"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו בינואר 2012 ".

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Budicort® Turbuhaler® 100 micrograms / dose, inhalation powder

Budicort® Turbuhaler® 200 micrograms / dose

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose contains budesonide 100 micrograms or 200 micrograms.

3. PHARMACEUTICAL FORM

Breath-actuated metered dose Inhalation powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Budicort is recommended in patients with bronchial asthma.

4.2 Posology and method of administration

The dosage of Budicort Turbuhaler is individual.

Budicort Turbuhaler is for oral inhalation

When transferring patients to Turbuhaler from other devices, treatment should be individualised, The drug and method of delivery should be considered.

The dosage should be individualised.

The dose should always be reduced to the minimum needed to maintain good asthma control.

Adults (including elderly) and children over 12 years of age: When starting treatment, during periods of severe asthma and while reducing or discontinuing oral glucocorticosteroids, the dosage in adults should be 200 - 1600 micrograms daily, divided into 2-4 administrations.

In less severe cases and children over 12 years of age, 200 - 800 micrograms daily, in divided doses, may be used. During periods of severe asthma, the daily dosage can be increased to up to 1600 micrograms, in 2-4 divided doses.

Children 6 years-12 years of age: 200 - 800 micrograms daily, in divided doses. During periods of severe asthma, the daily dose can be increased up to 800 micrograms.

The maintenance dose should be the lowest possible.

It is possible that the patient will not taste or perceive any medicine when Budicort Turbuhaler is used; this is because such a small amount of substance is dispensed.

In patients where an increased therapeutic effect is desired, an increased dose of Budicort is recommended because of the lower risk of systemic effects as compared with a combined treatment with oral glucocorticosteroids.

Patients dependant on oral glucocorticosteroids

Budicort Turbuhaler may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. For further information on the withdrawal of oral corticosteroids, see section 4.4.

Patients should be reminded of the importance of taking prophylactic therapy regularly, even when they are asymptomatic. A short-acting inhaled bronchodilator should be made available for the relief of acute asthma symptoms.

There is no experience of treatment of patients with impaired hepatic or renal function. Since budesonide is predominantly eliminated through hepatic metabolism, increased exposure may be expected in patients with severe cirrhosis of the liver.

Instructions for correct use of Budicort Turbuhaler:

It is important that the inhaler is used correctly. A detailed description of how the Turbuhaler is used is supplied with every pack.

Instructions for the correct use of Budicort Turbuhaler

Turbuhaler is inspiratory flow-driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient:

- To carefully read the instructions for use in the patient information leaflet, which is packed with each Turbuhaler
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece
- To rinse the mouth out with water and spit it out, or to brush the teeth after inhaling the prescribed dose, to minimise the risk of oropharyngeal thrush

The patient may not taste or feel any medication when using Turbuhaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to budesonide.

4.4 Special warnings and special precautions for use

In order to minimise the risk of Candida infections in the oral cavity and throat, the patient should be instructed to rinse the mouth with water after each dose administration.

Patients must be warned to contact the physician if the effect of the treatment diminishes in general, as repeated inhalations for severe asthma attacks must not delay the initiation of other important therapy. If there is a sudden deterioration the treatment must be supplemented with a short course of oral steroidsBudicort Turbuhaler is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required. If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for increased anti-inflammatory therapy, eg, higher doses of inhaled budesonide or a course of oral glucocorticosteroid.

Special care is needed in patients with quiescent lung tuberculosis, fungal and viral infections in the airways.

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, 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.

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.
Steroid-dependent patients: When transferral from oral steroids to Budicort Turbuhaler is started, the patient should be in a relatively stable phase. A high dose of Budicort Turbuhaler is then given in combination with the previously used oral steroid dose for about 10 days.

After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute Budicort for the oral steroid.

During transfer from oral therapy to Budicort, 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. During the withdrawal of oral steroids, patients may feel unwell in a non-specific way, even though respiratory function is maintained or improved. Patients should be encouraged to continue with Budicort therapy whilst withdrawing the oral steroid, unless there are clinical signs to indicate the contrary. 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.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If a severe reaction occurs, treatment should be reassessed and an alternative therapy instituted if necessary.

Patients who have previously been dependent on oral steroids may, as a result of prolonged systemic steroid therapy, experience the effects of impaired adrenal function. Recovery may take a considerable amount of time after cessation of oral steroid therapy, hence oral steroid-dependent patients transferred to budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances, HPA axis functions should be monitored regularly.

Acute exacerbations of asthma may need an increase in the dose of Budicort or additional treatment with a short course of oral corticosteroid and/or an antibiotic, if

there is an infection. The patient should be advised to use a short-acting inhaled bronchodilator as rescue medication to relieve acute asthma symptoms.

If patients find short-acting bronchodilator treatment ineffective or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for or an increase in their regular therapy, e.g., higher doses of inhaled budesonide or the addition of a long-acting beta agonist, or for a course of oral glucocorticosteroid.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. These patients should be instructed to carry a steroid warning card indicating their needs. Treatment with supplementary systemic steroids or Budicort should not be stopped abruptly.

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 adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

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 is 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.

In vivo studies have shown that oral administration of ketoconazole and itraconazole (known inhibitors of CYP3A4 activity in the liver and in the intestinal mucosa causes an increase in the systemic exposure to budesonide. Concomitant treatment with ketoconazole and itraconazole or other potent CYP3A4 inhibitors should be avoided (see section 4.5 Interactions). If this is not possible, the time interval between administration of the interacting drugs should be as long as possible. A reduction in the dose of budesonide should also be considered.

4.5 Interactions with other medicinal products and other forms of interaction

Budesonide has not been observed to interact with any drug used for the treatment of asthma or COPD.

At recommended doses, cimetidine has slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

No clinically relevant interactions with other agents for asthma are known.

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.

4.6 Pregnancy and lactation

Pregnancy

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. Animal studies have shown that, glucocorticosteroids can induce malformations (see Section 5.3), but with the recommended dosage this is judged not to be relevant for humans

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 Turbuhaler no effects on the suckling child are anticipated. Budicort Turbuhaler can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Budicort Turbuhaler does not affect the ability to drive or ~~to~~ use machines.

4.8 Undesirable effects

Up to 10 % of patients treated may be expected to experience adverse reactions of a local nature.

Clinical trials, literature reports and post-marketing experience suggest that the following adverse drug reactions may occur:

Common (>1/100)	*Airways*: Candida infections in the oral cavity and throat, mild throat irritation, cough, hoarseness.
Rare (<1/1000)	*General:* Angio-oedema, anaphylactic reaction
	Skin: Urticaria, rash, dermatitis, skin bruising
	Airways: Bronchospasm
	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 sensitivity.

When using inhalation steroids, the patient must rinse the mouth with water after every dose on account of the risk of Candida infection in the oral cavity and throat.

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see Section 4.4).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

4.9 Overdose

Acute overdose with Budicort Turbuhaler, even in high doses, is not expected to cause any clinical problems. If used chronically in high doses, systemic effects of glucocorticosteroids such as hypercortisolism and adrenal suppression can occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:.Inhalation drugs for obstructive airway diseases . ATC Code: RO3B A02.

Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action effects,.

Long-term studies show that 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.

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory effects, such as inhibited release of inflammatory mediators and inhibition of cytokine-mediated immune response are probably important. The activity of budesonide, measured as its affinity for glucocorticosteroid receptors is approx. 15 times higher than that of prednisolone.

Budesonide has anti-inflammatory effects, which manifested themselves as reduced bronchial obstruction during both the early and the late phase of an allergic reaction. In hyper-reactive patients budesonide reduces the histamine and metacholine reactivity in the airways.
Studies have shown that the earlier budesonide treatment is inititated after the onset of asthma, the better 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 prednisolone 10mg, as shown by ACTH tests.

In children over the age of 3 years no systemic effects have been detected with doses up to 400 micrograms/day. In the dose range 400-800 micrograms/day biochemical signs of a systemic effect may occur, while such signs are common with daily doses in excess of 800 micrograms.

Growth

Asthma, like inhaled corticosteroids, can delay 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.

5.2 Pharmacokinetic properties

Absorption

Inhaled budesonide is absorbed rapidly, and peak plasma concentrations are reached within 30 minutes after inhalation. In studies, the average deposition of budesonide in the lungs after inhalation via Turbuhaler has been shown to be 25-35 % of the given dose. The systemic bioavailability is approx. 38 %.

Distribution and metabolism

Binding to plasma proteins is approx. 90 %. The volume of distribution is approx. 3 litres/kg. Budesonide undergoes extensive (approx. 90 %) first-passage metabolism in the liver to metabolites with low glucocorticosteroid activity. The glucocorticosteroid activity for the main metabolites, 6-beta-hydroxybutesonide and 16-alpha hydroxyprednisolone, is less than 1 % of that of budesonide.

Elimination

Budesonide is eliminated through metabolism, which 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 the plasma after intravenous administration is on average 4 hours. The pharmacokinetics of budesonide are proportional to the dose at relevant dosages.

The pharmacokinetics of budesonide in children and in patients with impaired renal function are not known. Exposure to budesonide may be greater in patients with hepatic disease.

5.3 Preclinical safety data

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclomethasone dipropionate, fluocinolone acetonide).

Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe than, or similar to, those observed after administration of the other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex.

An increased incidence of brain gliomas in male rats, in a carcinogenicity study, could not be verified in a repeat study in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide, as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows no indication that budesonide, or other glucocorticosteroids, induce brain gliomas or primary hepatocellular neoplasms in man.

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.

In toxicity studies budesonide caused only 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 seem to be relevant in humans at the recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticosteroids, in increased risk 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Budicort Turbuhaler contains no excipients

6.2 Incompatibilities

Not relevant.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Must be stored with the protective cap in place.

Do not store above 30°C.

6.5 Nature and content of container

Budicort Turbuhaler is an inspiration-driven multi-dose powder inhaler made of plastic. One inhaler of 100 micrograms / dose contains 200 doses. One inhaler of 200 micrograms / dose contains 100 doses.

6.6 Instructions for use and handling and for destruction

No special requirements.

7. MANUFACTURER

AstraZeneca AB

Sweden

8. License Holder and importer

AstraZeneca (Israel) Ltd.,

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