# PACKAGE INSERT

## 1. NAME OF THE MEDICINAL PRODUCT

Budiair 200 micrograms pressurised inhalation solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered actuation contains 200 micrograms of budesonide.
For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Pressurised inhalation, solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Budiair is indicated for patients with bronchial asthma who require maintenance treatment with glucocorticosteroids for control of the underlying airways inflammation.

### 4.2 Posology and Method of Administration

Posology should be adjusted according to the single patient and relating to severity of asthma and therapy phase.
When transferring a patient to Budiair from other inhalation devices, the treatment should be individualised. The previous active substance, dose regimen, and method of delivery should be considered.
The maintenance dose is individual, and should be the minimum dose allowing suppression of symptoms. Budiair is a symptomatic therapy with no demonstrated effect on acute disorders.
Initially, at the beginning of inhaled corticosteroid therapy, for therapy during periods of severe asthma or when scaling down or withdrawing oral corticosteroids, the recommended dosage is:

- **Adults:** 200 micrograms (1 puff) 2-4 times daily. During the periods of severe asthma, the daily posology can be increased up to a maximum of 1600 micrograms.
- **Children > 12 years old:** 200-800 micrograms daily divided into 2-4 administrations.
- **Children from 6 to 12 years of age:** 200-400 micrograms daily divided into 2-4 administrations. The age limit depends on the possibility of properly using the product.

The dose should be reduced to the minimum needed to maintain good asthma control.
Contains alcohol, not suitable for children <6 years old.
**Patients not treated with corticosteroids:** the therapeutic effect of budesonide generally occurs within 10 days of therapy start: however, for patients with abundant bronchial secretion, such as to hinder mucosal absorption of the active ingredient, short-term concomitant treatment (about two weeks) with oral corticosteroids is recommended. This should be started at full dosage and reduced gradually until maintenance with Budiar only is achieved. Asthma exacerbations due to bacterial infections should be treated with antibiotics while increasing the posology of Budiair.
**Patients treated with corticosteroids:** switch from oral corticosteroidal therapy to treatment with Budiair requires special attention, due to the slow reactivation of those hypothalamic functions impaired by the prolonged oral corticosteroidal therapy. Introducing Budiair into therapy should occur when the patient is relatively stabilised.
Budiair will have to be administered concomitantly with oral corticosteroids for about 10 days; then this should be gradually reduced, down to the minimum dose that, combined with Budiair, ensures a stable response. In many cases it is possible to completely withdraw the oral therapy, whilst in some patients it will be necessary to continue treatment with a minimum oral corticosteroids dose. Nevertheless, in some cases when switching from oral therapy to Budiair, the systemic steroidal effect may decrease, with occurrence of rhinitis, eczema, headache, muscular and articular pain, and, rarely, of nausea and vomiting. Should these events occur, the physician shall evaluate the opportunity to maintain the patient on inhalation therapy. It might take a long time to recover the physiological production of natural corticosteroids, and in some conditions, such as physical stress due to severe infections, injuries or surgery, it may be necessary to combine Budiair with oral corticosteroidal therapy; also in case of asthma exacerbations, especially when associated with increased viscosity and formation of mucus plugs, a short-term concomitant treatment with oral steroids may be necessary. It is of utmost importance that the patient follows the instructions for use.

**Method of Administration**

**For use, perform the following operations:**

**The successful result of treatment depends on a correct use of the inhaler.**
Inhaler's working test: before using the inhaler for the first time, or if it has not been used for three days or more, remove the mouthpiece cover by gently squeezing its sides and release one puff into the air to make sure that the inhaler works properly.
For use, carefully follow the instructions below:

1. Hold the inhaler upright between thumb and index, with the mouthpiece downwards;
2. Remove the mouthpiece cover;
3. Breathe out steadily, then place the mouthpiece firmly between the lips;
4. Start breathing in steadily and deeply through your mouth and press down once on the top of the inhaler. After the inhalation, hold your breath as long as possible, remove the inhaler from your mouth.
5. If you need to take another puff, if recommended for you by your doctor, repeat steps 3-4.

Once completed the prescribed number of inhalations, replace the mouthpiece cover.
Rinse your mouth with water to remove any excess medicine (do not swallow).
The mouthpiece should always be kept clean. For cleaning, remove the pressurised canister and rinse the mouthpiece in lukewarm water. Leave to dry thoroughly in a warm place. Avoid excessive heat.
Inhalation in children should be supervised by an adult person. It is useful to close the child's nostrils during inhalation.
Clinical efficacy of Budiair inhaler in use with a spacer device has not been demonstrated.
Hence, for patients who cannot coordinate the release of dose and inhalation, monitoring of the patient's asthma control is advisable if Budiair inhaler is used together with a spacer device.

## 4.3 Contraindications

History of hypersensitivity to budesonide or any of the excipients.

## 4.4 Special Warnings and Precautions for Use

Budiair is not indicated for the treatment of acute dyspnoea or status asthmaticus. These conditions should be treated with standard therapy.
Patients should be instructed about the correct use of the inhaler.
In order to minimize 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.
Budiair provides a prophylactic therapy of the asthmatic disease: therefore, it should be administered regularly at the prescribed doses and as long as directed by the physician and should not be stopped abruptly.

In case of gastrointestinal ulcer, strict medical surveillance is advisable throughout therapy duration.
The transfer of patients treated with oral corticosteroids to the inhaled corticosteroid and their subsequent management requires special care. The patients should be in a reasonably stable state before initiating a high dose of inhaled corticosteroid in addition to their usual maintenance dose of systemic corticosteroid. (see also Section 4.2 Posology and Method of Administration). After about 10 days, withdrawal of the systemic corticosteroid is started by reducing the daily dose gradually to the lowest possible level. It may be possible to completely replace the oral corticosteroid with inhaled corticosteroid.
Transferred patients whose adrenocortical function is impaired may need supplementary systemic corticosteroid during periods of stress. This applies also to patients who have received prolonged treatment with high doses of inhaled corticosteroids. They may also have impaired adrenocortical function which may result in clinically significant adrenal suppression and may need systemic corticosteroid cover during periods of stress.
During transfer from oral therapy to inhaled budesonide symptoms may appear that had previously been suppressed by systemic treatment with glucocorticosteroids, with occurrence of rhinitis, eczema, headache, muscular and articular pain, and, rarely, of nausea and vomiting. Specific treatment should be co-administered to treat these conditions.
Some patients may feel unwell in a non-specific way during the withdrawal of systemic corticosteroids despite maintenance or even improvement in respiratory function. Such patients should be encouraged to continue treatment with inhaled budesonide and withdrawal of oral corticosteroid unless there are clinical signs to indicate the contrary, for example signs which might indicate adrenal insufficiency.
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.
When despite a well monitored treatment, an acute episode of dyspnoea occurs, a rapid acting inhaled bronchodilator should be used and medical reassessment should be considered. If despite maximum doses of inhaled corticosteroids asthma symptoms are not adequately controlled, patients may require short-term treatment with systemic corticosteroids.
It is important that the inhaled corticosteroid dose be the minimum effective for asthma control, and that it is regularly adjusted. In fact, possible systemic effects, such as acute adrenal suppression, delayed growth of children and adolescents, reduction of bone mineral density, cataract, glaucoma, may arise following long-term treatment with high dose inhaled corticosteroids. Very rare cases of acute adrenal crises occurred in young patients exposed to doses higher than those recommended (about 1000 mcg/day) for prolonged periods (several months or years). Adrenal insufficiency symptoms are initially aspecific and include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting; specific symptoms occurring with inhaled corticosteroids also include hypoglycemia with impaired consciousness and/or seizures. Situations that might potentially determine an adrenal crisis are: traumas, surgery, infections and rapid reduction of dosage. Patients receiving high doses should be strictly monitored and their dose gradually reduced. Monitoring the adrenal reserve may also be necessary.

**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.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. In case of growth retardation, therapy should be reviewed in order to reduce the glucocorticoid dosage to the lowest possible dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.
Patients who have previously been dependent on oral corticosteroids may, as a result of prolonged systemic corticosteroid therapy, experience effects of impaired adrenal function. Recovery may take a considerable

amount of time after cessation of oral corticosteroid therapy and hence oral steroid-dependent patients transferred to budesonide may remain at risk from impaired adrenocortical function for some considerable time. In such circumstances hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.
To reduce the risk of oral candidiasis and hoarseness patients should be advised to rinse out the mouth properly or brush the teeth after each administration of inhaled corticosteroid.
Exacerbation of clinical symptoms of asthma may be due to acute respiratory tract bacterial infections and treatment with appropriate antibiotics may be required. Such patients may need to increase the dose of inhaled budesonide and a short course of oral corticosteroids may be required. A rapid-acting inhaled bronchodilator should be used as "rescue" medication to relieve acute asthma symptoms.
Special care and adequate specific therapeutic control of patients with active and quiescent pulmonary tuberculosis is necessary before commencing treatment with Budiair. Similarly patients with fungal, viral or other infections of the airways require close observation and special care and should use Budiair only if they are also receiving adequate treatment for such infections.
In patients with excessive mucous secretion in the respiratory tract, short-term therapy with oral corticosteroids may be necessary.
In patients with severe hepatic dysfunction, treatment with inhaled budesonide can result in a reduced elimination rate and hence enhanced systemic availability. Possible systemic effects may then result and therefore HPA axis function in these patients should be monitored at regular intervals.
Concomitant treatment with ketoconazole and itraconazole or other potent CYP3A4 inhibitors should be avoided (see Section 4.5 Interaction with other medicinal products and other forms of interaction).
This product contains small amounts of ethanol (less than 10 mg per dose) and glycerol.
These amounts are negligible and do not represent any risk for the patient at usual therapeutic doses.

**4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**

In patients undergoing treatment with oral corticosteroids, switching to the use of only Budiair by inhalation should occur gradually. After stabilising the patient, Budiair is combined to the therapy and oral corticosteroid dose is progressively reduced, while regularly assessing the patient's general conditions. This is necessary due to the slow reactivation of adrenal function, compromised by prolonged use of oral corticosteroids (see 4.2 "Posology and Method of Administration").
Concomitant treatment with ketoconazole and itraconazole should be avoided, as their oral administration can increase systemic exposure to budesonide. Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide.
The product contains a small quantity of ethanol. There is the theoretical potential for interactions with disulfiram or metronidazole in particularly sensitive patients treated with these drugs.

**4.6 Pregnancy and Lactation**

Data on adequate number of exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended dose.
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.

During pregnancy, inhaled budesonide should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.
It is not known whether budesonide passes into human breast milk. Administration of inhaled budesonide to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

**4.7 Effects on Ability to Drive and Use Machines**

None

**4.8 Undesirable Effects**

The following adverse drug reactions may occur:

***Common (>1/100, <1/10)***

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|---|---|
| Respiratory system disorders: | hoarseness, cough and throat irritation. |
| Gastrointestinal disorders: | oropharyngeal candidiasis, difficulty in swallowing. |

***Uncommon (>1/1,000, <1/100)***

| | |
|---|---|
| Eye disorders | blurred vision |

***Rare (>1/10,000, <1/1000)***

| | |
|---|---|
| Skin and appendages disorders: | easy bruising, skin thinning, urticaria, rash, dermatitis, pruritus, erythema. |
| Psychiatric disorders: | depression, aggressive reactions, irritability, anxiety, psychosis, behavioural changes in children, restlessness, increased motorial activity. |
| Endocrine disorders: | hypocorticism, hypercorticism. |
| Respiratory system disorders: | bronchospasm |
| Body as a whole - general disorders: | anaphylactic shock, angioedema, immediate and delayed hypersensitivity reactions. |
| Musculoskeletal, connective tissue and bone disorders: | growth retardation in children and adolescents. |

***Very rare including isolated cases (<1/10,000)***

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|---|---|
| Psychiatric disorders: | nervousness. |
| Endocrine disorders: | adrenal suppression. |
| Eye disorders: | cataract, glaucoma. |
| Respiratory system disorders: | dysphonia. |
| Gastrointestinal disorders: | dysgeusia, nausea, glossodynia, stomatitis, dry mouth. |
| Musculoskeletal, connective tissue and bone disorders: | decreased bone density, back pain. |

Treatment with inhaled budesonide may result in candida infection in the oropharynx.
Experience has shown that candida infection occurs less often when inhalation is performed before meals and/or when the mouth is rinsed after inhalation. In most cases this condition responds to topical anti-fungal therapy without discontinuing treatment with inhaled budesonide.
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, and susceptibility to infections. The ability to adapt to stress may be impaired.
The systemic effects described, however, are much less likely to occur with inhaled budesonide than with oral corticosteroids.

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases, with an immediate increase in wheezing after dosing. If a severe reaction occurs, treatment should be reassessed and an alternative therapy instituted if necessary (see section 4.4).

### 4.9 Overdose

Overdose with Budiair is very unlikely, and generally does not cause any significant clinical effects.

Symptoms of overdose

The acute toxicity of budesonide is low. Chronic use in excessive doses can result in systemic glucocorticosteroid effects, such as increased susceptibility to infection, hypercorticism and adrenal suppression. Atrophy of the adrenal cortex can occur and the ability to adapt to stress can be impaired.

Therapeutic management of overdose

For acute overdosage, no special emergency action needs to be taken. The treatment with inhaled budesonide should be continued at the recommended dose to control asthma. HPA axis function recovers in a few days.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC: R03B A02 other drugs for obstructive airway disease, inhalants, glucocorticoids.

Budesonide, the active ingredient of Budiair, is a synthetic, non-halogenated corticosteroid for topic inhalation use only, endowed with potent anti-inflammatory activity and, at the recommended doses, devoid of systemic effects or of activity inhibiting the adrenocortical function.

Improvement in asthma control following inhalation of budesonide can occur within 24 hours of commencing the treatment although maximum benefit is achieved after a few weeks of continuous treatment.

The precise mechanism of corticosteroid actions on inflammation in asthma is not known.

Budesonide has been shown to have a wide range of inhibitory effects against several cell types (e.g., eosinophils, macrophages, mast cells, lymphocytes, and neutrophils) and mediators (e.g., cytokines, leukotrienes, eicosanoids, and histamine) involved in allergic and non-allergic respiratory inflammation. These actions of budesonide may contribute to its efficacy in asthma resulting in a reduction of hypersecretion, hyperreactivity and reducing the occurrence of bronchospasm. In patients with hyperreactivity the administration of budesonide reduces airway reactivity after stimulation with histamine or methacholine.

### 5.2 Pharmacokinetic Properties

Budesonide is provided as a mixture of two epimers (22R and 22S). In glucocorticoid receptor affinity studies, the 22R form is twice as active as the 22S epimer. These two forms of budesonide do not interconvert.

***Absorption***

Budesonide is a moderately lipophilic drug with high affinity for the glucocorticoid receptors, that is rapidly absorbed by the airway mucosa.

Approximately 20 minutes after administration by inhalation budesonide forms esters with the intracellular fatty acids via a reversible conjugation process that is able to prolong the local anti-inflammatory activity at pulmonary level.

The quantity absorbed into circulation, partly through the lungs and partly swallowed by oral route, varies between 10 and 30% and is rapidly and widely metabolised at the hepatic level to yield poorly active metabolites. Bonding to plasma proteins is 88% and the distribution volume is approximately 3L/kg.

***Metabolism:***
Budesonide is mainly eliminated by metabolism. Budesonide is rapidly and extensively metabolised in liver via cytochrome P4503A4 to two major metabolites. The in vitro glucocorticoid activity of these metabolites is less than 1% of that of the parent compound. Negligible metabolic inactivation has been observed in human lung and serum preparations.

***Excretion:***
Budesonide is excreted in urine and faeces as conjugated and non-conjugated metabolites.
The elimination half-life after inhalation is approximately ***3*** hours.

***Special patient populations:***
The exposure to budesonide may be increased in patients with liver disease. The pharmacokinetics of budesonide in children and in patients with impaired renal function are not known.

**5.3 Preclinical Safety Data**

The toxicity observed in animal studies with budesonide was associated with exaggerated pharmacological activity.
No genotoxic effects of budesonide have been observed in conventional genotoxicity tests.
In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). Similar effects are considered unlikely to occur in humans at therapeutic doses.
Specific tolerability studies by inhalation proved the good local tolerability of this budesonide formulation propelled with HFA 134a.
The HFA 134a propellant did not show any toxic effects, even at concentrations far higher than those recommended for human use, when administered by daily nebulisation to different animal species for up to two years.
Studies on the effects of the propellant HFA 134a on reproductive function and embryofoetal development in animals failed to detect any clinically important adverse events. It is therefore unlikely that adverse events can occur in humans.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of Excipients**

1,1,1,2 Tetrafluoroethane (HFA 134a )
Ethanol, anhydrous
Glycerol

**6.2 Incompatibilities**

Not known

**6.3 Shelf Life**

18 months.

**6.4 Special Precautions for Storage**

Pressurised container. Do not pierce, expose to heat, even if empty, freeze and expose to direct sunlight. Store below 25°C

**6.5 Nature and Contents of Container**

***Primary container:*** mono-bloc aluminium canister, pressurised with metering valve, equipped either with a standard actuator with mouthpiece cover or with a polypropylene Jet actuator-spacer with mouthpiece cover.

***Outer package:*** printed thin-cardboard box.
Presentation: pressurised canister providing 200 inhalations
Package:
- pressurised canister with standard actuator, providing 200 actuations

**6.6 Instructions for Use and Handling**

The package contains a pressurised container equipped with a standard actuator .
Do not dispose in the environment after use.

**Manufactured by:**

**Chiesi Farmaceutici SpA**
**26/A, via Palermo – Parma, Italy**

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