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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

Budesonide 100 micrograms/actuation.

Budesonide 200 micrograms/actuation.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Breath-actuated metered dose powder inhaler.

4. Clinical particulars

4.1 Therapeutic indications

Budicort is recommended in patients with bronchial asthma.

4.2 Posology and method of administration

Posology

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 the active substance.

4.4 Special warnings and precautions for use

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis, and in patients with fungal or viral infections in the airways.

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 Turbohaler is started, the patient should be in a relatively stable phase. A high dose of Budicort Turbohaler 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 this occurs, treatment with inhaled budesonide should be discontinued immediately, the patient assessed and 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 shortacting inhaled bronchodilator as rescue medication to relieve acute asthma symptoms.

Budicort 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 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.

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 of impaired adrenal function. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid treatment 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 may occur with any inhaled corticosteroids, 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, 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.

Reduced liver function affects the elimination of corticosteroids causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects.

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.

Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term treatment. A reduction in the dose of budesonide should also be considered (see section 4.5).

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary (see section 4.2).

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Visual disturbance

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.

Paediatric population

Influence on growth

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. The benefit of the corticosteroid therapy and the possible risk of growth suppression must be carefully weighed. In addition, **consideration should be given to referring the patient to a paediatric respiratory specialist.**

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of budesonide is primarily mediated by CYP3A4. Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects (see section 4.4 and section 5.2).

The combination of Budicort with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. If Budicort is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible. A reduction of the budesonide dose could be considered.

Limited data about this interaction for high-dose inhaled budesonide indicate that marked increases 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).

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Most results from prospective epidemiological studies and world-wide post-marketing data have not been able to detect an increased risk for adverse effects for the foetus and newborn child from the use of inhaled budesonide during pregnancy. In animal studies, glucocorticosteroids have been shown to induce malformations (see Section 5.3). 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. It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy. As with other drugs administered during pregnancy, the benefit of the administration of budesonide for the mother should be weighed against the risks to 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.

Breast-feeding

Budesonide is excreted in breast milk. However, at therapeutic doses of Budicort Turbohaler no effects on the suckling child are anticipated. Budicort Turbohaler can be used during breast feeding.

Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

In a pharmacokinetic study, the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification.

Based on data from inhaled budesonide and the fact that budesonide exhibits linear PK properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low.

4.7 Effects on ability to drive and use machines

Budicort Turbohaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

SOC	Frequency	Adverse Drug Reaction
Infections and infestations	Common	Oropharyngeal candidiasis
		Pneumonia (in COPD patients)

Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction
Endocrine disorders	Rare	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation*
Psychiatric disorders	Uncommon	Anxiety
		Depression
	Rare	Psychomotor hyperactivity
		Sleep disorders
		Aggression
		Behavioural changes (predominantly in children)
Nervous System Disorders	Uncommon	Tremor**
Eye disorders	Uncommon	Cataract
		Vision, blurred (see also section 4.4)
	Not Known	Glaucoma
Respiratory, thoracic and mediastinal disorders	Common	Cough
		Hoarseness
		Throat irritation
	Rare	Bronchospasm
		Dysphonia
		Hoarseness***
Skin and subcutaneous tissue disorders	Rare	Bruising
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasm

* refer to Paediatric population, below

** based on the frequency reported in clinical trials

*** rare in children

Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity (see section 4.4).

Description of selected adverse reactions

The candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dosing will minimise the risk.

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

In placebo-controlled studies, cataract was also uncommonly reported in the placebo group.

Clinical trials with 13119 patients on inhaled budesonide and 7278 patients on placebo have been pooled. The frequency of anxiety was 0.52% on inhaled budesonide and 0.63% on placebo; that of depression was 0.67% on inhaled budesonide and 1.15% on placebo.

Paediatric population

Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by an online form:

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

Symptoms

Acute overdosage with Budicort Turbohaler, even in excessive doses, is not expected to be a clinical problem. The only harmful effect that follows inhalation of large amounts of the drug over a short period is suppression of hypothalamic-pituitary-adrenal (HPA) function.

Management

No special emergency action needs to be taken. Treatment with Budicort Turbohaler should be continued at the recommended dose to control the asthma.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: R03B A02.

Topical anti-inflammatory effect

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Antiinflammatory actions, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

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.

Airway reactivity

Budesonide has also been shown to decrease airway reactivity to histamine and methacholine in hyper-reactive patients.

Exercise-induced asthma

Therapy with inhaled budesonide has effectively been used for prevention of exercise-induced asthma.

Growth

In short term studies a small and generally transient reduction in growth has been observed, which usually occurs within the first year of treatment. Long-term observational studies suggest that children and adolescents treated with

inhaled corticosteroids on average achieve their adult target height. However, in one study children who had been treated with high dose inhaled budesonide (400 micrograms daily) for up to 6 years without titration to the lowest effective dose were found on average to be 1.2 cm shorter as adults than those treated with placebo over the same period. See section 4.4 about titration to the lowest effective dose and about monitoring the growth in children.

Paediatric Population

Slit lamp examinations were performed in 157 children (5-16 years old), treated with an average daily dose of 504 µg for 3-6 years. Findings were compared with 111 age-matched asthmatic children. Inhaled budesonide was not associated with an increased occurrence of posterior subcapsular cataract.

Influence on plasma cortisol concentration

Studies in healthy volunteers with Budicort Turbohaler have shown dose-related effects on plasma and urinary cortisol. At recommended doses, Budicort Turbohaler, causes less effect on the adrenal function than prednisolone 10mg, as shown by ACTH tests.

5.2 Pharmacokinetic properties

Absorption

Following oral inhalation via Budicort Turbohaler, peak plasma concentrations of budesonide (4.0 nmol/L after a dose of 800 µg) occur within 30 minutes. Maximum plasma concentration and area under the plasma concentration time profile increase linearly with dose, but are slightly (20-30%) higher following repeated doses (3 weeks treatment) than after a single dose. Lung deposition in healthy subjects was estimated to 34% ±10% of the metered dose (arithmetic mean ± SD), while 22% was retained in the mouthpiece and the rest (approximately 45% of the metered dose) was swallowed.The maximal plasma concentration after inhalation of 1 milligram budesonide is about 3.5 nmol/L and is reached after about 20 minutes.

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

Biotransformation

Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6βhydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

Excretion

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours**.**

Linearity

The kinetics of budesonide are dose-proportional at clinically relevant doses.

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.

Paediatric safety data

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 2.3 hours in asthmatic children. This is about the same as in healthy adults. In asthmatic children treated with Budicort Turbohaler (800 µg single dose), plasma concentration reached Cmax (4.85 nmol/L) at 13.8 minutes after inhalation, and then decreased rapidly; AUC was 10.3 nmol·h/L. The value for AUC is generally comparable to that observed in adults at the same dose, however, the Cmax value tends to be higher in children. Lung deposition in children (31% of the nominal dose) is similar to that measured in healthy adults (34% of nominal dose).

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.

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 Turbohaler contains only active drug, budesonide. There are no propellants, lubricants, preservatives, carrier substances or other additives.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product indicated on the package materials.

6.4 Special precautions for storage

Do not store above 30°C.
Must be stored with a protective cap in place

6.5 Nature and contents of container

Polyethylene container consisting of a cover screwed onto a bottom plate. Inside this is the inhaler with its main parts: a mouthpiece, a dosing mechanism and a substance store.

The device also contains a desiccant.

200 micrograms/actuation, 100 actuations.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

See section 4.2.

7. Manufacturer

AstraZeneca AB

Sweden

8. License Holder and Importer

AstraZeneca (Israel) Ltd.

P.O.B 1455, Hod Hasharon 4524075, Israel