

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202129Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZETONNA™Nasal Aerosol safely and effectively. See full prescribing information for ZETONNA™Nasal Aerosol.

ZETONNA™ (ciclesonide) Nasal Aerosol
For Intranasal Use Only
Initial U.S. Approval: 2006

INDICATIONS AND USAGE

ZETONNA Nasal Aerosol is a corticosteroid indicated for treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. (1.1)

DOSAGE AND ADMINISTRATION

For Intranasal use only

- 1 actuation per nostril once daily. (74 mcg per day) (2.1)

DOSAGE FORMS AND STRENGTHS

- Nasal Aerosol: 37 mcg of ciclesonide per actuation. (3)
- Supplied in a 6.1 g canister containing 60 actuations. (16)

CONTRAINDICATIONS

- Patients with a known hypersensitivity to ciclesonide or any of the ingredients of ZETONNA Nasal Aerosol. (4)

WARNINGS AND PRECAUTIONS

- Epistaxis, ulceration, nasal septal perforations, *Candida albicans* infection impaired wound healing. Prior to initiating therapy, examine patients for evidence of septal perforation, erosions, ulceration, nasal surgery, and trauma. Avoid spraying ZETONNA Nasal Aerosol directly onto the nasal septum. Avoid use in patients with recent septal perforation, nasal erosion, nasal ulcers, nasal surgery, or nasal trauma. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Discontinue ZETONNA Nasal Aerosol if erosions, ulcerations or perforations occur. (5.1)

- Development of glaucoma or cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, or cataracts. (5.2)
- Cases of hypersensitivity reactions following administration of ciclesonide with manifestations such as angioedema, with swelling of the lips, tongue and pharynx have been reported. (5.3)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chicken pox or measles in susceptible individuals. Use caution in patients with the above because of the potential for worsening of these infections. (5.4)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ZETONNA Nasal Aerosol slowly. (5.5)
- Potential reduction in growth velocity in children. (5.6, 8.4) Monitor growth routinely in pediatric patients receiving ZETONNA Nasal Aerosol.

ADVERSE REACTIONS

The most common adverse reactions (≥2% incidence) included nasal discomfort, headache and epistaxis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.

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

Revised: 01/2012

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118 **FULL PRESCRIBING INFORMATION**

119 **1 INDICATIONS AND USAGE**

120 **1.1 Treatment of Allergic Rhinitis**

121 ZETONNA™ (ciclesonide) Nasal Aerosol is indicated for the treatment of symptoms associated
122 with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

123 **2 DOSAGE AND ADMINISTRATION**

124 Administer ZETONNA Nasal Aerosol by the intranasal route only. Prior to initial use,
125 ZETONNA Nasal Aerosol must be primed by actuating three times. If ZETONNA Nasal
126 Aerosol is not used for ten consecutive days, it must be primed by actuating three times. If
127 ZETONNA Nasal Aerosol is dropped, the canister and actuator may become separated. If this
128 happens, reassemble ZETONNA Nasal Aerosol and test spray once into the air before using.
129 Illustrated patient's instructions for proper use accompany each package of ZETONNA Nasal
130 Aerosol.

131 **2.1 Allergic Rhinitis**

132 *Adults and Adolescents (12 Years of Age and Older):* The recommended dose of ZETONNA
133 Nasal Aerosol is 1 actuation per nostril once daily (37 mcg per actuation). The maximum total
134 daily dosage should not exceed 1 actuation in each nostril (74 mcg per day).

135 **3 DOSAGE FORMS AND STRENGTHS**

136 ZETONNA Nasal Aerosol is provided at strength of 37 mcg per actuation strength containing
137 60 actuations per canister.

138 **4 CONTRAINDICATIONS**

139 ZETONNA Nasal Aerosol is contraindicated in patients with a known hypersensitivity to
140 ciclesonide or any of the ingredients of ZETONNA Nasal Aerosol [*see Warnings and*
141 *Precautions (5.3)*].

142 **5 WARNINGS AND PRECAUTIONS**

143 **5.1 Local Nasal Effects**

144 Epistaxis and Nasal Ulceration: In clinical trials of 2 to 26 weeks in duration, epistaxis was
145 observed more frequently in patients treated with ZETONNA Nasal Aerosol than those who
146 received placebo. In the 26-week open-label extension of the perennial allergic rhinitis trial,
147 nasal ulceration was identified in 4 of 824 patients administered ZETONNA Nasal Aerosol
148 (148 mcg). [*see Adverse Reactions (6)*]

149 Nasal Septal Perforation: Nasal septal perforation has been reported in patients following the
150 intranasal application of ZETONNA Nasal Aerosol. Three short-term placebo-controlled trials
151 (2 weeks) and one long-term (26 weeks with placebo control and 26 weeks open-label extension
152 without placebo control) trial were conducted in patients with seasonal and perennial allergic
153 rhinitis. Nasal septal perforations were reported in 2 patients out of 2335 treated with
154 ZETONNA Nasal Aerosol compared with none of 892 treated with placebo.

155 Before starting ZETONNA Nasal Aerosol conduct a nasal examination to ensure that patients are
156 free of nasal disease other than allergic rhinitis. Periodically monitor patients with nasal
157 examinations during treatment for adverse effects in the nasal cavity. If an adverse reaction
158 (e.g. erosion, ulceration, perforation) is noted, discontinue ZETONNA Nasal Aerosol. Avoid
159 spraying ZETONNA Nasal Aerosol directly onto the nasal septum.

160 Candida Infection: In clinical trials with another formulation of ciclesonide, the development of
161 localized infections of the nose or pharynx with *Candida albicans* has occurred. If such an
162 infection develops with ZETONNA Nasal Aerosol, it may require treatment with appropriate
163 local therapy and discontinuation of ZETONNA Nasal Aerosol.

164 Impaired Wound Healing: Because of the inhibitory effect of corticosteroids on wound healing,
165 patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should
166 not use ZETONNA Nasal Aerosol until healing has occurred.

167 **5.2 Glaucoma and Cataracts**

168 Nasal and inhaled corticosteroids may result in the development of glaucoma and cataracts.
169 Therefore, close monitoring is warranted in patients with a change in vision or with a history of
170 increased intraocular pressure, glaucoma, or cataracts.

171 **5.3 Hypersensitivity**

172 ZETONNA Nasal Aerosol is contraindicated in patients with a known hypersensitivity to
173 ciclesonide or any of the ingredients of ZETONNA Nasal Aerosol. Cases of hypersensitivity
174 reactions following administration of ciclesonide with manifestations such as angioedema, with
175 swelling of the lips, tongue and pharynx, have been reported.

176 **5.4 Immunosuppression**

177 Patients who are using drugs that suppress the immune system are more susceptible to infections
178 than healthy individuals. Chicken pox and measles, for example, can have a more serious or even
179 fatal course in susceptible children or adults using corticosteroids. In children or adults who
180 have not had these diseases or been properly immunized, particular care should be taken to avoid
181 exposure. How the dose, route, and duration of corticosteroid administration affect the risk of
182 developing a disseminated infection is not known. The contribution of the underlying disease or
183 prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chicken
184 pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is
185 exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be
186 indicated. (See the respective package inserts for complete VZIG and IG prescribing
187 information). If chickenpox develops, treatment with antiviral agents may be considered.

188 Corticosteroids should be used with caution, if at all, in patients with active or quiescent
189 tuberculosis infections of the respiratory tract; or in patients with untreated local or systemic
190 fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex
191 because of the potential for worsening of these infections.

192 **5.5 Hypothalamic-Pituitary-Adrenal Axis Effect**

193 Hypercorticism and Adrenal Suppression: When intranasal corticosteroids are used at higher
194 than recommended dosages or in susceptible individuals at recommended dosages, systemic
195 corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such
196 changes occur, the dosage of ZETONNA Nasal Aerosol should be discontinued slowly,
197 consistent with accepted procedures for discontinuing oral steroid therapy.

198 The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied
199 by signs of adrenal insufficiency. In addition, some patients may experience symptoms of
200 corticosteroid withdrawal, e.g., joint and muscular pain, lassitude, and depression. Patients
201 previously treated for prolonged periods with systemic corticosteroids and transferred to topical
202 corticosteroids should be carefully monitored for acute adrenal insufficiency in response to
203 stress. In those patients who have asthma or other clinical conditions requiring long-term
204 systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a
205 severe exacerbation of their symptoms.

206 **5.6 Effect on Growth**

207 Corticosteroids may cause a reduction in growth velocity when administered to pediatric
208 patients. Monitor the growth routinely (e.g., via stadiometry) in pediatric patients receiving
209 ZETONNA Nasal Aerosol. [*see Pediatric Use (8.4)*]

210 **6 ADVERSE REACTIONS**

211 Systemic and local corticosteroid use may result in the following:

- 212 • Epistaxis, ulcerations, nasal septal perforations, *Candida albicans* infection, impaired wound
213 healing [*see Warnings and Precautions (5.1)*]
- 214 • Glaucoma and cataracts [*see Warnings and Precautions (5.2)*]
- 215 • Immunosuppression [*see Warnings and Precautions (5.4)*]
- 216 • Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see*
217 *Warnings and Precautions (5.5, 5.6), Use in Specific Populations (8.4)*]

218 **6.1 Clinical Trials Experience**

219 The safety data described below for adults and adolescents 12 years of age and older are based
220 on 4 clinical trials evaluating doses of ciclesonide nasal aerosol from 74 to 282 mcg. Three of
221 the clinical trials were 2 to 6 weeks in duration and one trial was 26 weeks in duration with an
222 additional 26-week open-label extension. Data from the first 6 weeks of the 26-week trial were
223 pooled with data from the three 2-week trials. Short-term data (2 to 6 weeks) included
224 3001 patients with seasonal and perennial allergic rhinitis, of these, 884 received

ZETONNA Nasal Aerosol 74 mcg once daily and 892 received placebo. The short-term data included 1098 (36.6%) males, 1903 (63.4%) females, 2587 (86.2%) Caucasians, 320 (10.7%) Blacks, 49 (1.6%) Asians, and 45 (1.5%) patients classified as Other. The 26-week trial was conducted in 1110 patients with perennial allergic rhinitis [394 (35.5%) males and 716 (64.5%) females, ages 12 to 78 years old] treated with ZETONNA Nasal Aerosol 74 mcg, 148 mcg or placebo once daily. Of these patients, 298 were treated with 74 mcg ZETONNA Nasal Aerosol, 505 with 148 mcg, and 307 with placebo. The racial distribution in this trial included 922 (83.1%) Caucasians, 146 (13.2%) Blacks, 18 (1.6%) Asians, and 24 (2.2%) patients classified as Other. The 26-week open-label extension included 824 patients [295 (35.8%) males and 529 (64.2%) females, ages 12 to 79 years old] given ZETONNA Nasal Aerosol 148 mcg once daily. The racial distribution in the open-label extension included 690 (83.7%) Caucasians, 104 (12.6%) Blacks, 15 (1.8%) Asians, and 15 (1.8%) patients classified as Other.

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

Adults and Adolescents 12 Years of Age and Older in Short-Term (2-6 weeks) Trials:

In three short-term trials and the first 6 weeks of one long-term trial, conducted in the US, 884 patients with a history of seasonal or perennial allergic rhinitis were treated with ZETONNA Nasal Aerosol 74 mcg daily. Adverse reactions did not differ appreciably based on age, gender, or race. The table below displays reactions that occurred with an incidence of at least 2.0% and more frequently with ZETONNA Nasal Aerosol 74 mcg than with placebo in seasonal or perennial allergic rhinitis clinical trials of 2 to 6 weeks duration.

247

Table 1: Adverse Reactions Occurring with a Frequency of at least 2.0% and Greater than Placebo from Controlled Clinical Trials 2 to 6 Weeks in Duration in Patients 12 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis

Adverse Reaction	ZETONNA Nasal Aerosol 74 mcg Once Daily N = 884 (%)	Placebo N = 892 (%)
Nasal discomfort ^a	28 (3.2)	16 (1.8)
Headache	27 (3.1)	11 (1.2)
Epistaxis	26 (2.9)	24 (2.7)

^a Nasal discomfort includes both nasal discomfort and instillation site discomfort

252

When considering the data from higher doses evaluated in the short-term trials, epistaxis demonstrated a dose response. In addition, two patients treated with ZETONNA Nasal Aerosol 74 mcg experienced nasal septal perforations in the short-term trials compared to no patients treated with placebo.

Approximately 1.2% of patients treated with ZETONNA Nasal Aerosol 74 mcg in clinical trials discontinued because of adverse reactions; this rate was similar for patients treated with placebo.

259 Discontinuations due to local adverse reactions were similar in ZETONNA Nasal Aerosol
260 74 mcg treated patients (0.8%) compared to placebo treated patients (0.8%). Local adverse
261 reactions leading to discontinuation that occurred only in ZETONNA Nasal Aerosol treated
262 patients included ear infection, nasal discomfort, nasal dryness, nasal mucosal/septum disorders,
263 pharyngitis, streptococcal pharyngitis, sinus headache, and tonsillitis.

264 ***Pediatric Patients Aged 2 to 11 Years:***

265 Trials of ZETONNA Nasal Aerosol have not been conducted in pediatric patients aged 2 to
266 11 years.

267 ***Long-Term (26-Week Double-Blind and 26-Week Open-Label) Safety Trial:***

268 In one 26-week double-blind, placebo-controlled safety trial that included 1110 adult and
269 adolescent patients with perennial allergic rhinitis, additional adverse reactions, with an
270 incidence of at least 2%, that occurred more frequently with ZETONNA Nasal Aerosol than with
271 placebo were upper respiratory tract infection, urinary tract infection, oropharyngeal pain, nasal
272 mucosal/septum disorders, viral upper respiratory tract infection, cough, influenza, bronchitis,
273 streptococcal pharyngitis, muscle strain, and nausea. Nasal discomfort (5.7%) and epistaxis
274 (11.4%) were also more frequent in the 26-week safety trial compared to clinical trials 2 to
275 6 weeks in duration. Nasal mucosal/septum disorders and cough demonstrated a dose response.

276 Discontinuations due to adverse reactions were higher in ZETONNA Nasal Aerosol treated
277 patients compared to placebo treated patients and demonstrated a dose response. Local adverse
278 reactions leading to discontinuation were also higher in ZETONNA Nasal Aerosol 74 mcg
279 treated patients (1.7%) compared to placebo treated patients (0.7%). The only local adverse
280 reaction leading to discontinuation that occurred in ZETONNA Nasal Aerosol treated patients
281 and was not observed in the 2- to 6-week trials was upper respiratory tract infection.

282 A total of 824 patients with perennial allergic rhinitis who completed the 26-week double-blind
283 trial enrolled into an open-label extension and received ZETONNA Nasal Aerosol 148 mcg for
284 26 weeks. Additional adverse reactions, observed with an incidence of at least 2% were
285 sinusitis, nasopharyngitis, and back pain.

286 A total of 4 nasal septal ulcerations were also reported in the 26-week open-label extension.

287 There were no reports of nasal septal perforations in the long-term safety trial.

288 **6.2 Post-marketing Experience**

289 Additional adverse reactions have been identified during worldwide post-marketing use with
290 other formulations of ciclesonide, ALVESCO[®] Inhalation Aerosol and OMNARIS[®] Nasal
291 Spray. Because these reactions are reported voluntarily from a population of uncertain size, it is
292 not always possible to reliably estimate their frequency or establish a causal relationship to drug
293 exposure.

294 ALVESCO[®] Inhalation Aerosol: immediate or delayed hypersensitivity reactions such as
295 angioedema with swelling of the lips, tongue, and pharynx.

296 OMNARIS[®] Nasal Spray: nasal congestion, nasal ulcer, and dizziness. Localized infections of
297 the nose or mouth with *Candida albicans* have also occurred with OMNARIS[®] Nasal Spray.

298 **7 DRUG INTERACTIONS**

299 *In vitro* studies and clinical pharmacology studies suggested that des-ciclesonide has no potential
300 for metabolic drug interactions or protein binding-based drug interactions [*see Clinical*
301 *Pharmacology (12.3)*]. In a drug interaction study, co-administration of orally inhaled
302 ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the
303 exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of
304 ciclesonide remained unchanged. Erythromycin, a moderate inhibitor of cytochrome P450 3A4,
305 had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin following oral
306 inhalation of ciclesonide [*see Clinical Pharmacology (12.3)*].

307 **8 USE IN SPECIFIC POPULATIONS**

308 **8.1 Pregnancy**

309 Teratogenic Effects: Pregnancy Category C.

310 There are no adequate and well-controlled trials in pregnant women. ZETONNA Nasal Aerosol
311 should be used during pregnancy only if the potential benefit justifies the potential risk to the
312 fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed
313 to physiologic, doses suggests that rodents are more prone to teratogenic effects from
314 corticosteroids than humans.

315 Oral administration of ciclesonide in rats at approximately 120 times the maximum
316 recommended human daily intranasal dose (MRHDID) in adults (on a mcg/m² basis at a
317 maternal dose of 900 mcg/kg/day) produced no teratogenicity or other fetal effects. However,
318 subcutaneous administration of ciclesonide in rabbits at similar to MRHDID (on a mcg/m² basis
319 at a maternal dose of 5 mcg/kg/day) produced fetal toxicity. This included fetal loss, reduced
320 fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin
321 effects. No toxicity was observed at 1/4 of the MRHDID in adults (on a mcg/m² basis at a
322 maternal dose of 1 mcg/kg/day).

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

325 **8.3 Nursing Mothers**

326 It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are
327 excreted in human milk. In a study with lactating rats, minimal but detectable levels of
328 radiolabeled ciclesonide were recovered in milk. Caution should be used when ZETONNA
329 Nasal Aerosol is administered to nursing women.

330 **8.4 Pediatric Use**

331 The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of
332 age and older have been established. The safety and efficacy of ZETONNA Nasal Aerosol for
333 treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 11 years of age
334 and younger have not been established.

335 Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in
336 growth velocity in pediatric patients. This effect has been observed in the absence of laboratory
337 evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth
338 velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients
339 than some commonly used tests of HPA-axis function. The long-term effects of this reduction in
340 growth velocity associated with intranasal corticosteroids, including the impact on final adult
341 height, are unknown. The potential for “catch-up” growth following discontinuation of treatment
342 with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients
343 receiving intranasal corticosteroids, including ZETONNA Nasal Aerosol, should be monitored
344 routinely (e.g., via stadiometry). A 52-week, multi-center, double-blind, randomized, placebo-
345 controlled parallel-group trial was conducted to assess the effect of orally inhaled ciclesonide
346 (ALVESCO[®] Inhalation Aerosol) on growth rate in 609 pediatric patients with mild persistent
347 asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or
348 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the
349 baseline, treatment and follow-up periods. The primary comparison was the difference in growth
350 rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn
351 from this trial because compliance could not be assured. Ciclesonide blood levels were also not
352 measured during the one-year treatment period. There was no difference in efficacy measures
353 between the placebo and the orally inhaled ciclesonide (ALVESCO[®] Inhalation Aerosol) groups.

354 The potential growth effects of prolonged treatment should be weighed against clinical benefits
355 obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To
356 minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the
357 lowest dose that effectively controls his/her symptoms.

358 The potential for ZETONNA Nasal Aerosol to cause growth suppression in susceptible patients
359 or when given at higher than recommended dosages cannot be ruled out.

360 **8.5 Geriatric Use**

361 Clinical trials of ZETONNA Nasal Aerosol did not include sufficient numbers of patients age
362 65 and over to determine whether they responded differently from younger patients. Other
363 reported clinical experience has not identified differences in responses between the elderly and
364 younger patients. In general, dose selection for an elderly patient should be cautious reflecting
365 the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease
366 or other drug therapy.

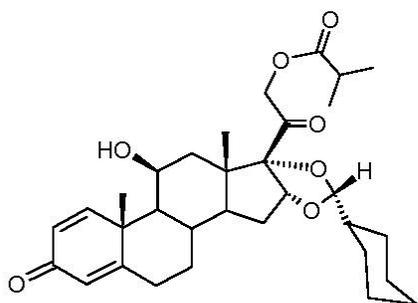
367 **10 OVERDOSAGE**

368 Chronic overdose may result in signs or symptoms of hypercorticism [*see Warnings and*
369 *Precautions (5.5)*]. There are no data on the effects of acute or chronic overdose with
370 ZETONNA Nasal Aerosol.

371 **11 DESCRIPTION**

372 The active component of ZETONNA Nasal Aerosol is ciclesonide, a non-halogenated
373 glucocorticoid having the chemical name pregna -1,4-diene-3,20-dione, 16,17-[[R-

374 cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-(11 β ,16 α)-
375 Ciclesonide is delivered as the R-epimer. The empirical formula is C₃₂H₄₄O₇ and its molecular
376 weight is 540.7. Its structural formula is as follows:



377
378 Ciclesonide is a white to yellow-white powder. It is soluble in dehydrated alcohol, acetone,
379 dichloromethane, and chloroform. ZETONNA Nasal Aerosol is comprised of a pressurized,
380 metered-dose aerosol canister and actuator, which is fitted with a dose indicator. ZETONNA
381 Nasal Aerosol is intended for intranasal use only. Each canister contains a solution of ciclesonide
382 in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. After priming, ZETONNA
383 Nasal Aerosol 37 mcg delivers 50 mcg of ciclesonide from the valve and 37 mcg of ciclesonide
384 from the actuator. This product delivers 50 microliters (59.3 milligrams) of solution as fine
385 particle mist from the valve with each actuation.

386 12 CLINICAL PHARMACOLOGY

387 12.1 Mechanism of Action

388 Ciclesonide is a pro-drug that is enzymatically hydrolyzed to a pharmacologically active
389 metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide or RM1) following intranasal
390 application. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid
391 receptor that is 120 times higher than the parent compound.

392 The precise mechanism through which ciclesonide affects allergic rhinitis symptoms is not
393 known. Corticosteroids have been shown to have a wide range of effects on multiple cell types
394 (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators
395 (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic inflammation.

396 12.2 Pharmacodynamics

397 Adrenal Function: In a 6-week, randomized, double-blind, placebo-controlled, parallel-group
398 trial in adolescents and adults 12-73 years of age with perennial allergic rhinitis, daily doses of
399 148 mcg and 282 mcg of ZETONNA Nasal Aerosol were compared to placebo nasal aerosol.
400 Dexamethasone 6 mg was used as an active control during the last 4 days of the trial. Adrenal
401 function was assessed by 24-hr serum cortisol AUC before and after the treatment. At the end of
402 6 weeks of treatment, the mean (SE) change from baseline in serum cortisol AUC₍₀₋₂₄₎
403 was -5.0 (4.6) mcg•hour/dL, -2.6 (4.6) mcg•hour/dL, and -4.6 (5.0) mcg•hour/dL for placebo
404 (n=57), 148 mcg ZETONNA Nasal Aerosol (n=60), and 282 mcg ZETONNA Nasal Aerosol
405 (n=50), respectively. The difference from placebo for the change from baseline in serum cortisol

406 AUC₍₀₋₂₄₎ was -2.4 mcg•hour/dL (95% CI: -15.1, 10.2) and -0.5 mcg•hour/dL (95% CI: -13.9,
407 13.0) for 148 mcg/day and 282 mcg/day treatments, respectively. The effects observed with the
408 active control (dexamethasone, n=18) validate the sensitivity of the study to assess the effect of
409 ciclesonide on the HPA axis.

410 **12.3 Pharmacokinetics**

411 Absorption: Ciclesonide and des-ciclesonide have negligible oral bioavailability (both less than
412 1%) due to low gastrointestinal absorption and high first-pass metabolism. The intranasal
413 administration of ciclesonide at recommended doses results in negligible serum concentrations of
414 ciclesonide. However, the known active metabolite (des-ciclesonide) is detected in the serum of
415 some patients after nasal inhalation of ciclesonide. The bioanalytical assay used has a lower
416 limit of quantification of 10 pg/mL, for both ciclesonide and des-ciclesonide, respectively.

417 The low systemic exposure of des-ciclesonide following ciclesonide nasal aerosol administration
418 was confirmed in a crossover trial in 29 healthy adults. The median C_{max} of des-ciclesonide was
419 59 pg/mL following a single dose of ciclesonide nasal aerosol (296 mcg) compared to
420 602 pg/mL following a single dose of orally inhaled ciclesonide (320 mcg) and 12 pg/mL
421 following a single dose of ciclesonide aqueous nasal spray (300 mcg). The pharmacokinetics of
422 intranasally administered ciclesonide have been assessed in perennial allergic rhinitis patients
423 resulting in similar exposure compared to healthy subjects.

424 Distribution: Following intravenous administration of 800 mcg of ciclesonide, the volumes of
425 distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and 12.1 L/kg,
426 respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins
427 averaged ≥ 99% each, with ≤ 1% of unbound drug detected in the systemic circulation. Des-
428 ciclesonide is not significantly bound to human transcortin.

429 Metabolism: Ciclesonide is hydrolyzed to a biologically active metabolite, des-ciclesonide, by
430 esterases. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites
431 mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser extent by CYP 2D6. The
432 full range of potentially active metabolites of ciclesonide has not been characterized. After
433 intravenous administration of ¹⁴C-ciclesonide, 19.3% of the resulting radioactivity in the plasma
434 is accounted for by ciclesonide or des-ciclesonide; the remainder may be a result of other, as yet,
435 unidentified multiple metabolites.

436 Elimination: Following intravenous administration of 800 mcg of ciclesonide, the clearance
437 values of ciclesonide and des-ciclesonide were high (approximately 152 L/hr and 228 L/hr,
438 respectively). ¹⁴C-ciclesonide was predominantly excreted via the feces after intravenous
439 administration (66%) indicating that excretion through bile is the major route of elimination.
440 Approximately 20% or less of drug related radioactivity was excreted in the urine.

441 Special Populations:

442 Hepatic Impairment: Compared to healthy subjects, the systemic exposure (C_{max} and AUC) in
443 patients with liver impairment increased in the range of 1.4 to 2.7-fold after ex-actuator
444 administration of 1280 mcg ciclesonide via oral inhalation. Dose adjustment in liver impairment
445 is not necessary.

446 Renal Impairment: Trials in renally-impaired patients were not conducted since renal excretion
447 of des-ciclesonide is a minor route of elimination ($\leq 20\%$).

448 Drug-Drug Interactions: Ciclesonide inhibited human recombinant cytochrome P450 enzymes at
449 high concentration (3 microM) *in vitro*, but clinically relevant metabolic interactions are not
450 anticipated. Based on *in vitro* studies in human liver microsomes, ciclesonide and des-
451 ciclesonide appear to have no inhibitory or induction potential on the metabolism of other drugs
452 metabolized by cytochrome P450 enzymes. *In vitro* studies demonstrated that the plasma protein
453 binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential
454 for protein binding-based drug interactions.

455 In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole,
456 a strong inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of the active
457 metabolite of ciclesonide, des-ciclesonide, by approximately 3.6-fold at steady state, while levels
458 of ciclesonide remained unchanged.

459 In another drug interaction study, co-administration of orally inhaled ciclesonide and oral
460 erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no effect on the
461 pharmacokinetics of either des-ciclesonide or erythromycin.

462 **13 NONCLINICAL TOXICOLOGY**

463 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

464 Ciclesonide demonstrated no carcinogenic potential in mice in a study of oral doses up to
465 900 mcg/kg (approximately 60 times the maximum recommended human daily intranasal dose
466 (MRHDID) in adults based on mcg/m²/day) in mice for 104 weeks, nor in a study in rats of
467 inhalation doses up to 193 mcg/kg (approximately 25 times the maximum human daily intranasal
468 dose in adults and adolescents 12 years of age or older based on mcg/m²/day) for 104 weeks.

469 Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not
470 clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However,
471 ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference
472 corticosteroid (dexamethasone) in this study showed similar findings.

473 No evidence of impairment of fertility was observed in a reproductive study conducted in male
474 and female rats both dosed orally up to 900 mcg/kg/day (approximately 120 times MRHDID in
475 adults based on mcg/m²/day).

476 **14 CLINICAL STUDIES**

477 **14.1 Seasonal and Perennial Allergic Rhinitis**

478 *Adults and Adolescent Patients 12 Years of Age and Older:*

479 The efficacy of ZETONNA Nasal Aerosol was evaluated in one randomized, double-blind,
480 parallel-group, multicenter, placebo-controlled dose-ranging trial (74 mcg, 148 mcg, and
481 282 mcg once daily) and 3 confirmatory trials (74 mcg and 148 mcg once daily) in adolescents
482 and adults with allergic rhinitis. Efficacy endpoints were evaluated at 2 weeks for the two

483 seasonal allergic rhinitis trials and at 6 weeks for the perennial allergic rhinitis trial. These trials
484 were all conducted in the United States. A total of 3001 patients were included in these 4 trials.
485 The dose-ranging trial included a total of 513 patients [193 males (37.6%) and 320 females
486 (62.4%)], of whom 65 (12.7%) were adolescents. The three confirmatory trials included a total of
487 2488 patients (905 males and 1583 females) of whom 170 were adolescents, ages 12 to 18 years.
488 Patients enrolled in the trials were 12 to 81 years of age with a history of seasonal or perennial
489 allergic rhinitis, a positive skin test to at least one relevant allergen, and active symptoms of
490 allergic rhinitis at study entry. Assessment of efficacy in these trials was based on patient
491 recording of four nasal symptoms (runny nose, nasal itching, sneezing, and nasal congestion) on
492 a 0-3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) as reflective
493 or instantaneous total nasal symptom scores (rTNSS and iTNSS respectively). Reflective
494 scoring required the patients to record symptom severity over the previous 12 hours; the
495 instantaneous scoring required patients to record symptom severity over the previous 10 minutes.

496 Additional secondary efficacy variables were assessed, including the total ocular symptom score
497 (TOSS) in the seasonal allergic rhinitis trials and the Rhinoconjunctivitis Quality of Life
498 Questionnaire with Standardised Activities [RQLQ(S)] in both seasonal and perennial allergic
499 rhinitis trials. TOSS is calculated as the sum of the patients' scoring of the three individual
500 ocular symptoms (itching, tearing, and redness) on a 0 to 3 categorical severity scale (0 = absent,
501 1 = mild, 2 = moderate, 3 = severe) as reflective (rTOSS) or instantaneous (iTOSS) scores. To
502 assess efficacy, rTOSS and iTOSS were evaluated as described above for the TNSS. Patients
503 perceptions of disease specific quality of life were evaluated through the use of the RQLQ(S),
504 which assesses the impact of allergic rhinitis symptoms and treatment through 28 items in
505 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye
506 symptoms, and emotional) on a 7-point scale where 0 = not troubled and 6 = extremely troubled.
507 An overall RQLQ(S) score is calculated from the average of the domain scores. An absolute
508 difference of ≥ 0.5 in mean change from baseline over placebo is considered the minimally
509 clinically important difference (MCID) for the RQLQ(S).

510 *Dose-Ranging Trial:* There was a 2-week placebo-controlled, double-blind, dose-ranging trial
511 that evaluated efficacy of three doses of ZETONNA Nasal Aerosol (74 mcg, 148 mcg, and
512 282 mcg once daily) in patients with seasonal allergic rhinitis. The primary efficacy endpoint
513 was the difference from placebo in the change from baseline of the average of morning and
514 evening reflective total nasal symptom score (rTNSS) averaged over the 2-week treatment
515 period. The rTNSS showed a statistically significant estimated treatment difference from
516 placebo of 0.81 (95% CI: 0.32, 1.29); 0.90 (95% CI: 0.40, 1.39); and 0.66 (95% CI: 0.16, 1.16)
517 for 282 mcg, 148 mcg and 74 mcg, respectively.

518 *Confirmatory Seasonal Allergic Rhinitis Trials:* There were two 2-week placebo-controlled,
519 double-blind confirmatory trials that evaluated efficacy of two doses of ZETONNA Nasal
520 Aerosol (74 mcg and 148 mcg once daily) in patients with seasonal allergic rhinitis. The primary
521 efficacy endpoint was the difference from placebo in the change from baseline of the average of
522 morning and evening rTNSS averaged over the 2-week treatment period. Table 2 displays the
523 efficacy results from one of these trials in patients with seasonal allergic rhinitis. The other trial
524 showed similar results. In these trials, ZETONNA Nasal Aerosol 74 mcg once daily was
525 statistically significantly different from placebo. Statistically significant differences in the
526 morning pre-dose iTNSS indicate that the effect was maintained over the full 24-hour dosing
527 interval. ZETONNA Nasal Aerosol 74 mcg demonstrated a statistically significant decrease from

528 baseline in the rTOSS compared to placebo. Similarly, a clinically significant decrease (≥ 0.5)
 529 from baseline compared to placebo for the RQLQ(S) was also shown. ZETONNA Nasal Aerosol
 530 148 mcg once daily did not provide an efficacy benefit over the 74 mcg once daily dose.

531 *Confirmatory Perennial Allergic Rhinitis Trial:* There was one 26-week placebo-controlled,
 532 double-blind trial that evaluated efficacy of two doses of ZETONNA Nasal Aerosol (74 mcg and
 533 148 mcg once daily) in patients with perennial allergic rhinitis. The primary efficacy endpoint
 534 was the difference from placebo in the change from baseline of the average of morning and
 535 evening rTNSS averaged over the first 6 weeks of treatment. In this trial, ZETONNA Nasal
 536 Aerosol 74 mcg once daily was statistically significantly different from placebo (Table 2) in
 537 decreasing nasal symptom scores. Statistically significant differences in the morning pre-dose
 538 instantaneous total nasal symptom score indicate that the effect was maintained over the full
 539 24-hour dosing interval. ZETONNA Nasal Aerosol 74 mcg did not demonstrate a clinically
 540 significant change from baseline in the overall RQLQ(S) compared to placebo. TOSS was not
 541 evaluated in this trial. ZETONNA Nasal Aerosol 148 mcg once daily did not provide an efficacy
 542 benefit over the 74 mcg once daily dose.

543

544 **Table 2: Mean Changes in Efficacy Variables in Adult and Adolescent Patients With**
 545 **Seasonal or Perennial Allergic Rhinitis**

Treatment	N	Mean Baseline ^a	LS Mean Change from Baseline	Difference from Placebo ^b		
				Estimate (LS Mean)	95% CI	p-value ^c
Seasonal Allergic Rhinitis						
Reflective Total Nasal Symptom Score						
Ciclesonide 74 mcg	237	9.3	-1.5	0.9	0.6, 1.3	<0.001
Placebo	235	9.1	-0.5			
Instantaneous Total Nasal Symptom Score						
Ciclesonide 74 mcg	237	8.7	-1.3	0.9	0.5, 1.3	<0.001
Placebo	235	8.6	-0.5			
Reflective Total Ocular Symptom Score						
Ciclesonide 74 mcg	237	5.8	-0.8	0.5	0.3, 0.8	0.001
Placebo	235	5.7	-0.2			
Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities						
Ciclesonide 74 mcg	237	4.0	-0.8	0.6	0.4, 0.8	<0.001
Placebo	234	4.0	-0.2			
Perennial Allergic Rhinitis						
Reflective Total Nasal Symptom Score						
Ciclesonide 74 mcg	298	8.5	-2.0	0.7	0.4, 1.0	<0.001

Treatment	N	Mean Baseline ^a	LS Mean Change from Baseline	Difference from Placebo ^b		
				Estimate (LS Mean)	95% CI	p-value ^c
Placebo	307	8.6	-1.3			
Instantaneous Total Nasal Symptom Score						
Ciclesonide 74 mcg	298	7.7	-1.8	0.6	0.3, 0.9	<0.001
Placebo	307	7.7	-1.2			

546 **a** Baseline for rTNSS, iTNSS, and rTOSS are averages of the AM and PM responses obtained during the Run-in
547 Period up to 6 days prior to randomization and includes AM score prior to randomization. Baseline for morning
548 iTNSS is the average of the AM responses obtained during the Run-in Period up to 6 days prior to randomization
549 and includes the AM score prior to randomization. Baseline RQLQ(S) is from the randomization visit assessment.
550 **b** Estimates (LS Mean), 95% Confidence Intervals, and p-values were obtained from ANCOVA analyses with
551 treatment and center as fixed effects and baseline as covariate in the model.
552 **c** P-values are significant at the 0.025 level based on Bonferroni correction.

553

554 *Onset of Action:* Onset of action was evaluated in both 2-week seasonal and one 6-week
555 perennial allergic rhinitis trials by frequent recording of instantaneous symptom score. In these
556 trials, onset of effect was seen after 36 hours following the first dose. Maximum benefit is
557 usually achieved within 1 to 2 weeks after initiation of dosing.

558 *Pediatric Patients Aged 11 Years and Younger:* Efficacy of ZETONNA Nasal Aerosol in
559 patients 11 years of age and younger has not been established [*see Use in Specific Populations*
560 (8.4)].

561 16 HOW SUPPLIED/STORAGE AND HANDLING

562 ZETONNA Nasal Aerosol is supplied as a pressurized aluminum canister with a purple and
563 white plastic actuator integrated with a dose indicator and a cap. The contents of one 6.1 gram
564 canister provide 60 actuations, after initial priming. Each actuation delivers 37 mcg of
565 ciclesonide from the nasal actuator. Prior to initial use, or when not used for ten consecutive
566 days, ZETONNA Nasal Aerosol must be primed by actuating three times. If ZETONNA Nasal
567 Aerosol is dropped, the canister and actuator may become separated. If this happens, ZETONNA
568 Nasal Aerosol should be reassembled and actuated once into the air to test before using. The
569 actuator and canister should be discarded after reaching zero in the indicator window since the
570 amount of ciclesonide delivered per spray thereafter may be substantially less than the labeled
571 dose.

572 The ZETONNA Nasal Aerosol canister should only be used with the ZETONNA Nasal Aerosol
573 actuator. The actuator is fitted with a dose indicator and should not be used with other inhalation
574 aerosol medications. The correct amount of medication in each inhalation cannot be ensured
575 after the labeled number of actuations from the canister has been used, even though the inhaler
576 may not feel completely empty and may continue to operate. Illustrated patient's instructions for
577 proper use accompany each package of ZETONNA Nasal Aerosol.

578 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled**
579 **Room Temp]. For optimal results, canister should be at room temperature when used.**

580 **CONTENTS UNDER PRESSURE**

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

583 **Keep out of reach of children. Avoid spraying in eyes or directly onto the nasal septum.**

584 **ZETONNA Nasal Aerosol 37 mcg, 60 metered actuations; net fill weight 6.1 g.**

585 **NDC Number 63402-737-60**

586 **17 PATIENT COUNSELING INFORMATION**

587 See FDA-Approved Patient Labeling accompanying the product.

588 **17.1 Local Nasal Effects**

589 Patients should be informed that treatment with ZETONNA Nasal Aerosol may lead to adverse
590 reactions, which include nasal septal perforation, epistaxis, and nasal ulceration. In addition,
591 ciclesonide is associated with candidal infection, and nasal corticosteroids are associated with
592 impaired wound healing. Do not spray ZETONNA Nasal Aerosol directly onto the nasal septum.
593 Patients who have experienced recent nasal septal perforation, nasal erosion, nasal ulcers, nasal
594 surgery, or nasal trauma should not use ZETONNA Nasal Aerosol until healing has occurred
595 [*see Warnings and Precautions (5.1)*].

596 **17.2 Glaucoma and Cataracts**

597 Patients should be informed that glaucoma and cataracts are associated with nasal and inhaled
598 corticosteroid use. Patients should inform his/her health care provider if a change in vision is
599 noted while using ZETONNA Nasal Aerosol [*see Warnings and Precautions (5.2)*].

600 **17.3 Immunosuppression**

601 Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid
602 exposure to chickenpox or measles, and if exposed, to consult their physician without delay.
603 Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial,
604 viral or parasitic infections, or ocular herpes simplex [*see Warnings and Precautions (5.4)*].

605 **17.4 Use Daily**

606 Patients should use ZETONNA Nasal Aerosol on a regular, once daily basis since its
607 effectiveness depends on its regular use. In clinical trials, the onset of effect was seen after
608 36 hours following the first dose. Maximum benefit is usually achieved within 1 to 2 weeks after
609 initiation of dosing. Initial assessment of response should be made during this timeframe and
610 periodically until the patient's symptoms are stabilized. The patient should take the medication
611 as directed and should not exceed the prescribed dosage. The patient should contact the
612 physician if symptoms do not improve by a reasonable time or if the condition worsens.

613 **17.5 Keep Spray Out of Eyes and Off Nasal Septum**

614 Patients should be informed to avoid spraying ZETONNA Nasal Aerosol in their eyes or directly
615 on the nasal septum.

616 **17.6 Storage and Handling**

617 Patients should use the ZETONNA Nasal Aerosol canister only with the ZETONNA Nasal
618 Aerosol actuator supplied with the product. The dose indicator display window will show a red
619 zone when it is about time to replace the ZETONNA Nasal Aerosol. Replace ZETONNA Nasal
620 Aerosol when the indicator shows zero.

621

622



624

625 Manufactured for:

626 **Sunovion Pharmaceuticals Inc.**

627 Marlborough, MA 01752 USA

628 Made in the United Kingdom

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630

631

632 For customer service, call 1-888-394-7377

633 To report adverse events, call 1-877-737-7226

634 For medical information, call 1-800-739-0565

635

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637 January 2012

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639 620392213

Patient Information

ZETONNA™ <<Ze toe' nah>> (ciclesonide) Nasal Aerosol

Note: For Use in the Nose Only.

- **Do not** spray ZETONNA Nasal Aerosol in your eyes or directly onto your nasal septum (the wall between the 2 nostrils).
- **Do not** use your ZETONNA Nasal Aerosol near heat or an open flame.

Read this Patient Information leaflet before you start using ZETONNA Nasal Aerosol and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about ZETONNA Nasal Aerosol, ask your healthcare provider or pharmacist.

What is ZETONNA Nasal Aerosol?

ZETONNA Nasal Aerosol is a prescription medicine that treats seasonal and year-round allergy symptoms in adults and children 12 years of age and older.

ZETONNA Nasal Aerosol contains ciclesonide, which is a man-made (synthetic) corticosteroid. Corticosteroids are natural substances found in the body and reduce inflammation. When you spray ZETONNA Nasal Aerosol into your nose, it may help reduce nasal symptoms of allergic rhinitis (inflammation of the lining of the nose) such as stuffy nose, runny nose, itching and sneezing. ZETONNA Nasal Aerosol may also help you if you have red, itchy, and watery eyes.

It is not known if ZETONNA Nasal Aerosol is safe and effective in children 11 years of age and younger.

Who should not use ZETONNA Nasal Aerosol?

Do not use ZETONNA Nasal Aerosol if you are allergic to ciclesonide or any of the ingredients in ZETONNA Nasal Aerosol. See the end of this Patient Information leaflet for a complete list of ingredients in ZETONNA Nasal Aerosol.

What should I tell my healthcare provider before using ZETONNA Nasal Aerosol?

Before you use ZETONNA Nasal Aerosol tell your healthcare provider if you:

- have had recent nose problems such as a hole in the cartilage of your nose, nasal ulcers, nasal surgery, or nasal injury.

- 677 • have or have had eye problems such as increased intraocular pressure,
678 glaucoma, or cataracts.
- 679 • have any infections including tuberculosis or ocular herpes simplex.
- 680 • have not had or been vaccinated for chicken pox or measles.
- 681 • are pregnant or plan to become pregnant. It is not known if ZETONNA Nasal
682 Aerosol will harm your unborn baby. Talk to your healthcare provider about the
683 best way to feed your baby if you are using ZETONNA Nasal Aerosol.
- 684 • are breastfeeding or plan to breastfeed. It is not known if ZETONNA Nasal
685 Aerosol passes into your breast milk. Talk to your healthcare provider about the
686 best way to feed your baby if you are using ZETONNA Nasal Aerosol.

687
688 **Tell your healthcare provider about all the medicines you take**, including
689 prescription and non-prescription medicines, vitamins, and herbal supplements.
690

691 Know the medicines you take. Keep a list of them to show your doctors and pharmacist
692 when you get a new medicine.

693 **How should I use ZETONNA Nasal Aerosol?**

- 694 • Read the Instructions for Use at the end of this leaflet for specific information
695 about the right way to use ZETONNA Nasal Aerosol.
- 696 • Use ZETONNA Nasal Aerosol exactly as your healthcare provider tells you to
697 use it. Do not take more of your medicine or take it more often than your
698 healthcare provider tells you.
- 699 • ZETONNA Nasal Aerosol is used 1 time each day, 1 spray in each nostril. Do
700 not use more than a total of 1 spray in each nostril per day.
- 701 • ZETONNA Nasal Aerosol may begin to work within 36 hours after you take your
702 first dose. Maximum benefit is usually achieved within 1 to 2 weeks after
703 initiation of dosing.
- 704 • If your symptoms do not improve or get worse, call your healthcare provider.

705 706 **What are the possible side effects of ZETONNA Nasal** 707 **Aerosol?**

708 **ZETONNA Nasal Aerosol may cause serious side effects, including:**

- 709 • **nose bleeds and nasal ulcers.** Call your healthcare provider right away if you
710 start to have more nose bleeds or nasal ulcers.
- 711 • **hole in the cartilage in the nose (nasal septal perforation).** Stop using
712 ZETONNA Nasal Aerosol and call your doctor right away if you have symptoms
713 of a nasal perforation. Symptoms of nasal perforation may include:

- 714
 - crusting in the nose
- 715
 - nosebleeds
- 716
 - runny nose
- 717
 - whistling sound when you breathe
- 718
 - **thrush (*Candida*), a fungal infection in your nose, mouth, or throat.** Tell
- 719 your healthcare provider if you have any redness or white colored patches in
- 720 your mouth or throat.
- 721
 - **slow wound healing.** You should not use ZETONNA Nasal Aerosol until your
- 722 nose has healed, if you have a sore in your nose, if you have had surgery in your
- 723 nose, or if your nose has been injured.
- 724
 - **eye problems such as glaucoma and cataracts.** If you have a history of
- 725 glaucoma or cataracts or have a family history of eye problems, you should have
- 726 regular eye exams while you use ZETONNA Nasal Aerosol.
- 727
 - **immune system problems that may increase your risk of infections.** You
- 728 are more likely to get infections if you take medicines that may weaken your
- 729 body's ability to fight infections. Avoid contact with people who have contagious
- 730 diseases such as chicken pox or measles while you use ZETONNA Nasal
- 731 Aerosol. Symptoms of an infection may include:
 - 732
 - fever
 - 733
 - pain
 - 734
 - aches
 - 735
 - chills
 - 736
 - feeling tired
 - 737
 - nausea
 - 738
 - vomiting
- 739
 - **adrenal insufficiency.** Adrenal insufficiency is a condition in which the adrenal
- 740 glands do not make enough steroid hormones. Call your healthcare provider
- 741 right away if you experience the following symptoms of adrenal insufficiency:
 - 742
 - tiredness
 - 743
 - weakness
 - 744
 - dizziness
 - 745
 - nausea
 - 746
 - vomiting
- 747
 - **slowed or delayed growth in children.** A child's growth should be checked
- 748 regularly while using ZETONNA Nasal Aerosol.
- 749
 - **allergic reactions.** Call your healthcare provider right away if you experience
- 750 swelling of the lips, tongue, or throat.
- 751
- 752 The most common side effects with ZETONNA Nasal Aerosol include:
 - 753
 - Nasal discomfort

- 754 • Headache
755 • Nose bleeds

756
757 Tell your doctor if you have any side effect that bothers you or that does not go away.
758

759 These are not all the possible side effects of ZETONNA Nasal Aerosol.
760

761 For more information, ask your doctor or pharmacist.
762

763 **Call your healthcare provider for medical advice about side effects. You may**
764 **report side effects to FDA at 1-800-FDA-1088.**
765

766 **How should I store ZETONNA Nasal Aerosol?**

- 767 • Store ZETONNA Nasal Aerosol at room temperature between 59°F and 86°F
768 (15°C to 30°C).
- 769 • **Do not** puncture the ZETONNA Nasal Aerosol canister.
- 770 • **Do not** store the ZETONNA Nasal Aerosol canister near heat or a flame.
771 Temperatures above 120°F (49°C) may cause the canister to burst.
- 772 • **Do not** throw the ZETONNA Nasal Aerosol canister into a fire or an incinerator.
- 773 • Safely throw away medicine that is out of date or no longer needed.
- 774 • Keep ZETONNA Nasal Aerosol clean and dry at all times.

775
776 **Keep ZETONNA Nasal Aerosol and all medicines out of the reach of children.**
777

778 **General Information About the Safe and Effective Use of ZETONNA Nasal Aerosol**

779 Medicines are sometimes prescribed for purposes other than those listed in a Patient
780 Information leaflet. Do not use ZETONNA Nasal Aerosol for a condition for which it was
781 not prescribed. Do not give ZETONNA Nasal Aerosol to other people, even if they have
782 the same symptoms that you have. It may harm them.

783 This Patient Information summarizes the most important information about ZETONNA
784 Nasal Aerosol. If you would like more information, talk with your healthcare provider.
785 You can ask your pharmacist or healthcare provider for information about ZETONNA
786 Nasal Aerosol that is written for health professionals. You may want to read this leaflet
787 again. Please **DO NOT THROW IT AWAY** until you have finished your medicine.
788

789 For more information, go to www.ZETONNA.com or call 1-888-394-7377.
790

791 **What are the ingredients in ZETONNA Nasal Aerosol?**

792 Active ingredient: ciclesonide

793 Inactive ingredients: HFA propellant and ethanol

794

795 **Instructions for Use**

796
797 **ZETONNA™ <<Ze toe' nah>>**
798 **(ciclesonide)**
799 **Nasal Aerosol**

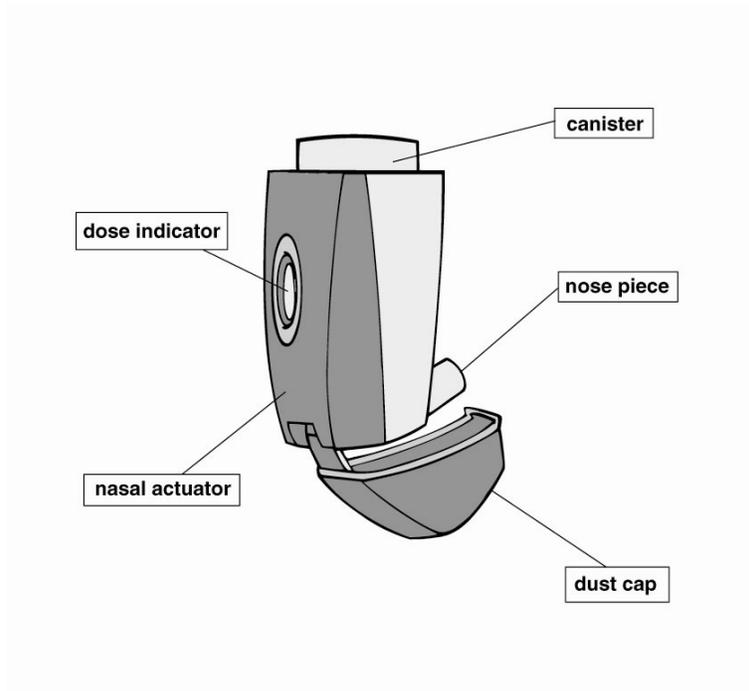
800
801 Read these Instructions for Use for ZETONNA Nasal Aerosol before you start using it
802 and each time you get a refill. There may be new information. This leaflet does not
803 take the place of talking to your doctor about your medical condition or treatment.
804

805 **Note: For Use in the Nose Only.**

- 806 • **Do not** spray ZETONNA Nasal Aerosol in your eyes or directly onto your nasal
807 septum (the wall between your 2 nostrils).
- 808 • **Do not** use your ZETONNA Nasal Aerosol near heat or an open flame.

809
810 **The Parts of Your ZETONNA Nasal Aerosol**

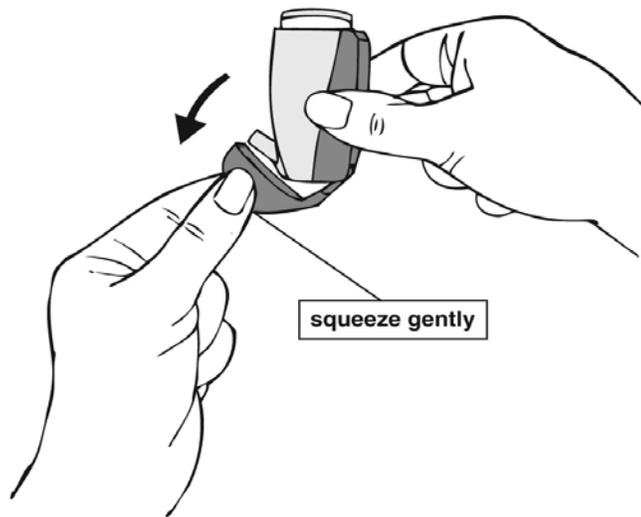
811 ZETONNA Nasal Aerosol comes as a canister fitted into a nasal actuator with a dose
812 indicator. Do not use the actuator with a canister of medicine from any other inhaler.
813 Do not use the ZETONNA Nasal Aerosol canister with an actuator from any other
814 inhaler. (See **Figure A**)
815



816
817
818 **Figure A**
819
820
821

822 **Priming Your ZETONNA Nasal Aerosol For Use**

- 823
- Remove ZETONNA Nasal Aerosol from its package.
 - **Before you use ZETONNA Nasal Aerosol for the first time** or if you have not used your medicine for 10 days in a row, you will need to prime your ZETONNA Nasal Aerosol.
 - Open the purple plastic dust cap by gently squeezing both sides and pulling the cap away from the nasal actuator. Hold the nasal actuator upright. (See **Figure B**)
- 827
- 828
- 829
- 830



831 **Figure B**

- 832
- 833
- 834
- Spray 3 times into the air away from the face, by pressing down fully on the top of the canister three times (See **Figure C**). Make sure the canister returns to its original position after each spray.
- 835
- 836
- 837
- 838



839
840
841

Figure C

842 **Using Your ZETONNA Nasal Aerosol**

843 Step 1. Open the purple plastic dust cap.

844

845 Step 2. Hold the nasal actuator upright, with the nose piece pointing upwards,
846 between your thumb and forefinger (and middle finger) (See **Figure D**).
847

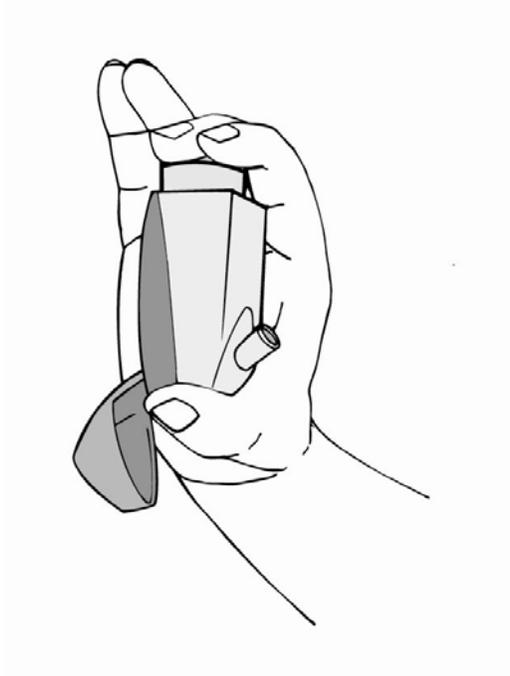


Figure D

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Step 3. Tilt your head back slightly and insert the end of the nose piece into 1 nostril, pointing it slightly toward the outside nostril wall away from the nasal septum (the wall between the 2 nostrils), while holding your other nostril closed with 1 finger (See **Figure E**). **Do not get any spray in your eyes or directly on your nasal septum.**



856
857

Figure E

858 Step 4. Press down on the canister to release 1 spray and at the same time breathe
859 in gently through the nostril. Hold your breath for a few seconds then breathe out slowly
860 through your mouth.

861

862 Step 5. Remove the nose piece from your nostril. Make sure the canister has
863 returned to its original position and repeat steps 2-4 for the second spray in your other
864 nostril.

865

866 Step 6. Replace the protective purple dust cap on the nasal actuator.

867

868 Step 7. Avoid blowing your nose for the next 15 minutes.

869

870 **Cleaning Your Nasal Actuator**

871

872 The outside of the nose piece should be cleaned weekly, by wiping with a clean, dry
873 tissue or cloth (see **Figure F**).

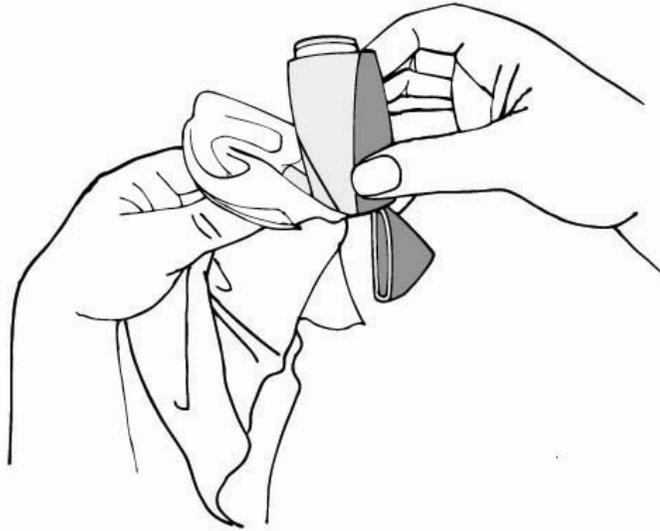
874

875 **Do not wash or put any part of the ZETONNA Nasal Aerosol canister or actuator**
876 **in water.**

877

878

879



880
881
882 **Figure F**
883

884 **How to Tell if Your ZETONNA Nasal Aerosol Is Empty**

- 885
- 886 • Each canister of ZETONNA Nasal Aerosol contains enough medicine for you to
887 spray medicine 60 times (or 30 times for sample size product). This does not
count the first 3 priming sprays.
 - 888 • The actuator of your ZETONNA Nasal Aerosol is fitted with a dose indicator
889 which shows you how much medicine is left after each use. The dose indicator
890 will display the number of sprays remaining in groups of 5 or 10 actuations.
 - 891 • The display window will begin showing a green color. As you continue to use the
892 medicine, the window will show a yellow color. A yellow color in the window
893 means that you need to replace your medicine soon. When the medicine is
894 almost empty, the window will show a red color.
 - 895 • When the window shows red and you see the dose indicator read zero, “0”
896 (see **Figure G**), you should throw away the canister and nasal actuator.

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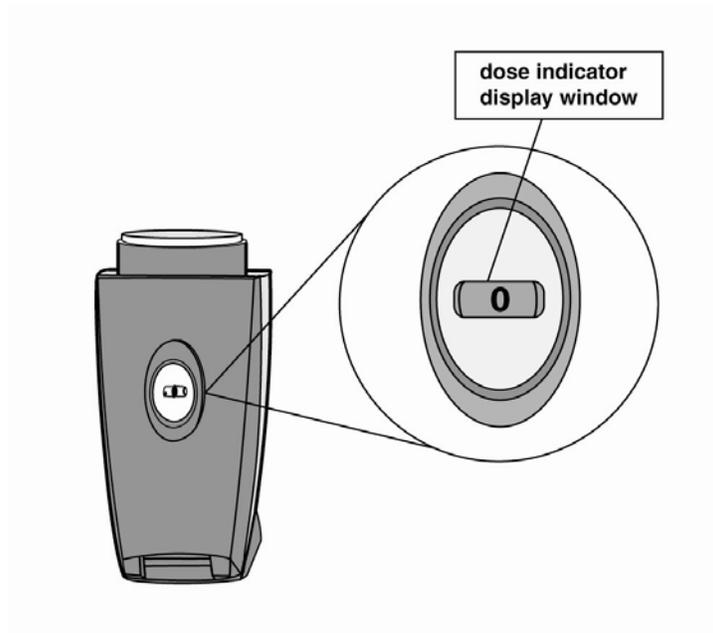


Figure G

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- **Do not** throw your ZETONNA Nasal Aerosol canister in the fire or an incinerator.
- **Do not** use your ZETONNA Nasal Aerosol after zero is shown in the window of the dose indicator even though it may look like there is medicine left in the canister. You may not get the right amount of medicine.
- Talk with your healthcare provider before your supply of ZETONNA Nasal Aerosol runs out to see if you should get a refill of your medicine.

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What to Do if You Drop Your ZETONNA Nasal Aerosol

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- If you drop your ZETONNA Nasal Aerosol, the canister may become separated from the actuator. If this happens, insert the canister into the actuator as shown in **Figure H**, test spray once into the air away from your face, then use as described above.

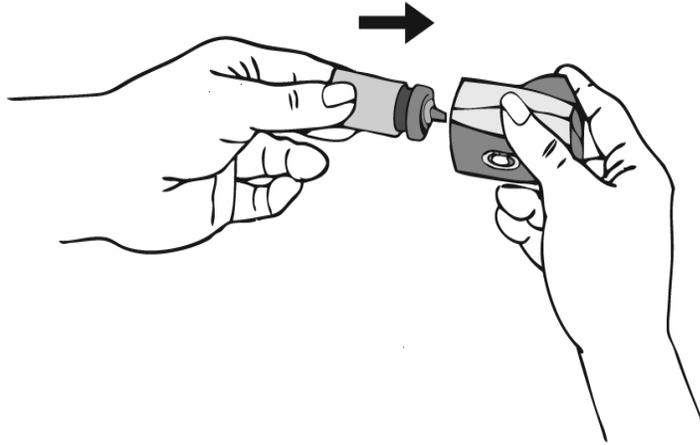


Figure H

- If the ZETONNA Nasal Aerosol is dropped, the dose counter may not work. It is recommended to keep track of the number of sprays taken from your ZETONNA Nasal Aerosol based on your records.

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



Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA
Made in the United Kingdom

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For customer service, call 1-888-394-7377

Revised: January 2012
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66961 73760 6300 (4)

Usual Dosage: See Prescribing Information.
Store at 25°C (77°F); excursions between 15°–30°C (59°–86°F) permitted [see USP].
Avoid spraying in eyes.
Keep out of reach of children.

Manufactured for
Sunovion Pharmaceuticals Inc
Marlborough MA 01752 USA
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NDC 63402 737 60 Net Contents 6.1 g

Zetonna™
(ciclesonide) Nasal Aerosol
37 mcg per actuation

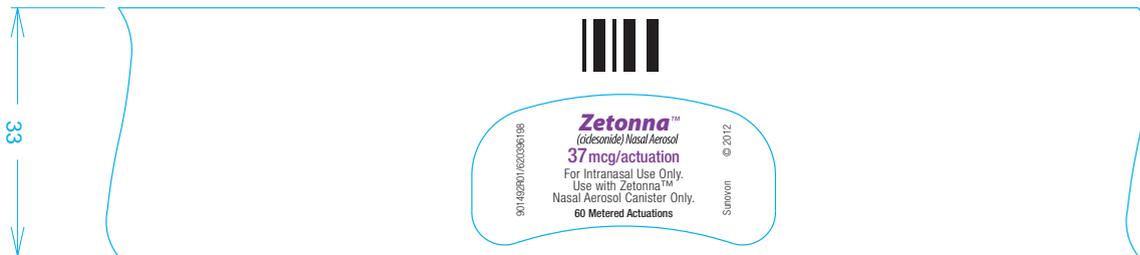
For Intranasal Use Only.
Use with Zetonna™ Nasal Aerosol Actuator Only.

60 Metered Actuations
Rx Only

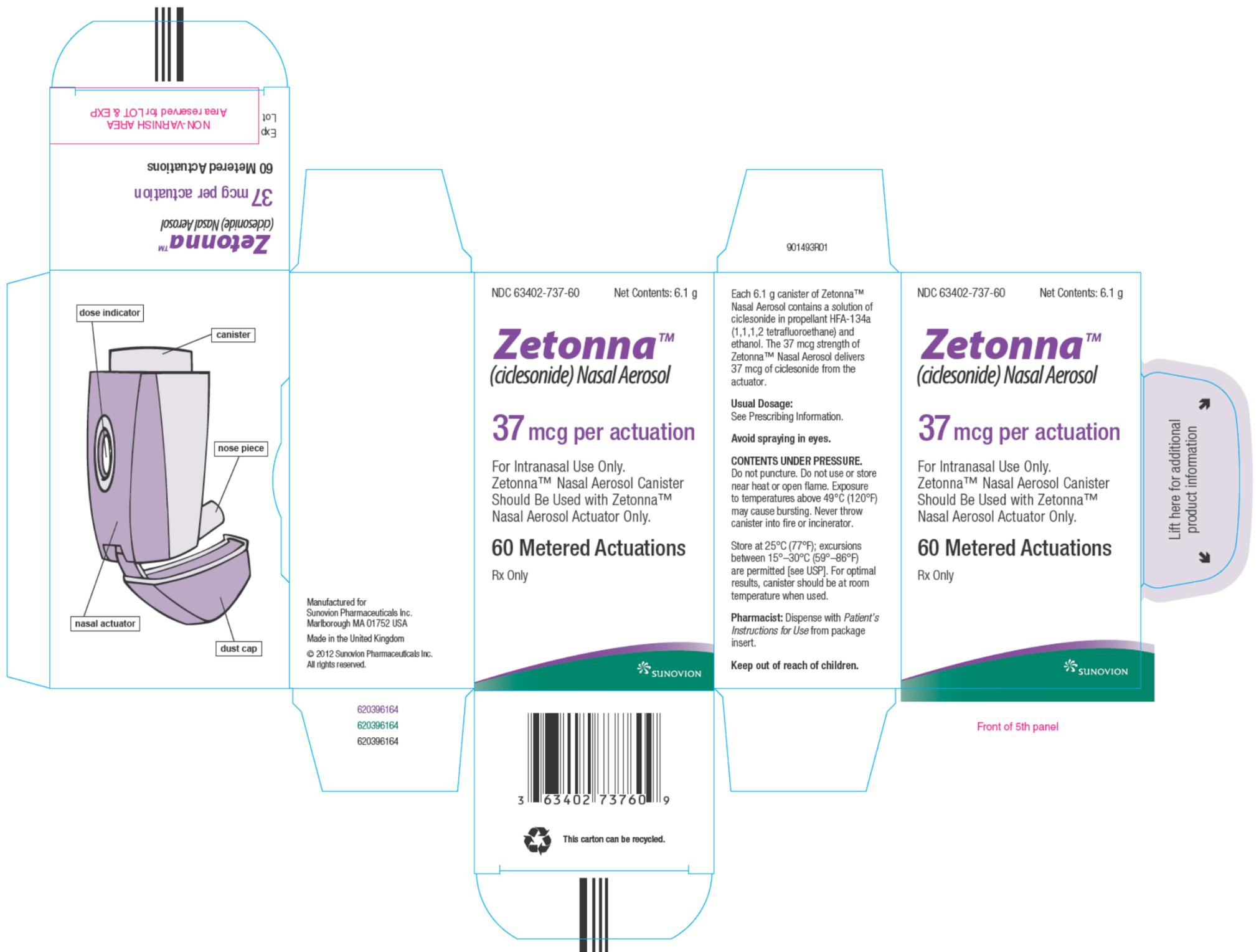
 **SUNOVION**

Exp: Lot:



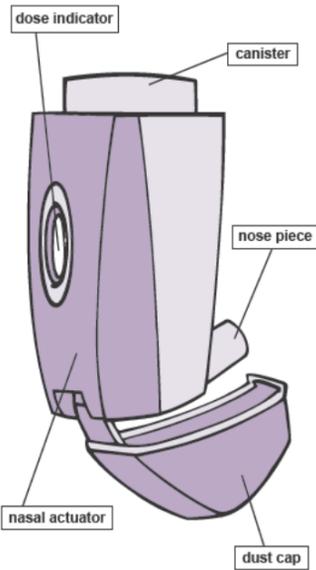


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Area reserved for LOT & EXP

60 Metered Actuations
37 mcg per actuation
Zetonna™
(ciclesonide) Nasal Aerosol



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NDC 63402-737-60 Net Contents: 6.1 g

Zetonna™ (ciclesonide) Nasal Aerosol

37 mcg per actuation

For Intranasal Use Only. Zetonna™ Nasal Aerosol Canister Should Be Used with Zetonna™ Nasal Aerosol Actuator Only.

60 Metered Actuations

Rx Only

Each 6.1 g canister of Zetonna™ Nasal Aerosol contains a solution of ciclesonide in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. The 37 mcg strength of Zetonna™ Nasal Aerosol delivers 37 mcg of ciclesonide from the actuator.

Usual Dosage: See Prescribing Information.

Avoid spraying in eyes.

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

Store at 25°C (77°F); excursions between 15°–30°C (59°–86°F) are permitted [see USP]. For optimal results, canister should be at room temperature when used.

Pharmacist: Dispense with *Patient's Instructions for Use* from package insert.

Keep out of reach of children.

NDC 63402-737-60 Net Contents: 6.1 g

Zetonna™ (ciclesonide) Nasal Aerosol

37 mcg per actuation

For Intranasal Use Only. Zetonna™ Nasal Aerosol Canister Should Be Used with Zetonna™ Nasal Aerosol Actuator Only.

60 Metered Actuations

Rx Only

Lift here for additional product information

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