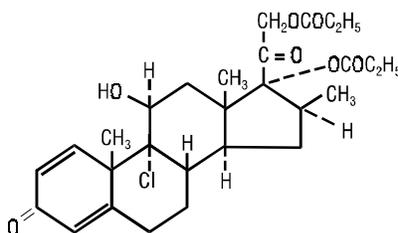


PRODUCT INFORMATION

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-11 β ,17,21-trihydroxy-16 β -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.

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

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

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

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

50 **Distribution:** The tissue distribution at steady-state for beclomethasone dipropionate is moderate
51 (20 L) but more extensive for B-17-MP (424 L). There is no evidence of tissue storage of
52 beclomethasone dipropionate or its metabolites. Plasma protein binding is moderately high (87%).

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

58 **Elimination:** The elimination of beclomethasone dipropionate and B-17-MP after intravenous
59 administration are characterized by high plasma clearance (150 and 120 L/hour) with corresponding
60 terminal elimination half-lives of 0.5 and 2.7 hours. Following oral administration of tritiated
61 beclomethasone dipropionate, approximately 60% of the dose was excreted in the feces within
62 96 hours, mainly as free and conjugated polar metabolites. Approximately 12% of the dose was
63 excreted as free and conjugated polar metabolites in the urine. The renal clearance of
64 beclomethasone dipropionate and its metabolites is negligible.

65 **Pharmacodynamics:** The effects of beclomethasone dipropionate on hypothalamic-pituitary-adrenal
66 (HPA) function have been evaluated in adult volunteers by other routes of administration. Studies
67 with beclomethasone dipropionate by the intranasal route may demonstrate that there is more or that
68 there is less absorption by this route of administration. There was no suppression of early morning
69 plasma cortisol concentrations when beclomethasone dipropionate was administered in a dose of
70 1,000 mcg per day for 1 month as an oral aerosol or for 3 days by intramuscular injection. However,
71 partial suppression of plasma cortisol concentrations was observed when beclomethasone
72 dipropionate was administered in doses of 2,000 mcg per day either by oral aerosol or intramuscular
73 injection. Immediate suppression of plasma cortisol concentrations was observed after single doses
74 of 4,000 mcg of beclomethasone dipropionate. Suppression of HPA function (reduction of early
75 morning plasma cortisol levels) has been reported in adult patients who received 1,600-mcg daily

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

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

78

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

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

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

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

94

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

97

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

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

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

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

114 Persons who are on drugs that suppress the immune system are more susceptible to infections
115 than healthy individuals. Chickenpox and measles, for example, can have a more serious or even

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

116 fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have
117 not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and
118 duration of corticosteroid administration affects the risk of developing a disseminated infection is not
119 known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is
120 also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
121 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG)
122 may be indicated. (See the respective package inserts for complete VZIG and IG prescribing
123 information.) If chickenpox develops, treatment with antiviral agents may be considered.

124

125 **PRECAUTIONS:**

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

128 Rare instances of nasal septum perforation have been spontaneously reported.

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

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

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

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

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

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

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

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

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

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

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

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

163 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Treatment of rats for a total of 95 weeks,
164 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic
165 activity. Mutagenic studies have not been performed.

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

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

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

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

183 **Pediatric Use:** Safety and effectiveness in children below 6 years of age have not been established.
184

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

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

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

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

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

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

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

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

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

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

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

208

209 **OVERDOSAGE:** When used at excessive doses, systemic corticosteroid effects such as
210 hypercorticism and adrenal suppression may appear. If such changes occur, BECONASE Inhalation
211 Aerosol should be discontinued slowly consistent with accepted procedures for discontinuing oral
212 steroid therapy. The oral LD₅₀ of beclomethasone dipropionate is greater than 1 g/kg in rodents. One
213 canister of BECONASE Inhalation Aerosol contains 8.4 mg of beclomethasone dipropionate;
214 therefore, acute overdosage is unlikely.

215

216 **DOSAGE AND ADMINISTRATION:**

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

221 **Children 6 to 12 Years of Age:** The usual dosage is one inhalation in each nostril three times a day
222 (252 mcg per day). BECONASE Inhalation Aerosol is *not* recommended for children below 6 years of
223 age since safety and efficacy studies have not been conducted in this age-group.

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

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

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

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

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

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

240

241 **HOW SUPPLIED:** BECONASE Inhalation Aerosol is supplied in a 6.7-g canister containing 80
242 metered doses (NDC 0173-0468-00) and in a 16.8-g canister containing 200 metered doses (NDC
243 0173-0336-02), each with beige compact actuator and patient's instructions.

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

247

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

250

251

252 **GlaxoWellcome**

253

Glaxo Wellcome Inc.

254

Research Triangle Park, NC 27709

255

256

March 2, 2001

RL-

257

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

258

259

260

BECONASE®

261

(beclomethasone dipropionate, USP)

262

Inhalation Aerosol

263

264

Patient's Instructions for Use

265

266

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

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Before using the inhaler for the first time, you must **remove the cap from the inhaler canister**

270

and insert the canister into the accompanying beige compact actuator. To open the actuator, place

271

your thumb on the notch at the bottom of the actuator and pull up on the front cover. After the

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canister is firmly inserted into the actuator, you will see the words "SHAKE BEFORE USE. THIS END

273

UP." on the top of the canister.
After each use of the inhaler, close the cover of the actuator.

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

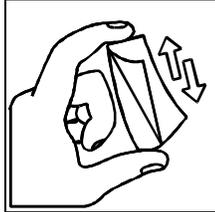
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275 **To Take a Dose From the Inhaler:**

276 1. Gently blow your nose to clear the nostrils.

277 2. **SHAKE THE INHALER WELL** (Figure 1).

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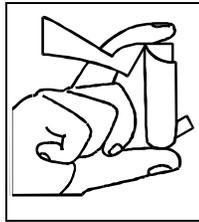
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Figure 1

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

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Figure 2

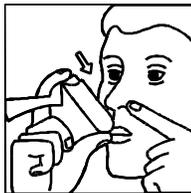
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289 4. Carefully insert the nasal piece on the actuator into one nostril and close the other nostril with one
290 finger (Figure 3).

291

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

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296

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Figure 3

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

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BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

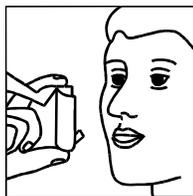


Figure 4

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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.

BECONASE® (beclomethasone dipropionate, USP) Inhalation Aerosol

337 **GlaxoWellcome**
338 Glaxo Wellcome Inc.
339 Research Triangle Park, NC 27709
340
341 March 2, 2001

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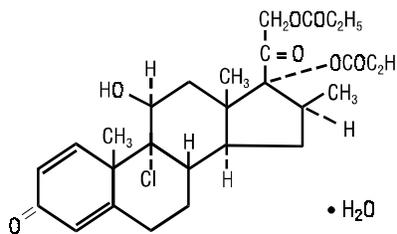
PRODUCT INFORMATION

1
2 **BECONASE AQ®**
3 **(beclomethasone**
4 **dipropionate, monohydrate)**
5 **Nasal Spray, 0.042%***

7 *Calculated on the dried basis.
8 For Intranasal Use Only

SHAKE WELL
BEFORE USE.

9
10 **DESCRIPTION:** Beclomethasone dipropionate, monohydrate, the active component of BECONASE
11 AQ Nasal Spray, is an anti-inflammatory steroid having the chemical name 9-chloro-11 β ,17,21-
12 trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, monohydrate and the
13 following chemical structure:
14



15
16
17 Beclomethasone 17,21-dipropionate is a diester of beclomethasone, a synthetic halogenated
18 corticosteroid. Beclomethasone dipropionate, monohydrate is a white to creamy-white, odorless
19 powder with a molecular weight of 539.06. It is very slightly soluble in water, very soluble in
20 chloroform, and freely soluble in acetone and in alcohol.

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

27 After initial priming (three to four actuations), each actuation of the pump delivers from the nasal
28 adapter 100 mg of suspension containing beclomethasone dipropionate, monohydrate equivalent to
29 42 mcg of beclomethasone dipropionate. Each bottle of BECONASE AQ Nasal Spray will provide at
30 least 200 metered doses.

31
32 **CLINICAL PHARMACOLOGY: Mechanism of Action:** Following topical administration,
33 beclomethasone dipropionate produces ~~potent~~ anti-inflammatory and vasoconstrictor effects. The
34 mechanisms responsible for the anti-inflammatory action of beclomethasone dipropionate are
35 unknown. Corticosteroids have been shown to have a wide range of effects on multiple cell types
36 (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g.,

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

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

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

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

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

54 **Distribution:** The tissue distribution at steady-state for beclomethasone dipropionate is moderate
55 (20 L) but more extensive for B-17-MP (424 L). There is no evidence of tissue storage of
56 beclomethasone dipropionate or its metabolites. Plasma protein binding is moderately high (87%).

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

62 **Elimination:** The elimination of beclomethasone dipropionate and B-17-MP after intravenous
63 administration are characterized by high plasma clearance (150 and 120 L/hour) with corresponding
64 terminal elimination half-lives of 0.5 and 2.7 hours. Following oral administration of tritiated
65 beclomethasone dipropionate, approximately 60% of the dose was excreted in the feces within
66 96 hours, mainly as free and conjugated polar metabolites. Approximately 12% of the dose was
67 excreted as free and conjugated polar metabolites in the urine. The renal clearance of
68 beclomethasone dipropionate and its metabolites is negligible.

69 **Pharmacodynamics:** The effects of beclomethasone dipropionate on hypothalamic-pituitary-adrenal
70 (HPA) function have been evaluated in adult volunteers by other routes of administration. Studies
71 with beclomethasone dipropionate by the intranasal route may demonstrate that there is more or that
72 there is less absorption by this route of administration. There was no suppression of early morning
73 plasma cortisol concentrations when beclomethasone dipropionate was administered in a dose of
74 1000 mcg/day for 1 month as an oral aerosol or for 3 days by intramuscular injection. However,
75 partial suppression of plasma cortisol concentrations was observed when beclomethasone
76 dipropionate was administered in doses of 2000 mcg/day either by oral aerosol or intramuscular

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

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

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

90

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

93 Results from two clinical trials have shown that significant symptomatic relief was obtained within
94 3 days. However, symptomatic relief may not occur in some patients for as long as 2 weeks.
95 BECONASE AQ Nasal Spray should not be continued beyond 3 weeks in the absence of significant
96 symptomatic improvement. BECONASE AQ Nasal Spray should not be used in the presence of
97 untreated localized infection involving the nasal mucosa.

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

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

104

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

107

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

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

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

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

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

123 Persons who are on drugs that suppress the immune system are more susceptible to infections
124 than healthy individuals. Chickenpox and measles, for example, can have a more serious or even
125 fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have
126 not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and
127 duration of corticosteroid administration affect the risk of developing a disseminated infection is not
128 known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is
129 also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
130 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG)
131 may be indicated. (See the respective package inserts for complete VZIG and IG prescribing
132 information.) If chickenpox develops, treatment with antiviral agents may be considered.

133

134 **PRECAUTIONS:**

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

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

139 Rare instances of nasal septum perforation have been spontaneously reported.

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

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

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

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

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

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

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

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

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

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

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

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

179 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Treatment of rats for a total of 95 weeks,
180 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic
181 activity. Mutagenic studies have not been performed.

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

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

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

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

199 **Pediatric Use:** The safety and effectiveness of BECONASE AQ Nasal Spray have been established
200 in children aged 6 years and above through evidence from extensive clinical use in adult and
201 pediatric patients. The safety and effectiveness of BECONASE AQ Nasal Spray in children below
202 6 years of age have not been established.

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

207

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

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

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

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

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

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

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

229

230 **OVERDOSAGE:** When used at excessive doses, systemic corticosteroid effects such as
231 hypercorticism and adrenal suppression may appear. If such changes occur, BECONASE AQ Nasal
232 Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral
233 steroid therapy. The oral LD₅₀ of beclomethasone dipropionate is greater than 1 g/kg in rodents. One
234 bottle of BECONASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate
235 equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

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

236

237 **DOSAGE AND ADMINISTRATION:**

238 **Adults and Children 12 Years of Age and Older:** The usual dosage is one or two inhalations (42 to
239 84 mcg) in each nostril twice a day (total dose, 168 to 336 mcg/day).

240 **Children 6 to 12 Years of Age:** Patients should be started with one inhalation in each nostril twice a
241 day; patients not adequately responding to 168 mcg or those with more severe symptoms may use
242 336 mcg (two inhalations in each nostril). BECONASE AQ Nasal Spray is *not* recommended for
243 children below 6 years of age.

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

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

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

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

257

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

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

262

263 *Calculated on the dried basis.

264

265 **Rx only**

266

267

268 **GlaxoWellcome**

269 Glaxo Wellcome Inc.

270 Research Triangle Park, NC 27709

271

272 March 2, 2001

RL-

273

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

274

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

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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).

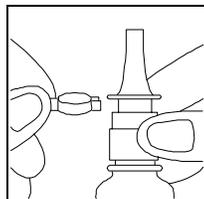


Figure 1

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.

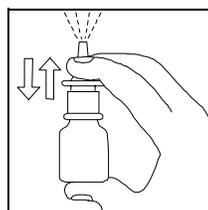


Figure 2

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).

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

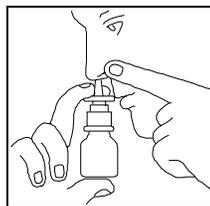


Figure 3

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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.

315

316

5. Then breathe out through the mouth.

317

318

6. Repeat in the other nostril.

319

320

7. Replace the plastic dust cap and safety clip.

321

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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.

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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.

329

330

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.

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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.

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

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343 **GlaxoWellcome**
344 Glaxo Wellcome Inc.
345 Research Triangle Park, NC 27709
346
347 March 2, 2001

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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.