

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BECLOMETHASONE DIPROPIONATE HFA INHALATION AEROSOL safely and effectively. See full prescribing information for BECLOMETHASONE DIPROPIONATE HFA INHALATION AEROSOL.

BECLOMETHASONE DIPROPIONATE HFA inhalation aerosol, for oral inhalation use

Initial U.S. Approval: 1976

INDICATIONS AND USAGE

Beclomethasone dipropionate HFA inhalation aerosol is a corticosteroid indicated for:

- Maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. (1)

Important Limitations:

- Not indicated for the relief of acute bronchospasm. (1)

DOSAGE AND ADMINISTRATION

For oral inhalation only. (2.1)

- Starting dosage is based on prior asthma therapy and disease severity. (2.2)
- Treatment of asthma in patients 12 years and older: 40 mcg, 80 mcg, 160 mcg, or 320 mcg twice daily. (2.2)
- Treatment of asthma in patients 5 to 11 years of age: 40 or 80 mcg twice daily. (2.2)
- Discard beclomethasone dipropionate HFA inhalation aerosol inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. (2.1)

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: 40 or 80 mcg per actuation (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. (4)
- Hypersensitivity to any of the ingredients of beclomethasone dipropionate HFA inhalation aerosol. (4)

WARNINGS AND PRECAUTIONS

- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth with water without swallowing after inhalation. (5.1)
- Deterioration of asthma and acute episodes: Do not use beclomethasone dipropionate HFA inhalation aerosol for

relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)

- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to beclomethasone dipropionate HFA inhalation aerosol. (5.3)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. Use with caution in patients with these infections because of the potential for worsening of these infections. (5.4)
- Paradoxical Bronchospasm: Bronchospasm, with an immediate increase in wheezing, may occur after dosing. Treat bronchospasm immediately with inhaled, short-acting bronchodilator and discontinue beclomethasone dipropionate HFA inhalation aerosol. (5.5)
- Hypersensitivity Reactions: Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm may occur. Discontinue beclomethasone dipropionate HFA inhalation aerosol if such reactions occur. (5.6)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue beclomethasone dipropionate HFA inhalation aerosol slowly. (5.7)
- Effects on growth: Monitor growth of pediatric patients. (5.8)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.9)
- Eye Disorders: Monitor patients with change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts closely. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 3\%$ and $>$ placebo) include headache, pharyngitis, oral symptoms (inhalation route), and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Beclomethasone dipropionate HFA inhalation aerosol is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older.

Important Limitations of Use:

- Beclomethasone dipropionate HFA inhalation aerosol is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer beclomethasone dipropionate HFA inhalation aerosol by the orally inhaled route in patients 5 years of age and older. Beclomethasone dipropionate HFA inhalation aerosol does not require shaking prior to use. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

Use of beclomethasone dipropionate HFA inhalation aerosol with a spacer device in children less than 5 years of age is not recommended [*see Use in Specific Populations (8.4)*].

Patients should be instructed on the proper use of their inhaler. Consistent dose delivery is achieved, whether using the 40 or 80 mcg strengths, due to proportionality of the 2 products (i.e., 2 actuations of 40 mcg strength should provide a dose comparable to 1 actuation of the 80 mcg strength).

Priming: Patients should prime beclomethasone dipropionate HFA inhalation aerosol by actuating into the air twice before using for the first time or if beclomethasone dipropionate HFA inhalation aerosol has not been used for over 10 days. Avoid spraying in the eyes or face when priming beclomethasone dipropionate HFA inhalation aerosol.

Dose Counter: Beclomethasone dipropionate HFA inhalation aerosol has a dose counter window located on the back of the actuator. When the patient receives the inhaler, “122” will appear in the viewing window until it has been primed 2 times, at which point the total number of actuations will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of one (e.g., 120, 119, 118, etc). When the dose counter reaches “20”, it is a reminder to the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill.

Discard beclomethasone dipropionate HFA inhalation aerosol inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

2.2 Recommended Dosage

Adults and Adolescents 12 years of age and older

The starting dosage is based on previous asthma therapy and disease severity, including consideration of the patients' current control of asthma symptoms and risk of future exacerbation. The recommended starting dosage for patients 12 years of age and older who are not on an inhaled corticosteroid is 40 to 80 mcg twice daily, approximately 12 hours apart. For patients switching to beclomethasone dipropionate HFA inhalation aerosol from another inhaled corticosteroid product, select the appropriate starting dosage strength of beclomethasone dipropionate HFA inhalation aerosol based on the strength of the previous inhaled corticosteroid product and disease severity: 40, 80, 160 or 320 mcg twice daily. For patients who do not respond adequately to the initial dosage after 2 weeks of therapy, increasing the dosage may provide additional asthma control. The maximum recommended dosage for patients 12 years of age and older is 320 mcg twice daily.

Pediatric Patients 5 to 11 years

The starting dosage is based on previous asthma therapy and disease severity, including consideration of the patients' current control of asthma symptoms and risk of future exacerbation. The recommended starting dosage for patients aged 5 to 11 years of age is 40 mcg twice daily, approximately 12 hours apart. For patients who do not respond adequately to beclomethasone dipropionate HFA inhalation aerosol 40 mcg after 2 weeks of therapy, increasing the dosage to beclomethasone dipropionate HFA inhalation aerosol 80 mcg twice daily may provide additional asthma control. The maximum recommended dosage for patients 5 to 11 years of age is 80 mcg twice daily.

General Dosing Recommendations

The onset and degree of symptom relief will vary in individual patients. Improvement in asthma symptoms can occur within 24 hours of the beginning of treatment and should be expected within the first or second week, but maximum benefit should not be expected until 3 to 4 weeks of therapy. Improvement in pulmonary function is usually apparent within 1 to 4 weeks after the start of therapy.

If a dosage regimen of beclomethasone dipropionate HFA inhalation aerosol fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options (e.g., replacing the current strength of beclomethasone dipropionate HFA inhalation aerosol with a higher strength, or adding additional controller therapies) should be considered.

As with any inhaled corticosteroid, physicians are advised to titrate the dose of beclomethasone dipropionate HFA inhalation aerosol downward over time to the lowest level that maintains proper asthma control. This is particularly important in children since a controlled study has shown that beclomethasone dipropionate HFA inhalation aerosol has the potential to affect growth in children.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Aerosol: Beclomethasone dipropionate HFA inhalation aerosol is a pressurized, metered-dose aerosol with a dose counter intended for oral inhalation containing beclomethasone dipropionate, USP in the following 2 strengths:

Beclomethasone dipropionate HFA inhalation aerosol 40 mcg is supplied in a pressurized aluminum canister with a plastic actuator (beige actuator with light blue dust cap). Each actuation delivers 50 mcg of beclomethasone dipropionate, USP from the valve and 40 mcg from the actuator. Beclomethasone dipropionate HFA inhalation aerosol 40 mcg is available as a 120-inhalation/8.7 g canister.

Beclomethasone dipropionate HFA inhalation aerosol 80 mcg is supplied in a pressurized aluminum canister with a plastic actuator (dark pink actuator with gray dust cap). Each actuation delivers 100 mcg of beclomethasone dipropionate, USP from the valve and 80 mcg from the actuator. Beclomethasone dipropionate HFA inhalation aerosol 80 mcg is available as a 120-inhalation/8.7 g canister.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

Beclomethasone dipropionate HFA inhalation aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

4.2 Hypersensitivity

Beclomethasone dipropionate HFA inhalation aerosol is contraindicated in patients with known hypersensitivity to beclomethasone dipropionate or any of the ingredients in beclomethasone dipropionate HFA inhalation aerosol [see *Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Local Effects

Localized infections with *Candida albicans* have occurred in the mouth and pharynx in some patients receiving beclomethasone dipropionate HFA inhalation aerosol. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with beclomethasone dipropionate HFA inhalation aerosol therapy, but at times therapy with beclomethasone dipropionate HFA inhalation aerosol may need to be temporarily interrupted under close medical supervision. Rinsing the mouth with water without swallowing after inhalation is advised.

5.2 Deterioration of Asthma and Acute Episodes

Beclomethasone dipropionate HFA inhalation aerosol is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta-2 agonist, not beclomethasone dipropionate HFA inhalation aerosol, should be used to relieve acute symptoms such as shortness of breath. Instruct patients to contact their physician immediately if episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with beclomethasone dipropionate HFA inhalation aerosol. During such episodes, patients may require therapy with oral corticosteroids.

5.3 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed in patients who are transferred from systemically active corticosteroids to beclomethasone dipropionate HFA inhalation aerosol 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 hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections (particularly gastroenteritis) or other conditions with severe electrolyte loss. Although beclomethasone dipropionate HFA inhalation aerosol may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid that is necessary for coping with these emergencies.

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

Patients requiring oral or other systemic corticosteroids should be weaned slowly from oral or other systemic corticosteroid use after transferring to beclomethasone dipropionate HFA inhalation aerosol. Lung function (FEV₁ or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral or other systemic 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.

Transfer of patients from systemic corticosteroid therapy to beclomethasone dipropionate HFA inhalation aerosol may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

5.4 Immunosuppression

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection. Nor is the contribution of the underlying disease and/or prior corticosteroid treatment known. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

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, parasitic or viral infections; or ocular herpes simplex.

5.5 Paradoxical Bronchospasm

Inhaled corticosteroids may produce inhalation induced bronchospasm with an immediate increase in wheezing after dosing that may be life-threatening. If inhalation induced bronchospasm occurs following dosing with beclomethasone dipropionate HFA inhalation aerosol, it should be treated immediately with an inhaled, short-

acting bronchodilator. Treatment with beclomethasone dipropionate HFA inhalation aerosol should be discontinued and alternate therapy instituted.

5.6 Immediate Hypersensitivity Reactions

Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm, may occur after administration of beclomethasone dipropionate HFA inhalation aerosol. Discontinue beclomethasone dipropionate HFA inhalation aerosol if such reactions occur [*see Contraindications (4.2)*].

5.7 Hypercorticism and Adrenal Suppression

Beclomethasone dipropionate HFA inhalation aerosol will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since beclomethasone dipropionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of beclomethasone dipropionate HFA inhalation aerosol in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with beclomethasone dipropionate HFA inhalation aerosol 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.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when beclomethasone dipropionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of beclomethasone dipropionate HFA inhalation aerosol should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.8 Effects on Growth

Orally inhaled corticosteroids, including beclomethasone dipropionate HFA inhalation aerosol, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving beclomethasone dipropionate HFA inhalation aerosol routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including beclomethasone dipropionate HFA inhalation aerosol, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [*see Use in Specific Populations (8.4)*].

5.9 Reduction in Bone Mineral Density

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 outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

5.10 Eye Disorders

Glaucoma, increased intraocular pressure, blurred vision and cataracts have been reported following the use of long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a

change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma and/or cataracts while using beclomethasone dipropionate HFA inhalation aerosol.

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection [see Warnings and Precautions (5.1)]
- Immunosuppression [see Warnings and Precautions (5.4)]
- Hypercorticism and adrenal suppression [see Warnings and Precautions (5.7)]
- Growth effects [see Warnings and Precautions (5.8) and Use in Specific Populations (8.4)]
- Eye Disorders [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following reporting rates of common adverse experiences are based upon 4 clinical trials in which 1196 patients (671 female and 525 male adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with beclomethasone dipropionate HFA inhalation aerosol (doses of 40, 80, 160, or 320 mcg twice daily) or CFC-BDP (doses of 42, 168, or 336 mcg twice daily) or placebo. Table 1 below includes all events reported by patients taking beclomethasone dipropionate HFA inhalation aerosol (whether considered drug related or not) that occurred at a rate over 3% for beclomethasone dipropionate HFA inhalation aerosol. In considering these data, difference in average duration of exposure and clinical trial design should be taken into account.

Table 1 Adverse Events Reported by at Least 3% of the Patients for Beclomethasone Dipropionate HFA Inhalation Aerosol by Treatment and Daily Dose

Adverse Events	Placebo (N=289) %	Beclomethasone Dipropionate HFA Inhalation Aerosol			
		Total (N=624) %	80 to 160 mcg (N=233) %	320 mcg (N=335) %	640 mcg (N=56) %
Headache	9	12	15	8	25
Pharyngitis	4	8	6	5	27
Upper Respiratory Tract Infection	11	9	7	11	5
Rhinitis	9	6	8	3	7
Increased Asthma Symptoms	18	3	2	4	0
Oral Symptoms Inhalation Route	2	3	3	3	2
Sinusitis	2	3	3	3	0
Pain	<1	2	1	2	5
Back Pain	1	1	2	<1	4
Dysphonia	2	<1	1	0	4

Other adverse events that occurred in these clinical trials using beclomethasone dipropionate HFA inhalation aerosol with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were nausea, dysmenorrhea, and coughing. Oropharyngeal candidiasis occurred in <1% of patients in both beclomethasone dipropionate HFA inhalation aerosol and placebo treatment groups.

Pediatric Studies

In two 12-week placebo-controlled studies in steroid naive pediatric patients 5 to 12 years of age, no clinically relevant differences were found in the pattern, severity, or frequency of adverse events compared with those reported in adults, with the exception of conditions which are more prevalent in a pediatric population generally.

6.2 Postmarketing Experience

In addition to adverse reactions experienced in the clinical trials, the following adverse events have been reported during post-approval use of beclomethasone dipropionate HFA inhalation aerosol. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Local Effects: Localized infections with *Candida albicans* have occurred in patients treated with beclomethasone dipropionate HFA inhalation aerosol or other orally inhaled corticosteroids [see *Warnings and Precautions* (5.1)].

Psychiatric and Behavioral Changes: Aggression, depression, sleep disorders, psychomotor hyperactivity, and suicidal ideation have been reported (primarily in children).

Eye Disorders: Blurred vision, central serous chorioretinopathy (CSC).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with beclomethasone dipropionate HFA inhalation aerosol or beclomethasone dipropionate in pregnant women. There are clinical considerations with the use of inhaled corticosteroids (ICS), including beclomethasone dipropionate, in pregnant women [see *Clinical Considerations*]. Also, no published studies, including studies of large birth registries, have to date related the use of ICS to any increases in congenital malformations or other adverse perinatal outcomes. Thus, available human data do not establish the presence or absence of drug-associated risk to the fetus. In animal reproduction studies, beclomethasone dipropionate resulted in adverse developmental effects in mice and rabbits at subcutaneous doses equal to or greater than approximately 0.75 times the maximum recommended human daily inhalation dose (MRHDID) in adults (0.64 mg/day) [see *Data*]. In rats exposed to beclomethasone dipropionate by inhalation, dose-related gross injury to the fetal adrenal glands was observed at doses greater than 180 times the MRHDID, but there was no evidence of external or skeletal malformations or embryoletality at inhalation doses up to 440 times the MRHDID.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the US general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk

The risk of complications to the mother and developing fetus from inadequate control of asthma must be balanced against the risks from exposure to beclomethasone dipropionate. In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight and small for gestational age for the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Labor or Delivery

There are no specific human data regarding any adverse effects of inhaled beclomethasone dipropionate on labor and delivery.

Data

Animal Data

In an embryofetal development study in pregnant rats, beclomethasone dipropionate administration during organogenesis from gestation days 6 to 15 at inhaled doses 180 times the MRHDID in adults and higher (on a mg/m^2 basis at maternal doses of 11.5 and 28.3 $\text{mg}/\text{kg}/\text{day}$) produced dose-dependent gross injury (characterized by red foci) of the adrenal glands in fetuses. There were no findings in the adrenal glands of rat fetuses at an inhaled dose that was 40 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 2.4 $\text{mg}/\text{kg}/\text{day}$). There was no evidence of external or skeletal malformations or embryoletality in rats at inhaled doses up to 440 times the MRHDID (on a mg/m^2 basis at maternal doses up to 28.3 $\text{mg}/\text{kg}/\text{day}$).

In an embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 18 at subcutaneous doses equal to and greater than 0.75 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 0.1 $\text{mg}/\text{kg}/\text{day}$ and higher) produced adverse developmental effects (increased incidence of cleft palate). A no-effect dose in mice was not identified. In a second embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 13 at subcutaneous doses equal to and greater than 2.3 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 0.3 $\text{mg}/\text{kg}/\text{day}$) produced embryoletal effects (increased fetal resorptions) and decreased pup survival.

In an embryofetal development study in pregnant rabbits, beclomethasone dipropionate administration during organogenesis from gestation days 7 to 16 at subcutaneous doses equal to and greater than 0.75 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 0.025 $\text{mg}/\text{kg}/\text{day}$ and higher) produced external and skeletal malformations and embryoletal effects (increased fetal resorptions). There were no effects in fetuses of pregnant rabbits administered a subcutaneous dose 0.2 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 0.006 $\text{mg}/\text{kg}/\text{day}$).

8.2 Lactation

Risk Summary

There are no data available on the presence of beclomethasone dipropionate in human milk, the effects on the breastfed child, or the effects on milk production. However, other inhaled corticosteroids have been detected in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for beclomethasone dipropionate HFA inhalation aerosol and any potential adverse effects on the breastfed child from beclomethasone dipropionate or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Impairment of fertility was observed in rats and dogs at oral doses of beclomethasone dipropionate corresponding to 250 and 25 times the MRHDID for adults on a mg/m² basis, respectively [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

Eight-hundred and thirty-four children between the ages of 5 and 12 were treated with HFA beclomethasone dipropionate (HFA-BDP) in clinical trials. The safety and effectiveness of beclomethasone dipropionate HFA inhalation aerosol in children below 5 years of age have not been established.

Use of beclomethasone dipropionate HFA inhalation aerosol with a spacer device in children less than 5 years of age is not recommended. *In vitro* dose characterization studies were performed with beclomethasone dipropionate HFA inhalation aerosol 40 mcg/actuation with the OptiChamber and AeroChamber Plus[®] spacer utilizing inspiratory flows representative of children under 5 years old. These studies indicated that the amount of medication delivered through the spacing device decreased rapidly with increasing wait times of 5 to 10 seconds as shown in Table 2. If beclomethasone dipropionate HFA inhalation aerosol is used with a spacer device, it is important to inhale immediately.

Based on the average inspiratory flow rates generated by children 6 months to 5 years old, the projected daily dose derived from beclomethasone dipropionate HFA inhalation aerosol 40 mcg at one puff per day at various wait times is depicted in Table 2 below:

Table 2 Average Daily Dose Based on Wait Time in Pediatric Patients

	Wait time, seconds	Mean medication delivery through AeroChamber mcg/actuationⁱ	Body Weight 50th percentile, kgⁱⁱ	Medication delivered per dose, mcg/kg^{iii, iv}
Age 6 months, Flow rate 4.8 L/min	0	11.5	7.6	1.2
Age 2 years, Flow rate 8.2 L/min	0	14.1	13.5	0.83
Age 2 years, Flow rate 8.2 L/min	5	5.4	13.5	0.32
Age 2 years, Flow rate 8.2 L/min	10	3.9	13.5	0.23
Age 5 years, Flow rate 11.0 L/min	0	17.5	18	0.78

ⁱ Summary Report; Pediatric Dose Characterization of beclomethasone dipropionate HFA inhalation aerosol with Spacer; 3M Pharmaceutical Development, July 21, 2004

ⁱⁱ CDC Growth charts, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

ⁱⁱⁱ Includes an estimated 20% loss in the masks

^{iv} Beclomethasone dipropionate HFA inhalation aerosol 40 mcg in an average adult without using a spacer delivers approximately 0.4 mcg/kg, or bid, 0.8 mcg/kg/day.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. A 12-month, randomized, controlled clinical trial evaluated the effects of HFA beclomethasone dipropionate without spacer versus CFC beclomethasone dipropionate with large-volume spacer on growth in children age 5 to 11. A total of 520 patients were enrolled, of whom 394 received HFA-BDP (100 to 400 mcg/day ex-valve) and 126 received CFC-BDP (200 to 800 mcg/day ex-valve). Similar control of asthma was noted in each treatment arm. When comparing results at month 12 to baseline, the mean

growth velocity in children treated with HFA-BDP was approximately 0.5 cm/year less than that noted with children treated with CFC-BDP via large-volume spacer. The long-term effects of the 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.

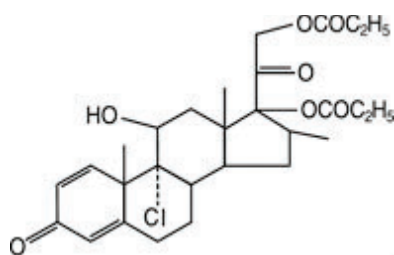
The growth of children and adolescents receiving orally inhaled corticosteroids, including beclomethasone dipropionate HFA inhalation aerosol, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including beclomethasone dipropionate HFA inhalation aerosol, each patient should be titrated to his/her lowest effective dose [*see Dosage and Administration (2.2)*].

8.5 Geriatric Use

Clinical studies of beclomethasone dipropionate HFA inhalation aerosol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical 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.

11 DESCRIPTION

The active component of beclomethasone dipropionate HFA inhalation aerosol 40 mcg inhalation aerosol and beclomethasone dipropionate HFA inhalation aerosol 80 mcg inhalation aerosol is beclomethasone dipropionate, USP, a corticosteroid having the chemical name 9-chloro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. Beclomethasone dipropionate, USP (BDP) is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. Beclomethasone differs from dexamethasone in having a chlorine at the 9-alpha carbon in place of a fluorine, and in having a 16 beta-methyl group instead of a 16 alpha-methyl group. Beclomethasone dipropionate, USP is a white to creamy white, odorless powder with a molecular formula of C₂₈H₃₇ClO₇ and a molecular weight of 521.1. Its chemical structure is:



Beclomethasone dipropionate HFA inhalation aerosol is a pressurized, metered-dose aerosol with a dose counter intended for oral inhalation only. Each unit contains a solution of beclomethasone dipropionate, USP in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. Beclomethasone dipropionate HFA inhalation aerosol 40 mcg delivers 40 mcg of beclomethasone dipropionate, USP from the actuator and 50 mcg from the valve. Beclomethasone dipropionate HFA inhalation aerosol 80 mcg delivers 80 mcg of beclomethasone dipropionate, USP from the actuator and 100 mcg from the valve. Both products deliver 50 microliters (59 milligrams) of solution formulation from the valve with each actuation. The 40 mcg canisters and the 80 mcg canisters provide 120 inhalations each. Beclomethasone dipropionate HFA inhalation aerosol should be "primed" or actuated twice prior to taking the first dose from a new canister, or when the inhaler has not been

used for more than 10 days. Avoid spraying in the eyes or face while priming beclomethasone dipropionate HFA inhalation aerosol. This product does not contain chlorofluorocarbons (CFCs).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Beclomethasone dipropionate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines). These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monoester, 17 monopropionate (17-BMP). Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. The clinical significance of these findings is unknown.

Studies in patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of beclomethasone dipropionate HFA inhalation aerosol.

12.2 Pharmacodynamics

HPA Axis Effects

The effects of beclomethasone dipropionate HFA inhalation aerosol on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 40 corticosteroid-naïve patients. Beclomethasone dipropionate HFA inhalation aerosol, at doses of 80, 160 or 320 mcg twice daily was compared with placebo and 336 mcg twice daily of beclomethasone dipropionate in a CFC propellant based formulation (CFC-BDP). Active treatment groups showed an expected dose-related reduction in 24-hour urinary-free cortisol (a sensitive marker of adrenal production of cortisol). Patients treated with the highest dose recommended of beclomethasone dipropionate HFA inhalation aerosol (320 mcg twice daily) had a 37.3% reduction in 24-hour urinary-free cortisol compared to a reduction of 47.3% produced by treatment with 336 mcg twice daily of CFC-BDP. There was a 12.2% reduction in 24-hour urinary-free cortisol seen in the group of patients that received 80 mcg twice daily of beclomethasone dipropionate HFA inhalation aerosol and a 24.6% reduction in the group of patients that received 160 mcg twice daily. An open label study of 354 asthma patients given beclomethasone dipropionate HFA inhalation aerosol at recommended doses for one year assessed the effect of beclomethasone dipropionate HFA inhalation aerosol treatment on the HPA axis (as measured by both morning and stimulated plasma cortisol). Less than 1% of patients treated for one year with beclomethasone dipropionate HFA inhalation aerosol had an abnormal response (peak less than 18 mcg/dL) to short-cosyntropin test.

12.3 Pharmacokinetics

Beclomethasone dipropionate (BDP) undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption. The pharmacokinetics of 17-BMP has been studied in asthmatics given single doses.

Absorption

The mean peak plasma concentration ($C_{\max}$) of BDP was 88 pg/ml at 0.5 hour after inhalation of 320 mcg using beclomethasone dipropionate HFA inhalation aerosol (4 actuations of the 80 mcg/actuation strength). The mean peak plasma concentration of the major and most active metabolite, 17-BMP, was 1419 pg/ml at 0.7 hour after inhalation of 320 mcg of beclomethasone dipropionate HFA inhalation aerosol. When the same nominal dose is provided by the two beclomethasone dipropionate HFA inhalation aerosol strengths (40 and 80 mcg/actuation), equivalent systemic pharmacokinetics can be expected. The $C_{\max}$ of 17-BMP increased dose proportionally in the dose range of 80 and 320 mcg.

Metabolism

Three major metabolites are formed via cytochrome P450-3A catalyzed biotransformation: beclomethasone-17-monopropionate (17-BMP), beclomethasone-21-monopropionate (21-BMP) and beclomethasone (BOH). Lung slices metabolize BDP rapidly to 17-BMP and more slowly to BOH. 17-BMP is the most active metabolite.

Distribution

The *in vitro* protein binding for 17-BMP was reported to be 94% to 96% over the concentration range of 1000 to 5000 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of BDP or its metabolites.

Elimination

The major route of elimination of inhaled BDP appears to be via hydrolysis. More than 90% of inhaled BDP is found as 17-BMP in the systemic circulation. The mean elimination half-life of 17-BMP is 2.8 hours. Irrespective of the route of administration (injection, oral or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine.

Special Populations

Formal pharmacokinetic studies using beclomethasone dipropionate HFA inhalation aerosol were not conducted in any special populations.

Pediatrics

The pharmacokinetics of 17-BMP, including dose and strength proportionalities, is similar in children and adults, although the exposure is highly variable. In 17 children (mean age 10 years), the $C_{\max}$ of 17-BMP was 787 pg/ml at 0.6 hour after inhalation of 160 mcg (4 actuations of the 40 mcg/actuation strength of HFA beclomethasone dipropionate). The systemic exposure to 17-BMP from 160 mcg of HFA-BDP administered without a spacer was comparable to the systemic exposure to 17-BMP from 336 mcg CFC-BDP administered with a large volume spacer in 14 children (mean age 12 years). This implies that approximately twice the systemic exposure to 17-BMP would be expected for comparable mg doses of HFA-BDP without a spacer and CFC-BDP with a large volume spacer.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of treatment-related increases in the incidence of tumors in this study at the highest dose, which is approximately 37 and 72 times the MRHDID in adults and children, respectively, on a mg/m² basis.

Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 250 times the MRHDID in adults on a mg/m² basis). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 25 times the MRHDID in adults on a mg/m² basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 17 times the MRHDID in adults on a mg/m² basis).

14 CLINICAL STUDIES

Blinded, randomized, parallel, placebo-controlled and active-controlled clinical studies were conducted in 940 adult asthma patients to assess the efficacy and safety of beclomethasone dipropionate HFA inhalation aerosol in the treatment of asthma. Fixed doses ranging from 40 mcg to 160 mcg twice daily were compared to placebo, and doses ranging from 40 mcg to 320 mcg twice daily were compared with doses of 42 mcg to 336 mcg twice daily of an active CFC-BDP comparator. These studies provided information about appropriate dosing through a range of asthma severity. A blinded, randomized, parallel, placebo-controlled study was conducted in 353 pediatric patients (age 5 to 12 years) to assess the efficacy and safety of HFA beclomethasone dipropionate in the treatment of asthma. Fixed doses of 40 mcg and 80 mcg twice daily were compared with placebo in this study. In these adult and pediatric efficacy trials, at the doses studied, measures of pulmonary function [forced expiratory volume in 1 second (FEV₁) and morning peak expiratory flow (AM PEF)] and asthma symptoms were significantly improved with beclomethasone dipropionate HFA inhalation aerosol treatment when compared to placebo.

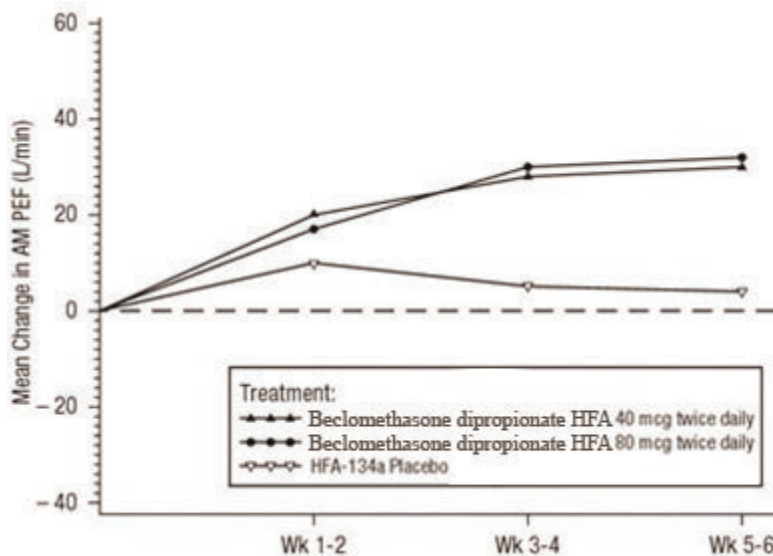
In controlled clinical trials with adult patients not adequately controlled with beta-agonist alone, beclomethasone dipropionate HFA inhalation aerosol was effective at improving asthma control at doses as low as 40 mcg twice daily (80 mcg/day). Comparable asthma control was achieved at lower daily doses of beclomethasone dipropionate HFA inhalation aerosol than with CFC-BDP. Treatment with increasing doses of both beclomethasone dipropionate HFA inhalation aerosol and CFC-BDP generally resulted in increased improvement in FEV₁. In this trial the improvement in FEV₁ across doses was greater for beclomethasone dipropionate HFA inhalation aerosol than for CFC-BDP, indicating a shift in the dose response curve for beclomethasone dipropionate HFA inhalation aerosol.

14.1 Adult and Adolescent Patients Greater Than 12 Years of Age

Patients not Previously Receiving Corticosteroid Therapy

In a 6-week clinical trial, 270 steroid-naïve patients with symptomatic asthma being treated with as-needed beta-agonist bronchodilators, were randomized to receive either 40 mcg twice daily of beclomethasone dipropionate HFA inhalation aerosol, 80 mcg twice daily of beclomethasone dipropionate HFA inhalation aerosol, or placebo. Both doses of beclomethasone dipropionate HFA inhalation aerosol were effective in improving asthma control with significantly greater improvements in FEV₁, AM PEF, and asthma symptoms than with placebo. Shown below is the change from baseline in AM PEF during this trial.

A 6-Week Clinical Trial in Patients with Mild to Moderate Asthma Not on Corticosteroid Therapy Prior to Study Entry: Mean Change in AM PEF

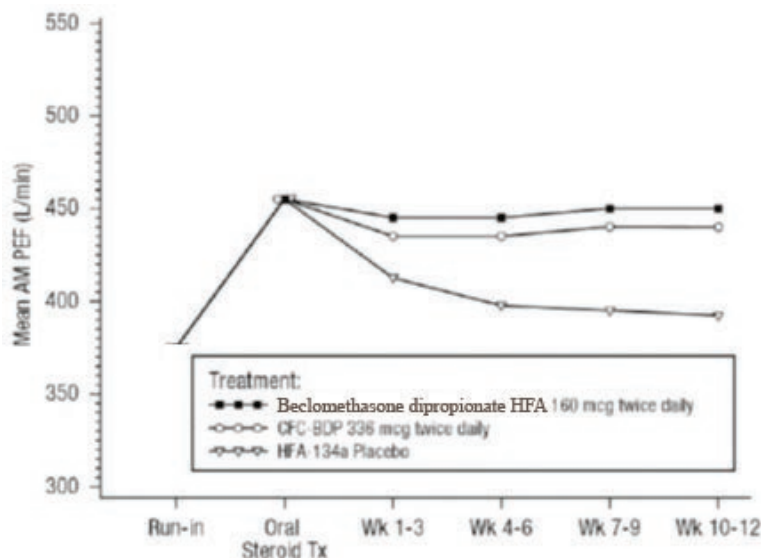


In a 6-week clinical trial, 256 patients with symptomatic asthma being treated with as-needed beta-agonist bronchodilators, were randomized to receive either 160 mcg twice-daily of beclomethasone dipropionate HFA inhalation aerosol (delivered as either 40 mcg/actuation or 80 mcg/actuation) or placebo. Treatment with beclomethasone dipropionate HFA inhalation aerosol significantly improved asthma control, as assessed by FEV₁, AM PEF, and asthma symptoms, when compared to treatment with placebo. Comparable improvement in AM PEF was seen for patients receiving 160 mcg twice-daily beclomethasone dipropionate HFA inhalation aerosol from the 40 mcg and 80 mcg strength products.

Patients Responsive to a Short Course of Oral Corticosteroids

In another clinical trial, 347 patients with symptomatic asthma, being treated with as-needed inhaled beta-agonist bronchodilators and, in some cases, inhaled corticosteroids, were given a 7 to 12-day course of oral corticosteroids and then randomized to receive either 320 mcg daily of beclomethasone dipropionate HFA inhalation aerosol, 672 mcg of CFC-BDP, or placebo. Patients treated with either beclomethasone dipropionate HFA inhalation aerosol or CFC-BDP had significantly better asthma control, as assessed by AM PEF, FEV₁ and asthma symptoms, and fewer study withdrawals due to asthma symptoms, than those treated with placebo over 12 weeks of treatment. A daily dose of 320 mcg beclomethasone dipropionate HFA inhalation aerosol administered in divided doses provided comparable control of AM PEF and FEV₁ as 672 mcg of CFC-BDP. Shown below are the mean AM PEF results from this trial.

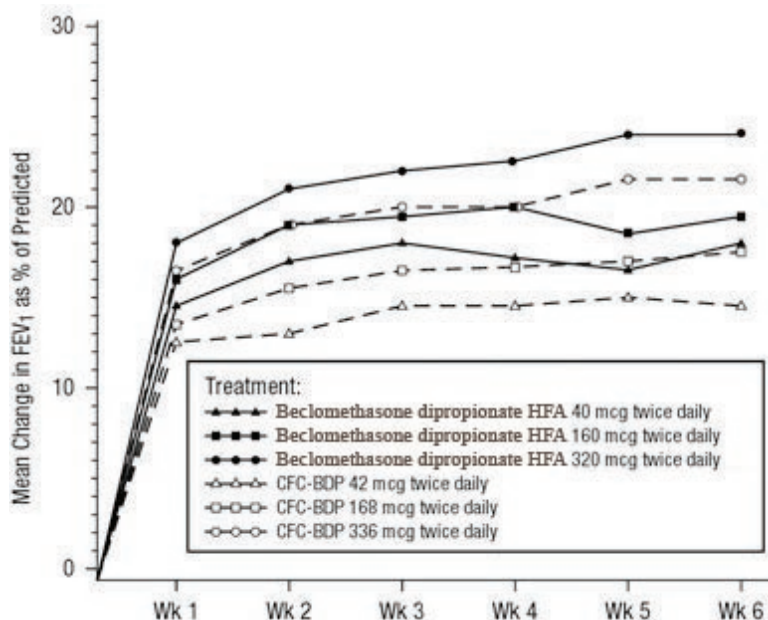
A 12-Week Clinical Trial in Moderate Symptomatic Patients with Asthma Responding to Oral Corticosteroid Therapy: Mean AM PEF by Study Week



Patients Previously on Inhaled Corticosteroids

In a 6-week clinical trial, 323 patients who exhibited a deterioration in asthma control during an inhaled corticosteroid washout period were randomized to daily treatment with either 40, 160, or 320 mcg twice-daily beclomethasone dipropionate HFA inhalation aerosol or 42, 168 or 336 mcg twice-daily CFC-BDP. Treatment with increasing doses of both beclomethasone dipropionate HFA inhalation aerosol and CFC-BDP resulted in increased improvement in FEV₁, FEF_{25-75%} (forced expiratory flow over 25% to 75% of the vital capacity) and asthma symptoms. Shown below is the change from baseline in FEV₁ as percent predicted after 6 weeks of treatment.

A 6-Week Dose Response Clinical Trial in Patients with Inhaled Corticosteroid-Dependent Asthma: Mean Change in FEV₁ as Percent of Predicted



14.2 Pediatric Patients 5 to 12 Years of Age

In one 12-week clinical trial, pediatric patients (age 5 to 12 years) with symptomatic asthma (N=353) being treated with as-needed beta-agonist bronchodilators were randomized to receive either 40 mcg or 80 mcg twice

daily of HFA beclomethasone dipropionate or placebo. Both doses were effective in improving asthma control with significantly greater improvements in FEV₁ (9% and 10% predicted change from baseline at week 12 in FEV₁ percent predicted, respectively) than with placebo (4% predicted change).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Beclomethasone dipropionate HFA inhalation aerosol is supplied in 2 strengths:

Beclomethasone dipropionate HFA inhalation aerosol **40 mcg** is available in a box of one 8.7 g canister containing 120 actuations with a beige plastic actuator with a dose counter and light blue dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC 69238-1289-4.

Beclomethasone dipropionate HFA inhalation aerosol **80 mcg** is available in a box of one 8.7 g canister containing 120 actuations with a dark pink plastic actuator with a dose counter and gray dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC 69238-1290-4.

The correct amount of medication in each inhalation cannot be assured after 120 actuations from the 8.7 g canister even though the canister is not completely empty. Patients should be informed to discard the beclomethasone dipropionate HFA inhalation aerosol inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). For optimal results, the canister should be at room temperature when used.

Beclomethasone dipropionate HFA inhalation aerosol canister should only be used with the beclomethasone dipropionate HFA inhalation aerosol actuator and the actuator should not be used with any other inhalation drug product.

Store beclomethasone dipropionate HFA inhalation aerosol when not being used, so that the product rests on the concave end of the canister with plastic actuator on top.

CONTENTS UNDER PRESSURE

Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw container into fire or incinerator.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Risks Associated with Corticosteroid Therapy

- **Local Effects:** Advise patients that localized infections with *Candida albicans* have occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with beclomethasone dipropionate HFA inhalation aerosol therapy, but at times therapy with beclomethasone dipropionate HFA inhalation

aerosol may need to be temporarily interrupted under close medical supervision. Rinsing the mouth with water without swallowing after inhalation is advised [*see Warnings and Precautions (5.1)*].

- **Immunosuppression**: Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex [*see Warnings and Precautions (5.4)*].
- **Hypercorticism and Adrenal Suppression**: Advise patients that beclomethasone dipropionate HFA inhalation aerosol may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, instruct patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to beclomethasone dipropionate HFA inhalation aerosol [*see Warnings and Precautions (5.7)*].
- **Reduction in Bone Mineral Density**: Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk and that they should be monitored and, where appropriate, be treated for this condition [*see Warnings and Precautions (5.9)*].
- **Reduced Growth Velocity**: Inform patients that orally inhaled corticosteroids, including beclomethasone dipropionate HFA inhalation aerosol, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route [*see Warnings and Precautions (5.8)*].
- **Eye Disorders**: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma, cataracts, blurred vision); regular eye examinations should be considered [*see Warnings and Precautions (5.10)*].

Not for Acute Symptoms

- Advise patients that beclomethasone dipropionate HFA inhalation aerosol is not intended for use in the treatment of acute asthma. Acute asthma symptoms should be treated with an inhaled, short-acting beta-2 agonist such as albuterol. Instruct the patient to contact their healthcare provider immediately if there is any deterioration of their asthma [*see Warnings and Precautions (5.2)*].

Susceptibility to Infections

- Warn persons who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex [*see Warnings and Precautions (5.4)*].

Use Daily for Best Effect

- Advise patients to use beclomethasone dipropionate HFA inhalation aerosol at regular intervals, since its effectiveness depends on regular use. Maximum benefit may not be achieved for 1 week or longer after starting treatment. If symptoms do not improve after 2 weeks of therapy or if the condition worsens, patients should be instructed to contact their physician.

Proper Use and Care of the Inhaler

- **Priming**: Priming is essential to ensure appropriate beclomethasone dipropionate content in each actuation. Instruct patients to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 10 days by releasing two sprays into the air, away from the face.
- **Cleaning**: For normal hygiene, the mouthpiece of the inhaler should be cleaned weekly with a clean, dry tissue or cloth. DO NOT WASH OR PUT ANY PART OF THE INHALER IN WATER.

- **Dose Counter:** Inform patients that beclomethasone dipropionate HFA inhalation aerosol has a dose counter window located on the back of the actuator. When the patient receives the inhaler, “122” will appear in the viewing window until it has been primed 2 times, at which point the total number of actuations will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of one (e.g., 120, 119, 118, etc). When the dose counter displays “20”, it is a reminder to the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. Inform patients to discard the beclomethasone dipropionate HFA inhalation aerosol inhaler when the dose counter displays 0, or after the expiration date on the product, whichever comes first.

Discontinuing Beclomethasone Dipropionate HFA Inhalation Aerosol

- Do not stop beclomethasone dipropionate HFA inhalation aerosol use abruptly. Instruct the patient to contact their healthcare provider immediately if use of beclomethasone dipropionate HFA inhalation aerosol is discontinued.

Rx only

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

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Manufactured In Ireland

OptiChamber is a registered trademark of Respironics Healthscan, Inc. and AeroChamber Plus is a registered trademark of Trudell Medical International Trudell Partnership Holdings Limited and Packard Medical Supply Centre Ltd.

Attention Pharmacist: Detach “Patient Information and Instructions for Use” from package insert and dispense with the product.

PATIENT INFORMATION

Beclomethasone Dipropionate (be” kloe meth’ a sone dye proe’ pee oh nate) HFA Inhalation Aerosol

What is beclomethasone dipropionate HFA inhalation aerosol?

Beclomethasone dipropionate HFA inhalation aerosol is an inhaled prescription medicine used as a maintenance treatment for the prevention and control of asthma in people 5 years of age and older.

- Beclomethasone dipropionate HFA inhalation aerosol is not used to relieve sudden breathing problems.

It is not known if beclomethasone dipropionate HFA inhalation aerosol is safe and effective in children less than 5 years of age.

Who should not use beclomethasone dipropionate HFA inhalation aerosol?

Do not use beclomethasone dipropionate HFA inhalation aerosol:

- to treat sudden severe symptoms of asthma.
- as a rescue inhaler.
- if you are allergic to beclomethasone dipropionate or any of the ingredients in beclomethasone dipropionate HFA inhalation aerosol. See the end of this leaflet for a complete list of ingredients in beclomethasone dipropionate HFA inhalation aerosol.

What should I tell my healthcare provider before using beclomethasone dipropionate HFA inhalation aerosol?

Before using beclomethasone dipropionate HFA inhalation aerosol, tell your healthcare provider about all of your medical conditions, including if you:

- are exposed to chickenpox or measles
- have or have had tuberculosis (TB) or any untreated fungal, bacterial or viral infections, or eye infections caused by herpes.
- have weak bones (osteoporosis).
- have an immune system problem
- have or have had eye problems, such as blurred vision, increased pressure in your eye (glaucoma), or cataracts.
- are pregnant or plan to become pregnant. It is not known if beclomethasone dipropionate HFA inhalation aerosol will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if beclomethasone dipropionate HFA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use beclomethasone dipropionate HFA inhalation aerosol.

Tell your healthcare provider about all of the medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use beclomethasone dipropionate HFA inhalation aerosol?

Read the step-by-step instructions for using beclomethasone dipropionate HFA inhalation aerosol at the end of this Patient Information leaflet.

- Use beclomethasone dipropionate HFA inhalation aerosol exactly as your healthcare provider tells you to. **Do not** use beclomethasone dipropionate HFA inhalation aerosol more often than it is prescribed.
- **Do not** change or stop using beclomethasone dipropionate HFA inhalation aerosol or other asthma medicines used to treat your breathing problems unless your healthcare provider tells you to. Your healthcare provider will change your medicines as needed.
- You must use beclomethasone dipropionate HFA inhalation aerosol regularly. It may take 1 to 4 weeks, or longer, after you start using beclomethasone dipropionate HFA inhalation aerosol for your asthma symptoms to get better. **Do not** stop using beclomethasone dipropionate HFA inhalation aerosol, even if you are feeling better, unless your healthcare provider tells you to.
- Beclomethasone dipropionate HFA inhalation aerosol comes in 2 strengths (40 and 80 mcg). Your healthcare provider has prescribed the strength that is best for you. Pay attention to the differences between beclomethasone dipropionate HFA inhalation aerosol and your other inhaled medicines, including their prescribed use and the way they look.
- Beclomethasone dipropionate HFA inhalation aerosol does not relieve sudden asthma symptoms. Always have a rescue inhaler with you to treat sudden symptoms. Use your rescue inhaler if you have breathing problems between doses of beclomethasone dipropionate HFA inhalation aerosol. If you do not have a rescue inhaler, call your healthcare provider to have a rescue inhaler prescribed for you.
- Rinse your mouth with water **without swallowing** after each dose of beclomethasone dipropionate HFA inhalation aerosol. This will help lessen the chance of getting a yeast infection (thrush) in your mouth and throat.
- **Do not** spray beclomethasone dipropionate HFA inhalation aerosol in your face or eyes. If you accidentally get beclomethasone dipropionate HFA inhalation aerosol in your eyes, rinse your eyes with water and if redness or irritation continues, call your healthcare provider.

What should I avoid while using beclomethasone dipropionate HFA inhalation aerosol?

If you have not had, or have not been vaccinated against, chickenpox or measles, you should stay away from people who are infected.

What are the possible side effects of beclomethasone dipropionate HFA inhalation aerosol?

Beclomethasone dipropionate HFA inhalation aerosol may cause serious side effects, including:

- **fungal infections (thrush) in your mouth and throat.** You may develop a yeast infection (Candida albicans) in your mouth and throat. Tell your healthcare provider if you have any redness or white colored patches in your mouth or throat. Rinse your mouth with water **without swallowing** after using beclomethasone dipropionate HFA inhalation aerosol to help prevent an infection in your mouth or throat.
- **worsening asthma or sudden asthma attacks.** You should contact your healthcare provider right away if you do not get relief from your sudden asthma attacks, after using your rescue inhaler, during your treatment with beclomethasone dipropionate HFA inhalation aerosol.
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency that can lead to death can happen when you stop taking oral corticosteroid medicines and start using inhaled corticosteroid medicines. Adrenal insufficiency can also happen in people who take higher doses of beclomethasone dipropionate HFA inhalation aerosol than recommended over a long period of time. When your body is under stress such as from fever, trauma (such as a car accident), infection, or surgery, adrenal insufficiency can get worse. Signs and symptoms of adrenal insufficiency may include:
 - feeling tired or exhausted (fatigue)
 - lack of energy
 - weakness

- dizziness or feeling faint
- nausea and vomiting
- low blood pressure (hypotension)
- **immune system effects and a higher chance for infections.** Tell your healthcare provider about any signs or symptoms of infection such as:
 - fever
 - pain
 - body aches
 - chills
 - feeling tired
 - nausea
 - vomiting
- **increased wheezing (bronchospasm) right after using** beclomethasone dipropionate HFA inhalation aerosol. Always have a rescue inhaler with you to treat sudden wheezing.
- **serious allergic reactions.** Stop using beclomethasone dipropionate HFA inhalation aerosol and call your healthcare provider or get emergency medical help right away if you get any of the following signs or symptoms of an serious allergic reaction:
 - hives
 - swelling of your lips, tongue, or face
 - rash
 - breathing problems
- **slowed growth in children.** Children should have their growth checked regularly while using beclomethasone dipropionate HFA inhalation aerosol.
- **lower bone density.** This may be a problem for people who already have a higher chance for low bone density (osteoporosis).
- **eye problems.** If you have had glaucoma, cataracts or blurred vision in the past, you should have regular eye exams while using beclomethasone dipropionate HFA inhalation aerosol.

The most common side effects of beclomethasone dipropionate HFA inhalation aerosol include:

- headache
- throat irritation (pharyngitis)
- sinus irritation (sinusitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of beclomethasone dipropionate HFA inhalation aerosol. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store beclomethasone dipropionate HFA inhalation aerosol?

- Store beclomethasone dipropionate HFA inhalation aerosol at room temperature between 68°F to 77°F (20°C to 25°C).
- **Your beclomethasone dipropionate HFA inhalation aerosol canister should only be used with the beclomethasone dipropionate HFA inhalation aerosol actuator. Do not use any other medicines in your beclomethasone dipropionate HFA inhalation aerosol actuator.**
- The contents of your beclomethasone dipropionate HFA inhalation aerosol canister are under pressure. **Do not** puncture the beclomethasone dipropionate HFA inhalation aerosol canister.
- **Do not** store your beclomethasone dipropionate HFA inhalation aerosol canister near heat or a flame.

Temperatures above 120°F may cause the canister to burst.

- **Do not** throw your beclomethasone dipropionate HFA inhalation aerosol canister into a fire or incinerator.
- When not in use, store beclomethasone dipropionate HFA inhalation aerosol so that the product rests on the concave end of the canister with the plastic actuator on top.

Keep beclomethasone dipropionate HFA inhalation aerosol and all medicines out of the reach of children.

General information about the safe and effective use of beclomethasone dipropionate HFA inhalation aerosol.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use beclomethasone dipropionate HFA inhalation aerosol for a condition for which it was not prescribed. Do not give beclomethasone dipropionate HFA inhalation aerosol to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about beclomethasone dipropionate HFA inhalation aerosol that is written for health professionals.

What are the ingredients in beclomethasone dipropionate HFA inhalation aerosol?

Active ingredient: beclomethasone dipropionate, USP

Inactive ingredients: propellant HFA-134a and ethanol

For more information, go to www.amneal.com or call 1-877-835-5472.

Distributed by:

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Instructions for Use

Beclomethasone Dipropionate (be'' kloe meth' a sone dye proe' pee oh nate) HFA Inhalation Aerosol

It is important that you read these instructions before using beclomethasone dipropionate HFA inhalation aerosol.

Correct and regular use of the inhaler will prevent or lessen the severity of asthma attacks.

- **Do not** use the beclomethasone dipropionate HFA inhalation aerosol actuator with a canister of medicine from any other inhaler.
- **Do not** use a beclomethasone dipropionate HFA inhalation aerosol canister with an actuator from any other inhaler, including another beclomethasone dipropionate HFA inhalation aerosol inhaler.

The parts of your beclomethasone dipropionate HFA inhalation aerosol:

- There are 2 main parts of your beclomethasone dipropionate HFA inhalation aerosol inhaler including the:
 - metal canister that holds the medicine (See Figure A)
 - plastic actuator that sprays the medicine from the canister (See Figure A)

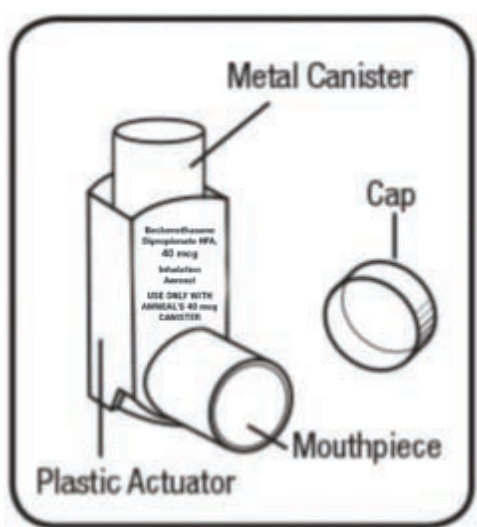


Figure A

- The inhaler has a cap that covers the mouthpiece of the actuator to protect it from dust (See Figure A). The cap should be removed before use.
- The inhaler comes with a dose counter located on the back of the actuator (See Figure B). The dose counter window will show you the number of actuations (puffs) of medicine remaining in units of **one (1)**. The inhaler contains “**120**” actuations (puffs).

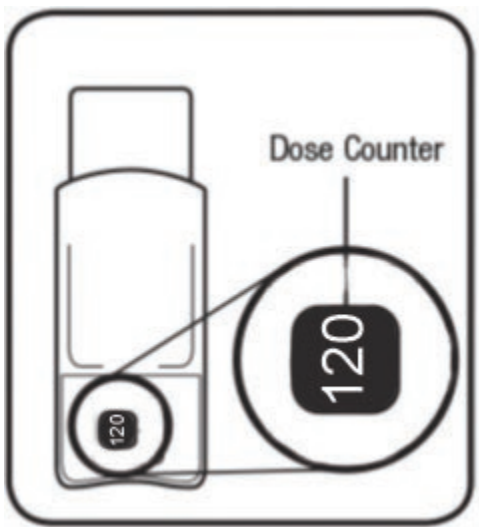


Figure B

- The first time you use beclomethasone dipropionate HFA inhalation aerosol inhaler, the dose counter will show “120” actuations remaining (See Figure B). Each time you press the metal canister, a puff of medicine is released and the dose counter will count down.
- When the dose counter reaches 0, it will continue to show 0 and you should replace your beclomethasone dipropionate HFA inhalation aerosol inhaler.
- The dose counter cannot be reset and is permanently inserted into the actuator. Never change the numbers for the dose counter or touch the white component inside the actuator.

Do not remove the metal canister from the plastic actuator.

Before using your beclomethasone dipropionate HFA inhalation aerosol inhaler:

Remove the cap from the mouthpiece of the actuator (See Figure C). Check the mouthpiece for objects before use. Make sure the metal canister is fully inserted into the actuator.

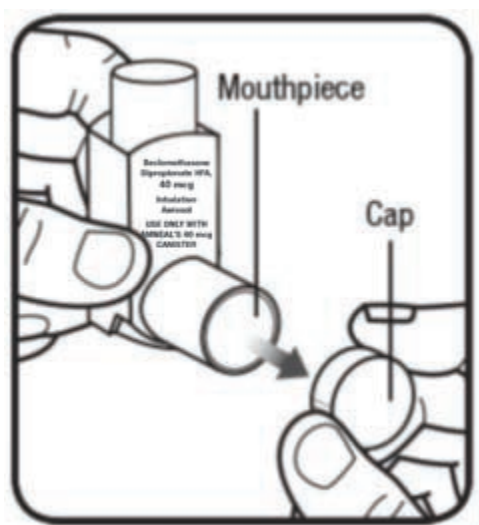


Figure C

Priming your beclomethasone dipropionate HFA inhalation aerosol inhaler:

Before you use your beclomethasone dipropionate HFA inhalation aerosol inhaler for the first time or if you have not used your beclomethasone dipropionate HFA inhalation aerosol inhaler for more than 10 days, you will need to prime your beclomethasone dipropionate HFA inhalation aerosol inhaler.

- Before priming, the inhaler will show “122” in the dose counter window until it has been primed 2 times, at which point the total number of actuations will be displayed (See Figure D).

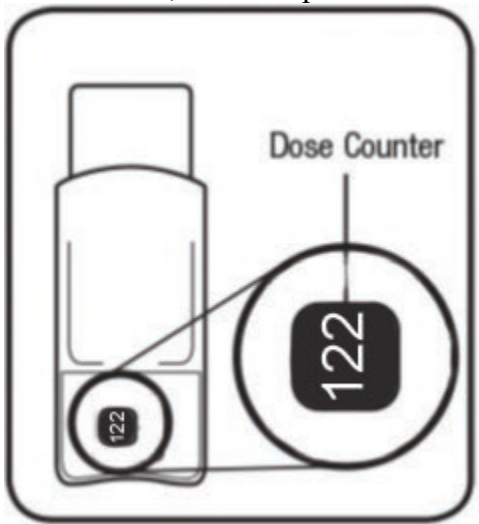


Figure D

- Hold the beclomethasone dipropionate HFA inhalation aerosol inhaler in the upright position and with the mouthpiece pointing away from you.
- Press down on the metal canister **2** times and release **2** actuations (puffs) into the air and away from your face.
- After priming 2 times, the dose counter should read “**120**”.
 - Your beclomethasone dipropionate HFA inhalation aerosol inhaler is now ready to use.

Using your beclomethasone dipropionate HFA inhalation aerosol inhaler:

Step 1: Remove the cap from the mouthpiece of the actuator (See Figure C). Check the mouthpiece for objects before use. Make sure the metal canister is fully inserted into the actuator.

Step 2: Breathe out as fully as you comfortably can. Hold the inhaler in the upright position (See Figure E). Close your lips around the mouthpiece, keeping your tongue below it.

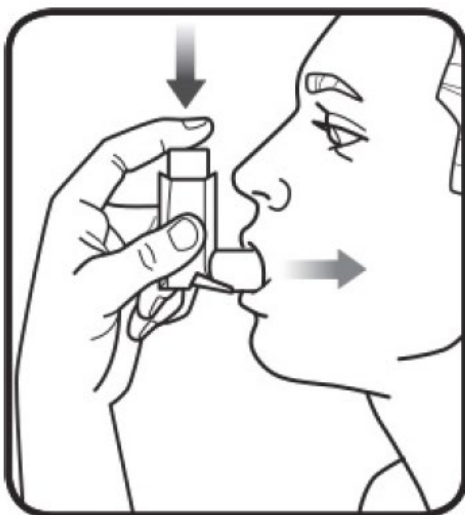


Figure E

Step 3: While breathing in deeply and slowly, press down on the metal canister with your finger (See Figure E). When you have finished breathing in, hold your breath as long as you comfortably can (5 to 10 seconds).

Step 4: Take your finger off the metal canister and remove the inhaler from your mouth. Breathe out gently.

If your healthcare provider has told you to take more than 1 inhalation per dose, repeat steps 1 through 4.

After using your beclomethasone dipropionate HFA inhalation aerosol inhaler:

- Replace the cap over the mouthpiece right away after use.
- You should rinse your mouth with water **without swallowing** after you finish using beclomethasone dipropionate HFA inhalation aerosol.
- Clean the mouthpiece of your beclomethasone dipropionate HFA inhalation aerosol inhaler weekly with a clean, dry tissue or cloth.
- **Do not** wash or put any part of your inhaler in water.

When to replace your beclomethasone dipropionate HFA inhalation aerosol inhaler:

- It is important that you pay attention to the number of actuations (puffs) left in your beclomethasone dipropionate HFA inhalation aerosol inhaler by reading the dose counter.
- **When the dose counter on the actuator reads “20”**, you should refill your prescription or ask your healthcare provider if you need another prescription for beclomethasone dipropionate HFA inhalation aerosol inhaler.
- When the dose counter reaches “0” **throw away your beclomethasone dipropionate HFA inhalation aerosol inhaler** or by the expiration date on the beclomethasone dipropionate HFA inhalation aerosol inhaler package, whichever comes first.
- **Do not** use beclomethasone dipropionate HFA inhalation aerosol past the expiration date.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

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