Aeronide® 200 MCG

Each metered dose contains:
Budesonide 200 mcg

Pressurised metered-dose inhaler

โปรดอ่านรายละเอียดเพิ่มเติมในเอกสารกำกับยา
ใบอนุญาตโฆษณาเลขที่ ฆศ. 179/2556

AeroCare

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Aeronide® 200 MCG

Each puff contains: Budesonide 200 mcg

1. MECHANISM OF ACTION:

Pharmacology:

1.1 Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has an approximately 200-fold higher affinity for the glucocorticoid receptor and a 1,000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, cytokines) involved in allergic and nonallergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma. Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including budesonide inhalation-driven, multi-dose dry powder inhaler and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first-pass hepatic degradation of orally absorbed drug (85% to 95%), and the low potency of metabolites.

1.2 The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1,400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Improvement in the control of asthma symptoms following inhalation of budesonide inhalation suspension can occur within 2 to 8 days of beginning treatment, although maximum benefit may not be achieved for 4 to 6 weeks.

2. INDICATION:

For the maintenance treatment of bronchial asthma as prophylactic therapy

3. POSOLOGY AND METHOD OF ADMINISTRATION:

Aeronide 200 mcg is for oral inhalation use only.

Asthma:

Children 1 – 8 years of age:

Recommended Dosages in Children 1 – 8 years of age

Previous therapy	Recommended starting dose	Highest recommended dose
Bronchodilators alone	500 mcg/day administered either once daily or twice daily in divided doses	500 mcg/day
Inhaled corticosteroids	500 mcg/day administered either once daily or twice daily in divided doses	1000 mcg/day
Oral corticosteroids	1000 mcg/day administered either as 500 mcg twice daily or 1000 mcg once daily	1000 mcg/day

Dosage adjustment: If once-daily treatment does not provide adequate control of asthma symptoms, the total daily dose should be increased or administered as a divided dose.

Symptomatic children not responding to nonsteroidal therapy (e.g., bronchodilator, mast-cell stabilizer): A starting dose of 200 mcg once daily may also be considered.

Children 7 years of age and above:

- Recommended dose is 200 to 800 mcg daily in divided into 2 to 4 administrations
- In children with mild to moderate asthma who have not previously received inhaled glucocorticosteroids, or who are already controlled on inhaled steroids (e.g. budesonide or beclomethasone dipropionate): 200 to 400 mcg daily may be used in divided into 2 administrations.
- During periods of severe asthma, the daily dose can be increased up to 800 mcg.

Adults and children over 12 years of age:

- Recommended dose is 200 to 1600 mcg daily divided into 2 to 4 administrations.
- In less severe cases 200 to 800 mcg daily (200 to 400 mcg may be used in patients with mild to moderate asthma who have not previously received inhaled glucocorticosteroids and up to 800 mcg may be used by patients with mild to moderate asthma already controlled on inhaled steroids e.g. budesonide or beclomethasone dipropionate, administered twice daily.)
- In more severe cases 800 to 1600 mcg daily. Administration twice daily (morning and evening) is usually sufficient. In severe asthma and during exacerbations some patients may benefit from dividing the daily dose into 3 to 4 administrations per day. In mild asthmatics requiring up to 400 mcg daily for symptom control, the dose could be given once daily in the morning or in the evening.

The maintenance dose should be individualised and should be the lowest dose which leaves the patient symptom-free. Recommended doses are 100 to 400 mcg/ daily. This may be given as a twice daily dose, or as a once daily dose given in the morning or the evening.

4. CONTRAINDICATIONS:

- Hypersensitivity to budesonide or any of the ingredients in its preparations.
- Budesonide is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

5. PRECAUTIONS:

5.1 **Steroid withdrawal:** Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids (eg, budesonide) because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.

5.2 **Acute stress/severe asthma attack:** During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction.

5.3 **Transfer from systemic steroids:** Transfer of patients from systemic corticosteroid therapy to budesonide may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (eg, rhinitis, conjunctivitis, eczema).

5.4 **Compromised immune system:** Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on immunosuppressant doses of corticosteroids. In children or adult patients who have not had these diseases, or who have not been properly vaccinated, 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 unknown.

5.5 **Acute asthma:** Budesonide is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

5.6 **Bronchospasm:** If bronchospasm occurs following dosing with budesonide, it should be treated immediately with a fast-acting inhaled bronchodilator.

5.7 **Inhalation suspension:** For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. Read patient instructions before using.

5.8 **Systemic corticosteroid effects:**

- Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response
- Although patients in clinical trials have received budesonide powder for inhalation on a continuous basis for periods of 1 to 2 years and budesonide inhalation suspension on a continuous basis for up to 1 year, the long-term local and systemic effects of budesonide in human subjects are not completely known. In particular, the effects resulting from chronic use of budesonide on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

5.9 **Vision:** Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

5.10 **Special risk patients:** Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex.

5.11 **Carcinogenesis:** In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis).

5.12 **Mutagenesis:** Budesonide was not mutagenic or clastogenic.

5.13 **Fertility impairment:** No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

5.14 **Monitoring:** A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment.

6. WARNINGS:

6.1 Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids (eg, budesonide) because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA-axis function.

6.2 Patients who have been previously maintained on greater than or equal to 20 mg/day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

6.3 During this period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although budesonide may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

6.4 During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

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

6.6 **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.

6.7 **Steroid-dependent patients:** When transferral from oral steroids to Aeronide 200 mcg is started, the patient should be in a relatively stable phase. A high dose of Aeronide 200 mcg 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 Aeronide 200 mcg for the oral steroid.

6.8 During transfer from oral therapy to Aeronide 200 mcg, 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.

6.9 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.

6.10 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.

6.11 Acute exacerbations of asthma may need an increase in the dose of Aeronide 200 mcg 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.

6.12 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.

6.13 Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may result in clinically significant adrenal suppression.

6.14 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.

6.15 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.

6.16 Reduced liver function may affect the elimination of glucocorticosteroids.

6.17 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.

7. DRUG INTERACTIONS:

- In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse reactions.
- Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

8. PREGNANCY:

8.1 **Teratogenic Effects:** As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats.

8.2 Experience with oral corticosteroids in pharmacologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

8.3 Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy.

8.4 These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

8.5 Nevertheless, because the studies in humans cannot rule out the possibility of harm, budesonide inhalation should be used during pregnancy only if clearly needed.

8.6 **Nonteratogenic Effects:** Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

9. LACTATION:

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

10. PEDIATRIC USE:

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. To minimize the systemic effects of inhaled corticosteroids, including budesonide inhalation suspension, each patient should be titrated to his or her lowest effective dose.

11. GERIATRIC USE:

Of the 215 patients in 3 clinical trials of budesonide inhalation suspension in adult patients, 65 (30%) were greater than or equal to 65 years of age, while 22 (10%) were greater than or equal to 75 years of age. No overall differences in safety were observed between these patients and younger patients.

12. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

It does not affect the ability to drive or to use machines.

13. UNDESIRABLE EFFECTS:

Adverse reactions with ≥ 3% incidence reported by patients on budesonide inhalation suspension

Adverse reactions	Vehicle placebo (n = 227) %	Budesonide inhalation suspension total daily dose		
		0.25 mg (n = 178) %	0.5 mg (n = 223) %	1 mg (n = 317) %
Respiratory				
Respiratory tract infection	36%	34%	35%	38%
Rhinitis	9%	7%	11%	12%
Coughing	5%	5%	9%	8%
GI				
Gastroenteritis	4%	5%	5%	5%
Vomiting	3%	2%	4%	4%
Diarrhea	2%	4%	4%	2%
Abdominal pain	2%	3%	2%	3%

14. OVERDOSE:

14.1 The potential for acute toxic effects following overdose of budesonide inhalation is low.

14.2 In mice the minimal lethal inhalation dose was 100 mg/kg (approximately 410 or 120 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m^2 basis). In rats there were no deaths at an inhalation dose of 68 mg/kg (approximately 550 or 160 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m^2 basis).

14.3 **Sign and Symptoms:** 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. No special emergency action needs to be taken.

14.4 **Treatment:** Treatment should be continued at the recommended dose to control the asthma.

15. 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: RO3B A02.

16. PHARMACOKINETIC PROPERTIES:

16.1 Absorption:

In asthmatic children 4 to 6 years of age, the total absolute bioavailability (ie, lung + oral) following administration of budesonide inhalation suspension via jet nebulizer was approximately 6% of the labeled dose. The peak plasma concentration of budesonide occurred 10 to 30 minutes after start of nebulization.

16.2 Distribution:

In asthmatic children 4 to 6 years of age, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults.

16.3 Metabolism:

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16-hydroxy-prednisolone and 6ß-hydroxybudesonide. The corticosteroid activity of each of these 2 metabolites is less than 1% of that of the parent compound. No qualitative difference between the in vitro and in vivo metabolic patterns have been detected.

16.4 Excretion:

Budesonide is excreted in urine and faces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

16.5 Special Populations:

Hepatic Function Impairment: Reduced liver function may affect the elimination of corticosteroids.

Children: - Following IV dosing in children age 10 to 14 years, plasma half-life was shorter than in adults (1.5 hours vs 2 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.

17. 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.

18. INFORMATION FOR THE PATIENT:

For instructions on the proper use of Aeronide 200 mcg and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the accompanying patient information and instructions carefully.

- Patients should take Aeronide 200 mcg at regular intervals once or twice a day as directed, since its effectiveness depends on regular use.
- The effects of mixing Aeronide 200 mcg with other nebulizable medications have not been adequately assessed. Aeronide 200 mcg should be administered separately in the nebulizer.
- Aeronide 200 mcg is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.
- Aeronide 200 mcg should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask.
- Ultrasonic nebulizers are not suitable for the adequate administration of Aeronide 200 mcg and, therefore, are not recommended.
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis.
- Improvement in asthma control following treatment with Aeronide 200 mcg can occur within 2 to 8 days of beginning treatment, although maximum benefit may not be achieved for 4 to 6 weeks after starting treatment.
- Care should be taken to avoid exposure to chickenpox and measles.
- Aeronide 200 mcg should be stored upright at controlled room temperature 20° to 25°C (68° to 77°F) and protected from light. Aeronide 200 mcg should not be refrigerated or frozen.

HOW SUPPLIED/STORAGE AND HANDLING

Available pack: Aeronide 200 mcg is supplied in the following packs as a pressurized aluminum canister sealed with a metering valve, actuator and dust cap canister contains 200 metered actuations providing 200 micrograms of Budesonide.

Storage: Keep in tight containers, protected from light, Store below 30°C

Handling precaution:

- Keep out of reach of children. Avoid spraying in eyes.
- Contents under pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 50°C may cause bursting. Never throw container into fire or incinerator.
- Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL BEFORE EACH SPRAY.
- It does not contain chlorofluorocarbons (CFCs) as the propellant.

AeroCare

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