonide.

The amount of budesonide delivered to a patient varies between 11 and 22 % of the amount administered in the nebuliser, and depends on factors such as
- nebulisation time
- volume fill
- technical performance of the compressor (propeller unit) and the nebuliser
- patient's tidal volume
- use of face-mask or mouthpiece.

The air-flow rate through the nebuliser is also important. In order to obtain the maximum available dose of budesonide a flow rate of 5-8 l/min is required. The fill volume should be 2-4 ml.
The available dose for small children is maximised by the use of a closely fitting face- mask.

The single-dose unit must be shaken carefully before being opened.

The nebuliser chamber must be cleaned after every administration. Wash the chamber and mouthpiece or face-mask with warm tap water and use a mild detergent.
Rinse thoroughly and dry the

chamber by connecting it to the compressor or air inlet. See also the nebuliser manufacturer's instructions.		
Concomitant treatment with ketoconazole, itrakonazole or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the interval between administrations of the medications should be as long as possible (see 4.5).	Special care is needed in patients with pulmonary tuberculosis and viral infections of the airways.	**4.4 Special warnings and special precautions for use**
Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.	Non steroid-dependent patients: A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2 weeks) additional oral corticosteroid regimen can be given initially. After the course of the oral drug, Budicort Respules alone should be sufficient therapy. Steroid-dependent patients: When transfer from oral corticosteroid to treatment with Budicort is initiated, the patient should be in a relatively stable phase. Budicort is then given, in combination with the previously used oral steroid dose, for about 10 days.	
During transfer from oral steroid therapy to Budicort, patients may experience previous symptoms such as muscle and joint pain. In these cases a temporary increase of the oral steroid dose may be necessary. If, in isolated cases, fatigue, headache, nausea, vomiting or similar symptoms occur, a generally inadequate steroid effect should be suspected.	After that, the oral steroid dose should be gradually reduced (by, for example, 2.5 mg prednisolone or the equivalent each month), to the lowest possible level. In many cases, it is possible to completely substitute Budicort for the oral corticosteroid.	
Replacement of systemic steroid treatment by Pulmicort sometimes reveals allergies, e.g. rhinitis and eczema that were previously controlled by the systemic treatment.	During transfer from oral therapy to Budicort, a generally lower systemic corticosteroid action will be experienced, which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain, despite maintenance or even improvement in pulmonary function. Specific treatment should be initiated for these conditions.	
Regular monitoring of growth is recommended in children and adolescents receiving long-term treatment with corticosteroids, irrespective of the administration form. The benefits of corticosteroid		

treatment must be placed in relation to possible risks of inhibition of growth. Patients must be instructed to contact their physician if the effect of the treatment generally diminishes, as repeated inhalations for severe asthma attacks must not delay the initiation of other important therapy. In the event of acute deterioration the treatment should be supplemented with a course of oral steroid for a short period.	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.		
Decreased liver function may affect the ability to eliminate budesonide.			
Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. 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~~.~~ and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important therefore that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.	It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids be regularly monitored. If growth is slowed, therapy should be reviewed, with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist. Reduced liver function may affect the elimination of glucocorticosteroids. The plasma clearance following an intravenous dose of budesonide however was similar in cirrhotic patients and in healthy subjects. After oral ingestion systemic availability of budesonide was increased by compromised liver function due to decreased first pass metabolism. The clinical relevance of this to treatment with Budicort is unknown as no		

	data exist for inhaled budesonide, but increases in plasma levels and hence an increased risk of systemic adverse effects could be expected. The nebuliser chamber should be cleaned after every administration. Wash the nebuliser chamber and mouthpiece or face-mask in hot water using a mild detergent. Rinse well and dry, by connecting the nebuliser chamber to the compressor or air inlet.	
No clinically relevant interactions with asthma agents are known. Ketoconazole 200 mg once daily increased the plasma concentrations of oral budesonide (3 mg in a single dose) on average six-fold when administered simultaneously. When ketoconazole was administered 12 hours after budesonide the concentration increased on average three-fold. Information on this interaction is lacking for inhaled budesonide, but greatly increased plasma levels are expected there too. Since there is an absence of data to permit dosage recommendations, the combination should be avoided. If this is not possible, the interval between administration of ketoconazole and budesonide should be as long as possible. A reduction of the budesonide dose must also be considered. Other potent inhibitors of CYP3A4, i.e. itrakonazole also cause a marked increase in the plasma levels of budesonide. At recommended doses, cimetidine has slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.	The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide, (see Section 4.4 Special Warnings and Special Precautions for Use and Section 5.2 Pharmacokinetic Properties). Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide.	**4.5 Interactions with other medicinal products and other forms of interaction**
Data on approximately 2000 exposed pregnancies have not revealed any increased risk of malformations a result of treatment with budesonide.Animal studies have shown that, glucocorticosteroidscan induce malformations (see Section 5.3), but this is judged not to be	Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled in Animal studies glucocorticosteroids have been shown to induce malformations (see Section 5.3),	**4.6 Pregnancy and lactation**

relevant for humans with the recommended dosage. Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range. Lactation Budesonide is excreted in breast milk. However, at therapeutic doses of Budicort Nebulizer suspension no effects on the suckling child are anticipated. Budicort pMDI can be used during breast-feeding.	This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. The administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risk for the foetus. Inhaled glucocorticosteroids should be considered in preference to oral glucocorticosteroids because of the lower systemic effects at the doses required to achieve similar pulmonary responses. Budesonide is excreted in breast milk. However, at therapeutic doses of Budicort Respules no effects on the suckling child are anticipated. Budicort Respules can be used during breast feeding.	
Up to 10 % of treated patients may be expected to experience side effects of a local nature. Common (> 1/100) Airways: Candida infection in the oropharynx, mild irritation in the throat, coughing, hoarseness Rare (< 1/1000) General:Angioedema, anaphylactic reaction skin: Urticaria, rash, dermatitis, skin bruising airways: Bronchospasm and anaphylactic reaction Psychiatric disorders Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children). Nervousness, restlessness In rare cases signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of the adrenal gland and reduction of growth velocity, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous steroid exposure, and individual		**4.8 Undesirable effects**

sensitivity. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Facial skin irritation has been reported in some cases when a face mask ~~has been~~ was used. ~~.~~ In order to prevent this, the face should be washed when a face-mask is used. Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for ~~long~~ periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Acute overdose with Budicort suspension for nebuliser, even high doses, is not expected to cause any clinical problems. If it is used chronically in high doses, systemic effects of glucocorticosteroids such as hypercortisolism and adrenal suppression may occur. Budesonide has anti-inflammatory effects shown as reduced bronchial obstruction during both the early and the late phase of an allergic reaction. Budesonide reduces histamine and methacholine activity in the airways in hyperreactive patients. Studies have shown that the earlier the treatment with budesonide is initiated after the onset of asthma, the better is the lung function that can be expected. Studies in healthy volunteers with Budicort Turbuhaler have shown dose-related effects on plasma and urinary cortisol. At recommended doses, Budicort Turbuhaler, causes significantly less effect on the adrenal function than prednisone 10 mg, as shown by ACTH tests.	Budicort Respules contains 0.1 mg/ml disodium edetate which has been shown to cause bronchoconstriction at levels above 1.2 mg/ml. Acute overdose with Budicort should not present a clinical problem.	**4.9 Overdose**

In children over the age of 3 years, no systemic effects have been detected with doses up to 400 micrograms per day. In the range 400-800 micrograms per day biochemical signs of a systemic effect may occur. With daily doses in excess of 800 micrograms such signs are common. This information applies to Budicort administered as inhalation spray and inhalation powder. The asthma itself, like inhaled corticosteroids, can retard growth. Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment ~~(see section 4.4)~~. Inhalation therapy with budesonide is effective in preventing effort-induced asthma. <u>*ABSORPTION*</u> Inhaled budesonide is rapidly absorbed. The peak plasma concentration is reached within 60 minutes after the start of nebulisation and is approximately 4 nmol/litre after a dose of 2 mg. In adults the pulmonary distribution of budesonide, administrated via nebuliser, is approximately 15% of the nominal dose. The systemic availability, following inhalation via jet nebuliser, is also approximately 15% of the nominal dose, of which a small fraction comes from swallowed drug. *Distribution and metabolism* Binding to plasma proteins is approx. 90 %. The volume of distribution is approx. 3 l/kg. Budesonide undergoes extensive (~	A clinical study in asthmatics comparing inhaled and oral budesonide at doses calculated to achieve similar systemic bioavailability demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract. In a provocation study pre-treatment with budesonide for four weeks has shown decreased bronchial constriction in immediate as well as late asthmatic reactions. Onset of effect After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, improvement in lung function has been shown to occur within 2 days of initiation of treatment although maximum benefit may not be achieved for up to 4 weeks. Exercise-induced asthma Therapy with inhaled budesonide has effectively been used for prevention of exercise-induced asthma. Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment ~~(see section 4.4)~~.	**5.1 Pharmacodynamic properties**

90 %) first pass metabolism in the liver to metabolites with low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide. *Elimination* Budesonide is eliminated by means of metabolism that is catalysed principally by the enzyme CYP3A4. The metabolites are excreted in the urine in unchanged or conjugated form. Only negligible amounts of unchanged budesonide are recovered in the urine. Budesonide has a high systemic clearance (approx. 1.2 litres/min) and the half-life in plasma after intravenous administration is on average 4 hours. The pharmacokinetics of budesonide are proportional to the dose at clinically relevant doses. *Children:* In 4-6 years old asthmatic children, the maximal plasma concentration occurs within 20 minutes after start of nebulisation and is approximately 2.4 nmol/L after a 1 mg dose. In 4-6 years old asthmatic patients the pulmonary distribution of budesonide, administrated via nebulisator, is 6% of the nominal dose, and the systemic availability of budesonide following inhalation via a jet nebuliser (Pari LC Jet Plus with Pari Master compressor) is approximately 6% of the nominal dose. Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance, which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2 hours in asthmatic children. This is about the same as in healthy adults. The exposure (Cmax and AUC) of budesonide following administration of a single 1 mg	Budesonide undergoes an extensive biotransformation in the liver, to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes. In a study, 100 mg ketoconazole taken twice daily, increased plasma levels of concomitantly administered oral budesonide (single dose of 10 mg) on average, by 7.8-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected. Of the fraction of budesonide which is swallowed, approximately 90% is inactivated at first passage through the liver. The maximal plasma concentration after inhalation of 1 mg budesonide, delivered via dry powder inhaler, is about 3.5 nmol/L and is reached after about 20 minutes	**5.2 Pharmacokinetic properties**

dose by nebulisation to 4-6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebuliser system.

The pharmacokinetics of budesonide in patients with impaired renal function are unknown. Exposure to budesonide may be increased in patients with hepatic disease.

In toxicity studies budesonide has only caused the expected glucocorticoid effects.

Budesonide has not exhibited any genotoxic effects.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not appear to be relevant in humans at the recommended doses.

5.3 Preclinical safety data

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
אזהרות	תופעות אלו עלולות לאותת שמחלת האסתמה שלך אינה תחת שליטה, ויתכן שתצטרך/י טיפול אחר או נוסף באופן מידי	עליך לפנות לרופא מייד אם חלה החמרה במחלת האסתמה שלך. החמרה עלולה להצביע על צורך בשינוי במינון או בטיפול אחר.
הריון והנקה		יש להתייעץ עם הרופא לפני השימוש בבודיקורט בזמן ההריון כיוון שחומרת האסתמה והטיפול לו את זקוקה עשויים להשתנות ויתכן כי יהיה צורך לבצע התאמה מחודשת של הטיפול. בודסוניד (החומר הפעיל של התרופה) מופרש בחלב האם, בהנקה יש להתייעץ עם הרופא לפני השימוש בבודיקורט.
תגובות בין-תרופתיות:		תרופות מסויימות עלולות להשפיע או להיות מושפעות מהטיפול בבודיקורט, לדוגמא תרופות המכילות קטוקונזול או איטרקונזול (לטיפול בזיהומים פטרייתיים).
תופעות לוואי		שינוי נוסח: סרפדת תגובות אלרגיות כולל פריחה בעור, דרמטיטיס (דלקת עור), אנגיואדמה (התנפחות בפנים, בשפתיים בלשון ו/ או בגרון, לעיתים עם קשיי נשימה או בליעה) אם הופיעה התנפחות יש להיוועץ ברופא מייד; , עווית הסימפונות (היצרות שרירידרכי הנשימה); חבלות בעור. **תופעות לוואי-אחרות שדווחו:** הפרעות בשינה, עצבנות, חוסר מנוחה, דיכאון, חרדה ו/ או רגזנות רבה. תופעות לוואי אלו נראות בדרך כלל בתדירות רבה יותר בילדים.