

1 XXXXXX-XX

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3 **TRADENAME<sup>®</sup> 180 mcg**

4 (budesonide inhalation powder, 180 mcg)

5

6 **TRADENAME<sup>®</sup> 90 mcg**

7 (budesonide inhalation powder, 90 mcg)

8

9 **For Oral Inhalation Only.**

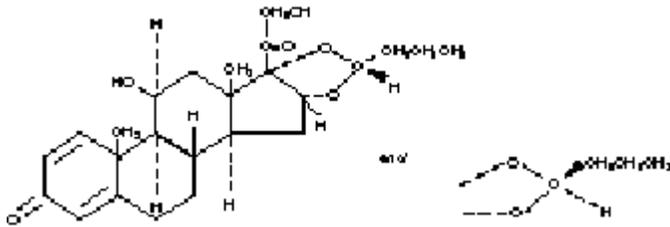
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11 **Rx only**

12

13 **DESCRIPTION**

14 Budesonide, the active component of TRADENAME, is  
15 a corticosteroid designated chemically as (RS)-11 $\beta$ ,  
16 16 $\alpha$ , 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione  
17 cyclic 16,17-acetal with butyraldehyde. Budesonide is  
18 provided as a mixture of two epimers (22R and 22S).  
19 The empirical formula of budesonide is C<sub>25</sub>H<sub>34</sub>O<sub>6</sub> and its  
20 molecular weight is 430.5. Its structural formula is:



21

22 Budesonide is a white to off-white, tasteless, odorless  
23 powder that is practically insoluble in water and in  
24 heptane, sparingly soluble in ethanol, and freely soluble  
25 in chloroform. Its partition coefficient between octanol  
26 and water at pH 7.4 is  $1.6 \times 10^3$ .

27

28 TRADENAME is an inhalation-driven multi-dose dry  
29 powder inhaler containing a formulation of 1 mg per  
30 actuation of micronized budesonide and micronized  
31 lactose (which may contain trace or residual levels of  
32 milk proteins). Each actuation of TRADENAME 180  
33 mcg delivers 160 mcg budesonide from the mouthpiece  
34 and each actuation of TRADENAME 90 mcg delivers  
35 80 mcg budesonide from the mouthpiece (based on *in*  
36 *vitro* testing at 60 L/min for 2 sec). Each TRADENAME  
37 180 mcg contains 120 actuations and each  
38 TRADENAME 90 mcg contains 60 actuations.

39

40 *In vitro* testing has shown that the dose delivery for  
41 TRADENAME is dependent on airflow through the  
42 device, as evidenced by a decrease in the fine particle  
43 dose at a flow rate of 30 L/min to a value that is  
44 approximately 40-50% of that produced at 60 L/min. At  
45 a flow rate of 40 L/min, the fine particle dose is  
46 approximately 70% of that produced at 60 L/min.  
47 Patient factors such as inspiratory flow rates will also  
48 affect the dose delivered to the lungs of patients in  
49 actual use (see *Patient's Instructions for Use*). In  
50 asthmatic children age 6 to 17 (N=516, FEV<sub>1</sub> 2.29  
51 [0.97–4.28]) peak inspiratory flow (PIF) through  
52 TRADENAME was 72.5 [19.1 – 103.6] L/min).  
53 Inspiratory flows were not measured in the adult pivotal  
54 study. Patients should be carefully instructed on the use  
55 of this drug product to assure optimal dose delivery.

56

57

## 58 **CLINICAL PHARMACOLOGY**

### 59 **Mechanism of Action**

60 Budesonide is an anti-inflammatory corticosteroid that  
61 exhibits potent glucocorticoid activity and weak  
62 mineralocorticoid activity. In standard *in vitro* and  
63 animal models, budesonide has approximately a 200-  
64 fold higher affinity for the glucocorticoid receptor and a  
65 1000-fold higher topical anti-inflammatory potency than  
66 cortisol (rat croton oil ear edema assay). As a measure of  
67 systemic activity, budesonide is 40 times more potent  
68 than cortisol when administered subcutaneously and 25  
69 times more potent when administered orally in the rat  
70 thymus involution assay.

71

72 The activity of TRADENAME is due to the parent drug,  
73 budesonide. In glucocorticoid receptor affinity studies,  
74 the 22R form was two times as active as the 22S epimer.  
75 *In vitro* studies indicated that the two forms of  
76 budesonide do not interconvert.

77

78 The precise mechanism of corticosteroid actions on  
79 inflammation in asthma is not known. Inflammation is  
80 an important component in the pathogenesis of asthma.  
81 Corticosteroids have been shown to have a wide range  
82 of inhibitory activities against multiple cell types (eg,  
83 mast cells, eosinophils, neutrophils, macrophages, and  
84 lymphocytes) and mediators (eg, histamine, eicosanoids,  
85 leukotrienes, and cytokines) involved in allergic and  
86 non-allergic-mediated inflammation. These anti-  
87 inflammatory actions of corticosteroids may contribute  
88 to their efficacy in asthma.

89

90 Studies in asthmatic patients have shown a favorable  
91 ratio between topical anti-inflammatory activity and  
92 systemic corticosteroid effects over a wide range of  
93 doses from TRADENAME or inhaled budesonide. This  
94 is explained by a combination of a relatively high local  
95 anti-inflammatory effect, extensive first pass hepatic  
96 degradation of orally absorbed drug (85-95%), and the  
97 low potency of formed metabolites (see below).

98

## 99 **Pharmacokinetics**

### 100 **Absorption**

101 After oral administration of budesonide, peak plasma  
102 concentration was achieved in about 1 to 2 hours and the  
103 absolute systemic availability was 6-13%. In contrast,  
104 most of budesonide delivered to the lungs is  
105 systemically absorbed. In healthy subjects, 34% of the  
106 metered dose was deposited in the lungs (as assessed by  
107 plasma concentration method and using a different  
108 budesonide containing dry-powder inhaler) with an  
109 absolute systemic availability of 39% of the metered  
110 dose. Peak steady-state plasma concentrations of  
111 budesonide delivered from TRADENAME in adults  
112 with asthma (n=39) occurred at approximately 10  
113 minutes post-dose and averaged 0.6 and 1.6 nmol/L at  
114 doses of 180 mcg once daily and 360 mcg twice daily,  
115 respectively.

116

117 In asthmatic patients, budesonide showed a linear  
118 increase in AUC and  $C_{max}$  with increasing dose after  
119 both a single dose and repeated dosing of inhaled  
120 budesonide.

121

#### 122 Distribution

123 The volume of distribution of budesonide was  
124 approximately 3 L/kg. It was 85-90% bound to plasma  
125 proteins. Protein binding was constant over the  
126 concentration range (1-100 nmol/L) achieved with, and  
127 exceeding, recommended doses of TRADENAME.  
128 Budesonide showed little or no binding to corticosteroid  
129 binding globulin. Budesonide rapidly equilibrated with  
130 red blood cells in a concentration independent manner  
131 with a blood/plasma ratio of about 0.8.

132

#### 133 Metabolism

134 *In vitro* studies with human liver homogenates have  
135 shown that budesonide is rapidly and extensively  
136 metabolized. Two major metabolites formed via  
137 cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)  
138 catalyzed biotransformation have been isolated and  
139 identified as 16 $\alpha$ -hydroxyprednisolone and 6 $\beta$ -  
140 hydroxybudesonide. The corticosteroid activity of each  
141 of these two metabolites is less than 1% of that of the  
142 parent compound. No qualitative differences between  
143 the *in vitro* and *in vivo* metabolic patterns have been  
144 detected. Negligible metabolic inactivation was  
145 observed in human lung and serum preparations.

146

#### 147 Excretion/Elimination

148 The 22R form of budesonide was preferentially cleared  
149 by the liver with systemic clearance of 1.4 L/min vs. 1.0  
150 L/min for the 22S form. The terminal half-life, 2 to 3  
151 hours, was the same for both epimers and was  
152 independent of dose. Budesonide was excreted in urine  
153 and feces in the form of metabolites. Approximately  
154 60% of an intravenous radiolabeled dose was recovered  
155 in the urine. No unchanged budesonide was detected in  
156 the urine.

157

#### 158 Special Populations

159 No clinically relevant pharmacokinetic differences have  
160 been identified due to race, sex, or advanced age.

161

162 **Pediatric**

163 Following intravenous dosing in pediatric patients age  
164 10-14 years, plasma half-life was shorter than in adults  
165 (1.5 hours vs. 2.0 hours in adults). In the same  
166 population following inhalation of budesonide via a  
167 pressurized metered-dose inhaler, absolute systemic  
168 availability was similar to that in adults.

169

170 Peak steady-state plasma concentrations of budesonide  
171 delivered via TRADENAME in children and  
172 adolescents with asthma (n=14) occurred at  
173 approximately 15 to 30 minutes post-dose and averaged  
174 0.4 and 1.5 nmol/L at doses of 180 mcg once daily and  
175 360 mcg twice daily, respectively.

176

177 **Hepatic Insufficiency**

178 Reduced liver function may affect the elimination of  
179 corticosteroids. The pharmacokinetics of budesonide  
180 were affected by compromised liver function as  
181 evidenced by a doubled systemic availability after oral  
182 ingestion. The intravenous pharmacokinetics of  
183 budesonide were, however, similar in cirrhotic patients  
184 and in healthy subjects.

185

186 **Drug-Drug Interactions**

187 Ketoconazole, a potent inhibitor of cytochrome P450  
188 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic  
189 enzyme for corticosteroids, increased plasma levels of  
190 orally ingested budesonide. At recommended doses,  
191 cimetidine had a slight but clinically insignificant effect  
192 on the pharmacokinetics of oral budesonide. For more  
193 information, please see PRECAUTIONS, Drug  
194 Interactions.

195

196 **Pharmacodynamics**

197 To confirm that systemic absorption is not a significant  
198 factor in the clinical efficacy of inhaled budesonide, a  
199 clinical study in patients with asthma was performed  
200 comparing 400 mcg budesonide administered via a  
201 pressurized metered-dose inhaler with a tube spacer to  
202 1400 mcg of oral budesonide and placebo. The study  
203 demonstrated the efficacy of inhaled budesonide but not  
204 orally ingested budesonide, despite comparable systemic  
205 levels. Thus, the therapeutic effect of conventional doses  
206 of orally inhaled budesonide are largely explained by its  
207 direct action on the respiratory tract.

208

209 Generally, budesonide has a relatively rapid onset of  
210 action for an inhaled corticosteroid. Improvement in  
211 asthma control following inhalation of budesonide can  
212 occur within 24 hours of beginning treatment although  
213 maximum benefit may not be achieved for 1 to 2 weeks,  
214 or longer.

215

216 Inhaled budesonide has been shown to decrease airway  
217 reactivity in various challenge models, including  
218 histamine, methacholine, sodium metabisulfite, and  
219 adenosine monophosphate in patients with hyperreactive  
220 airways. The clinical relevance of these models is not  
221 certain.

222

223 Pretreatment with inhaled budesonide 1600 mcg daily  
224 (800 mcg twice daily) for 2 weeks reduced the acute  
225 (early-phase reaction) and delayed (late-phase reaction)  
226 decrease in FEV<sub>1</sub> following inhaled allergen challenge.

227

228 The effects of inhaled budesonide on the hypothalamic-  
229 pituitary-adrenal (HPA) axis were studied in 905 adults  
230 and 404 pediatric patients with asthma. For most  
231 patients, the ability to increase cortisol production in  
232 response to stress, as assessed by cosyntropin (ACTH)  
233 stimulation test, remained intact with inhaled  
234 budesonide treatment at recommended doses. For adult  
235 patients treated with 100, 200, 400, or 800 mcg twice  
236 daily for 12 weeks, 4%, 2%, 6%, and 13% respectively,  
237 had an abnormal stimulated cortisol response (peak  
238 cortisol <14.5 mcg/dL assessed by liquid  
239 chromatography following short-cosyntropin test) as  
240 compared with 8% of patients treated with placebo.  
241 Similar results were obtained in pediatric patients. In  
242 another study in adults, doses of 400, 800 and 1600 mcg  
243 of inhaled budesonide twice daily for 6 weeks were  
244 examined; 1600 mcg twice daily (twice the maximum  
245 recommended dose) resulted in a 27% reduction in  
246 stimulated cortisol (6-hour ACTH infusion) while 10 mg  
247 prednisone resulted in a 35% reduction. In this study, no  
248 patient taking doses of 400 and 800 mcg twice daily met  
249 the criterion for an abnormal stimulated cortisol  
250 response (peak cortisol <14.5 mcg/dL assessed by liquid  
251 chromatography) following ACTH infusion. An open-  
252 label, long-term follow-up of 1133 patients for up to 52  
253 weeks confirmed the minimal effect on the HPA axis  
254 (both basal and stimulated plasma cortisol) of inhaled  
255 budesonide when administered at doses ranging from  
256 100 to 800 mcg twice daily. In patients who had  
257 previously been oral steroid-dependent, use of inhaled  
258 budesonide at doses ranging from 100 to 800 mcg twice  
259 daily was associated with higher stimulated cortisol  
260 response compared with baseline following 1 year of  
261 therapy.

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268 The administration of inhaled budesonide via a different  
269 dry-powder inhaler in doses up to 800 mcg/day (mean  
270 daily dose 445 mcg/day) or via a pressurized metered-  
271 dose inhaler in doses up to 1200 mcg/day (mean daily  
272 dose 620 mcg/day) to 216 pediatric patients (age 3 to 11  
273 years) for 2 to 6 years had no significant effect on  
274 statural growth compared with non-corticosteroid  
275 therapy in 62 matched control patients. However, the  
276 long-term effect of inhaled budesonide on growth is not  
277 fully known.

278

### 279 **Clinical Studies**

280 The safety and efficacy of TRADENAME were  
281 evaluated in two 12-week, double-blind, randomized,  
282 parallel-group, placebo-controlled clinical studies  
283 conducted at sites in the United States and Asia  
284 involving 1137 patients aged 6 to 80 years with mild to  
285 moderate asthma. Study 1 evaluated TRADENAME  
286 180 mcg, PULMICORT TURBUHALER 200 mcg, and  
287 placebo, each administered as 1 inhalation once daily or  
288 2 inhalations twice daily in patients 18 years of age and  
289 older with mild to moderate asthma previously treated  
290 with inhaled corticosteroids. The delivered dose of  
291 TRADENAME 180 mcg and PULMICORT  
292 TURBUHALER 200 mcg are the same; each delivers  
293 160 mcg from the mouthpiece. Study 2 evaluated  
294 TRADENAME 90 mcg, 2 inhalations once daily or 4  
295 inhalations twice daily, PULMICORT TURBUHALER  
296 200 mcg, 1 inhalation once daily or 2 inhalations twice  
297 daily, and placebo in pediatric patients aged 6 to 17  
298 years with mild to moderate asthma. Both of the studies  
299 had a 2-week placebo treatment run-in period followed  
300 by a 12-week randomized treatment period. The  
301 primary endpoint was the difference between baseline  
302 and the mean of the treatment-period FEV<sub>1</sub> (adults) or  
303 FEV<sub>1</sub> % predicted (children).

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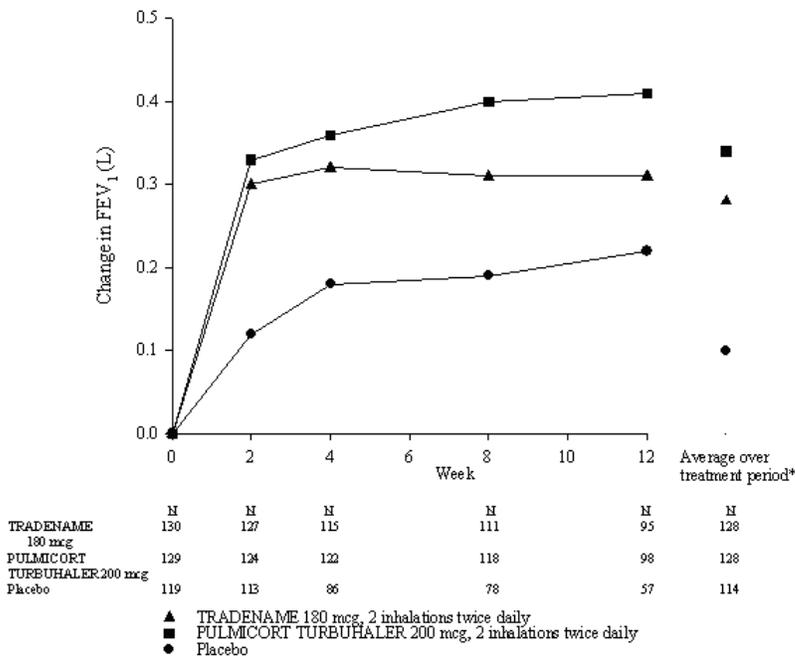
305

305 **Adult Patients with Asthma (Study 1)**

306 This study enrolled 621 patients aged  $\geq 18$  to 80 years  
 307 with mild-to-moderate asthma (mean baseline %  
 308 predicted FEV<sub>1</sub> 64.3%) whose symptoms were  
 309 previously controlled on inhaled corticosteroids. Mean  
 310 change from baseline in FEV<sub>1</sub> in the TRADENAME  
 311 180 mcg, 2 inhalations twice-daily group was 0.28 liters,  
 312 as compared to 0.10 liters in the placebo group  
 313 ( $p < 0.001$ ). Secondary endpoints of morning and  
 314 evening peak expiratory flow rate, daytime asthma  
 315 symptom severity, nighttime asthma symptom severity,  
 316 daily rescue medication use, and the percentage of  
 317 patients who met predefined asthma related withdrawal  
 318 criteria showed differences from baseline favoring  
 319 TRADENAME over placebo. The responses of  
 320 TRADENAME compared with PULMICORT  
 321 TURBUHALER tended to be lower.

322

323 **12-Week Trial in Adult Patients with Mild to**  
 324 **Moderate Asthma (Study 1)**  
 325 **Mean Change from Baseline in FEV<sub>1</sub> (L)**  
 326



\* Average over treatment period: values are adjusted treatment means for the average difference during the treatment period using last observation carried forward (primary endpoint).  
 Comparison of TRADENAME 180 mcg, 2 inhalations twice daily vs placebo for Average over treatment period:  $p < 0.001$   
 One inhalation of TRADENAME 180 mcg and one inhalation of PULMICORT TURBUHALER 200 mcg result in the same delivered dose of 160 mcg.

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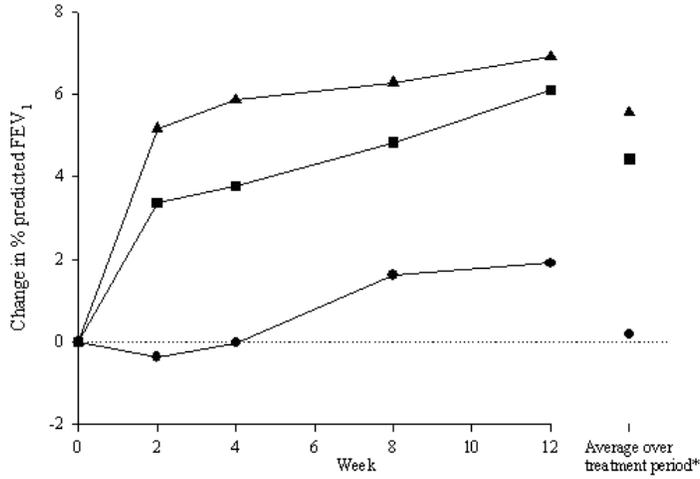
328

328 **Pediatric and Adolescent Patients with Asthma**  
329 **(Study 2)**

330 This study enrolled 516 patients aged 6 to 17 years with  
331 mild asthma (mean baseline % predicted FEV<sub>1</sub> 84.9%).  
332 The study population included patients previously  
333 treated with inhaled corticosteroids for no more than 30  
334 days before the study began (4%) and patients who were  
335 naïve to inhaled corticosteroids (96%). Mean change  
336 from baseline in % predicted FEV<sub>1</sub> during the 12-week  
337 treatment period in the TRADENAME 90 mcg, 4  
338 inhalations twice daily treatment group was 5.6  
339 compared with 0.2 in the placebo group (p<0.001).  
340 Secondary endpoints of morning and evening PEF  
341 showed differences from baseline favoring  
342 TRADENAME over placebo.  
343

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**12-Week Trial in Pediatric Patients With Mild Asthma (Study 2)**  
**Mean Change from Baseline in Percent Predicted FEV<sub>1</sub>**



	N	N	N	N	N	N
TRADENAME 90 mcg	98	86	87	81	75	90
PULMICORT TURBUHALER 200 mcg	99	97	95	91	85	98
Placebo	104	96	96	91	85	101

- ▲ TRADENAME 90 mcg, 4 inhalations twice daily
- PULMICORT TURBUHALER 200 mcg, 2 inhalations twice daily
- ◆ Placebo

\* Average over treatment period: values are adjusted treatment means for the average difference during the treatment period using last observation carried forward (primary endpoint).  
 Comparison of TRADENAME 90 mcg, 4 inhalations twice daily vs placebo for Average over treatment period: p<0.001  
 Two inhalations of TRADENAME 90 mcg and one inhalation of PULMICORT TURBUHALER 200 mcg result in the same delivered dose of 160 mcg.

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351 **INDICATIONS AND USAGE**

352 TRADENAME is indicated for the maintenance  
353 treatment of asthma as prophylactic therapy in adult and  
354 pediatric patients six years of age or older. It is also  
355 indicated for patients requiring oral corticosteroid  
356 therapy for asthma. Many of those patients may be able  
357 to reduce or eliminate their requirement for oral  
358 corticosteroids over time.

359

360 TRADENAME is NOT indicated for the relief of acute  
361 bronchospasm.

362

363

364 **CONTRAINDICATIONS**

365 TRADENAME is contraindicated in the primary  
366 treatment of status asthmaticus or other acute episodes  
367 of asthma where intensive measures are required.

368

369 TRADENAME is contraindicated in patients with  
370 known hypersensitivity to any component of the  
371 formulation.

372

373

374 **WARNINGS**

375 Particular care is needed for patients who are transferred  
376 from systemically active corticosteroids to  
377 TRADENAME because deaths due to adrenal  
378 insufficiency have occurred in asthmatic patients during  
379 and after transfer from systemic corticosteroids to less  
380 systemically available inhaled corticosteroids. After  
381 withdrawal from systemic corticosteroids, a number of  
382 months are required for recovery of hypothalamic-  
383 pituitary-adrenal (HPA) function.

384

385 Patients who have been previously maintained on 20 mg  
386 or more per day of prednisone (or its equivalent) may be  
387 most susceptible, particularly when their systemic  
388 corticosteroids have been almost completely withdrawn.  
389 During this period of HPA suppression, patients may  
390 exhibit signs and symptoms of adrenal insufficiency  
391 when exposed to trauma, surgery, or infection  
392 (particularly gastroenteritis) or other conditions  
393 associated with severe electrolyte loss. Although  
394 TRADENAME may provide control of asthma  
395 symptoms during these episodes, in recommended doses  
396 it supplies less than normal physiological amounts of  
397 glucocorticoid systemically and does NOT provide the  
398 mineralocorticoid activity that is necessary for coping  
399 with these emergencies.

400

401 During periods of stress or a severe asthma attack,  
402 patients who have been withdrawn from systemic  
403 corticosteroids should be instructed to resume oral  
404 corticosteroids (in large doses) immediately and to  
405 contact their physicians for further instruction. These  
406 patients should also be instructed to carry a medical  
407 identification card indicating that they may need  
408 supplementary systemic corticosteroids during periods  
409 of stress or a severe asthma attack.

410

411 Patients requiring oral corticosteroids should be weaned  
412 slowly from systemic corticosteroid use after  
413 transferring to TRADENAME. Lung function (FEV<sub>1</sub> or  
414 AM PEF), beta-agonist use, and asthma symptoms  
415 should be carefully monitored during withdrawal of oral  
416 corticosteroids. In addition to monitoring asthma signs  
417 and symptoms, patients should be observed for signs and  
418 symptoms of adrenal insufficiency such as fatigue,  
419 lassitude, weakness, nausea and vomiting, and  
420 hypotension.

421

422 Transfer of patients from systemic corticosteroid therapy  
423 to TRADENAME may unmask allergic conditions  
424 previously suppressed by the systemic corticosteroid  
425 therapy, eg, rhinitis, conjunctivitis, arthritis, eosinophilic  
426 conditions, and eczema.

427

428 Patients who are on drugs that suppress the immune  
429 system are more susceptible to infection than healthy

430 individuals. Chicken pox and measles, for example, can  
431 have a more serious or even fatal course in susceptible  
432 pediatric patients or adults on immunosuppressant doses  
433 of corticosteroids. In pediatric or adult patients who  
434 have not had these diseases, particular care should be  
435 taken to avoid exposure. How the dose, route, and  
436 duration of corticosteroid administration affects the risk  
437 of developing a disseminated infection is not known.  
438 The contribution of the underlying disease and/or prior  
439 corticosteroid treatment to the risk is also not known. If  
440 exposed, therapy with varicella zoster immune globulin  
441 (VZIG) or pooled intravenous immunoglobulin (IVIG),  
442 as appropriate, may be indicated. If exposed to measles,  
443 prophylaxis with pooled intramuscular immunoglobulin  
444 (IG) may be indicated. (See the respective package  
445 inserts for complete VZIG and IG prescribing  
446 information.) If chicken pox develops, treatment with  
447 antiviral agents may be considered.

448

449 TRADENAME is not a bronchodilator and is not  
450 indicated for rapid relief of bronchospasm or other acute  
451 episodes of asthma.

452

453 As with other inhaled asthma medications,  
454 bronchospasm, with an immediate increase in wheezing,  
455 may occur after dosing. If bronchospasm occurs  
456 following dosing with TRADENAME, it should be  
457 treated immediately with a fast-acting inhaled  
458 bronchodilator. Treatment with TRADENAME should  
459 be discontinued and alternate therapy instituted.

460

461 Patients should be instructed to contact their physician  
462 immediately when episodes of asthma not responsive to  
463 their usual doses of bronchodilators occur during  
464 treatment with TRADENAME. During such episodes,  
465 patients may require therapy with oral corticosteroids.

466

467

468 **PRECAUTIONS**

469 **General**

470 During withdrawal from oral corticosteroids, some  
471 patients may experience symptoms of systemically  
472 active corticosteroid withdrawal, eg, joint and/or  
473 muscular pain, lassitude, and depression, despite  
474 maintenance or even improvement of respiratory  
475 function (see DOSAGE AND ADMINISTRATION).

476

477 In responsive patients, TRADENAME may permit  
478 control of asthma symptoms with less suppression of  
479 HPA-axis function than therapeutically equivalent oral  
480 doses of prednisone. Since budesonide is absorbed into  
481 the circulation and can be systemically active, the  
482 beneficial effects of TRADENAME in minimizing HPA  
483 dysfunction may be expected only when recommended  
484 dosages are not exceeded and individual patients are  
485 titrated to the lowest effective dose. Since individual  
486 sensitivity to effects on cortisol production exists,  
487 physicians should consider this information when  
488 prescribing TRADENAME.

489

490 Because of the possibility of systemic absorption of  
491 inhaled corticosteroids, patients treated with  
492 TRADENAME should be observed carefully for any  
493 evidence of systemic corticosteroid effects. Particular  
494 care should be taken in observing patients  
495 postoperatively or during periods of stress for evidence  
496 of inadequate adrenal response.

497

498 It is possible that systemic corticosteroid effects such as  
499 hypercorticism, reduced bone mineral density, and  
500 adrenal suppression may appear in a small number of  
501 patients, particularly at higher doses. If such changes  
502 occur, TRADENAME should be reduced slowly,  
503 consistent with accepted procedures for management of  
504 asthma symptoms and for tapering of systemic steroids.

505

506 Orally inhaled corticosteroids, including budesonide,  
507 may cause a reduction in growth velocity when  
508 administered to pediatric patients. A reduction in growth  
509 velocity may occur as a result of inadequate control of  
510 asthma or from use of corticosteroids for treatment. The  
511 potential effects of prolonged treatment on growth  
512 velocity should be weighed against the clinical benefits  
513 obtained and the risks associated with alternative  
514 therapies. To minimize the systemic effects of orally  
515 inhaled corticosteroids, including TRADENAME, each  
516 patient should be titrated to his/her lowest effective dose  
517 (see PRECAUTIONS, Pediatric Use).

518

519 Although patients in clinical trials have received inhaled  
520 budesonide on a continuous basis for periods of 1 to 2  
521 years, the long-term local and systemic effects of  
522 TRADENAME in human subjects are not completely  
523 known. In particular, the effects resulting from chronic  
524 use of TRADENAME on developmental or  
525 immunological processes in the mouth, pharynx,  
526 trachea, and lung are unknown.

527

528 In clinical trials with TRADENAME, localized  
529 infections with *Candida albicans* occurred in the mouth  
530 and pharynx in some patients. These infections may  
531 require treatment with appropriate antifungal therapy  
532 and/or discontinuance of treatment with TRADENAME.

533

534 Inhaled corticosteroids should be used with caution, if at  
535 all, in patients with active or quiescent tuberculosis  
536 infection of the respiratory tract, untreated systemic  
537 fungal, bacterial, viral or parasitic infections, or ocular  
538 herpes simplex.

539

540 Rare instances of glaucoma, increased intraocular  
541 pressure, and cataracts have been reported following the  
542 inhaled administration of corticosteroids.

543

544 **Information for Patients**

545 Patients being treated with TRADENAME should  
546 receive the following information and instructions. This  
547 information is intended to aid the patient in the safe and  
548 effective use of the medication. It is not a disclosure of  
549 all possible adverse or intended effects. For proper use  
550 of TRADENAME and to attain maximum improvement,  
551 the patient should read and follow the accompanying  
552 *Patient's Instructions for Use*.

553

554 • Patients should use TRADENAME at regular  
555 intervals as directed since its effectiveness  
556 depends on regular use. The patient should not  
557 alter the prescribed dosage unless advised to do  
558 so by the physician.

559 • Patients should be advised that TRADENAME is  
560 not a bronchodilator and is not intended to treat  
561 acute or life-threatening episodes of asthma.

562 • Patients should be advised that the effectiveness  
563 of TRADENAME depends on proper use of the  
564 device and inhalation-administering technique:

565 ○ 1) TRADENAME must be in the upright  
566 position (mouthpiece on top) during  
567 loading in order to provide the correct  
568 dose.

569 ○ 2) TRADENAME must be primed when  
570 the unit is used for the very first time. To  
571 prime the unit, it must be held in an  
572 upright position and the brown grip  
573 turned fully in one direction as far as it  
574 will go, then twisted fully back again in  
575 the other direction as far as it will go.  
576 One of the twisting movements will  
577 produce an audible click. This procedure  
578 must be repeated.

579 ○ 3) To load the first dose, the grip must be  
580 turned fully in one direction and then  
581 fully in the other direction until it clicks.

582 ○ 4) After the first dose, it is not necessary  
583 to prime the unit. However, it must be  
584 loaded in the upright position  
585 immediately prior to use as described  
586 above.

587 ○ 5) Patients should be advised not to shake  
588 the inhaler.

- 589 • Patients should place the mouthpiece between  
590 the lips and inhale forcefully and deeply. The  
591 powder is then delivered to the lungs.
- 592 • Patients should not exhale through  
593 TRADENAME.
- 594 • Due to the small volume of powder, patients may  
595 not sense the presence of any medication  
596 entering the lungs when inhaling from  
597 TRADENAME. This lack of sensation does not  
598 indicate that the patient is not receiving benefit  
599 from TRADENAME.
- 600 • Patients should be advised that rinsing the mouth  
601 with water without swallowing after each dosing  
602 may decrease the risk of the development of oral  
603 candidiasis.
- 604 • Patients should be instructed that they will  
605 receive a new TRADENAME unit each time  
606 they refill their prescription. Patients should be  
607 advised to discard the whole device after the  
608 labeled number of inhalations has been used. The  
609 dose indicator window tells how many doses are  
610 left in the inhaler. The inhaler is empty when the  
611 number zero (“0”) on the red background reaches  
612 the middle of the window.
- 613 • TRADENAME should not be used with a spacer.
- 614 • The mouthpiece should not be bitten or chewed.
- 615 • Replace the cover securely after each opening.
- 616 • Patients should keep TRADENAME clean and  
617 dry at all times.
- 618 • Patients should be advised that improvement in  
619 asthma control following inhalation of  
620 budesonide can occur within 24 hours of  
621 beginning treatment although maximum benefit  
622 may not be achieved for 1 to 2 weeks, or longer.  
623 If symptoms do not improve in that time frame,  
624 or if the condition worsens, the patient should be  
625 instructed not to increase the dosage, but to  
626 contact the physician.
- 627 • Patients whose systemic corticosteroids have  
628 been reduced or withdrawn should be instructed  
629 to carry a warning card indicating that they may  
630 need supplemental systemic corticosteroids  
631 during periods of stress or an asthma attack that  
632 does not respond to bronchodilators.

- 633 • Patients should be advised not to stop the use of  
634 TRADENAME abruptly.
- 635 • Patients should be warned to avoid exposure to  
636 chicken pox or measles and if they are exposed,  
637 to consult their physicians without delay.
- 638 • Long-term use of inhaled corticosteroids,  
639 including budesonide, may increase the risk of  
640 some eye problems (cataracts or glaucoma).  
641 Regular eye examinations should be considered.
- 642 • Women considering the use of TRADENAME  
643 should consult with their physician if they are  
644 pregnant or intend to become pregnant, or if they  
645 are breast-feeding a baby.
- 646 • Patients considering use of TRADENAME  
647 should consult with their physician if they are  
648 allergic to budesonide or any other orally inhaled  
649 corticosteroid.
- 650 • Patients should inform their physician of other  
651 medications they are taking as TRADENAME  
652 may not be suitable in some circumstances and  
653 the physician may wish to use a different  
654 medicine.

655

### 656 **Drug Interactions**

657 In clinical studies, concurrent administration of  
658 budesonide and other drugs commonly used in the  
659 treatment of asthma has not resulted in an increased  
660 frequency of adverse events. The main route of  
661 metabolism of budesonide, as well as other  
662 corticosteroids, is via cytochrome P450 (CYP)  
663 isoenzyme 3A4 (CYP3A4). After oral administration of  
664 ketoconazole, a potent inhibitor of CYP3A4, the mean  
665 plasma concentration of orally administered budesonide  
666 increased. Concomitant administration of other known  
667 inhibitors of CYP3A4 (eg, itraconazole, clarithromycin,  
668 erythromycin, etc.) may inhibit the metabolism of, and  
669 increase the systemic exposure to, budesonide. Care  
670 should be exercised when budesonide is coadministered  
671 with long-term ketoconazole and other known CYP3A4  
672 inhibitors.

673

674 **Carcinogenesis, Mutagenesis, Impairment of**  
675 **Fertility**

676 Long-term studies were conducted in rats and mice  
677 using oral administration to evaluate the carcinogenic  
678 potential of budesonide.

679

680 In a 104-week oral study in Sprague-Dawley rats, a  
681 statistically significant increase in the incidence of  
682 gliomas was observed in male rats receiving an oral dose  
683 of 50 mcg/kg/day (less than the maximum recommended  
684 daily inhalation dose in adults and children on a mcg/m<sup>2</sup>  
685 basis). No tumorigenicity was seen in male and female  
686 rats at respective oral doses up to 25 and 50 mcg/kg (less  
687 than the maximum recommended daily inhalation dose  
688 in adults and children on a mcg/m<sup>2</sup> basis). In two  
689 additional two-year studies in male Fischer and Sprague-  
690 Dawley rats, budesonide caused no gliomas at an oral  
691 dose of 50 mcg/kg (less than the maximum  
692 recommended daily inhalation dose in adults and  
693 children on a mcg/m<sup>2</sup> basis). However, in the male  
694 Sprague-Dawley rats, budesonide caused a statistically  
695 significant increase in the incidence of hepatocellular  
696 tumors at an oral dose of 50 mcg/kg (less than the  
697 maximum recommended daily inhalation dose in adults  
698 and children on a mcg/m<sup>2</sup> basis). The concurrent  
699 reference corticosteroids (prednisone and triamcinolone  
700 acetate) in these two studies showed similar findings.

701

702 There was no evidence of a carcinogenic effect when  
703 budesonide was administered orally for 91 weeks to  
704 mice at doses up to 200 mcg/kg/day (less than the  
705 maximum recommended daily inhalation dose in adults  
706 and children on a mcg/m<sup>2</sup> basis).

707

708 Budesonide was not mutagenic or clastogenic in six  
709 different test systems: Ames *Salmonella*/microsome  
710 plate test, mouse micronucleus test, mouse lymphoma  
711 test, chromosome aberration test in human lymphocytes,  
712 sex-linked recessive lethal test in *Drosophila*  
713 *melanogaster*, and DNA repair analysis in rat hepatocyte  
714 culture.

715

716 In rats, budesonide had no effect on fertility at  
717 subcutaneous doses up to 80 mcg/kg (less than the  
718 maximum recommended human daily inhalation dose on  
719 a mcg/m<sup>2</sup> basis).

720

721 At 20 mcg/kg/day (less than the maximum  
722 recommended human daily inhalation dose on a mcg/m<sup>2</sup>  
723 basis), decreases in maternal body weight gain, prenatal  
724 viability, and viability of the young at birth and during  
725 lactation were observed. No such effects were noted at 5  
726 mcg/kg (less than the maximum recommended human  
727 daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

728

### 729 **Pregnancy**

#### 730 **Teratogenic Effects: Pregnancy Category B**

731 As with other glucocorticoids, budesonide produced  
732 fetal loss, decreased pup weight, and skeletal  
733 abnormalities at subcutaneous doses of 25 mcg/kg/day  
734 in rabbits (less than the maximum recommended human  
735 daily inhalation dose on a mcg/m<sup>2</sup> basis) and 500  
736 mcg/kg/day in rats (approximately 3 times the maximum  
737 recommended human daily inhalation dose on a mcg/m<sup>2</sup>  
738 basis). No teratogenic or embryocidal effects were  
739 observed in rats when budesonide was administered by  
740 inhalation at doses up to 250 mcg/kg/day (equivalent to  
741 the maximum recommended human daily inhalation  
742 dose on a mcg/m<sup>2</sup> basis).

743

744 Experience with oral corticosteroids since their  
745 introduction in pharmacologic as opposed to physiologic  
746 doses suggests that rodents are more prone to  
747 teratogenic effects from corticosteroids than humans.

748

749 Studies of pregnant women, however, have not shown  
750 that inhaled budesonide increases the risk of  
751 abnormalities when administered during pregnancy. The  
752 results from a large population-based prospective cohort  
753 epidemiological study reviewing data from three  
754 Swedish registries covering approximately 99% of the  
755 pregnancies from 1995-1997 (i.e., Swedish Medical  
756 Birth Registry; Registry of Congenital Malformations;  
757 Child Cardiology Registry) indicate no increased risk for  
758 congenital malformations from the use of inhaled  
759 budesonide during early pregnancy. Congenital  
760 malformations were studied in 2,014 infants born to  
761 mothers reporting the use of inhaled budesonide for  
762 asthma in early pregnancy (usually 10-12 weeks after  
763 the last menstrual period), the period when most major  
764 organ malformations occur. The rate of recorded  
765 congenital malformations was similar compared with the  
766 general population rate (3.8 % vs. 3.5%, respectively).  
767 In addition, after exposure to inhaled budesonide, the  
768 number of infants born with orofacial clefts was similar  
769 to the expected number in the normal population (4  
770 children vs. 3.3, respectively).

771

772 These same data were utilized in a second study  
773 bringing the total to 2,534 infants whose mothers were  
774 exposed to inhaled budesonide. In this study, the rate of  
775 congenital malformations among infants whose mothers  
776 were exposed to inhaled budesonide during early  
777 pregnancy was not different from the rate for all  
778 newborn babies during the same period (3.6%).

779

780 Despite the animal findings, it would appear that the  
781 possibility of fetal harm is remote if the drug is used  
782 during pregnancy. Nevertheless, because the studies in  
783 humans cannot rule out the possibility of harm,  
784 TRADENAME should be used during pregnancy only if  
785 clearly needed.

786

#### 787 **Nonteratogenic Effects**

788 Hypoadrenalism may occur in infants born of mothers  
789 receiving corticosteroids during pregnancy. Such infants  
790 should be carefully observed.

791

792 **Nursing Mothers**

793 Corticosteroids are secreted in human milk. Because of  
794 the potential for adverse reactions in nursing infants  
795 from any corticosteroid, a decision should be made  
796 whether to discontinue nursing or discontinue the drug,  
797 taking into account the importance of the drug to the  
798 mother. Actual data for budesonide are lacking.

799

800 **Pediatric Use**

801 Safety and effectiveness of TRADENAME in pediatric  
802 patients below 6 years of age have not been established.

803

804 Clinical studies with inhaled budesonide included 704  
805 patients 6 to 17 years of age (n=204 treated with  
806 TRADENAME). The frequency of adverse events  
807 observed with TRADENAME in pediatric patients 6 to  
808 17 years of age was similar to that of patients 18 to 80  
809 years of age.

810

811 Controlled clinical studies have shown that orally  
812 inhaled corticosteroids may cause a reduction in growth  
813 velocity in pediatric patients. This effect has been  
814 observed in the absence of laboratory evidence of  
815 hypothalamic-pituitary-adrenal (HPA) axis suppression,  
816 suggesting that growth velocity is a more sensitive  
817 indicator of systemic corticosteroid exposure in pediatric  
818 patients than some commonly used tests of HPA-axis  
819 function. The long-term effects of this reduction in  
820 growth velocity associated with orally inhaled  
821 corticosteroids including the impact on final adult height  
822 are unknown. The potential for “catch up” growth  
823 following discontinuation of treatment with orally  
824 inhaled corticosteroids has not been adequately studied.

825

826 In a study of asthmatic children 5-12 years of age, those  
827 treated with PULMICORT TURBUHALER 200 mcg  
828 twice daily (n=311) had a 1.1-centimeter reduction in  
829 growth compared with those receiving placebo (n=418)  
830 at the end of one year; the difference between these two  
831 treatment groups did not increase further over three  
832 years of additional treatment. By the end of four years,  
833 children treated with PULMICORT TURBUHALER  
834 and children treated with placebo had similar growth  
835 velocities. Conclusions drawn from this study may be  
836 confounded by the unequal use of corticosteroids in the  
837 treatment groups and inclusion of data from patients  
838 attaining puberty during the course of the study.

839

840 The growth of pediatric patients receiving orally inhaled  
841 corticosteroids, including TRADENAME, should be  
842 monitored routinely (eg, via stadiometry). The potential  
843 growth effects of prolonged treatment should be  
844 weighed against clinical benefits obtained and the risks  
845 and benefits associated with alternative therapies. To  
846 minimize the systemic effects of inhaled corticosteroids,  
847 including TRADENAME, each patient should be titrated  
848 to his/her lowest effective dose.

849

### 850 **Geriatric Use**

851 Of the total number of patients in controlled clinical  
852 studies receiving inhaled budesonide, 153 (n=11 treated  
853 with TRADENAME ) were 65 years of age or older and  
854 one was age 75 years or older. No overall differences in  
855 safety were observed between these patients and  
856 younger patients. Clinical studies did not include  
857 sufficient numbers of patients aged 65 years and over to  
858 determine differences in efficacy between elderly and  
859 younger patients. Other reported clinical or medical  
860 surveillance experience has not identified differences in  
861 responses between the elderly and younger patients. In  
862 general, dose selection for an elderly patient should be  
863 cautious, usually starting at the low end of the dosing  
864 range, reflecting the greater frequency of decreased  
865 hepatic, renal, or cardiac function, and of concomitant  
866 disease or other drug therapy.

867

868

869 **ADVERSE REACTIONS**

870 The following adverse reactions were reported in  
 871 patients treated with TRADENAME 180 or 90 mcg in  
 872 two double-blind, placebo-controlled clinical trials in  
 873 which 226 patients age 6-80 years, previously receiving  
 874 bronchodilators, inhaled corticosteroids, or both, were  
 875 treated with TRADENAME, administered as 360 mcg  
 876 twice daily for 12 weeks.

877

878 The following table shows the incidence of adverse  
 879 events (whether considered drug-related or non-drug-  
 880 related by the investigators) that occurred at a rate of  
 881  $\geq 1\%$  in the TRADENAME group and were more  
 882 common than in the placebo group.

883

884 **Adverse Events with a  $\geq 1\%$  Incidence and with**  
 885 **incidence greater than placebo, reported by patients**  
 886 **on TRADENAME 180 or 90 mcg**

<b>Adverse Event</b>	<b>TRADENAME 360 mcg twice daily N=226 %</b>	<b>Placebo N=230 %</b>
Nasopharyngitis	9.3	8.3
Nasal congestion	2.7	0.4
Pharyngitis	2.7	1.7
Rhinitis allergic	2.2	1.3
Viral upper respiratory tract infection	2.2	1.3
Nausea	1.8	0.9
Viral gastroenteritis	1.8	0.4
Otitis media	1.3	0.9
Oral candidiasis	1.3	0.4
Average exposure duration (days)	76.2	68.2

887

888 **Long-Term Safety**

889 Non-placebo controlled long-term studies in children (at  
890 doses up to 360 mcg daily), and adolescent and adult  
891 subjects (at doses up to 720 mcg daily), treated for up to  
892 one year with TRADENAME, revealed a similar pattern  
893 and incidence of adverse events.

894

895 **Adverse Event Reports from Other Sources**

896 The following other adverse events occurred in placebo-  
897 controlled clinical trials with similar or lower  
898 budesonide doses with PULMICORT TURBUHALER  
899 with an incidence of  $\geq 1\%$  in the budesonide group and  
900 were more common than in the placebo group:

901  $\geq 3\%$ : respiratory infection, sinusitis, headache, pain,  
902 back pain, fever.

903  $\geq 1-3\%$ : neck pain, syncope, abdominal pain, dry mouth,  
904 vomiting, weight gain, fracture, myalgia, hypertonia,  
905 migraine, ecchymosis, insomnia, infection, taste  
906 perversion, voice alteration.

907

908 Higher doses of PULMICORT TURBUHALER 800  
909 mcg twice daily resulted in an increased incidence of  
910 voice alteration, flu syndrome, dyspepsia,  
911 gastroenteritis, nausea, and back pain, compared with  
912 doses of 400 mcg twice daily.

913

914 In a 20-week trial in adult asthmatics who previously  
915 required oral corticosteroids, the effects of inhaled  
916 budesonide with PULMICORT TURBUHALER 400  
917 mcg twice daily (N=53) and 800 mcg twice daily  
918 (N=53) were compared with placebo (N=53) on the  
919 frequency of reported adverse events. In considering  
920 these data, the increased average duration of exposure  
921 for inhaled budesonide patients (78 days for inhaled  
922 budesonide vs. 41 days for placebo) should be taken into  
923 account. Adverse events, whether considered drug-  
924 related or non-drug-related by the investigators, reported  
925 in more than five patients in the budesonide group and  
926 which occurred more frequently with budesonide than  
927 placebo are given (% inhaled budesonide and %  
928 placebo): asthenia (9% and 2%), headache (12% and  
929 2%), pain (10% and 2%), dyspepsia (8% and 0%),  
930 nausea (6% and 0%), oral candidiasis (10% and 0%),  
931 arthralgia (6% and 0%), cough increased (6% and 2%),  
932 respiratory infection (32% and 13%), rhinitis (6% and  
933 2%), sinusitis (16% and 11%).

934

935 Rare adverse events reported in the published literature  
936 or from worldwide marketing experience with any  
937 formulation of inhaled budesonide include: immediate  
938 and delayed hypersensitivity reactions including rash,  
939 contact dermatitis, urticaria, angioedema and  
940 bronchospasm; symptoms of hypocorticism and  
941 hypercorticism; glaucoma, cataracts; psychiatric  
942 symptoms including depression, aggressive reactions,  
943 irritability, anxiety and psychosis.

944

945

#### 946 **OVERDOSAGE**

947 The potential for acute toxic effects following overdose  
948 of TRADENAME is low. If used at excessive doses for  
949 prolonged periods, systemic corticosteroid effects such  
950 as hypercorticism may occur (see PRECAUTIONS).  
951 Another budesonide-containing dry powder inhaler at  
952 3200 mcg daily administered for 6 weeks caused a  
953 significant reduction (27%) in the plasma cortisol  
954 response to a 6-hour infusion of ACTH compared with  
955 placebo (+1%). The corresponding effect of 10 mg  
956 prednisone daily was a 35% reduction in the plasma  
957 cortisol response to ACTH.

958

959 The minimal inhalation lethal dose in mice was 100  
960 mg/kg (approximately 280 times the maximum  
961 recommended daily inhalation dose in adults and  
962 approximately 330 times the maximum recommended  
963 daily inhalation dose in children on a mcg/m<sup>2</sup> basis).  
964 There were no deaths following the administration of an  
965 inhalation dose of 68 mg/kg in rats (approximately 380  
966 times the maximum recommended daily inhalation dose  
967 in adults and approximately 450 times the maximum  
968 recommended daily inhalation dose in children on a  
969 mcg/m<sup>2</sup> basis). The minimal oral lethal dose was 200  
970 mg/kg in mice (approximately 560 times the maximum  
971 recommended daily inhalation dose in adults and  
972 approximately 670 times the maximum recommended  
973 daily inhalation dose in children on a mcg/m<sup>2</sup> basis) and  
974 less than 100 mg/kg in rats (approximately 560 times the  
975 maximum recommended daily inhalation dose in adults  
976 and approximately 670 times the maximum  
977 recommended daily inhalation dose in children based on  
978 a mcg/m<sup>2</sup> basis).

979

980 Post-marketing experience showed that acute overdose  
981 of inhaled budesonide commonly remained  
982 asymptomatic. The use of excessive doses (up to 6400  
983 mcg daily) for prolonged periods showed systemic  
984 corticosteroid effects such as hypercorticism.

985

986

## 987 **DOSAGE AND ADMINISTRATION**

988 TRADENAME should be administered by the orally  
989 inhaled route in asthmatic patients age 6 years and older.  
990 Individual patients will experience a variable onset and  
991 degree of symptom relief. Generally, budesonide has a  
992 relatively rapid onset of action for an inhaled  
993 corticosteroid. Improvement in asthma control following  
994 inhaled administration of budesonide can occur within  
995 24 hours of initiation of treatment, although maximum  
996 benefit may not be achieved for 1 to 2 weeks, or longer.  
997 The safety and efficacy of TRADENAME when  
998 administered in excess of recommended doses have not  
999 been established.

1000

1001 A definitive comparative therapeutic ratio between  
1002 TRADENAME and PULMICORT TURBUHALER has  
1003 not been established. For patients who have been on  
1004 PULMICORT TURBUHALER the dose of  
1005 TRADENAME may not be predicted by the dose of that  
1006 product. The clinical response of TRADENAME  
1007 compared with PULMICORT TURBUHALER tends to  
1008 be lower (see Clinical Studies). Any patient who is  
1009 switched from PULMICORT TURBUHALER to  
1010 TRADENAME should be dosed appropriately, taking  
1011 into account the dosing recommendations, and titrating  
1012 the dose as dictated by the clinical response.

1013

1014 **Adults (age 18 and older):** The recommended starting  
1015 dosage is 360 mcg twice daily. In some patients, a  
1016 starting dosage of 180 mcg twice daily may be adequate.  
1017 The maximum dosage should not exceed 720 mcg twice  
1018 daily.

1019

1020 **Children (age 6 to 17):** The recommended starting  
1021 dosage is 180 mcg twice daily. In some patients a  
1022 starting dosage of 360 mcg twice daily may be  
1023 appropriate. The maximum dosage should not exceed  
1024 360 mcg twice daily.

1025

#### 1026 **Dose Titration**

1027 As with any inhaled corticosteroid, physicians are  
1028 advised to select the dosage of TRADENAME that  
1029 would be appropriate based upon the patient's disease  
1030 severity and titrate the dosage of TRADENAME  
1031 downward over time to the lowest level that maintains  
1032 proper asthma control. In adult patients who are well  
1033 controlled, a dosage of 180 mcg twice daily may be  
1034 considered. In some adult patients, a starting dosage of  
1035 180 mcg twice daily may be adequate. If the 180 mcg  
1036 twice daily dosage of TRADENAME in adults does not  
1037 provide adequate control, the dosage should be  
1038 increased.

1039

1040 **Patients Maintained on Chronic Oral**  
1041 **Corticosteroids**

1042 Clinical studies with TRADENAME did not evaluate  
1043 patients on oral corticosteroids. However, clinical  
1044 studies with therapeutic doses of PULMICORT  
1045 TURBUHALER did show efficacy in the management  
1046 of asthmatics dependent or maintained on systemic  
1047 corticosteroids. If a patient is already on a systemic  
1048 corticosteroid for asthma control, TRADENAME should  
1049 be used concurrently with the patient's usual  
1050 maintenance dose of systemic corticosteroid. The  
1051 patient's asthma should be reasonably stable before  
1052 withdrawal of oral corticosteroids is initiated. After  
1053 approximately one week, gradual withdrawal of the  
1054 systemic corticosteroid may be started by reducing the  
1055 daily or alternate daily dose. The next reduction is made  
1056 after an interval of one or two weeks, depending on the  
1057 response of the patient. Generally, these decrements  
1058 should not exceed 2.5 mg of prednisone or its  
1059 equivalent. A slow rate of withdrawal is strongly  
1060 recommended. During reduction of oral corticosteroids,  
1061 patients should be carefully monitored for asthma  
1062 instability, including objective measures of airway  
1063 function, and for adrenal insufficiency (see  
1064 WARNINGS). During withdrawal, some patients may  
1065 experience symptoms of systemic corticosteroid  
1066 withdrawal, eg, joint and/or muscular pain, lassitude,  
1067 and depression, despite maintenance or even  
1068 improvement in pulmonary function. Such patients  
1069 should be encouraged to continue with TRADENAME  
1070 but should be monitored for objective signs of adrenal  
1071 insufficiency. If evidence of adrenal insufficiency  
1072 occurs, the systemic corticosteroid doses should be  
1073 increased temporarily and thereafter withdrawal should  
1074 continue more slowly. During periods of stress or a  
1075 severe asthma attack, transfer patients may require  
1076 supplementary treatment with systemic corticosteroids.

1077

1078 **Directions for Use**

1079 Illustrated *Patient's Instructions for Use* accompany  
1080 each package of TRADENAME.

1081

1082 Patients should be instructed to prime TRADENAME  
1083 prior to its initial use, and instructed to inhale deeply and  
1084 forcefully each time the unit is used. Rinsing the mouth

1085 after inhalation is also recommended (see further  
1086 instructions in PRECAUTIONS, Information for  
1087 Patients).

1088

1089

#### 1090 **HOW SUPPLIED**

1091 TRADENAME consists of a number of assembled  
1092 plastic details, the main parts being the dosing  
1093 mechanism, the storage unit for drug substance, and the  
1094 mouthpiece. The inhaler is protected by a white outer  
1095 tubular cover screwed onto the inhaler. The body of the  
1096 inhaler is white and the turning grip is brown. The  
1097 TRADENAME inhaler cannot be refilled and should be  
1098 discarded when empty.

1099

1100 TRADENAME is available in two strengths: 180  
1101 mcg/dose, 120 doses (NDC 0186-0916-12) with a target  
1102 fill weight of 225 mg (range 200-250), and 90 mcg/dose,  
1103 60 doses (NDC 0186-0917-06) with a target fill weight  
1104 of 165 mg (range 140-190).

1105

1106 The dose indicator window shows how many doses are  
1107 left in the inhaler. The inhaler is empty when the number  
1108 zero ("0") on the red background reaches the middle of  
1109 the window. If the unit is used beyond the point at which  
1110 the zero reaches the middle of the window, the correct  
1111 amount of medication may not be obtained and the unit  
1112 should be discarded.

1113

1114 Store in a dry place at controlled room temperature 20-  
1115 25°C (68-77°F) [see USP] with the cover tightly in  
1116 place. Keep out of the reach of children.

1117

1118 All trademarks are the property of the AstraZeneca  
1119 group of companies

1120

1121 © AstraZeneca 200X

1122

1123 Manufactured for: AstraZeneca LP, Wilmington, DE  
1124 19850

1125 By: AstraZeneca AB, Södertälje, Sweden

1126

1127 XXXXXX-XX

1128 Rev 7/11/06

1129

XXXXXX-XX

## Patient's Instructions For Use

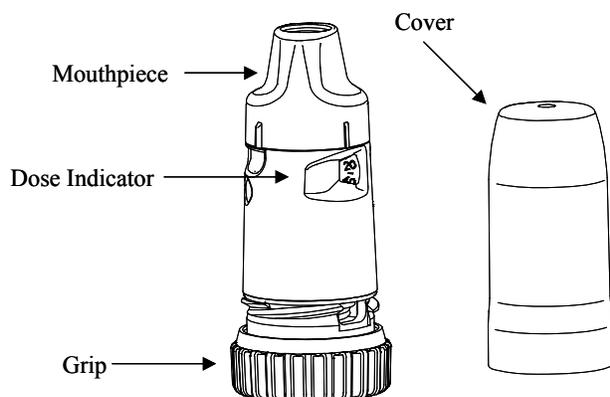
### **TRADENAME 180 mcg**

(budesonide inhalation powder, 180 mcg)

### **TRADENAME 90 mcg**

(budesonide inhalation powder, 90 mcg)

**For Oral Inhalation Only.**



**Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine. Following these instructions helps to ensure that you are inhaling the medication correctly.**

**FOR FURTHER INFORMATION ASK YOUR DOCTOR, HEALTHCARE PROFESSIONAL, OR PHARMACIST.**

## **WHAT YOU SHOULD KNOW ABOUT TRADENAME**

Your doctor or healthcare professional has prescribed TRADENAME 180 mcg or TRADENAME 90 mcg. Both contain a medication called budesonide, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing

problems. When inhaled regularly, corticosteroids also help to prevent attacks of asthma.

TRADENAME treats the inflammation—the “quiet part” of asthma that you cannot hear, see, or feel. When inflammation is left untreated, asthma symptoms and attacks can increase. TRADENAME works to prevent and reduce your asthma symptoms and attacks.

### **IMPORTANT POINTS TO REMEMBER ABOUT TRADENAME**

❶ **MAKE SURE** that this medicine is suitable for you (see “BEFORE USING YOUR TRADENAME”).

❷ It is important that you inhale each dose as your doctor or healthcare professional has advised.

❸ **DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU FEEL BETTER**, unless told to do so by your doctor or healthcare professional. Use TRADENAME as directed by your doctor or healthcare professional.

❹ **DO NOT** inhale more doses or use your TRADENAME more often than instructed by your doctor or healthcare professional.

❺ This medicine is **NOT** intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor or healthcare professional, and not as an emergency measure.

❻ Your doctor or healthcare professional may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor or healthcare professional if:

- an asthma attack does not respond to the additional medication,
- you require more of the additional medication than usual.

❼ If you also use another medicine by inhalation, you should consult your doctor or healthcare professional for instructions on when to use it in relation to using your TRADENAME.

## BEFORE USING YOUR TRADENAME

**AS WITH ALL MEDICATIONS, TELL YOUR DOCTOR OR HEALTHCARE PROFESSIONAL BEFORE STARTING TO TAKE THIS MEDICINE IF YOU:**

- are pregnant (or intending to become pregnant),
- are breast-feeding a baby,
- are allergic to budesonide or any other orally inhaled corticosteroid,
- have any infections,
- have or had tuberculosis,
- have osteoporosis,
- have recently been around anyone with chicken pox or measles,
- are planning to have surgery,
- have been taking an oral corticosteroid medicine like prednisone. You may have to follow specific instructions to avoid health risks associated with stopping the use of these types of medicines.

In some circumstances, this medicine may not be suitable and your doctor or healthcare professional may wish to prescribe a different medicine. Make sure that your doctor or healthcare professional knows what other medicines you are taking including prescription and non-prescription medicines, as well as any vitamins or dietary and herbal supplements.

## WHAT ARE THE POSSIBLE SIDE EFFECTS OF TRADENAME?

As with all inhaled corticosteroids, you should be aware of the following side effects:

- **Increased wheezing right after taking TRADENAME. Always have a short-acting bronchodilator medicine with you to treat sudden wheezing.** Short-acting bronchodilator medicines help to relax the muscles around the airways in your lungs. Wheezing happens when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

- **Immune system effects and a higher chance of infections.**
- **Eye problems including glaucoma and cataracts.** Eye examinations should be considered while using TRADENAME.
- A child's growth should be checked regularly while taking TRADENAME because of the potential for slowed growth.

Based on clinical trials, the most common side effects reported by patients using TRADENAME are:

- Sore nose and throat
- Stuffy nose
- Hay fever
- Viral infections in the upper respiratory tract

These are not all of the possible side effects of TRADENAME. For more information, ask your doctor, healthcare professional, or pharmacist.

## USING YOUR TRADENAME

- Follow the instructions shown in the section "HOW TO USE YOUR TRADENAME". If you have any questions, talk with your doctor, healthcare professional or pharmacist.
- It is important that you inhale each dose as directed by your doctor or healthcare professional. The pharmacy label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor, healthcare professional, or pharmacist.

## DOSAGE

- You can determine which strength of TRADENAME you have (either 180 mcg or 90 mcg) by looking at the label on the cover or by what is printed on the inhaler itself.
- Use as directed by your doctor or healthcare professional.
- It is **VERY IMPORTANT** that you follow your doctor or healthcare professional's instructions as to

how many inhalations to take and how often to use your TRADENAME.

- **DO NOT** inhale more doses or use your TRADENAME more often than your doctor or healthcare professional advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement, so **IT IS VERY IMPORTANT THAT YOU USE TRADENAME REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER**, unless told to do so by your doctor or healthcare professional.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

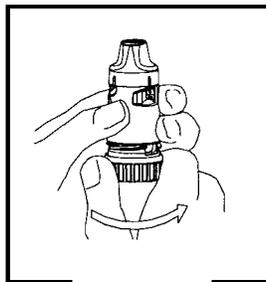
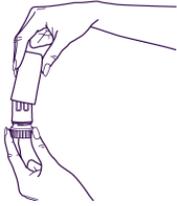
## **HOW TO USE YOUR TRADENAME**

Read the complete instructions carefully and use only as directed.

### **PRIMING INSTRUCTIONS:**

**Before you use a new TRADENAME for the first time, you should prime it.** To do this, turn the cover and lift it off. Hold TRADENAME upright (with mouthpiece up), then twist the brown grip as far as it will go in one direction and then fully back again in the other direction. Repeat. Now you are ready to take your first dose (see instructions for “TAKING A DOSE”). **You do not have to prime it any other time after this, even if you put it aside for a prolonged period of time.**

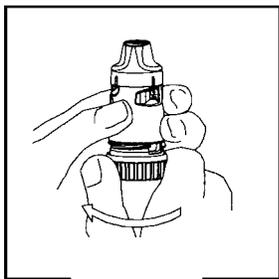
## **TAKING A DOSE:**



**Twist**

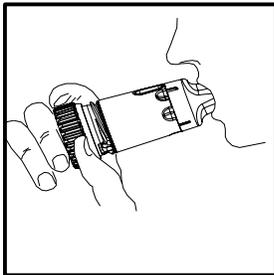
## **①LOADING A DOSE**

- Twist the cover and lift it off.
- In order to provide the correct dose, **TRADENAME must be held in the upright position (mouthpiece up) whenever a dose of medication is being loaded.**
- Twist the brown grip fully in one direction as far as it will go. Twist it fully back again in the other direction as far as it will go.
- You will hear a click during one of the twisting movements.
- Do not hold the mouthpiece when you load the inhaler.



**Click**

## ② INHALING THE DOSE



### Inhale

- Turn your head away from the inhaler and breathe out. **Do not shake the inhaler after loading it.**
- Place the mouthpiece in your mouth, close your lips around the mouthpiece, and inhale deeply and forcefully through the inhaler. You may not feel the medication.
- Do not chew or bite on the mouthpiece.
- Remove the inhaler from your mouth and exhale. **Do not blow or exhale into the mouthpiece.**
- If more than one dose is required, just repeat the steps above.
- **When you are finished, place the cover back on the inhaler and twist shut. Rinse your mouth with water. Do not swallow.**
- Do not use TRADENAME if it has been damaged or if the mouthpiece has become detached.

## CLEANING YOUR TRADENAME

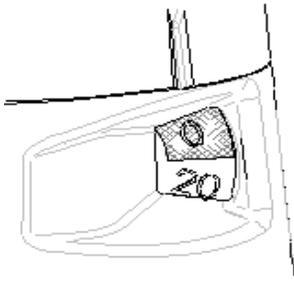
- **Keep your TRADENAME clean and dry at all times. Do not immerse it in water.**
- Wipe the outside of the mouthpiece regularly (once a week) with a dry tissue.
- **Do not use water or liquids when cleaning the mouthpiece.**
- Do not try to remove the mouthpiece or twist it unnecessarily.

## STORING YOUR TRADENAME

- After each use, place the white cover back on and twist it tightly into place.
- Store TRADENAME in a dry place at controlled room temperature, 68-77°F (20-25°C) with the cover tightly in place.
- Keep your TRADENAME in a secure place out of the **reach of young children.**
- **DO NOT** use after the date shown on the body of your inhaler.

## HOW TO KNOW WHEN YOUR TRADENAME IS EMPTY

- The label on the box or cover will tell you how many doses are in your TRADENAME.
- Your TRADENAME has a convenient dose indicator window just below the mouthpiece that shows you how many doses are left in the inhaler.



- **Your inhaler is empty when the number 0 on the red background has reached the middle of the window. At this time, your inhaler should be discarded, as it may no longer deliver the correct amount of medication.** (You may still hear a sound if you shake it—this sound is not the medicine. This sound is produced by the drying agent inside.)
- Remember, you will get a new inhaler each time you refill your prescription.
- **Do not immerse it in water to find out if it is empty. Simply check your dose indicator window.**

## **FURTHER INFORMATION ABOUT TRADENAME**

- TRADENAME delivers your medicine as a very fine powder. Because of this, you may not sense the presence of any medication entering your lungs when inhaling from TRADENAME. This lack of sensation does not mean that you are not getting your medication.
- TRADENAME should not be used with a spacer.
- TRADENAME contains only budesonide and lactose, an inactive ingredient.
- TRADENAME is specially designed to deliver only one dose at a time, no matter how often you click the brown grip, although the dose indicator will continue to advance. If you accidentally blow into your inhaler after loading a dose, simply follow the instructions for loading a new dose.

**This leaflet does not contain the complete information about your medicine. If you have any questions, or are not sure about something, then you should ask your doctor, healthcare professional, or pharmacist.**

**You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.**

**REMEMBER: This medicine has been prescribed for you by your doctor or healthcare professional. DO NOT give this medicine to anyone else.**

**USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR OR HEALTHCARE PROFESSIONAL.**

**If you have further questions about the use of TRADENAME, call: 1-800-236-9933.**

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