

1 **HIGHLIGHTS OF PRESCRIBING INFORMATION**
2 **These highlights do not include all the information needed to use**
3 **OMNARIS® Nasal Spray safely and effectively. See full prescribing**
4 **information for OMNARIS Nasal Spray.**

6 **OMNARIS® (ciclesonide) Nasal Spray**
7 **For Nasal Inhalation Only**
8 **Initial U.S. Approval: 2006**

9 -----INDICATIONS AND USAGE-----
10 OMNARIS Nasal Spray is a corticosteroid indicated for treatment of nasal
11 symptoms associated with seasonal allergic rhinitis in adults and children 6
12 years of age and older and perennial allergic rhinitis in adults and adolescents
13 12 years of age and older. (1.1, 1.2)

15 -----DOSAGE AND ADMINISTRATION-----
16 For Intranasal use only

- 2 sprays per nostril -once daily. (200 mcg) (2.1, 2.2)
- Priming Information: Gently shake and prime OMNARIS Nasal Spray before using for the first time or when not used for four consecutive days. (2)

21 -----DOSAGE FORMS AND STRENGTHS-----
22 • Nasal Spray: 50 mcg of ciclesonide in each 70-microliter spray. (3)
23 • Supplied in a 12.5 g bottle containing 120 sprays. (16)

24 -----CONTRAINDICATIONS-----
25 • Patients with a known hypersensitivity to ciclesonide or any of the
26 ingredients of OMNARIS Nasal Spray. (4)

27 -----WARNINGS AND PRECAUTIONS-----
28 • Epistaxis, *Candida albicans* infection, nasal septal perforation, impaired
29 wound healing. Monitor patients periodically for signs of adverse
30 effects on the nasal mucosa. Avoid spraying OMNARIS Nasal Spray
31 directly onto the nasal septum. Avoid use in patients with recent nasal
32 ulcers, nasal surgery, or nasal trauma. (5.1)

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34 • Development of glaucoma or cataracts. Monitor patients closely with a
35 change in vision or with a history of increased intraocular pressure,
36 glaucoma, and/or cataracts. (5.2)
37 • Potential worsening of existing tuberculosis; fungal, bacterial, viral, or
38 parasitic infections, or ocular herpes simplex. More serious or even
39 fatal course of chicken pox or measles in susceptible patients. Use
40 caution in patients with the above because of the potential for worsening
41 of these infections. (5.3)
42 • Hypercorticism and adrenal suppression with very high dosages or at the
43 regular dosage in susceptible individuals. If such changes occur,
44 discontinue OMNARIS Nasal Spray slowly. (5.4)
45 • Potential reduction in growth velocity in children. (5.5, 8.4) Monitor
46 growth routinely in pediatric patients receiving OMNARIS Nasal Spray.

48 -----ADVERSE REACTIONS-----
49 The most common adverse reactions (>2% incidence) included headache,
50 epistaxis, nasopharyngitis, ear pain, and pharyngolaryngeal pain. (6)

52 **To report SUSPECTED ADVERSE REACTIONS, contact Sepracor Inc.**
53 **at 1-877-737-7226 or FDA at 1-800-FDA-1088 or**
54 **www.fda.gov/medwatch for voluntary reporting of adverse events.**

56 -----USE IN SPECIFIC POPULATIONS-----
57 • Pregnancy: Use only if benefit justifies potential risk to fetus. (8.1)

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

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62 **Revised: June 2009**

63
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Seasonal Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

1.2 Treatment of Perennial Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with perennial allergic rhinitis in adults and adolescents 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Administer OMNARIS Nasal Spray by the intranasal route only. Prior to initial use, OMNARIS Nasal Spray must be gently shaken and then the pump must be primed by actuating eight times. If the product is not used for four consecutive days, it should be gently shaken and reprimed with one spray or until a fine mist appears. Illustrated patient's instructions for proper use accompany each package of OMNARIS Nasal Spray.

2.1 Seasonal Allergic Rhinitis

Adults and Children (6 Years of Age and Older): The recommended dose of OMNARIS Nasal Spray is 2 sprays per nostril once daily (200 mcg). The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).

2.2 Perennial Allergic Rhinitis

Adults and Adolescents (12 Years of Age and Older): The recommended dose of OMNARIS Nasal Spray is 2 sprays per nostril once daily (200 mcg). The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).

3 DOSAGE FORMS AND STRENGTHS

OMNARIS Nasal Spray is a metered-dose, manual-pump spray formulation containing a hypotonic aqueous suspension of ciclesonide. Once primed, each actuation of the pump delivers 50 mcg ciclesonide in a volume of 70 microliters from the nasal actuator.

4 CONTRAINDICATIONS

OMNARIS Nasal Spray is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of OMNARIS Nasal Spray [*see Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

Epistaxis: In clinical studies of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with OMNARIS Nasal Spray than those who received placebo. [*see Adverse Reactions (6)*].

Candida Infection: In clinical studies with OMNARIS Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS Nasal Spray. Therefore, patients using OMNARIS Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

157 Nasal Septal Perforation: Instances of nasal septal perforation have been reported in
158 patients following the intranasal application of corticosteroids. No cases of nasal septal
159 perforation were identified in clinical studies with OMNARIS Nasal Spray. Avoid spraying
160 OMNARIS Nasal Spray directly onto the nasal septum.

161 Impaired Wound Healing: Because of the inhibitory effect of corticosteroids on
162 wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or
163 nasal trauma should not use a nasal corticosteroid until healing has occurred.

164 **5.2 Glaucoma and Cataracts**

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

168 The risk of glaucoma was evaluated by assessments of intraocular pressure in
169 3 studies including 943 patients. Of these, 390 adolescents or adults were treated for up to
170 52 weeks and 186 children ages 2 to 11 received treatment with OMNARIS Nasal Spray
171 200 mcg daily for up to 12 weeks. In these studies, no significant differences in intraocular
172 pressure changes were observed between OMNARIS Nasal Spray 200 mcg and placebo-
173 treated patients. Additionally, no significant differences between OMNARIS Nasal Spray
174 200 mcg and placebo-treated patients were noted during the 52-week study of adults and
175 adolescent patients in whom thorough ophthalmologic assessments were performed including
176 evaluation of cataract formation using slit lamp examinations.

177 **5.3 Immunosuppression**

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

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

194 **5.4 Hypothalamic-Pituitary-Adrenal Axis Effect**

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

200 The replacement of a systemic corticosteroid with a topical corticosteroid can be
201 accompanied by signs of adrenal insufficiency. In addition, some patients may experience
202 symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and

203 depression. Patients previously treated for prolonged periods with systemic corticosteroids
204 and transferred to topical corticosteroids should be carefully monitored for acute adrenal
205 insufficiency in response to stress. In those patients who have asthma or other clinical
206 conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic
207 corticosteroid dosages may cause a severe exacerbation of their symptoms.

208 **5.5 Effect on Growth**

209 Corticosteroids may cause a reduction in growth velocity when administered to
210 pediatric patients. Monitor the growth routinely (e.g., via stadiometry) in pediatric patients
211 receiving OMNARIS Nasal Spray.

212 **6 ADVERSE REACTIONS**

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

- 214 • Epistaxis, nasal septal perforations, *Candida albicans* infection, impaired wound
215 healing [*see Warnings and Precautions (5.1)*]
- 216 • Cataracts and glaucoma [*see Warnings and Precautions (5.2)*]
- 217 • Immunosuppression [*see Warnings and Precautions (5.3)*]
- 218 • Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction
219 [*see Warnings and Precautions (5.4, 5.5), Use in Specific Populations (8.4)*]

220 **6.1 Clinical Trials Experience**

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

224 The safety data described below for adults and adolescents 12 years of age and older
225 are based on 3 clinical trials of 2 to 6 weeks duration and one 52 week trial. In the 3 trials of
226 2 to 6 weeks duration, 1524 patients (495 males and 1029 females, ages 12 to 86 years old)
227 with seasonal or perennial allergic rhinitis were treated with OMNARIS Nasal Spray 200,
228 100, 50, or 25 mcg or placebo once daily. The racial distribution in these three trials included
229 1374 Caucasians, 69 Blacks, 31 Asians, and 50 patients classified as Other. The 52-week trial
230 was conducted in 663 patients (227 males and 436 females, ages 12 to 73 years old) treated
231 with OMNARIS Nasal Spray 200 mcg or placebo once daily. The racial distribution in this
232 trial included 538 Caucasians, 69 Blacks, 16 Asians, and 40 patients classified as Other. The
233 data from pediatric patients are based upon 4 clinical trials in which 1541 children (871
234 males and 670 females, ages 2 to 11 years old) with seasonal or perennial allergic rhinitis
235 were treated with OMNARIS Nasal Spray 200, 100, or 25 mcg or placebo once daily for 2 to
236 12 weeks. The racial distribution in these four trials included 1136 Caucasians, 273 Blacks,
237 20 Asians, and 112 patients classified as Other.

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

239 ***Trials:*** In three short-term trials conducted in the US and Canada, 546 patients were treated
240 with OMNARIS Nasal Spray 200 mcg daily. Adverse reactions did not differ appreciably
241 based on age, gender, or race. Approximately 2% of patients treated with OMNARIS Nasal
242 Spray 200 mcg in clinical trials discontinued because of adverse reactions; this rate was
243 similar for patients treated with placebo. The table below displays reactions that occurred
244 with an incidence of 2% or greater and more frequently with OMNARIS Nasal Spray 200
245 mcg than with placebo in clinical trials of 2 to 6 weeks in duration.

246 **Table 1 Adverse Events from Controlled Clinical Trials 2 to 6 Weeks in Duration in**
247 **Patients 12 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis**
248

Adverse Event	OMNARIS Nasal Spray 200 mcg Once Daily (N =546) %	Placebo (N = 544) %
Headache	6.0	4.6
Epistaxis	4.9	2.9
Nasopharyngitis	3.7	3.3
Ear Pain	2.2	0.6

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Pediatric Patients Aged 6 to 11 Years in short-term (2-12 weeks) trials: In two short-term trials, conducted in the US and Canada, 913 patients were treated with OMNARIS (ciclesonide) Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. Adverse events did not differ appreciably based on age, gender, or race. In clinical trials, 1.6% and 2.7% of patients treated with OMNARIS Nasal Spray 200 mcg or 100 mcg, respectively, discontinued because of adverse reactions; these rates were lower than the rate in patients treated with placebo (2.8%). Table 2 displays adverse events that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg than with placebo.

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Table 2 Adverse Events from Controlled Clinical Trials 2 to 12 Weeks in Duration in Patients 6 to 11 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis

Adverse Event	OMNARIS Nasal Spray 200 mcg Once Daily (N =380) %	Placebo (N = 369) %
Headache	6.6	5.7
Nasopharyngitis	6.6	5.4
Pharyngolaryngeal pain	3.4	3.3

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Pediatric Patients Aged 2 to 5 Years in Short-Term (6-12 weeks) Trials: In two short-term trials conducted in the US 183 patients were treated with OMNARIS Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. The distribution of adverse events was similar to that seen in the 6 to 11 year old children.

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Long-Term (52-Week) Safety Trial: In a 52-week double-blind, placebo controlled safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 227 males and 436 females) with perennial allergic rhinitis, the adverse reaction profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse reactions, irrespective of drug relationship, that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg than with placebo were epistaxis, pharyngolaryngeal pain, sinusitis, headache, nasal discomfort, cough, bronchitis, influenza, back pain, and urinary tract infection. No patient experienced a nasal septal perforation or nasal ulcer during this long-term trial of OMNARIS Nasal Spray.

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6.2 Post-marketing Experience

The following adverse reactions have been reported in association with post marketing use of the product and are not listed above: nasal congestion, nasal ulcer and dizziness. Because these reactions are reported voluntarily from a population of uncertain size and are generally not confirmed with a health care professional, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

285 **7 DRUG INTERACTIONS**

286 *In vitro* studies and clinical pharmacology studies suggested that des-ciclesonide has
287 no potential for metabolic drug interactions or protein binding-based drug interactions [*see*
288 *Clinical Pharmacology (12.3)*]

289 In a drug interaction study, co-administration of orally inhaled ciclesonide and oral
290 ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of
291 des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide
292 remained unchanged. Erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no
293 effect on the pharmacokinetics of either des-ciclesonide or erythromycin following oral
294 inhalation of ciclesonide [*see Clinical Pharmacology (12.3)*].
295

296 **8 USE IN SPECIFIC POPULATIONS**

297 **8.1 Pregnancy**

298 Teratogenic Effects: Pregnancy Category C.

299 There are no adequate and well-controlled studies in pregnant women. OMNARIS
300 Nasal Spray should be used during pregnancy only if the potential benefit justifies the
301 potential risk to the fetus. Experience with oral corticosteroids since their introduction in
302 pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to
303 teratogenic effects from corticosteroids than humans. In addition, because there is a natural
304 increase in corticosteroid production during pregnancy, most women will require a lower
305 exogenous corticosteroid dose and many will not need corticosteroid treatment during
306 pregnancy.

307 Oral administration of ciclesonide in rats at approximately 35 times the maximum
308 human daily intranasal dose in adults based on mcg/m² produced no teratogenicity or other
309 fetal effects. However, subcutaneous administration of ciclesonide in rabbits at less than the
310 maximum human daily intranasal dose in adults based on mcg/m² produced fetal toxicity.
311 This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including
312 incomplete ossifications, and skin effects [*see Animal Toxicology and Pharmacology (13.2)*].

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

315 **8.3 Nursing Mothers**

316 It is not known if ciclesonide is excreted in human milk. However, other
317 corticosteroids are excreted in human milk. In a study with lactating rats, minimal but
318 detectable levels of ciclesonide were recovered in milk. Caution should be used when
319 OMNARIS Nasal Spray is administered to nursing women.

320 **8.4 Pediatric Use**

321 The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12
322 years of age and older have been established. The efficacy of OMNARIS Nasal Spray in
323 patients 6 to 11 years of age for treatment of the symptoms of seasonal allergic rhinitis was
324 demonstrated in one study in patients 6 to 11 years of age with seasonal allergic rhinitis. The
325 efficacy of OMNARIS Nasal Spray for the treatment of the symptoms of seasonal allergic
326 rhinitis in patients 5 years of age and younger has not been established. The efficacy of
327 OMNARIS Nasal Spray for the treatment of the symptoms of perennial allergic rhinitis in
328 patients 11 years of age and younger has not been established [*see Clinical Studies (14.1)*].
329 The safety of OMNARIS Nasal Spray in children 2 to 11 years of age was evaluated in 4
330 controlled clinical studies of 2 to 12 weeks duration [*see Clinical Pharmacology (12.2)*,
331 *Clinical Studies (14.1)*, and *Adverse Reactions (6.1)*].

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

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

356 **8.5 Geriatric Use**

357 Clinical studies of OMNARIS Nasal Spray did not include sufficient numbers of
358 subjects age 65 and over to determine whether they respond differently from younger
359 subjects. Other reported clinical experience has not identified differences in responses
360 between the elderly and younger patients. In general, dose selection for an elderly patient
361 should be cautious, usually starting at the low end of the dosing range, reflecting the greater
362 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or
363 other drug therapy.

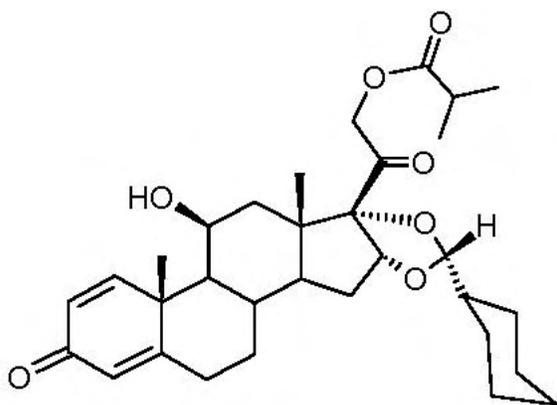
364 365 366 **10 OVERDOSAGE**

367 Chronic overdosage may result in signs or symptoms of hypercorticism [*see*
368 *Warnings and Precautions (5.4)*]

369 There are no data available on the effects of acute or chronic overdosage with
370 OMNARIS Nasal Spray.

371 372 **11 DESCRIPTION**

373 The active component of OMNARIS Nasal Spray is ciclesonide, a non-halogenated
374 glucocorticoid having the chemical name pregna -1,4-diene-3,20-dione, 16,17-[[R-
375 cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α)-.
376 Ciclesonide is delivered as the R-epimer. The empirical formula is C₃₂H₄₄O₇ and its
377 molecular weight is 540.7. Its structural formula is as follows:



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382 Ciclesonide is a white to yellow-white powder, practically insoluble in water and
 383 freely soluble in ethanol and acetone. OMNARIS Nasal Spray is a metered-dose, manual-
 384 pump spray formulation containing a hypotonic aqueous suspension of ciclesonide.
 385 OMNARIS Nasal Spray also contains microcrystalline cellulose, carboxymethylcellulose
 386 sodium, hypromellose, potassium sorbate and edetate sodium; and hydrochloric acid to adjust
 387 the pH to 4.5.

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389 12 CLINICAL PHARMACOLOGY

390 12.1 Mechanism of Action

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

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

400 12.2 Pharmacodynamics

401 Adrenal Function: In a 12-week study in children 6-11 years of age with perennial
 402 allergic rhinitis, daily doses of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray
 403 were compared to placebo nasal spray. Adrenal function was assessed by measurement of
 404 24-hour urinary free cortisol (in 32 to 44 patients per group) and morning plasma cortisol
 405 levels (in 45 to 61 patients per group) before and after 12 consecutive weeks of treatment.
 406 The ciclesonide-treated groups had a numerically greater decline in 24-hour urinary free
 407 cortisol compared to the placebo treated group. The differences (and 95% confidence
 408 intervals) from placebo in the mean change from baseline to 12 weeks were -0.81 (-4.0, 2.4),
 409 -0.08 (-3.1, 2.9), and -2.11 (-5.3, 1.1) mcg/day for 200 mcg, 100 mcg, and 25 mcg dose
 410 groups, respectively. The mean AM plasma cortisol value did not show any consistent
 411 treatment effect with differences (and 95% confidence intervals) from placebo in the mean
 412 change from baseline to 12 weeks of 0.35 (-1.4, 2.1), 0.12 (-1.5, 1.7), and -0.38 (-2.1, 1.3)

413 mcg/dL for 200 mcg, 100 mcg, and 25 mcg dose groups respectively. In this study, serum
414 was assayed for ciclesonide and des-ciclesonide [*see Clinical Pharmacology (12.3)*].

415 In a 6-week study in children 2 to 5 years of age with perennial allergic rhinitis, daily
416 doses of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray were compared to
417 placebo nasal spray. Adrenal function was assessed by measurement of 24-hour urinary free
418 cortisol (in 15 to 22 patients per group) and morning plasma cortisol levels (in 28 to 30
419 patients per group) before and after 6 consecutive weeks of treatment. The ciclesonide-
420 treated groups had a numerically greater decline in 24-hour urinary free cortisol compared to
421 the placebo treated group. The differences (and 95% confidence intervals) from placebo in
422 the mean change from baseline to 6 weeks were -2.04 (-4.4, 0.3), -1.96 (-4.5, 0.6), and
423 -1.76 (-4.3, 0.8) mcg/day for the 200 mcg, 100 mcg, and 25 mcg dose groups, respectively.
424 The plasma cortisol also decreased numerically after treatment with ciclesonide. The
425 differences (and 95% confidence intervals) from placebo in the mean change in plasma
426 cortisol from baseline to 6 weeks were -1.04 (-2.7, 0.7), -0.36 (-2.1, 1.4), and
427 -0.12 (-1.8, 1.6) mcg/dL for the 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. In
428 this study, serum was assayed for ciclesonide and des-ciclesonide [*see Clinical
429 Pharmacology (12.3)*].

430 There are no adequately conducted studies in adults and adolescents that assess the
431 effect of OMNARIS Nasal Spray on adrenal function.

432 **12.3 Pharmacokinetics**

433 Absorption: Ciclesonide and des-ciclesonide have negligible oral bioavailability
434 (both less than 1%) due to low gastrointestinal absorption and high first-pass metabolism.
435 The intranasal administration of ciclesonide at recommended doses results in negligible
436 serum concentrations of ciclesonide. However, the known active metabolite (des-
437 ciclesonide) is detected in the serum of some patients after nasal inhalation of ciclesonide.
438 The bioanalytical assay used has a lower limit of quantification of 25 pg/mL and 10 pg/mL,
439 for ciclesonide and des-ciclesonide, respectively.

440 In healthy adults treated for two weeks with 50 to 800 mcg of ciclesonide nasal spray
441 daily (n=6 in each treatment group), the peak serum concentrations of des-ciclesonide in all
442 subjects were found to be below 30 pg/mL. Of those treated with 800 mcg and 400 mcg
443 daily, 100% and 67% had detectable levels of des-ciclesonide, respectively. With daily doses
444 of 200 mcg or less, detectable serum levels of des-ciclesonide were not observed. The low
445 systemic exposure following ciclesonide nasal spray administration was confirmed in a
446 crossover study in twenty-nine healthy adults. The median C_{max} was less than 10 pg/mL and
447 602 pg/mL following a single dose of ciclesonide nasal spray (300 mcg) and orally inhaled
448 ciclesonide (Alvesco 320 mcg), respectively.

449 Distribution: Following intravenous administration of 800 mcg of ciclesonide, the
450 volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and
451 12.1 L/kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human
452 plasma proteins averaged ≥ 99% each, with ≤ 1% of unbound drug detected in the systemic
453 circulation. Des-ciclesonide is not significantly bound to human transcortin.

454 Metabolism: Ciclesonide is hydrolyzed to a biologically active metabolite, des-
455 ciclesonide, by esterases. Des-ciclesonide undergoes further metabolism in the liver to
456 additional metabolites mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser
457 extent by CYP 2D6. The full range of potentially active metabolites of ciclesonide has not
458 been characterized. After intravenous administration of ¹⁴C-ciclesonide, 19.3% of the

459 resulting radioactivity in the plasma is accounted for by ciclesonide or des-ciclesonide; the
460 remainder may be a result of other, as yet, unidentified multiple metabolites

461 Elimination: Following intravenous administration of 800 mcg of ciclesonide, the
462 clearance values of ciclesonide and des-ciclesonide were high (approximately 152 L/h and
463 228 L/h, respectively). ¹⁴C-labeled ciclesonide was predominantly excreted via the feces
464 after intravenous administration (66%) indicating that excretion through bile is the major
465 route of elimination. Approximately 20% or less of drug related radioactivity was excreted
466 in the urine.

467 Special Populations: The pharmacokinetics of intranasally administered ciclesonide
468 have not been assessed in patient subpopulations because the resulting blood levels of
469 ciclesonide and des-ciclesonide are insufficient for pharmacokinetic calculations. However,
470 population pharmacokinetic analysis showed that characteristics of des-ciclesonide after oral
471 inhalation of ciclesonide were not appreciably influenced by a variety of subject
472 characteristics such as body weight, age, race, and gender.

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

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

479 Pediatric: In pediatric subjects treated with 25 to 200 mcg of ciclesonide nasal spray
480 daily, serum concentrations of des-ciclesonide were below 45 pg/mL, with the exception of
481 one value of 64.5 pg/mL. In a 12-week study in children 6 to 11 years of age with perennial
482 allergic rhinitis, des-ciclesonide was detected in 50% of the subjects treated with 200 mcg
483 and in 5% of those treated with 100 mcg ciclesonide nasal spray daily. In a 6-week study in
484 children 2 to 5 years of age with perennial allergic rhinitis, des-ciclesonide was detected in
485 41%, 22%, and 13% of the subjects treated with 200 mcg, 100 mcg, and 25 mcg ciclesonide
486 nasal spray daily, respectively.

487 Drug-Drug Interactions: Based on in vitro studies in human liver microsomes, des-
488 ciclesonide appears to have no inhibitory or induction potential on the metabolism of other
489 drugs metabolized by cytochrome P450 enzymes. The inhibitory potential of ciclesonide on
490 cytochrome P450 isoenzymes has not been studied. In vitro studies demonstrated that the
491 plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid,
492 indicating no potential for protein binding-based drug interactions.

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

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

500

501 **13 NONCLINICAL TOXICOLOGY**

502 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

503 Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900
504 mcg/kg (approximately 20 and 10 times the maximum human daily intranasal dose in adults

505 and adolescents ≥ 12 years of age and children, 6-11 years of age, respectively, based on
506 mcg/m^2) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg
507 (approximately 8 and 5 times the maximum human daily intranasal dose in adults and
508 adolescents ≥ 12 years of age and children, 6-11 years of age, respectively, based on mcg/m^2)
509 in rats for 104 weeks. Ciclesonide was not mutagenic in an Ames test or in a forward
510 mutation assay and was not clastogenic in a human lymphocyte assay or in an in vitro
511 micronucleus test. However, ciclesonide was clastogenic in the in vivo mouse micronucleus
512 test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar
513 findings. No evidence of impairment of fertility was observed in a reproductive study
514 conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 35
515 times the maximum human daily intranasal dose in adults based on mcg/m^2).

516 **13.2 Animal Toxicology and Pharmacology**

517 Reproductive Toxicology Studies: Oral administration of ciclesonide in rats up to
518 900 mcg/kg (approximately 35 times the maximum human daily dose in adults based on
519 mcg/m^2) produced no teratogenicity or other fetal effects. However, subcutaneous
520 administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum daily intranasal
521 dose in adults based on mcg/m^2) or greater produced fetal toxicity. This included fetal loss,
522 reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications,
523 and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily
524 intranasal dose in adults based on mcg/m^2).

525
526

527 **14 CLINICAL STUDIES**

528 **14.1 Seasonal and Perennial Allergic Rhinitis**

529 *Adults and Adolescent Patients 12 Years of Age and Older:* The efficacy of
530 OMNARIS Nasal Spray was evaluated in 3 randomized, double-blind, parallel-group,
531 multicenter, placebo-controlled clinical trials of 2 to 6 weeks duration conducted in the
532 United States and Canada in adolescents and adults with allergic rhinitis. The three trials
533 included a total of 1524 patients (495 males and 1029 females) of whom 79 were
534 adolescents, ages 12 to 17 years. The racial distribution in these three trials included 1374
535 Caucasians, 69 Blacks, 31 Asians, and 50 patients classified as Other. Of the 1524 patients,
536 546 patients received OMNARIS Nasal Spray 200 mcg once daily administered as 2 sprays
537 in each nostril. Patients enrolled in the studies were 12 to 86 years of age with a history of
538 seasonal or perennial allergic rhinitis, a positive skin test to at least one relevant allergen, and
539 active symptoms of allergic rhinitis at study entry. Assessment of efficacy in these trials was
540 based on patient recording of four nasal symptoms (runny nose, nasal itching, sneezing, and
541 nasal congestion) on a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and
542 3=severe) as reflective or instantaneous scores. Reflective scoring required the patients to
543 record symptom severity over the previous 12 hours; the instantaneous scoring required
544 patients to record symptom severity at the time of recording. The results of these trials
545 showed that patients treated with OMNARIS Nasal Spray 200 mcg once daily exhibited
546 statistically significantly greater decreases in total nasal symptom scores than placebo treated
547 patients. Secondary measures of efficacy were also generally supportive.

548 *Dose Ranging Trial:* One of the three trials was a 2-week dose-ranging trial that
549 evaluated efficacy of four doses of OMNARIS Nasal Spray in patients with seasonal allergic
550 rhinitis. The primary efficacy endpoint was the difference from placebo in the change from
551 baseline of the sum of morning and evening reflective total nasal symptom score averaged

552 over the 2-week treatment period. Results of the primary efficacy endpoint are shown in
 553 Table 3. In this trial OMNARIS Nasal Spray 200 mcg once daily was statistically
 554 significantly different from placebo, but the lower doses were not statistically significantly
 555 different from placebo.

556 **Table 3 Mean change in reflective total nasal symptom score over 2 weeks in patients**
 557 **with seasonal allergic rhinitis**

Treatment	N	Baseline*	Change from Baseline	Difference from Placebo**		
				Estimate	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	144	18.8	-5.73	-1.35	(-2.43, -0.28)	0.014
Ciclesonide 100 mcg	145	18.7	-5.26	-0.88	(-1.96, 0.19)	0.11
Ciclesonide 50 mcg	143	18.4	-4.82	-0.44	(-1.52, 0.63)	0.42
Ciclesonide 25 mcg	146	18.7	-4.74	-0.35	(-1.42, 0.71)	0.51
Placebo	148	17.8	-4.38			

558 *Sum of AM and PM Scores; Maximum score = 24

559 ** Estimates, 95% Confidence Intervals, and p-values were obtained from repeated measures ANCOVA analysis with treatment, baseline,
 560 day, and treatment by day interaction effects included in the model.
 561

562 *Seasonal Allergic Rhinitis Trial:* The second trial was a 4-week single dose-level
 563 trial conducted in patients with seasonal allergic rhinitis. The primary efficacy endpoint in
 564 the seasonal allergic rhinitis trial was the difference from placebo in the change from baseline
 565 of the average of morning and evening reflective total nasal symptom score averaged over
 566 the first 2 weeks of treatment. In this trial, OMNARIS Nasal Spray 200 mcg once daily was
 567 statistically significantly different from placebo (Table 4). Statistically significant
 568 differences in the morning pre-dose instantaneous total nasal symptom score indicate that the
 569 effect was maintained over the full 24-hour dosing interval.

570 *Perennial Allergic Rhinitis Trial:* The third trial was a 6-week single dose level trial
 571 conducted in patients with perennial allergic rhinitis. The primary efficacy endpoint in the
 572 perennial allergic rhinitis trial was the difference from placebo in the change from baseline of
 573 the average of morning and evening reflective total nasal symptom score averaged over the
 574 6 weeks of treatment. In this trial, OMNARIS Nasal Spray 200 mcg once daily was
 575 statistically significantly different from placebo (Table 4). Statistically significant
 576 differences in the morning pre-dose instantaneous total nasal symptom score indicate that the
 577 effect was maintained over the full 24-hour dosing interval.

578 **Table 4 Mean changes in reflective total nasal symptom score and instantaneous total**
 579 **nasal symptom score in allergic rhinitis trials**

Treatment	n	Baseline*	Change from Baseline	Difference from Placebo**		
				Estimate	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	162	8.96	-2.40	-0.90	(-1.36, -0.45)	<0.001
Placebo	162	8.83	-1.50			
Seasonal Allergic Rhinitis Trial – Instantaneous total nasal symptom score						

Ciclesonide 200 mcg	162	8.45	-1.87	-0.84	(-1.30, -0.39)	<0.001
Placebo	162	8.33	-1.03			
Perennial Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	232	7.59	-2.51	-0.62	(-0.97, -0.28)	<0.001
Placebo	229	7.72	-1.89			
Perennial Allergic Rhinitis Trial – Instantaneous total nasal symptom score						
Ciclesonide 200 mcg	232	7.05	-1.99	-0.53	(-0.90, -0.17)	0.004
Placebo	229	7.05	-1.46			

580 *Mean of AM and PM score from reflective total nasal symptom score; Mean of AM score for instantaneous total nasal symptom score;
581 Maximum = 12
582 ** Estimates, 95% Confidence Intervals, and p-values were obtained from repeated measures ANCOVA analysis with treatment, baseline,
583 day, and treatment by day interaction effects included in the model.
584

585 *Onset of action:* Onset of action was evaluated in two environmental exposure unit
586 studies in patients with seasonal allergic rhinitis receiving a single dose of OMNARIS Nasal
587 Spray 200 mcg. Results from these two studies did not demonstrate a replicate onset of action
588 within the assessment period. Onset of action was also evaluated in the 4-week seasonal
589 allergic rhinitis and in the 6-week perennial allergic rhinitis trial by frequent recording of
590 instantaneous symptom score after the first dose. In these trials, onset of effect was seen
591 within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in
592 seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis.

593 *Pediatric Patients Aged 6 to 11 Years:* The efficacy of OMNARIS Nasal Spray was
594 evaluated in two randomized, double-blind, parallel-group, multicenter, placebo-controlled
595 clinical trials in 1282 patients 6 to 11 years of age with allergic rhinitis. Of the two trials,
596 one was 2 weeks in duration conducted in patients with seasonal allergic rhinitis that
597 evaluated efficacy of 200 mcg and 100 mcg of OMNARIS Nasal Spray once daily. The
598 other trial was 12 weeks in duration conducted in patients with perennial allergic rhinitis that
599 evaluated efficacy of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray once daily.
600 Of the total number of patients enrolled in the 2 studies, 380 were treated with 200 mcg of
601 OMNARIS Nasal Spray once daily. The primary efficacy endpoint was the difference from
602 placebo in the change from baseline of the average of morning and evening reflective total
603 nasal symptom score averaged over 2 weeks of treatment in the seasonal allergic rhinitis trial
604 and over the first 6 weeks of treatment in the perennial allergic rhinitis trial. In the 2-week
605 trial in patients with seasonal allergic rhinitis, the OMNARIS Nasal Spray 200 mcg once
606 daily dose was statistically significantly different from placebo, but the 100 mcg one daily
607 dose was not statistically significantly different from placebo. The efficacy results for the
608 seasonal allergic rhinitis trial are shown in Table 5.

609 **Table 5 Mean changes in reflective total nasal symptom score in 1 seasonal allergic**
610 **rhinitis trial in children 6 to 11 years of age**

Treatment	n	Baseline*	Change from Baseline	Difference from Placebo**		
				Estimate	95% CI	p-value
Reflective total nasal symptom score						
Ciclesonide 200 mcg	215	8.25	-2.46	-0.39	(-0.76, -0.02)	0.040

Ciclesonide 100 mcg	199	8.41	-2.38	-0.32	(-0.69, 0.06)	0.103
Placebo	204	8.41	-2.07			

*Mean of AM and PM score from reflective total nasal symptom score; Maximum = 12

** Estimates, 95% Confidence Intervals, and p-values were obtained from repeated measures ANCOVA analysis with treatment, baseline, day, and treatment by day interaction effects included in the model.

In the 12-week trial in patients with perennial allergic rhinitis none of the ciclesonide doses were statistically significantly different from placebo. The means and 95% confidence intervals for the differences (OMNARIS Nasal Spray minus placebo) between OMNARIS Nasal Spray 200 mcg, 100 mcg, and 25 mcg treatment groups and placebo were -0.31 (-0.75, 0.13), 0.02 (-0.41, 0.46), and 0.09 (-0.35, 0.53), respectively.

Pediatric Patients Aged 2 to 5 Years: Efficacy of OMNARIS Nasal Spray in patients 2 to 5 years of age has not been established [see *Pediatric Use (8.4)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

OMNARIS is supplied in an amber glass bottle and provides for nasal delivery with a manual metered pump. OMNARIS Nasal Spray is supplied with an oxygen absorber sachet and enclosed in a foil pouch. The contents of one 12.5 gram bottle provide 120 actuations, after initial priming. Each spray delivers 50 mcg of ciclesonide from the nasal actuator. Prior to initial use, OMNARIS Nasal Spray must be gently shaken and then the pump must be primed by actuating eight times. The OMNARIS Nasal Spray bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after removal from the foil pouch either after 120 sprays following initial priming (since the amount of ciclesonide delivered per spray thereafter may be substantially less than the labeled dose) or after 4 months. Patient instructions are also provided.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temp]. Do not freeze. Shake gently before use. Keep out of reach of children.

Omnaris Nasal Spray 50 mcg, 120 metered sprays; net fill weight 12.5 g. (NDC Number 63402-701-01)

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling accompanying the product

17.1 Local Nasal Effects

Patients should be informed that treatment with OMNARIS Nasal Spray may lead to adverse reactions, which include epistaxis and nasal ulceration. *Candida* infection may also occur with treatment with OMNARIS Nasal Spray. In addition, nasal corticosteroids are associated with nasal septal perforation and impaired wound healing. Avoid spraying OMNARIS Nasal Spray directly onto the nasal septum. Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use OMNARIS Nasal Spray until healing has occurred [see *Warning and Precautions (5.1)*].

653 **17.2 Cataracts and Glaucoma**

654 Patients should be informed that glaucoma and cataracts are associated with nasal and
655 inhaled corticosteroid use. Patients should inform his/her health care provider if a change in
656 vision is noted while using OMNARIS Nasal Spray [see *Warning and Precautions (5.2)*].

657 **17.3 Immunosuppression**

658 Patients who are on immunosuppressive doses of corticosteroids should be warned to
659 avoid exposure to chickenpox or measles, and if exposed, to consult their physician without
660 delay. Patients should be informed of potential worsening of existing tuberculosis, fungal,
661 bacterial, viral or parasitic infections, or ocular herpes simplex [see *Warning and Precautions*
662 *(5.3)*].

663 **17.4 Use Daily**

664 Patients should use OMNARIS Nasal Spray at regular intervals since its effectiveness
665 depends on its regular use. In clinical trials, the onset of effect was seen within 24 to 48
666 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic
667 rhinitis and 5 weeks in perennial allergic rhinitis. Initial assessment of response should be
668 made during this timeframe and periodically until the patients' symptoms are stabilized. The
669 patient should take the medication as directed and should not exceed the prescribed dosage.
670 The patient should contact the physician if symptoms do not improve by a reasonable time or
671 if the condition worsens.

672 **17.5 Keep Spray Out of Eyes**

673 Patients should be informed to avoid spraying OMNARIS Nasal Spray in their eyes.

674 **17.6 Storage and Handling**

675 It is important that the bottle is gently shaken prior to use to ensure that a consistent
676 amount is dispensed per actuation. The bottle should be discarded after 120 actuations
677 following initial priming or after 4 months after the bottle is removed from the foil pouch,
678 whichever occurs first.

679
680



681
682

683 Manufactured for:

684 Sepracor Inc.

685 Marlborough, MA 01752 USA

686 Made in Germany

687 OMNARIS is a registered trademark of Nycomed GmbH and is used with permission.

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

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

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

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