

Summary Product Characteristics

1. Name of the medicinal product

BUDECORT Inhaler with Dose Counter

2. Qualitative and quantitative composition

BUDECORT 100 Inhaler

Each actuation delivers:

Budesonide IP.....100 mcg

Suspended in CFC-free propellant.....HFA

BUDECORT 200 Inhaler

Each actuation delivers:

Budesonide IP.....200 mcg

Suspended in CFC-free propellant.....HFA

For the full list of excipients, see section 6.1

3. DOSAGE FORM

Inhalation aerosol

4. Clinical particulars

4.1 INDICATIONS

BUDECORT Inhaler is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

BUDECORT Inhaler is not indicated for the relief of acute bronchospasm.

4.2 Posology and method of administration

Adults (including elderly) and Children over 12 Years

200-1,600 mcg daily, in divided doses.

200 mcg twice daily, in the morning and in the evening. During periods of severe asthma the daily dosage can be increased up to 1600 mcg.

In less severe cases and children over 12 years of age, 200 - 800 micrograms daily, in divided doses, may be used.

In patients whose asthma is well controlled, the daily dose may be reduced below 400 mcg but should not go below 200 mcg.

Patients should be maintained on the lowest dose that will effectively control symptoms.

Children (less than 12 Years)

200-800 mcg daily, in divided doses.

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

Patients should be maintained on the lowest dose that will effectively control symptoms.

Patients (adults and children) with mild to moderate asthma, who have not previously received inhaled glucocorticosteroids or who are already controlled on inhaled steroids administered twice daily may be transferred to once daily dosing at the same equivalent total daily dose; the drug and method of delivery should be considered. The dose should subsequently be reduced to the minimum needed to maintain good asthma control.

Patients should be instructed to take the once daily dose in the evening. It is important that the dose is taken consistently and at a similar time each evening.

Patients, in particular those receiving once daily treatment, should be advised that if their asthma deteriorates (e.g. increased frequency of bronchodilator use or persistent respiratory symptoms) they should double their steroid dose, by administering it twice daily, and should contact their doctor as soon as possible.

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

BUDECORT Inhaler may be used with a **Cipla Zerostat VT/ Zerostat Spacer /Minizerostat spacer** device in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

4.3 Contraindications

History of hypersensitivity to budesonide or any of the excipients.

BUDECORT Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

4.4 Warnings and Precautions

Patients Not Dependent on Steroids:

Treatment with the recommended doses of budesonide inhaler usually gives a therapeutic benefit within 10 days. However, certain patients may have an excessive collection of mucous secretion in the bronchi. In these cases, a short course of oral corticosteroids (usually 1-2 weeks) should be given in addition to the aerosol. After the course of the oral drug, the inhaler alone should be sufficient therapy.

Steroid-Dependent Patients:

Transfer of patients on oral steroids to treatment with budesonide inhaler demands special care, mainly due to the slow restitution of the disturbed hypothalamic-pituitary-adrenal (HPA) axis function, caused by extended treatment with oral corticosteroids. When the budesonide inhaler treatment is initiated, the patient should be in a relatively stable phase. Budesonide inhaler is then given in combination with the previously used oral steroid dose for about 10 days.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to budesonide inhaler.

Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg or equivalent each month to the lowest possible level during therapy with budesonide inhaler. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

In many cases it may be possible to completely substitute the oral steroid with inhaled budesonide; however some patients may have to be maintained on a low dose of oral steroid together with inhaled budesonide.

During the withdrawal of oral steroids some patients may experience uneasiness and may feel generally unwell in a non-specific way even though respiratory function is maintained or improved. Patients should be encouraged to continue with inhaled budesonide 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.

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 and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly. These patients should be instructed to carry a steroid warning card indicating their needs.

Acute exacerbations of asthma may need an increase in the dose of budesonide 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 recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Such patients should be instructed to carry a steroid warning card indicating their needs. Treatment with supplementary systemic steroids or inhaled budesonide 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 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.

During transfer from oral therapy to budesonide inhaler, 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.

In clinical trials with budesonide, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. These infections may require treatment with appropriate antifungal therapy and/or discontinuance of treatment with budesonide.

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex..

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 (CSCS) which have been reported after use of systemic and topical corticosteroids.

Acute exacerbations of asthma may need an increase in the dose of budesonide 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.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. **BUDECORT Inhaler** should be discontinued immediately, the treatment should be reassessed and an alternative therapy instituted if necessary.

Paediatric Populations

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 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.

BUDECORT Inhaler is not intended for rapid relief of acute episodes of asthma or symptoms of asthma. In these situations an inhaled short-acting bronchodilator is required. Patients should be advised to have such 'rescue' medication with them at all times.

Patients should be reminded of the importance of taking prophylactic therapy regularly, even when they are asymptomatic. Patients should also be reminded of the risk of oropharyngeal Candida infection, due to drug deposition in the oropharynx. Advising the patient to rinse the mouth out with water after each dose will minimize the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid. However at times, the therapy with corticosteroid may need to be interrupted

Patients should be instructed in the proper use of their inhalation device and their technique should be checked to ensure optimum delivery of the inhaled drug to the lungs.

Reduced liver function may affect the elimination of glucocorticosteroids. However, the plasma clearance following an intravenous dose of budesonide 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 inhaled budesonide 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 the 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. If this is not possible, the time interval between administrations of the interacting drugs should be as long as possible. A reduction in the dose of budesonide should also be considered.

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg- Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Hypersensitivity reactions including anaphylaxis, rash, contact dermatitis, urticaria, angioedema, and bronchospasm have been reported with use of budesonide. Discontinue budesonide if such reactions occur.

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

If clinical symptoms become exacerbated by acute respiratory tract infections, treatment with appropriate antibiotics should be considered. The dose of budesonide can be adjusted as required and, in certain situations systemic treatment with glucocorticosteroids may be indicated.

If no improvement of symptoms or adequate asthma control is seen within 14 days of treatment, medical advice is sought for either adjusting the dose or clarifying correct inhalation procedure.

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post-menopausal status, tobacco use, advance age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

4.5 Drug Interactions

The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased.

Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, ketoconazole, erythromycin, HIV protease inhibitors and cobicistat-containing products.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known strong CYP3A4 inhibitors.

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).

Hepatic Impairment

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 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.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Pregnancy Category B. Results from a large prospective epidemiological study and from worldwide post marketing experience 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 doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. Administration of **BUDECORT Inhaler** during pregnancy requires that the benefits for the mother be weighed against the risks for the fetus. **BUDECORT Inhaler** should only be used during pregnancy if the expected benefits outweigh the potential risks. 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. Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Lactation

Budesonide, like other corticosteroids, is secreted in human milk. However, at therapeutic doses of budesonide no effects on the suckling child are anticipated. Budesonide 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

No effects on ability to drive and use machines have been observed.

4.8 Undesirable Effects

Clinical Experience

The following adverse reactions were reported in patients treated with budesonide.

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1116 adult and pediatric patients age 6-70 years (472 females and 644 males) were treated with budesonide (200 to 800 mcg twice daily for 12 to 20 weeks) or placebo.

Table 1 shows the incidence of adverse events in patients previously receiving bronchodilators and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6 to 17 years) and 332 male and 331 female adult patients (age 18 years and greater).

Table 1: Adverse Events with $\geq 3\%$ Incidence reported by Patients on Budesonide

		Budesonide		
Adverse Event	Placebo N=284 %	200 mcg twice daily N=286 %	400 mcg twice daily N=289 %	800 mcg twice daily N=98 %
Respiratory System				
Respiratory infection	17	20	24	19

Pharyngitis	9	10	9	5
Sinusitis	7	11	7	2
Voice alteration	0	1	2	6
Body As A Whole				
Headache	7	14	13	14
Flu syndrome	6	6	6	14
Pain	2	5	5	5
Back pain	1	2	3	6
Fever	2	2	4	0
Digestive System				
Oral candidiasis	2	2	4	4
Dyspepsia	2	1	2	4

Gastroenteritis	1	1	2	3
Nausea	2	2	1	3
Average Duration of Exposure (days)	59	79	80	80

The table above includes all events (whether considered drug-related or non-drug-related by the investigators) that occurred at a rate of $\geq 3\%$ in any one budesonide group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for budesonide patients should be taken into account.

The following other adverse events occurred in these clinical trials using budesonide with an incidence of 1 to 3% and were more common on budesonide than on placebo.

Body As A Whole: neck pain

Cardiovascular: syncope

Digestive: abdominal pain, dry mouth, vomiting

Metabolic and Nutritional: weight gain

Musculoskeletal: fracture, myalgia

Nervous: hypertonia, migraine

Platelet, Bleeding and Clotting: ecchymosis

Psychiatric: insomnia

Resistance Mechanisms: infection

Special Senses: taste perversion

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of budesonide 400 mcg twice daily (N=53) and 800 mcg twice daily (N=53) were compared with placebo (N=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or non-drug-related by the investigators, reported in more than five patients in the budesonide group and which occurred more frequently with budesonide than placebo are shown below (% budesonide and % placebo). In considering these data, the increased average duration of exposure for budesonide patients (78 days for budesonide vs. 41 days for placebo) should be taken into account.

Body as a Whole:

- Asthenia (9% and 2%)
- Headache (12% and 2%)
- Pain (10% and 2%)

Digestive:

- Dyspepsia (8% and 0%)
- Nausea (6% and 0%)
- Oral candidiasis (10% and 0%)

Musculoskeletal:

- Arthralgia (6% and 0%)

Respiratory:

- Cough increased (6% and 2%)
- Respiratory infection (32% and 13%)
- Rhinitis (6% and 2%)
- Sinusitis (16% and 11%)

Patients Receiving Budesonide Once Daily

The adverse event profile of once-daily administration of budesonide 200 mcg and 400 mcg, and placebo, was evaluated in 309 adult asthmatic patients in an 18-week study. The study population included both patients previously treated with inhaled corticosteroids, and patients not previously receiving corticosteroid therapy. There was no clinically relevant difference in the pattern of adverse events following once-daily administration of budesonide when compared with twice-daily dosing.

Pediatric Studies: In a 12-week placebo-controlled trial in 404 pediatric patients 6 to 18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6 to 12 years, 13 to 18 years) was comparable for budesonide (at 100, 200 and 400 mcg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Additional adverse events observed in clinical trials from the European data include:

Infections and Infestations: Pneumonia (in COPD patients)

Immune system disorders: Anaphylactic reaction

Endocrine disorders: Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation*

Psychiatric disorders: Psychomotor hyperactivity, sleep disorders, behavioural changes (predominantly in children)

Nervous system disorder: Tremor

Eye disorder: Vision blurred

Respiratory, thoracic and mediastinal disorders: Hoarseness, throat irritation, Dysphonia

Skin and subcutaneous tissue disorders: Bruising

Musculoskeletal and connective tissue disorders: Muscle spasm

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

Adverse Event Reports from Other Sources

1. Rare adverse events reported in the published literature or from worldwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis. If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com.
2. **Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdosage

Acute overdosage with budesonide, 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 the HPA axis function. No special emergency action needs to be taken. Treatment with **BUDECORT Inhaler** should be continued at the recommended dose to control the asthma.

5.0 PHARMACOLOGY

5.1 Pharmacodynamics

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1,000-fold higher topical anti-

inflammatory potency than cortisol (rat croton oil ear oedema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favourable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first-pass hepatic degradation of orally absorbed drug (85–95%), and the low potency of formed metabolites.

Generally, budesonide has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhalation of budesonide can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer.

Inhaled budesonide has been shown to decrease airway reactivity in various challenge models, including histamine, methacholine, sodium metabisulfite, and control adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pre-treatment with inhaled budesonide 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV₁ following inhaled allergen challenge.

The administration of budesonide in doses up to 800 mcg/day (mean daily dose 445 mcg/day) or via a pressurized metered-dose inhaler in doses up to 1200 mcg/day (mean daily dose 620 mcg/day) to 216 pediatric patients (age 3 to 11 years) for 2 to 6 years had no significant effect on statural growth compared with non-corticosteroid therapy in 62 matched control patients. However, the long-term effect of budesonide on growth is not fully known.

Paediatric Use

Safety and effectiveness of budesonide in pediatric patients below 6 years of age have not been established. Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids including the impact on final adult height are unknown.

The potential for “catch up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of pediatric patients receiving orally inhaled corticosteroids, including budesonide, should be monitored routinely (eg, via stadiometry).

The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks and benefits associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including budesonide, each patient should be titrated to his/her lowest effective dose.

Geriatric Use

No overall differences in safety were observed between these patients and younger patients. Clinical studies did not include sufficient numbers of patients aged 65 years and over to determine differences in efficacy between elderly and younger patients. Other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

5.2 Pharmacokinetics

Absorption:

Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide, peak plasma concentration was achieved in

about 1–2 hours and the absolute systemic availability was 6–13%, due to extensive first-pass metabolism. In contrast, most of the budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs (as assessed by plasma concentration method and using a budesonide-containing dry powder inhaler) with an absolute systemic availability of 39% of the metered dose. Peak steady-state plasma concentrations of budesonide administered by dry powder inhalation in adults with asthma averaged 0.6nmol/L and 1.6nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively. In asthmatic patients, budesonide showed a linear increase in the area under the curve (AUC) and $C_{\max}$ with increasing dose, after both a single dose and repeated dosing of inhaled budesonide.

Distribution:

The volume of distribution of budesonide was approximately 3 L/kg. It was 85–90% bound to plasma proteins. Protein binding was constant over the concentration range (1–100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration-independent manner, with a blood/plasma ratio of about 0.8.

Metabolism:

In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites, formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)-catalysed biotransformation, have been isolated and identified as 16alpha-hydroxyprednisolone and 6beta-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in the human lungs and in serum preparations.

Excretion/Elimination:

The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose. Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Population

No pharmacokinetic differences have been identified due to race, gender or advanced age.

Pediatric

Following intravenous dosing in pediatric patients age 10-14 years, plasma half-life was shorter than in adults (1.5 hours vs. 2.0 hours in adults). In the same population following inhalation of budesonide via a pressurized metered-dose inhaler, absolute systemic availability was similar to that in adults.

Hepatic Impairment

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy subjects.

5.3 Preclinical safety data

Non-clinical data with budesonide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential.

In animal studies on reproductive toxicity, glucocorticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal results do not seem to be relevant for humans given recommended doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tetrafluroethane (HFA-134a Propellant)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

19 ml aluminium aerosol container (Plain) with 50 mcl valve and 0.40 mm Aerosol actuator

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MAH

Cipla Ltd.

Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg,
Lower Parel, Mumbai: 400013.
India

Manufactured by

Cipla Ltd.

UNIT II

Plot No. L-139 to L-146

Verna Industrial Estate, Verna, Goa - 403722,
India.

8. MARKETING AUTHORISATION NUMBER(S)

Budecort 100 Inhaler- H1998/301/11639/R1.

Budecort 200 inhaler : H2002/206/R1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06.08.2025

10. DATE OF REVISION OF THE TEXT

Last Reviewed: 06.08.2025