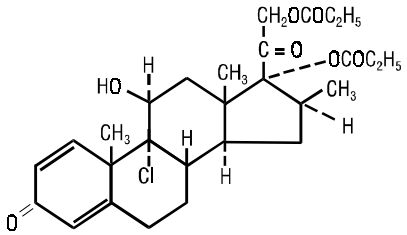
BECONASE®

(beclomethasone dipropionate, USP)

Inhalation Aerosol

For Nasal Inhalation Only

DESCRIPTION: Beclomethasone dipropionate, USP, the active component of BECONASE Inhalation Aerosol, is an anti-inflammatory steroid having the chemical name 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate and the following chemical structure:



Beclomethasone 17,21-dipropionate is a diester of beclomethasone, a synthetic halogenated corticosteroid. Beclomethasone dipropionate is a white to creamy-white, odorless powder with a molecular weight of 521.25. It is very slightly soluble in water, very soluble in chloroform, and freely soluble in acetone and in alcohol.

BECONASE Inhalation Aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of beclomethasone dipropionate-trichloromonofluoromethane clathrate in a mixture of propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each canister contains beclomethasone dipropionate-trichloromonofluoromethane clathrate having a molecular proportion of beclomethasone dipropionate to trichloromonofluoromethane between 3:1 and 3:2. Each actuation delivers from the compact actuator a quantity of clathrate equivalent to 42 mcg of beclomethasone dipropionate, USP. The contents of one 6.7-g canister provide at least 80 metered doses, and the contents of one 16.8-g canister provide at least 200 metered doses.

CLINICAL PHARMACOLOGY: Mechanism of Action: Following topical administration, beclomethasone dipropionate produces ~~potent~~ anti-inflammatory and vasoconstrictor effects. The mechanisms responsible for the anti-inflammatory action of beclomethasone dipropionate are unknown. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. The direct relationship of these findings to the effects of beclomethasone dipropionate on allergic rhinitis symptoms is not known.

Biopsies of nasal mucosa obtained during clinical studies showed no histopathologic changes when beclomethasone dipropionate was administered intranasally.

Beclomethasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is hydrolyzed via esterase enzymes to its active metabolite beclomethasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity.

Pharmacokinetics: *Absorption:* Beclomethasone dipropionate is sparingly soluble in water. When given by nasal inhalation in the form of an aqueous or aerosolized suspension, the drug is deposited primarily in the nasal passages. The majority of the drug is eventually swallowed. Following intranasal administration of aqueous beclomethasone dipropionate, the systemic absorption was assessed by measuring the plasma concentrations of its active metabolite B-17-MP, for which the absolute bioavailability following intranasal administration is 44% (~~of which~~ 43% of the administered dose came from the swallowed portion and only 1% of the total dose was bioavailable from the nose). The absorption of unchanged beclomethasone dipropionate following oral and intranasal dosing was undetectable (plasma concentrations <50 pg/mL).

Distribution: The tissue distribution at steady-state for beclomethasone dipropionate is moderate (20 L) but more extensive for B-17-MP (424 L). There is no evidence of tissue storage of beclomethasone dipropionate or its metabolites. Plasma protein binding is moderately high (87%).

Metabolism: Beclomethasone dipropionate is cleared very rapidly from the systemic circulation by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclomethasone-21-monopropionate (B-21-MP) and beclomethasone (BOH), are also formed, but these contribute little to systemic exposure.

Elimination: The elimination of beclomethasone dipropionate and B-17-MP after intravenous administration are characterized by high plasma clearance (150 and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 and 2.7 hours. Following oral administration of tritiated beclomethasone dipropionate, approximately 60% of the dose was excreted in the feces within 96 hours, mainly as free and conjugated polar metabolites. Approximately 12% of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of beclomethasone dipropionate and its metabolites is negligible.

Pharmacodynamics: The effects of beclomethasone dipropionate on hypothalamic-pituitary-adrenal (HPA) function have been evaluated in adult volunteers by other routes of administration. Studies with beclomethasone dipropionate by the intranasal route may demonstrate that there is more or that there is less absorption by this route of administration. There was no suppression of early morning plasma cortisol concentrations when beclomethasone dipropionate was administered in a dose of 1,000 mcg per day for 1 month as an oral aerosol or for 3 days by intramuscular injection. However, partial suppression of plasma cortisol concentrations was observed when beclomethasone dipropionate was administered in doses of 2,000 mcg per day either by oral aerosol or intramuscular injection. Immediate suppression of plasma cortisol concentrations was observed after single doses of 4,000 mcg of beclomethasone dipropionate. Suppression of HPA function (reduction of early morning plasma cortisol levels) has been reported in adult patients who received 1,600-mcg daily

doses of oral beclomethasone dipropionate for 1 month. In clinical studies using beclomethasone dipropionate intranasally, there was no evidence of adrenal insufficiency.

INDICATIONS AND USAGE: BECONASE Inhalation Aerosol is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

BECONASE Inhalation Aerosol is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies in patients with seasonal or perennial rhinitis have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Although systemic effects are minimal at recommended doses, BECONASE Inhalation Aerosol should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. BECONASE Inhalation Aerosol should not be used in the presence of untreated localized infection involving the nasal mucosa.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with BECONASE Inhalation Aerosol can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to BECONASE Inhalation Aerosol. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, BECONASE Inhalation Aerosol treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, cataracts, and cushingoid features. If such changes occur, BECONASE Inhalation Aerosol should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs that 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 nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to 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.

PRECAUTIONS:

General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression.

Rare instances of nasal septum perforation have been spontaneously reported.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal use of beclomethasone dipropionate.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with BECONASE Inhalation Aerosol.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of BECONASE Inhalation Aerosol may suppress HPA function.

BECONASE Inhalation Aerosol should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For BECONASE Inhalation Aerosol to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with BECONASE Inhalation Aerosol should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of BECONASE Inhalation Aerosol into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using BECONASE Inhalation Aerosol over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients should use BECONASE Inhalation Aerosol at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of BECONASE Inhalation

Aerosol are fully manifested. One to 2 weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of this unit and to attain maximum improvement, the patient should read and follow carefully the accompanying patient's instructions.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately 10 times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at 10 times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when BECONASE Inhalation Aerosol is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes.

Adverse reactions reported in controlled clinical trials and long-term open studies in patients treated with BECONASE Inhalation Aerosol are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of BECONASE Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients.

Rare cases of ulceration of the nasal mucosa and instances of nasal septum perforation have been spontaneously reported (see PRECAUTIONS).

Reports of headache, light-headedness, dryness and irritation of the nose and throat, and unpleasant taste and smell have been received. There are rare reports of loss of taste and smell.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the use of intranasal beclomethasone dipropionate (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of beclomethasone.

Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, i.e., Cushing's syndrome, could occur.

OVERDOSAGE: When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, BECONASE Inhalation Aerosol should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One canister of BECONASE Inhalation Aerosol contains 8.4 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

DOSAGE AND ADMINISTRATION:

Adults and Children 12 Years of Age and Older: The usual dosage is one inhalation (42 mcg) in each nostril two to four times a day (total dose, 168 to 336 mcg per day). Patients can often be maintained on a maximum dose of one inhalation in each nostril three times a day (252 mcg per day).

Children 6 to 12 Years of Age: The usual dosage is one inhalation in each nostril three times a day (252 mcg per day). BECONASE Inhalation Aerosol is *not* recommended for children below 6 years of age since safety and efficacy studies have not been conducted in this age-group.

In patients who respond to BECONASE Inhalation Aerosol, an improvement of the symptoms of seasonal or perennial rhinitis usually becomes apparent within a few days after the start of BECONASE Inhalation Aerosol therapy. However, symptomatic relief may not occur in some patients for as long as 2 weeks. BECONASE Inhalation Aerosol should not be continued beyond 3 weeks in the absence of significant symptomatic improvement.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of intended action. In such cases it is advisable to use a nasal vasoconstrictor during the first 2 to 3 days of BECONASE Inhalation Aerosol therapy.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of BECONASE Inhalation Aerosol.

CONTENTS UNDER PRESSURE: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

HOW SUPPLIED: BECONASE Inhalation Aerosol is supplied in a 6.7-g canister containing 80 metered doses (NDC 0173-0468-00) and in a 16.8-g canister containing 200 metered doses (NDC 0173-0336-02), each with beige compact actuator and patient's instructions.

Store between 2° and 30°C (36° and 86°F). **As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.**

WARNING: Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

March 2, 2001 RL-

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

BECONASE®

(beclomethasone dipropionate, USP)
Inhalation Aerosol

Patient's Instructions for Use

Before using your BECONASE Inhalation Aerosol, read complete instructions carefully.

Before using the inhaler for the first time, you must **remove the cap from the inhaler canister** and insert the canister into the accompanying beige compact actuator. To open the actuator, place your thumb on the notch at the bottom of the actuator and pull up on the front cover. After the canister is firmly inserted into the actuator, you will see the words "SHAKE BEFORE USE. THIS END UP." on the top of the canister.

After each use of the inhaler, close the cover of the actuator.

To Take a Dose From the Inhaler:

1. Gently blow your nose to clear the nostrils.

2. SHAKE THE INHALER WELL (Figure 1).

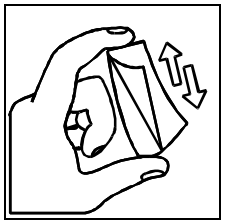


Figure 1

3. Snap open the cover of the actuator and hold the inhaler as shown in Figure 2.

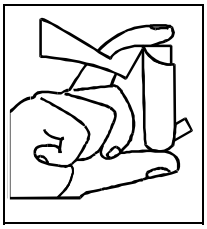


Figure 2

4. Carefully insert the nasal piece on the actuator into one nostril and close the other nostril with one finger (Figure 3).

5. While gently breathing in through the nostril, press down on the top of the canister to release the medication (Figure 3).

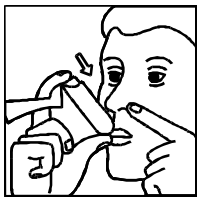


Figure 3

6. Now breathe out through the mouth (Figure 4).

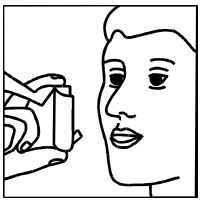


Figure 4

7. SHAKE THE INHALER AGAIN and then repeat steps 4 through 6 in the other nostril.

8. Close the actuator cover.

9. DISCARD THE CANISTER AFTER the date calculated by your doctor or pharmacist. The correct amount of medication in each inhalation cannot be assured after a specified number of inhalations even though the canister is not completely empty. Before the discard date you should consult your doctor to determine whether a refill is needed. Just as you should not take extra doses without consulting your doctor, you also should not stop BECONASE Inhalation Aerosol without consulting your doctor.

DOSAGE: Use only as directed by your doctor.

CLEANING: Remove the canister from the actuator and rinse the actuator's nasal piece in warm water once a day. Dry well and insert the canister back into the actuator.

CAUTION: BECONASE Inhalation Aerosol is not intended to give immediate relief of your nasal symptoms. Improvement with BECONASE Inhalation Aerosol may take a few days to develop, and it is important that you use it regularly at the times recommended by your doctor.

CONTENTS UNDER PRESSURE: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

Store between 2° and 30°C (36° and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

March 2, 2001 RL-

PRODUCT INFORMATION

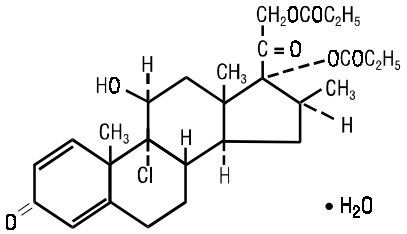
BECONASE AQ®

*(beclomethasone dipropionate, monohydrate) Nasal Spray, 0.042%**

***Calculated on the dried basis.** **SHAKE WELL**

For Intranasal Use Only **BEFORE USE.**

DESCRIPTION: Beclomethasone dipropionate, monohydrate, the active component of BECONASE AQ Nasal Spray, is an anti-inflammatory steroid having the chemical name 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, monohydrate and the following chemical structure:



Beclomethasone 17,21-dipropionate is a diester of beclomethasone, a synthetic halogenated corticosteroid. Beclomethasone dipropionate, monohydrate is a white to creamy-white, odorless powder with a molecular weight of 539.06. It is very slightly soluble in water, very soluble in chloroform, and freely soluble in acetone and in alcohol.

BECONASE AQ Nasal Spray is a metered-dose, manual pump spray unit containing a microcrystalline suspension of beclomethasone dipropionate, monohydrate equivalent to 0.042% w/w beclomethasone dipropionate, calculated on the dried basis, in an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% v/w phenylethyl alcohol. Hydrochloric acid may be added to adjust pH. The pH is between 4.5 and 7.0.

After initial priming (three to four actuations), each actuation of the pump delivers from the nasal adapter 100 mg of suspension containing beclomethasone dipropionate, monohydrate equivalent to 42 mcg of beclomethasone dipropionate. Each bottle of BECONASE AQ Nasal Spray will provide at least 200 metered doses.

CLINICAL PHARMACOLOGY: Mechanism of Action: Following topical administration, beclomethasone dipropionate produces ~~potent~~ anti-inflammatory and vasoconstrictor effects. The mechanisms responsible for the anti-inflammatory action of beclomethasone dipropionate are unknown. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g.,

histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. The direct relationship of these findings to the effects of beclomethasone dipropionate on allergic rhinitis symptoms is not known.

Biopsies of nasal mucosa obtained during clinical studies showed no histopathologic changes when beclomethasone dipropionate was administered intranasally.

Beclomethasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is hydrolyzed via esterase enzymes to its active metabolite beclomethasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity.

Pharmacokinetics: ***Absorption:*** Beclomethasone dipropionate is sparingly soluble in water. When given by nasal inhalation in the form of an aqueous or aerosolized suspension, the drug is deposited primarily in the nasal passages. The majority of the drug is eventually swallowed. Following intranasal administration of aqueous beclomethasone dipropionate, the systemic absorption was assessed by measuring the plasma concentrations of its active metabolite B-17-MP, for which the absolute bioavailability following intranasal administration is 44% (~~of which~~ 43% of the administered dose came from the swallowed portion and only 1% of the total dose was bioavailable from the nose). The absorption of unchanged beclomethasone dipropionate following oral and intranasal dosing was undetectable (plasma concentrations <50 pg/mL).

Distribution: The tissue distribution at steady-state for beclomethasone dipropionate is moderate (20 L) but more extensive for B-17-MP (424 L). There is no evidence of tissue storage of beclomethasone dipropionate or its metabolites. Plasma protein binding is moderately high (87%).

Metabolism: Beclomethasone dipropionate is cleared very rapidly from the systemic circulation by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclomethasone-21-monopropionate (B-21-MP) and beclomethasone (BOH), are also formed, but these contribute little to systemic exposure.

Elimination: The elimination of beclomethasone dipropionate and B-17-MP after intravenous administration are characterized by high plasma clearance (150 and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 and 2.7 hours. Following oral administration of tritiated beclomethasone dipropionate, approximately 60% of the dose was excreted in the feces within 96 hours, mainly as free and conjugated polar metabolites. Approximately 12% of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of beclomethasone dipropionate and its metabolites is negligible.

Pharmacodynamics: The effects of beclomethasone dipropionate on hypothalamic-pituitary-adrenal (HPA) function have been evaluated in adult volunteers by other routes of administration. Studies with beclomethasone dipropionate by the intranasal route may demonstrate that there is more or that there is less absorption by this route of administration. There was no suppression of early morning plasma cortisol concentrations when beclomethasone dipropionate was administered in a dose of 1000 mcg/day for 1 month as an oral aerosol or for 3 days by intramuscular injection. However, partial suppression of plasma cortisol concentrations was observed when beclomethasone dipropionate was administered in doses of 2000 mcg/day either by oral aerosol or intramuscular

injection. Immediate suppression of plasma cortisol concentrations was observed after single doses of 4000 mcg of beclomethasone dipropionate. Suppression of HPA function (reduction of early morning plasma cortisol levels) has been reported in adult patients who received 1600-mcg daily doses of oral beclomethasone dipropionate for 1 month. In clinical studies using beclomethasone dipropionate aerosol intranasally, there was no evidence of adrenal insufficiency. The effect of BECONASE AQ Nasal Spray on HPA function was not evaluated but would not be expected to differ from intranasal beclomethasone dipropionate aerosol.

In one study in asthmatic children, the administration of inhaled beclomethasone at recommended daily doses for at least 1 year was associated with a reduction in nocturnal cortisol secretion. The clinical significance of this finding is not clear. It reinforces other evidence, however, that topical beclomethasone may be absorbed in amounts that can have systemic effects and that physicians should be alert for evidence of systemic effects, especially in chronically treated patients (see PRECAUTIONS).

INDICATIONS AND USAGE: BECONASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and nonallergic (vasomotor) rhinitis.

Results from two clinical trials have shown that significant symptomatic relief was obtained within 3 days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. BECONASE AQ Nasal Spray should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. BECONASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

BECONASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with BECONASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to BECONASE AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of HPA suppression compared

to a therapeutic dose of either one alone. Therefore, BECONASE AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, cataracts, and cushingoid features. If such changes occur, BECONASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs that 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 nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to 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.

PRECAUTIONS:

General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone (see ADVERSE REACTIONS).

Rare instances of nasal septum perforation have been spontaneously reported.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the use of intranasal beclomethasone.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with BECONASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping BECONASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of BECONASE AQ Nasal Spray may suppress HPA function.

BECONASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For BECONASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with BECONASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications that

will permit effective penetration of BECONASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using BECONASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients being treated with BECONASE AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. Patients should use BECONASE AQ Nasal Spray at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of BECONASE AQ Nasal Spray are fully manifested. One to 2 weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of the unit and to attain maximum improvement, the patient should read and follow carefully the accompanying patient's instructions.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately 10 times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at 10 times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when BECONASE AQ Nasal Spray is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of BECONASE AQ Nasal Spray have been established in children aged 6 years and above through evidence from extensive clinical use in adult and pediatric patients. The safety and effectiveness of BECONASE AQ Nasal Spray in children below 6 years of age have not been established.

Glucocorticoids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any glucocorticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of glucocorticoids should be considered.

ADVERSE REACTIONS: In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with BECONASE AQ Nasal Spray are described below.

Mild nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness following the use of BECONASE AQ Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

Rare cases of ulceration of the nasal mucosa and instances of nasal septum perforation have been spontaneously reported (see PRECAUTIONS).

Reports of dryness and irritation of the nose and throat, and unpleasant taste and smell have been received. There are rare reports of loss of taste and smell.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the use of intranasal beclomethasone dipropionate (see PRECAUTIONS).

OVERDOSAGE: When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, BECONASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of BECONASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

DOSAGE AND ADMINISTRATION:

Adults and Children 12 Years of Age and Older: The usual dosage is one or two inhalations (42 to 84 mcg) in each nostril twice a day (total dose, 168 to 336 mcg/day).

Children 6 to 12 Years of Age: Patients should be started with one inhalation in each nostril twice a day; patients not adequately responding to 168 mcg or those with more severe symptoms may use 336 mcg (two inhalations in each nostril). BECONASE AQ Nasal Spray is *not* recommended for children below 6 years of age.

In patients who respond to BECONASE AQ Nasal Spray, an improvement of the symptoms of seasonal or perennial rhinitis usually becomes apparent within a few days after the start of BECONASE AQ Nasal Spray therapy. However, symptomatic relief may not occur in some patients for as long as 2 weeks. BECONASE AQ Nasal Spray should not be continued beyond 3 weeks in the absence of significant symptomatic improvement.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen.

In the presence of excessive nasal mucous secretion or edema of the nasal mucosa, the drug may fail to reach the site of intended action. In such cases it is advisable to use a nasal vasoconstrictor during the first 2 to 3 days of BECONASE AQ Nasal Spray therapy.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of BECONASE AQ Nasal Spray.

HOW SUPPLIED: BECONASE AQ Nasal Spray, 0.042%* is supplied in an amber glass bottle fitted with a metering atomizing pump and nasal adapter in a box of one (NDC 0173-0388-79) with patient's instructions for use. Each bottle contains 25 g of suspension.

Store between 15° and 30°C (59° and 86°F).

*Calculated on the dried basis.

Rx only

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

March 2, 2001 RL-

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

BECONASE AQ®
*(beclomethasone dipropionate, monohydrate) Nasal Spray, 0.042%**

***Calculated on the dried basis.** **SHAKE WELL BEFORE USE.**

Patient's Instructions for Use

Shake the spray well before using it. Read complete instructions carefully and use only as directed.

To Use:

1. Remove the safety clip and the plastic dust cap from the nasal applicator (Figure 1).

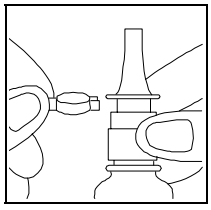


Figure 1

2. The very first time the spray is used, prime the pump into the air by pressing downward on the white collar, using your forefinger and middle finger while supporting the base of the bottle with your thumb. Press down and release the pump three to four times until a fine spray appears (Figure 2). The pump is now ready for use. It should be necessary to prime the pump only when using the spray for the first time each day.

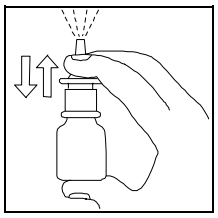


Figure 2

3. Gently blow your nose to clear the nostrils. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril (Figure 3).

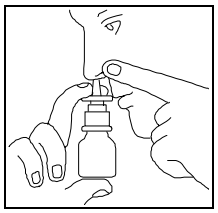


Figure 3

4. For each spray, press firmly downward once on the white collar, using your forefinger and middle finger while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril.

5. Then breathe out through the mouth.

6. Repeat in the other nostril.

7. Replace the plastic dust cap and safety clip.

8. The correct amount of medication in each spray cannot be assured after a specified number of sprays even though the bottle is not completely empty. Before the discard date you should consult your doctor to determine whether a refill is needed. Just as you should not take extra doses without consulting your doctor, you also should not stop BECONASE AQ Nasal Spray without consulting your doctor.

Cleansing: To clean the nasal applicator, remove the plastic dust cap and safety clip and then press gently upward on the white collar to free the nasal applicator. Wash the applicator and dust cap with cold water. Dry and replace with the plastic dust cap and safety clip back in position.

If the nasal applicator becomes blocked, remove the dust cap, unscrew the complete pump mechanism, and soak the pump in warm water for a few minutes. Rinse with cold water, dry, refit to bottle, and reprime the pump.

Caution: BECONASE AQ Nasal Spray is not intended to give rapid relief of your nasal symptoms. BECONASE AQ Nasal Spray controls the underlying disorders responsible for your attacks, so it is important that you use it regularly at the times recommended by your doctor. The full benefit of BECONASE AQ Nasal Spray may take a few days to develop.

Storage: Store between 15° and 30°C (59° and 86°F).

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marianne Mann
8/31/01 02:59:50 PM
signing as Acting Director for Dr. Meyer, Director.