

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-929

LABELING

1 XXXXXX-XX

2

3 **SYMBICORT 80/4.5**

4 *(budesonide 80 mcg and formoterol fumarate*

5 *dihydrate* 4.5 mcg) Inhalation Aerosol*

6 **SYMBICORT 160/4.5**

7 *(budesonide 160 mcg and formoterol fumarate*

8 *dihydrate* 4.5 mcg) Inhalation Aerosol*

9

10 *3.7 mcg formoterol as the free base, equivalent to 4.5

11 mcg formoterol fumarate dihydrate

12

13 **For Oral Inhalation Only**

14

15 **Rx only**

16

17 **WARNING**

18 Long-acting beta₂-adrenergic agonists may increase the
19 risk of asthma-related death. Therefore, when treating
20 patients with asthma, SYMBICORT should only be used
21 for patients not adequately controlled on other asthma-
22 controller medications (e.g., low-to-medium dose
23 inhaled corticosteroids) or whose disease severity
24 clearly warrants initiation of treatment with two
25 maintenance therapies. Data from a large placebo-
26 controlled US study that compared the safety of another
27 long-acting beta₂-adrenergic agonist (salmeterol) or
28 placebo added to usual asthma therapy showed an
29 increase in asthma-related deaths in patients receiving
30 salmeterol. This finding with salmeterol may apply to
31 formoterol (a long-acting beta₂-adrenergic agonist), one
32 of the active ingredients in SYMBICORT (see
33 WARNINGS).

34

35 **DESCRIPTION**

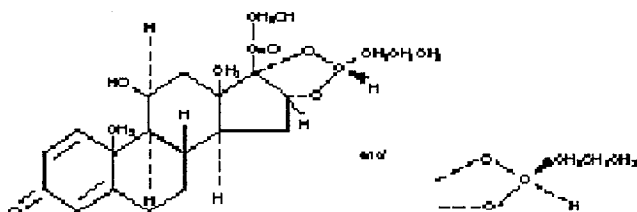
36 SYMBICORT 80/4.5 and SYMBICORT 160/4.5 each

37 contain micronized budesonide and micronized

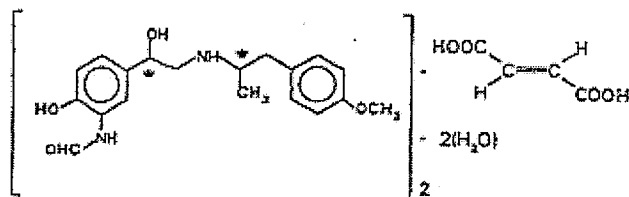
38 formoterol fumarate dihydrate for oral inhalation only.

39

40 One active component of SYMBICORT is budesonide,
 41 a corticosteroid designated chemically as (RS)-11 β ,
 42 16 α , 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione
 43 cyclic 16,17-acetal with butyraldehyde. Budesonide is
 44 provided as a mixture of two epimers (22R and 22S).
 45 The empirical formula of budesonide is C₂₅H₃₄O₆ and its
 46 molecular weight is 430.5. Its structural formula is:



49
 50
 51 Budesonide is a white to off-white, tasteless, odorless
 52 powder that is practically insoluble in water and in
 53 heptane, sparingly soluble in ethanol, and freely soluble
 54 in chloroform. Its partition coefficient between octanol
 55 and water at pH 7.4 is 1.6×10^3 .
 56
 57 The other active component of SYMBICORT is
 58 formoterol fumarate dihydrate, a selective β_2 -agonist
 59 designated chemically as (R*,R*)-($\pm$)-N-[2-hydroxy-5-
 60 [1-hydroxy-2-[[2-(4-methoxyphenyl)-1-
 61 methylethyl]amino]ethyl]phenyl]formamide, (E)-2-
 62 butendioate(2:1), dihydrate. The empirical formula of
 63 formoterol is C₄₂H₅₆N₄O₁₄ and its molecular weight is
 64 840.9. Its structural formula is:



67 Formoterol fumarate dihydrate is a powder which is
68 slightly soluble in water. Its octanol-water partition
69 coefficient at pH 7.4 is 2.6. The pKa of formoterol
70 fumarate dihydrate at 25°C is 7.9 for the phenolic group
71 and 9.2 for the amino group.

72
73 Each 10.2 g SYMBICORT 80/4.5 and SYMBICORT
74 160/4.5 canister is formulated as a hydrofluoroalkane
75 (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled
76 pressurized metered dose inhaler containing 120
77 actuations. After priming, each actuation meters either
78 91/5.1 mcg or 181/5.1 mcg from the valve and delivers
79 either 80/4.5 mcg or 160/4.5 mcg (budesonide
80 micronized/formoterol fumarate dihydrate micronized)
81 from the actuator. The actual amount of drug delivered
82 to the lung may depend on patient factors, such as the
83 coordination between actuation of the device and
84 inspiration through the delivery system. SYMBICORT
85 also contains povidone K25 USP as a suspending agent
86 and polyethylene glycol 1000 NF as a lubricant.

87
88 SYMBICORT should be primed before using for the
89 first time by releasing 2 test sprays into the air away
90 from the face, shaking well for 5 seconds before each
91 spray. In cases where the inhaler has not been used for
92 more than 7 days or when it has been dropped, prime the
93 inhaler again by shaking well for 5 seconds before each
94 spray and releasing 2 test sprays into the air away from
95 the face.

96
97

98 **CLINICAL PHARMACOLOGY**

99 **Mechanism of Action**

100 **SYMBICORT**

101 SYMBICORT contains both budesonide and formoterol;
102 therefore, the mechanisms of action described below for
103 the individual components apply to SYMBICORT.
104 These drugs represent two classes of medications (a
105 synthetic corticosteroid and a long-acting selective
106 beta₂-adrenoceptor agonist) that have different effects on
107 clinical, physiological, and inflammatory indices of
108 asthma.

109

110 **Budesonide**

111 Budesonide is an anti-inflammatory corticosteroid that
112 exhibits potent glucocorticoid activity and weak
113 mineralocorticoid activity. In standard *in vitro* and
114 animal models, budesonide has approximately a 200-
115 fold higher affinity for the glucocorticoid receptor and a
116 1000-fold higher topical anti-inflammatory potency than
117 cortisol (rat croton oil ear edema assay). As a measure of
118 systemic activity, budesonide is 40 times more potent
119 than cortisol when administered subcutaneously and 25
120 times more potent when administered orally in the rat
121 thymus involution assay.

122

123 In glucocorticoid receptor affinity studies, the 22R form
124 of budesonide was two times as active as the 22S
125 epimer. *In vitro* studies indicated that the two forms of
126 budesonide do not interconvert.

127

128 Inflammation is an important component in the
129 pathogenesis of asthma. Corticosteroids have a wide
130 range of inhibitory activities against multiple cell types
131 (e.g., mast cells, eosinophils, neutrophils, macrophages,
132 and lymphocytes) and mediators (e.g., histamine,
133 eicosanoids, leukotrienes, and cytokines) involved in
134 allergic and non-allergic-mediated inflammation. These
135 anti-inflammatory actions of corticosteroids may
136 contribute to their efficacy in asthma.

137

138 Studies in asthmatic patients have shown a favorable
139 ratio between topical anti-inflammatory activity and
140 systemic corticosteroid effects over a wide range of
141 doses of budesonide. This is explained by a combination
142 of a relatively high local anti-inflammatory effect,
143 extensive first pass hepatic degradation of orally
144 absorbed drug (85-95%), and the low potency of formed
145 metabolites.

146

146

147 **Formoterol:**

148 Formoterol fumarate is a long-acting selective beta₂-
149 adrenergic agonist (beta₂-agonist) with a rapid onset of
150 action. Inhaled formoterol fumarate acts locally in the
151 lung as a bronchodilator. *In vitro* studies have shown
152 that formoterol has more than 200-fold greater agonist
153 activity at beta₂-receptors than at beta₁-receptors. The *in*
154 *vitro* binding selectivity to beta₂- over beta₁-
155 adrenoceptors is higher for formoterol than for albuterol
156 (5 times), whereas salmeterol has a higher (3 times) beta
157 ₂-selectivity ratio than formoterol.

158

159 Although beta₂-receptors are the predominant adrenergic
160 receptors in bronchial smooth muscle and beta₁-
161 receptors are the predominant receptors in the heart,
162 there are also beta₂-receptors in the human heart
163 comprising 10%-50% of the total beta-adrenergic
164 receptors. The precise function of these receptors has not
165 been established, but they raise the possibility that even
166 highly selective beta₂-agonists may have cardiac effects.

167

168 The pharmacologic effects of beta₂-adrenoceptor agonist
169 drugs, including formoterol, are at least in part
170 attributable to stimulation of intracellular adenyl
171 cyclase, the enzyme that catalyzes the conversion of
172 adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine
173 monophosphate (cyclic AMP). Increased cyclic AMP
174 levels cause relaxation of bronchial smooth muscle and
175 inhibition of release of mediators of immediate
176 hypersensitivity from cells, especially from mast cells.

177

178 *In vitro* tests show that formoterol is an inhibitor of the
179 release of mast cell mediators, such as histamine and
180 leukotrienes, from the human lung. Formoterol also
181 inhibits histamine-induced plasma albumin
182 extravasation in anesthetized guinea pigs and inhibits
183 allergen-induced eosinophil influx in dogs with airway
184 hyper-responsiveness. The relevance of these *in vitro*
185 and animal findings to humans is unknown.

186

187 **Animal Pharmacology**

188 Studies in laboratory animals (minipigs, rodents, and
189 dogs) have demonstrated the occurrence of cardiac
190 arrhythmias and sudden death (with histologic evidence
191 of myocardial necrosis) when beta-agonists and
192 methylxanthines are administered concurrently. The
193 clinical significance of these findings is unknown.

194
195 **Pharmacokinetics**

196 **Symbicort**

197 In a single-dose study, higher than recommended doses
198 of SYMBICORT (12 inhalations of SYMBICORT
199 160/4.5 mcg) were administered to patients with
200 moderate asthma. Peak plasma concentrations for
201 budesonide of 4.5 nmol/L occurred at 20 minutes
202 following dosing and peak concentrations for formoterol
203 of 136 pmol occurred at 10 minutes following dosing.
204 Approximately 8% of the delivered dose of formoterol
205 was recovered in the urine as unchanged drug. This
206 study also demonstrated that the total systemic exposure
207 to budesonide from SYMBICORT was approximately
208 30% lower than from inhaled budesonide via a dry
209 powder inhaler (DPI) at the same delivered dose.
210 Following administration of SYMBICORT, the half-life
211 of the budesonide component was 4.7 hours and for the
212 formoterol component was 7.9 hours.

213
214 In a repeat dose study, the highest recommended dose of
215 SYMBICORT (160/4.5 mcg, 2 inhalations twice daily)
216 was administered to patients with moderate asthma and
217 healthy subjects for one week. Peak plasma
218 concentrations of budesonide (1.2 nmol/L) and
219 formoterol (28 pmol/L) occurred at 21 and 10 minutes,
220 respectively, in asthma patients. Peak plasma
221 concentrations for budesonide and formoterol were
222 about 30 to 40% higher in healthy subjects to that in
223 asthma patients. However, the total systemic exposure
224 was comparable to that in asthma patients.

225
226 Following administration of SYMBICORT (160/4.5
227 mcg, two or four inhalations twice daily) for five days in
228 healthy subjects, plasma concentrations of budesonide
229 and formoterol generally increased in proportion to
230 dose. Additionally in this study, the accumulation index

231 for the two inhalation groups was 1.32 for budesonide
232 and 1.77 for formoterol.

233

234 Special Populations

235 *Geriatric*

236 The pharmacokinetics of SYMBICORT in geriatric
237 patients have not been specifically studied.

238

239 *Pediatric*

240 Plasma concentrations of budesonide were measured
241 following administration of 4 inhalations of
242 SYMBICORT 160/4.5 mcg in a single dose study in
243 pediatric patients with asthma, 6-11 years of age. Urine
244 was collected for determination of formoterol excretion.
245 Peak budesonide concentrations of 1.4 nmol/L occurred
246 at 20 minutes post-dose. Approximately 3.5% of the
247 delivered formoterol dose was recovered in the urine as
248 unchanged formoterol. This study also demonstrated
249 that the total systemic exposure to budesonide from
250 SYMBICORT was approximately 30% lower than from
251 inhaled budesonide via a dry powder inhaler which was
252 also evaluated at the same delivered dose.

253

254 *Gender/Race*

255 Specific studies to examine the effects of gender and
256 race on the pharmacokinetics of SYMBICORT have not
257 been conducted. Population PK analysis of the
258 SYMBICORT data indicates that gender does not affect
259 the pharmacokinetics of budesonide and formoterol. No
260 conclusions can be drawn on the effect of race due to the
261 low number of non-Caucasians evaluated for PK.

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263 *Renal or Hepatic Insufficiency*

264 There are no data regarding the specific use of
265 SYMBICORT in patients with hepatic or renal
266 impairment. Reduced liver function may affect the
267 elimination of corticosteroids. Budesonide
268 pharmacokinetics was affected by compromised liver
269 function as evidenced by a doubled systemic availability
270 after oral ingestion. The intravenous budesonide
271 pharmacokinetics was, however, similar in cirrhotic
272 patients and in healthy subjects. Specific data with
273 formoterol is not available, but since formoterol is
274 primarily eliminated via hepatic metabolism, an
275 increased exposure can be expected in patients with
276 severe liver impairment.

277

278 *Drug-Drug Interactions*

279 A single dose crossover study was conducted to
280 compare the pharmacokinetics of eight inhalations of the
281 following: budesonide, formoterol, and budesonide plus
282 formoterol administered concurrently. The results of the
283 study indicated that there was no evidence of a
284 pharmacokinetic interaction between the two
285 components of SYMBICORT.

286

287 Ketoconazole, a potent inhibitor of cytochrome P450
288 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic
289 enzyme for corticosteroids, increased plasma levels of
290 orally ingested budesonide. At recommended doses,
291 cimetidine had a slight but clinically insignificant effect
292 on the pharmacokinetics of oral budesonide. Specific
293 drug-drug interaction studies with formoterol have not
294 been performed.

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296 **Budesonide**

297 **Absorption**

298 Orally inhaled budesonide is rapidly absorbed in the
299 lungs and peak concentration is typically reached within
300 20 minutes. After oral administration of budesonide,
301 peak plasma concentration was achieved in about 1 to 2
302 hours and the absolute systemic availability was 6-13%,
303 due to extensive first pass metabolism. In contrast, most
304 of the budesonide delivered to the lungs was
305 systemically absorbed. In healthy subjects, 34% of the
306 metered dose was deposited in the lung (as assessed by
307 plasma concentration method and using a budesonide
308 containing dry-powder inhaler) with an absolute
309 systemic availability of 39% of the metered dose. Peak
310 steady-state plasma concentrations of budesonide
311 administered by DPI in adults with asthma averaged 0.6
312 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice
313 daily, respectively.

314

315 In asthmatic patients, budesonide showed a linear
316 increase in AUC and C_{max} with increasing dose after
317 both a single dose and repeated dosing of inhaled
318 budesonide.

319

320 **Distribution**

321 The volume of distribution of budesonide was
322 approximately 3 L/kg. It was 85-90% bound to plasma
323 proteins. Protein binding was constant over the
324 concentration range (1-100 nmol/L) achieved with, and
325 exceeding, recommended inhaled doses. Budesonide
326 showed little or no binding to corticosteroid binding
327 globulin. Budesonide rapidly equilibrated with red blood
328 cells in a concentration independent manner with a
329 blood/plasma ratio of about 0.8.

330

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331 **Metabolism**

332 *In vitro* studies with human liver homogenates have
333 shown that budesonide was rapidly and extensively
334 metabolized. Two major metabolites formed via
335 cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)
336 catalyzed biotransformation have been isolated and
337 identified as 16 α -hydroxyprednisolone and 6 β -
338 hydroxybudesonide. The corticosteroid activity of each
339 of these two metabolites was less than 1% of that of the
340 parent compound. No qualitative differences between
341 the *in vitro* and *in vivo* metabolic patterns were detected.
342 Negligible metabolic inactivation was observed in
343 human lung and serum preparations.

344

345 **Excretion/Elimination**

346 Budesonide was excreted in urine and feces in the form
347 of metabolites. Approximately 60% of an intravenous
348 radiolabeled dose was recovered in the urine. No
349 unchanged budesonide was detected in the urine. The
350 22R form of budesonide was preferentially cleared by
351 the liver with systemic clearance of 1.4 L/min vs. 1.0
352 L/min for the 22S form. The terminal half-life, 2 to 3
353 hours, was the same for both epimers and was
354 independent of dose.

355

356 **Formoterol**

357 **Absorption**

358 Inhaled formoterol is rapidly absorbed; peak plasma
359 concentrations are typically reached at the first plasma
360 sampling time, within 5-10 minutes after dosing. As
361 with many drug products for oral inhalation, it is likely
362 that the majority of the inhaled formoterol delivered is
363 swallowed and then absorbed from the gastrointestinal
364 tract.

365

366 **Distribution**

367 Over the concentration range of 10-500 nmol/L, plasma
368 protein binding for the RR and SS enantiomers of
369 formoterol was 46 and 58%, respectively. The
370 concentrations of formoterol used to assess the plasma
371 protein binding were higher than those achieved in
372 plasma following inhalation of a single 54 mcg dose.

373

374 Metabolism and Excretion

375 The metabolism and excretion of formoterol were
376 studied in 4 healthy subjects following simultaneous
377 administration of radiolabeled formoterol via the oral
378 and IV routes. In that study, 62% of the radiolabeled
379 formoterol was excreted in the urine while 24% was
380 eliminated in the feces. The primary metabolism of
381 formoterol is by direct glucuronidation and by O-
382 demethylation followed by conjugation to inactive
383 metabolites. Secondary metabolic pathways include
384 deformylation and sulfate conjugation. CYP2D6 and
385 CYP2C have been identified as being primarily
386 responsible for O-demethylation.

387

388 Pharmacodynamics

389 Symbicort

390 In a single-dose cross-over study involving 201 patients
391 with persistent asthma, single-dose treatments of 4.5, 9,
392 and 18 mcg of formoterol in combination with 320 mcg
393 of budesonide delivered via SYMBICORT were
394 compared to budesonide 320 mcg alone. Dose-ordered
395 improvements in FEV₁ were demonstrated when
396 compared with budesonide. ECGs and blood samples
397 for glucose and potassium were obtained post dose. For
398 SYMBICORT, small mean increases in serum glucose
399 and decreases in serum potassium (+0.44 mmol/L and -
400 0.18 mmol/L at the highest dose, respectively) were
401 observed with increasing doses of formoterol, compared
402 to budesonide. In ECGs, SYMBICORT produced small
403 dose-related mean increases in heart rate (approximately
404 3 bpm at the highest dose), and QTc intervals (3-6 msec)
405 compared to budesonide alone. No subject had a QT or
406 QTc value $\geq$ 500 msec.

407

408 In the United States, five 12-week, active- and placebo-
409 controlled studies evaluated 2152 patients aged 12 and
410 older with asthma. Systemic pharmacodynamic effects
411 of formoterol (heart/pulse rate, blood pressure, QTc
412 interval, potassium, and glucose) were similar in patients
413 treated with SYMBICORT compared with patients
414 treated with formoterol dry inhalation powder 4.5 mcg,
415 2 inhalations twice daily. No patient had a QT or QTc
416 value $\geq$ 500 msec during treatment.

417

418 In 3 placebo-controlled studies in adolescents and adults
419 with asthma aged 12 and older, a total of 1232 patients
420 (553 patients in the SYMBICORT group) had evaluable
421 continuous 24-hour electrocardiographic monitoring.
422 Overall, there were no important differences in the
423 occurrence of ventricular or supraventricular ectopy and
424 no evidence of increased risk for clinically significant
425 dysrhythmia in the SYMBICORT group compared to
426 placebo.

427

428 Overall, no clinically important effects on HPA axis, as
429 measured by 24-hour urinary cortisol, were observed for
430 SYMBICORT-treated adult or adolescent patients at
431 doses up to 640/18 mcg/day compared to budesonide.

432

433 **Budesonide**

434 To confirm that systemic absorption is not a significant
435 factor in the clinical efficacy of inhaled budesonide, a
436 clinical study in patients with asthma was performed
437 comparing 400 mcg budesonide administered via a
438 pressurized metered dose inhaler with a tube spacer to
439 1400 mcg of oral budesonide and placebo. The study
440 demonstrated the efficacy of inhaled budesonide but not
441 orally ingested budesonide despite comparable systemic
442 levels. Thus, the therapeutic effect of conventional
443 doses of orally inhaled budesonide are largely explained
444 by its direct action on the respiratory tract.

445

446 Inhaled budesonide has been shown to decrease airway
447 reactivity to various challenge models, including
448 histamine, methacholine, sodium metabisulfite, and
449 adenosine monophosphate in patients with hyperreactive
450 airways. The clinical relevance of these models is not
451 certain.

452

453 Pretreatment with inhaled budesonide, 1600 mcg daily
454 (800 mcg twice daily) for 2 weeks reduced the acute
455 (early-phase reaction) and delayed (late-phase reaction)
456 decrease in FEV₁ following inhaled allergen challenge.

457

458 The systemic effects of inhaled corticosteroids are
459 related to the systemic exposure to such drugs.
460 Pharmacokinetic studies have demonstrated that in both
461 adults and children with asthma the systemic exposure
462 to budesonide is lower with SYMBICORT compared
463 with inhaled budesonide administered at the same
464 delivered dose via a dry powder inhaler (see
465 **CLINICAL PHARMACOLOGY, Pharmacokinetics,**
466 **SYMBICORT**). Therefore, the systemic effects (HPA
467 axis and growth) of budesonide delivered from
468 SYMBICORT would be expected to be no greater than
469 what is reported for inhaled budesonide when
470 administered at comparable doses via the dry powder
471 inhaler (see **PRECAUTIONS, Pediatric Use**).
472

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473 The effects of inhaled budesonide administered via a dry
474 powder inhaler on the hypothalamic-pituitary-adrenal
475 (HPA) axis were studied in 905 adults and 404 pediatric
476 patients with asthma. For most patients, the ability to
477 increase cortisol production in response to stress, as
478 assessed by cosyntropin (ACTH) stimulation test,
479 remained intact with budesonide treatment at
480 recommended doses. For adult patients treated with
481 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%,
482 2%, 6%, and 13% respectively, had an abnormal
483 stimulated cortisol response (peak cortisol <14.5
484 mcg/dL assessed by liquid chromatography following
485 short-cosyntropin test) as compared to 8% of patients
486 treated with placebo. Similar results were obtained in
487 pediatric patients. In another study in adults, doses of
488 400, 800 and 1600 mcg of inhaled budesonide twice
489 daily for 6 weeks were examined; 1600 mcg twice daily
490 (twice the maximum recommended dose) resulted in a
491 27% reduction in stimulated cortisol (6-hour ACTH
492 infusion) while 10 mg prednisone resulted in a 35%
493 reduction. In this study, no patient on budesonide at
494 doses of 400 and 800 mcg twice daily met the criterion
495 for an abnormal stimulated cortisol response (peak
496 cortisol <14.5 mcg/dL assessed by liquid
497 chromatography) following ACTH infusion. An open-
498 label, long-term follow-up of 1133 patients for up to 52
499 weeks confirmed the minimal effect on the HPA axis
500 (both basal and stimulated plasma cortisol) of
501 budesonide when administered at recommended doses.
502 In patients who had previously been oral steroid-
503 dependent, use of budesonide in recommended doses
504 was associated with higher stimulated cortisol response
505 compared to baseline following 1 year of therapy.

506

507 **Formoterol**

508 While the pharmacodynamic effect is via stimulation of
509 beta-adrenergic receptors; excessive activation of these
510 receptors commonly leads to skeletal muscle tremor and
511 cramps, insomnia, tachycardia, decreases in plasma
512 potassium, and increases in plasma glucose. Inhaled
513 formoterol, like other beta-adrenergic agonist drugs, can
514 produce dose-related cardiovascular effects and effects
515 on blood glucose and/or serum potassium (see
516 **PRECAUTIONS, General**). For Symbicort, these
517 effects are detailed in the **CLINICAL**

518 **PHARMACOLOGY,** **Pharmacodynamics,**
519 **SYMBICORT** section.

520

521 Use of long-acting beta₂-adrenergic agonist drugs can
522 result in tolerance to bronchoprotective and
523 bronchodilatory effects.

524

525 Rebound bronchial hyper-responsiveness after cessation
526 of chronic long-acting beta-agonists therapy has not
527 been observed.

528

529 **Clinical Studies**

530 SYMBICORT has been studied in patients with asthma
531 12 years of age and older. In two clinical studies
532 comparing SYMBICORT with the individual
533 components, improvements in most efficacy endpoints
534 were greater with SYMBICORT than with the use of
535 either budesonide or formoterol alone. In addition, one
536 clinical study showed similar results between
537 SYMBICORT and the concurrent use of budesonide and
538 formoterol at corresponding doses from separate
539 inhalers.

540

541 The safety and efficacy of SYMBICORT were
542 demonstrated in two randomized, double-blind, placebo-
543 controlled US clinical studies involving 1076 patients 12
544 years of age and older. Fixed SYMBICORT dosages of
545 160/9 mcg, and 320/9 mcg twice daily (each dose
546 administered as 2 inhalations of the 80/4.5- and 160/4.5-
547 mcg strengths, respectively) were compared with the
548 monocomponents (budesonide and formoterol) and
549 placebo to provide information about appropriate dosing
550 to cover a range of asthma severity.

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552 **Study 1: Clinical Study with SYMBICORT 160/4.5:**

553 This 12-week study evaluated 596 patients 12 years of
554 age and older by comparing: SYMBICORT 160/4.5
555 mcg, the free combination of budesonide 160 mcg plus
556 formoterol 4.5 mcg in separate inhalers, budesonide 160
557 mcg, formoterol 4.5 mcg, and placebo; each
558 administered as 2 inhalations twice daily. The study
559 included a 2-week run-in period with budesonide 80
560 mcg, 2 inhalations twice daily. Most patients had
561 moderate to severe asthma and were using moderate to
562 high doses of inhaled corticosteroids prior to study
563 entry. Randomization was stratified by previous inhaled
564 corticosteroid treatment (71.6% on moderate- and 28.4%
565 on high-dose inhaled corticosteroid). Mean percent
566 predicted FEV₁ at baseline was 68.1% and was similar
567 across treatment groups. The co-primary efficacy
568 endpoints were 12-hour-average post-dose FEV₁ at
569 week 2, and pre-dose FEV₁ averaged over the course of
570 the study. The study also required that patients who
571 satisfied a pre-defined asthma worsening criterion to be
572 withdrawn. The pre-defined asthma worsening criteria
573 were: a clinically important decrease in FEV₁ or peak
574 expiratory flow (PEF), increase in rescue albuterol use,
575 nighttime awakening due to asthma, emergency
576 intervention or hospitalization due to asthma, or
577 requirement for asthma medication not allowed by the
578 protocol. For the criterion of nighttime awakening due
579 to asthma, patients were allowed to remain in the study
580 at the discretion of the investigator if none of the other
581 asthma worsening criteria were met. The percentage of
582 patients withdrawing due to or meeting predefined
583 criteria for worsening asthma is shown in Table 1.

584

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584
585 **Table 1 – The number and percentage of patients**
586 **withdrawing due to or meeting predefined criteria**
587 **for worsening asthma (Study 1)**

588

	SYMBICORT 160/4.5 (N=124)	Budesonide 160 mcg plus Formoterol 4.5 mcg (N=115)	Budesonide 160 mcg (N=109)	Formoterol 4.5 mcg (N=123)	Placebo (N=125)
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event*†	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV ₁	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakening‡	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (13.8)	16 (12.8)

589 *These criteria were assessed on a daily basis irrespective of the
590 timing of the clinic visit, with the exception of FEV₁ which was
591 assessed at each clinic visit.

592 †Individual criteria are shown for patients meeting any
593 predefined asthma event, regardless of withdrawal status.

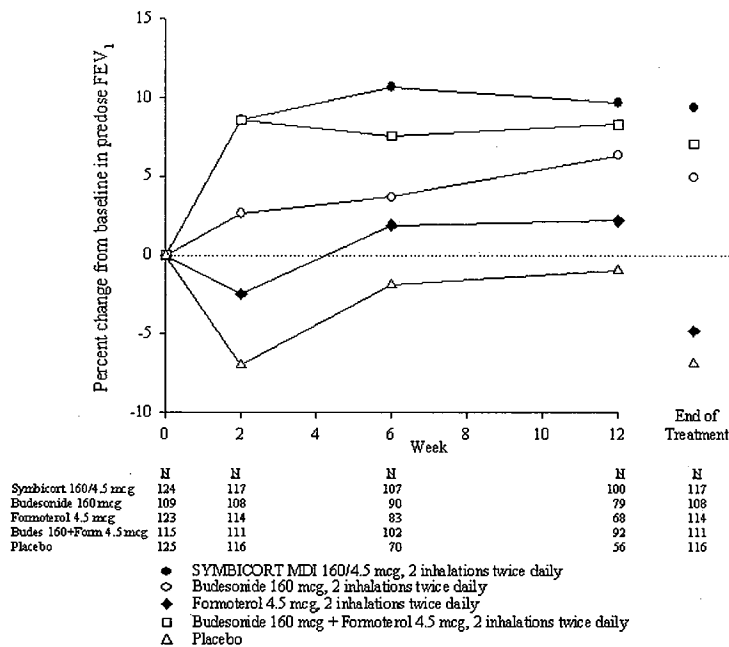
594 ‡For the criterion of nighttime awakening due to asthma, patients
595 were allowed to remain in the study at the discretion of the
596 investigator if none of the other criteria were met.

597

598 Mean percent change from baseline in FEV₁ measured
599 immediately prior to dosing (predose) over 12 weeks is
600 displayed in Figure 1. Because this study used
601 predefined withdrawal criteria for worsening asthma,
602 which caused a differential withdrawal rate in the
603 treatment groups, predose FEV₁ results at the last
604 available study visit (end of treatment, EOT) are also
605 provided. Patients receiving SYMBICORT 160/4.5 mcg

606 had significantly greater mean improvements from
 607 baseline in predose FEV₁ at the end of treatment (0.19
 608 L, 9.4%) compared with budesonide 160 mcg (0.10 L,
 609 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%), and
 610 placebo (-0.17 L, -6.9%).

611
 612 **Figure 1 - Mean Percent Change From Baseline in**
 613 **predose FEV₁ Over 12 Weeks (Study 1)**



614
 615 The effect of SYMBICORT 160/4.5 mcg 2 inhalations
 616 twice daily on selected secondary efficacy variables,
 617 including morning and evening PEF, albuterol rescue
 618 use, and asthma symptoms over 24 hours on a 0-3 scale
 619 is shown in Table 2.

620
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623 **Table 2 - Mean values for selected secondary efficacy**
 624 **variables (Study 1)**

625

Efficacy Variable	SYMBICORT 160/4.5 (N*=124)	Budesonide 160 mcg + Formoterol 4.5 mcg (N*=115)	Budesonide 160 mcg (N*=109)	Formoterol 4.5 mcg (N*=123)	Placebo (N*=125)
AM PEF (L/min)					
Baseline	341	338	342	339	355
Change from Baseline	35	28	9	-9	-18
PM PEF (L/min)					
Baseline	351	348	357	354	369
Change from Baseline	34	26	7	-7	-18
Albuterol rescue use					
Baseline	2.1	2.3	2.7	2.5	2.4
Change from Baseline	-1.0	-1.5	-0.8	-0.3	0.8
Average symptom score/day (0-3 scale)					
Baseline	0.99	1.03	1.04	1.04	1.08
Change from Baseline	-0.28	-0.32	-0.14	-0.05	0.10

626 *Number of patients (N) varies slightly due to the number of
 627 patients for whom data were available for each variable.
 628 Results shown are based on last available data for each
 629 variable.

630

631 The subjective impact of asthma on patients' health-
 632 related quality of life was evaluated through the use of
 633 the standardized Asthma Quality of Life Questionnaire
 634 (AQLQ(S)) (based on a 7-point scale where 1 =
 635 maximum impairment and 7 = no impairment). Patients
 636 receiving SYMBICORT 160/4.5 had clinically
 637 meaningful improvement in overall asthma-specific
 638 quality of life, as defined by a mean difference between
 639 treatment groups of >0.5 points in change from baseline

640 in overall AQLQ score (difference in AQLQ score of
641 0.70 [95% CI 0.47, 0.93] compared to placebo).

642

643 **Study 2: Clinical Study with SYMBICORT 80/4.5**

644 This 12-week study was similar in design to Study 1,
645 and included 480 patients 12 years of age and older.

646 This study compared: SYMBICORT 80/4.5 mcg,
647 budesonide 80 mcg, formoterol 4.5 mcg, and placebo;

648 each administered as 2 inhalations twice-daily. The
649 study included a 2-week placebo run-in period. Most

650 patients had mild to moderate asthma and were using
651 low to moderate doses of inhaled corticosteroids prior to

652 study entry. Mean percent predicted FEV₁ at baseline
653 was 71.3% and was similar across treatment groups.

654 Efficacy variables and endpoints were identical to those
655 in Study 1.

656

657 The percentage of patients withdrawing due to or
658 meeting predefined criteria for worsening asthma is

659 shown in Table 3. The method of assessment and
660 criteria used were identical to that in Study 1.

661

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662 **Table 3 - The number and percentage of patients**
663 **withdrawing due to or meeting predefined criteria**
664 **for worsening asthma (Study 2)**

	SYMBICORT 80/4.5 (N=123)	Budesonide 80 mcg (N=121)	Formoterol 4.5 mcg (N=114)	Placebo (N=122)
Patients withdrawn due to predefined asthma event*	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)
Patients with a predefined asthma event*†	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)
Decrease in FEV ₁	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)
Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)
Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)
Nighttime awakening‡	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

665 *These criteria were assessed on a daily basis irrespective of the
666 timing of the clinic visit, with the exception of FEV₁ which was
667 assessed at each clinic visit.

668 †Individual criteria are shown for patients meeting any
669 predefined asthma event, regardless of withdrawal status.

670 ‡For the criterion of nighttime awakening due to asthma, patients
671 were allowed to remain in the study at the discretion of the
672 investigator if none of the other criteria were met.

673

674 Mean percent change from baseline in predose FEV₁
675 over 12 weeks is displayed in Figure 2.

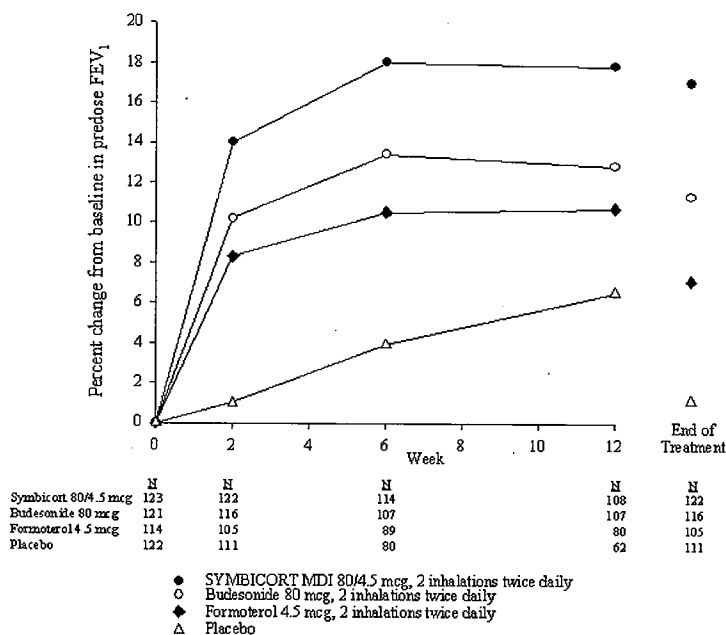
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677 **Figure 2 - Mean percent change from baseline in**
 678 **predose FEV₁ over 12 weeks (Study 2)**

679



680

681

682 Efficacy results for other secondary endpoints, including
 683 quality of life, were similar to those observed in Study 1.

684

685 **Onset and Duration of Action and Progression of** 686 **Improvement in Asthma Control**

687 The onset of action and progression of improvement in
 688 asthma control were evaluated in the 2 pivotal clinical
 689 studies. The median time to onset of clinically
 690 significant bronchodilation (>15% improvement in
 691 FEV₁) was seen within 15 minutes. Maximum
 692 improvement in FEV₁ occurred within 3 hours, and
 693 clinically significant improvement was maintained over
 694 12 hours. Figures 3 and 4 show the percent change from
 695 baseline in postdose FEV₁ over 12 hours on the day of
 696 randomization and on the last day of treatment for Study
 697 1.

698

699 Reduction in asthma symptoms and in albuterol rescue
 700 use, as well as improvement in morning and evening

701 PEF, occurred within 1 day of the first dose of
702 SYMBICORT; improvement in these variables were
703 maintained over the 12 weeks of therapy.

704

705 Following the initial dose of SYMBICORT, FEV₁
706 improved markedly during the first 2 weeks of
707 treatment, continued to show improvement at the Week
708 6 assessment, and was maintained through Week 12 for
709 both studies.

710

711 No diminution in the 12-hour bronchodilator effect was
712 observed with either SYMBICORT 80/4.5 mcg or
713 SYMBICORT 160/4.5 mcg as assessed by FEV₁
714 following 12 weeks of therapy or at the last available
715 visit.

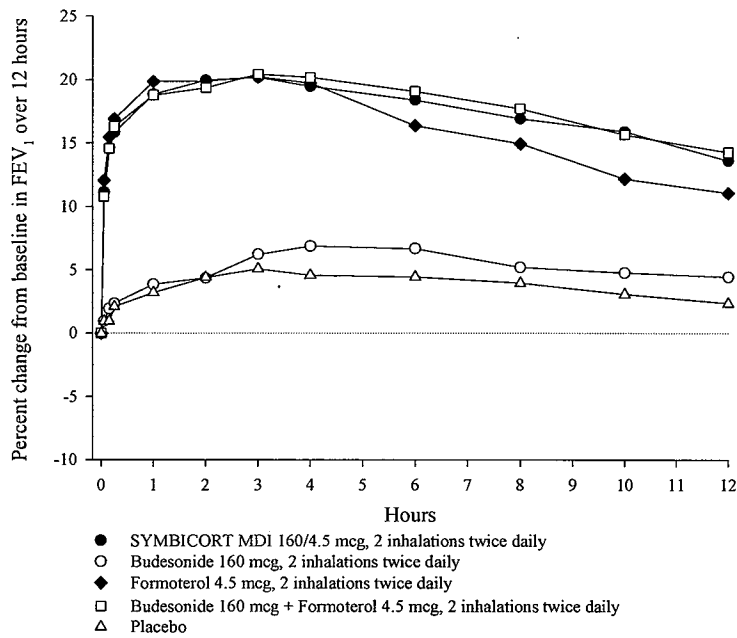
716

717 FEV₁ data from Study 1 evaluating SYMBICORT
718 160/4.5 mcg is displayed in Figures 3 and 4.

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719

720 **Figure 3 - Mean Percent Change From Baseline in**
721 **FEV₁ on Day of Randomization**
722 **(Study 1)**



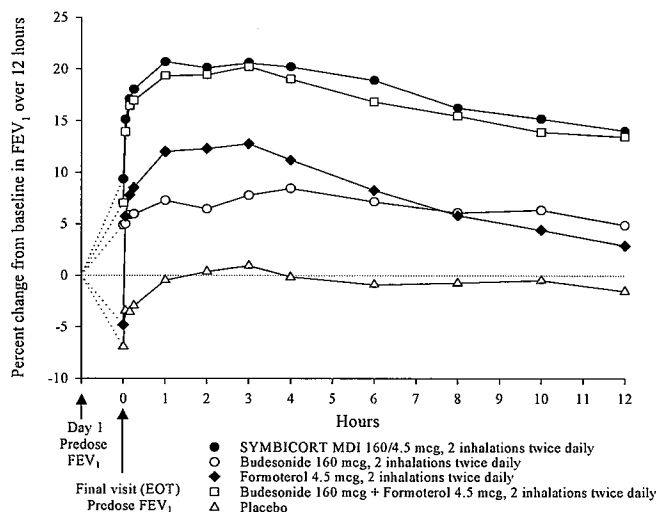
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Figure 4 - Mean Percent Change From Baseline in FEV₁ At End of Treatment (Study 1)



INDICATIONS AND USAGE

SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta₂-agonists.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

753 **CONTRAINDICATIONS**

754 SYMBICORT is contraindicated in the primary
755 treatment of status asthmaticus or other acute episodes
756 of asthma where intensive measures are required.

757

758 Hypersensitivity to any of the ingredients in
759 SYMBICORT contraindicates its use.

760

761

762 **WARNINGS**

763 Long-acting beta₂-adrenergic agonists may increase
764 the risk of asthma-related death. Therefore, when
765 treating patients with asthma, SYMBICORT should
766 only be used for patients not adequately controlled
767 on other asthma-controller medications (e.g., low-to-
768 medium dose inhaled corticosteroids) or whose
769 disease severity clearly warrants initiation of
770 treatment with two maintenance therapies.

771

772 • A 28-week, placebo controlled US study
773 comparing the safety of salmeterol with placebo,
774 each added to usual asthma therapy, showed an
775 increase in asthma-related deaths in patients
776 receiving salmeterol (13/13,176 in patients
777 treated with salmeterol vs 3/13,179 in patients
778 treated with placebo; RR 4.37, 95% CI 1.25,
779 15.34). The increased risk of asthma-related
780 death may represent a class effect of the long-
781 acting beta₂-adrenergic agonists, including
782 formoterol. No study adequate to determine
783 whether the rate of asthma-related death is
784 increased with SYMBICORT has been
785 conducted.

786

787 • Clinical studies with formoterol suggested a
788 higher incidence of serious asthma exacerbations
789 in patients who received formoterol than in those
790 who received placebo. The sizes of these studies
791 were not adequate to precisely quantify the
792 differences in serious asthma exacerbation rates
793 between treatment groups.

794

795 **SYMBICORT Should Not Be Initiated In Patients**
796 **During Rapidly Deteriorating Or Potentially Life-**
797 **Threatening Episodes Of Asthma.**

798

799 **Do Not Use SYMBICORT to Treat Acute Symptoms.**

800 SYMBICORT should not be used to treat acute
801 symptoms of asthma. An inhaled, short-acting beta₂-
802 agonist (e.g., albuterol), should be used to relieve acute
803 asthma symptoms. Therefore, when prescribing
804 SYMBICORT, the physician must also provide the
805 patient with an inhaled, short-acting beta₂-agonist for
806 treatment of symptoms that occur acutely, despite
807 regular twice-daily (morning and evening) use of
808 SYMBICORT.

809

810 When beginning treatment with SYMBICORT, patients
811 who have been taking oral or inhaled, short-acting beta₂-
812 agonists on a regular basis (e.g., 4 times a day) should
813 be instructed to discontinue the regular use of these
814 drugs. For patients on SYMBICORT, short-acting,
815 inhaled beta₂-agonists should only be used for
816 symptomatic relief of acute asthma symptoms (see
817 **PRECAUTIONS, Information for Patients**).

818

819 **Watch for Increasing Use of Inhaled, Short-Acting**
820 **Beta₂-Agonists, Which Is a Marker of Deteriorating**

821 **Asthma.** Asthma may deteriorate acutely over a period
822 of hours or chronically over several days or longer. If
823 the patient's inhaled, short-acting beta₂-agonist becomes
824 less effective, the patient needs more inhalations than
825 usual, or the patient develops a significant decrease in
826 lung function, these may be markers of destabilization of
827 asthma. In this setting, the patient requires immediate
828 reevaluation and reassessment of the treatment regimen,
829 giving special consideration to the possible need for
830 replacing the current strength of SYMBICORT with a
831 higher strength, adding additional inhaled corticosteroid,
832 or initiating systemic corticosteroids. Patients should
833 not use more than two actuations twice daily (morning
834 and evening) of SYMBICORT.

835

836 **SYMBICORT Should Not be Used For Transferring**
837 **Patients from Systemic Corticosteroid Therapy.**

838 Particular care is needed for patients who are transferred
839 from systemically active corticosteroids to inhaled
840 corticosteroids. Deaths due to adrenal insufficiency
841 have occurred in asthmatic patients during and after
842 transfer from systemic corticosteroids to less
843 systemically available inhaled corticosteroids. After
844 withdrawal from systemic corticosteroids, a number of
845 months may be required for recovery of HPA function.
846 Patients who have been previously maintained on 20 mg
847 or more per day of prednisone (or its equivalent) may be
848 most susceptible, particularly when their systemic
849 corticosteroids have been almost completely withdrawn.
850 During this period of HPA suppression, patients may
851 exhibit signs and symptoms of adrenal insufficiency
852 when exposed to trauma, surgery, or infection
853 (particularly gastroenteritis) or other conditions
854 associated with severe electrolyte loss. Although inhaled
855 corticosteroid therapy may provide control of asthma
856 symptoms during these episodes, in recommended doses
857 it supplies less than normal physiological amounts of
858 glucocorticoid systemically and does NOT provide the
859 mineralocorticoid activity that is necessary for coping
860 with these emergencies.

861
862 During periods of stress or a severe asthma attack,
863 patients who have been withdrawn from systemic
864 corticosteroids should be instructed to resume oral
865 corticosteroids (in large doses) immediately and to
866 contact their physicians for further instruction. These
867 patients should also be instructed to carry a medical
868 identification card indicating that they may need
869 supplementary systemic corticosteroids during periods
870 of stress or a severe asthma attack.

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872 **Do Not Use an Inhaled, Long-Acting Beta₂-Agonist in**
873 **Conjunction With SYMBICORT.** Patients who are
874 receiving SYMBICORT twice daily should not use
875 additional formoterol or other long-acting inhaled beta₂-
876 agonists (e.g., salmeterol) for prevention of exercise-
877 induced bronchospasm (EIB) or the maintenance
878 treatment of asthma. Additional benefit would not be
879 gained from using supplemental formoterol or
880 salmeterol for prevention of EIB since SYMBICORT
881 already contains an inhaled, long-acting beta₂-agonist.

882

883 **Do Not Exceed Recommended Dosage.** SYMBICORT
884 should not be used more often or at higher doses than
885 recommended. Fatalities have been reported in
886 association with excessive use of inhaled
887 sympathomimetic drugs in patients with asthma. The
888 exact cause of death is unknown, but cardiac arrest
889 following an unexpected development of a severe acute
890 asthmatic crisis and subsequent hypoxia is suspected. In
891 addition, data from clinical studies with formoterol dry
892 powder inhaler suggest that the use of doses higher than
893 recommended (24 mcg twice daily) is associated with an
894 increased risk of serious asthma exacerbations. In a 52-
895 week active-controlled safety study evaluating
896 SYMBICORT 160/4.5, patients treated with twice the
897 highest recommended dose of SYMBICORT
898 demonstrated a similar safety profile to that of patients
899 treated with the highest recommended dose.

900

901 **Paradoxical Bronchospasm.** As with other inhaled
902 asthma medications SYMBICORT, may produce
903 paradoxical bronchospasm, which may be life
904 threatening. If paradoxical bronchospasm occurs
905 following dosing with SYMBICORT, treatment with
906 SYMBICORT should be discontinued immediately and
907 alternate therapy should be instituted.

908

909 **Immediate Hypersensitivity Reactions.** Immediate
910 hypersensitivity reactions, such as urticaria,
911 angioedema, rash, and bronchospasm may occur after
912 administration of SYMBICORT.

913

914 **Cardiovascular Disorders.** SYMBICORT, like all
915 products containing sympathomimetic amines, should be
916 used with caution in patients with cardiovascular
917 disorders, especially coronary insufficiency, cardiac
918 arrhythmias, and hypertension. Formoterol, a component
919 of SYMBICORT, may produce a clinically significant
920 cardiovascular effect in some patients as measured by
921 pulse rate, blood pressure, and/or symptoms. Although
922 such effects are uncommon after administration of
923 SYMBICORT at recommended doses, if they occur, the
924 drug may need to be discontinued. In addition, beta-
925 agonists have been reported to produce
926 electrocardiogram (ECG) changes, such as flattening of
927 the T wave, prolongation of the QTc interval, and ST
928 segment depression. The clinical significance of these
929 findings is unknown.
930
931 **Discontinuation of Systemic Corticosteroids.**
932 Transfer of patients from systemic corticosteroid therapy
933 to inhaled corticosteroids may unmask conditions
934 previously suppressed by the systemic corticosteroid
935 therapy, e.g., rhinitis, conjunctivitis, eczema, and
936 arthritis.
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938 **Immunosuppression.** Persons who are using drugs that
939 suppress the immune system are more susceptible to
940 infections than healthy individuals. Chickenpox and
941 measles, for example, can have a more serious or even
942 fatal course in susceptible children or adults using
943 corticosteroids. In such children or adults who have not
944 had these diseases or been properly immunized,
945 particular care should be taken to avoid exposure. It is
946 unknown how the dose, route, and duration of
947 corticosteroid administration affect the risk of
948 developing a disseminated infection. The contribution
949 of the underlying disease and/or prior corticosteroid
950 treatment to the risk is also not known. If a patient on
951 immunosuppressant doses of corticosteroids is exposed
952 to chicken pox, therapy with varicella zoster immune
953 globulin (VZIG) or pooled intramuscular
954 immunoglobulin (IG), as appropriate may be indicated.
955 If exposed to measles, prophylaxis with pooled
956 intramuscular immunoglobulin (IG) may be indicated.
957 (See the respective package inserts for complete VZIG
958 and IG prescribing information.) If chickenpox
959 develops, treatment with antiviral agents may be
960 considered. The immune responsiveness to varicella
961 vaccine was evaluated in pediatric patients with asthma
962 ages 12 months to 8 years with budesonide inhalation
963 suspension (see **PRECAUTIONS, Drug Interactions**).
964

965

966

PRECAUTIONS

General

968 **Sympathomimetic Effects.** The cardiovascular and
969 central nervous system effects seen with all
970 sympathomimetic drugs (e.g., increased blood pressure,
971 heart rate, excitement) can occur after use of formoterol,
972 a component of SYMBICORT, and may require
973 discontinuation of SYMBICORT. SYMBICORT, like
974 all medications containing sympathomimetic amines,
975 should be used with caution in patients with
976 cardiovascular disorders, especially coronary
977 insufficiency, cardiac arrhythmias, and hypertension; in
978 patients with convulsive disorders, untreated
979 hypokalemia, or thyrotoxicosis; and in patients who are
980 unusually responsive to sympathomimetic amines.

981

982 As has been described with other beta-adrenergic
983 agonist bronchodilators, clinically important changes in
984 electrocardiograms, systolic and/or diastolic blood
985 pressure, and pulse rate were seen infrequently in
986 individual patients during controlled clinical studies
987 with SYMBICORT at recommended doses.

988

989 **Metabolic and Other Effects.** Long-term use of orally
990 inhaled corticosteroids, such as budesonide, a
991 component of SYMBICORT, may affect normal bone
992 metabolism resulting in a loss of bone mineral density.
993 In patients with major risk factors for decreased bone
994 mineral content, such as tobacco use, advanced age,
995 sedentary lifestyle, poor nutrition, family history or
996 osteoporosis, or chronic use of drugs that can reduce
997 bone mass (e.g., anticonvulsants and corticosteroids),
998 orally inhaled corticosteroids may pose an additional
999 risk.

1000

1001 Doses of the related beta₂-adrenoceptor agonist
1002 albuterol, when administered intravenously, have been
1003 reported to aggravate preexisting diabetes mellitus and
1004 ketoacidosis. High doses of beta-adrenergic agonist
1005 medications may produce significant hypokalemia in
1006 some patients, through intracellular shunting, which may
1007 have the potential to produce adverse cardiovascular
1008 effects. The decrease in serum potassium is usually
1009 transient, not requiring supplementation.

1010

1011 Clinically important changes in blood glucose and/or
1012 serum potassium were seen rarely during clinical studies
1013 with SYMBICORT at recommended doses.

1014

1015 During withdrawal from oral corticosteroids, some
1016 patients may experience symptoms of systemically
1017 active corticosteroid withdrawal, e.g., joint and/or
1018 muscular pain, lassitude, and depression, despite
1019 maintenance or even improvement of respiratory
1020 function.

1021

1022 Budesonide, a component of SYMBICORT, will often
1023 permit control of asthma symptoms with less
1024 suppression of HPA function than therapeutically
1025 equivalent oral doses of prednisone. Since budesonide is
1026 absorbed into the circulation and can be systemically

1027 active, patients should not exceed the recommended
1028 dosage of SYMBICORT. Individual patients should be
1029 titrated to the lowest effective dose in order to minimize
1030 HPA dysfunction. Since individual sensitivity to effects
1031 on cortisol production exists, physicians should consider
1032 this information when prescribing SYMBICORT.

1033

1034 Because of the possibility of systemic absorption of
1035 inhaled corticosteroids, patients treated with
1036 SYMBICORT should be observed carefully for any
1037 evidence of systemic corticosteroid effects. Particular
1038 care should be taken in observing patients
1039 postoperatively or during periods of stress for evidence
1040 of inadequate adrenal response.

1041

1042 It is possible that systemic corticosteroid effects such as
1043 hypercorticism and adrenal suppression may appear in a
1044 small number of patients, particularly at higher doses. If
1045 such changes occur, the total daily dose of
1046 SYMBICORT should be reduced slowly, consistent with
1047 accepted procedures for management of asthma
1048 symptoms and for tapering of systemic steroids.

1049

1050 Budesonide, a component of SYMBICORT, may cause
1051 a reduction in growth velocity when administered to
1052 pediatric patients. Patients should be maintained on the
1053 lowest dose of SYMBICORT that effectively controls
1054 their asthma (see **PRECAUTIONS, Pediatric Use**).

1055

1056 The long-term effects resulting from chronic use of
1057 budesonide on developmental or immunological
1058 processes in the mouth, pharynx, trachea, and lung are
1059 unknown. The local and systemic effects of
1060 SYMBICORT in humans have been studied for up to
1061 one year (see **ADVERSE REACTIONS, Long Term
1062 Safety**).

1063

1064 Rare instances of glaucoma, increased intraocular
1065 pressure, and cataracts have been reported following the
1066 inhaled administration of corticosteroids, including
1067 budesonide, a component of SYMBICORT.

1068

1069

1070

1071

1072

1073 Lower respiratory tract infections, including pneumonia,
1074 have been reported following the inhaled administration
1075 of corticosteroids, including budesonide, a component of
1076 SYMBICORT. In the 3 placebo-controlled US clinical
1077 studies, the incidence of lower respiratory tract
1078 infections, including pneumonia, was low, with no
1079 consistent evidence of increased risk for SYMBICORT
1080 compared to placebo.

1081

1082 In clinical studies with SYMBICORT, localized
1083 infections with *Candida albicans* have occurred in the
1084 mouth and pharynx. If oropharyngeal candidiasis
1085 develops, it should be treated with appropriate local or
1086 systemic (ie, oral) antifungal therapy while still
1087 continuing with SYMBICORT therapy, but at times the
1088 dose of SYMBICORT may need to be temporarily
1089 decreased or interrupted under close medical
1090 supervision.

1091

1092 Inhaled corticosteroids should be used with caution, if at
1093 all, in patients with active or quiescent tuberculosis
1094 infection of the respiratory tract, untreated systemic
1095 fungal, bacterial, viral or parasitic infections, or ocular
1096 herpes simplex.

1097

1098 **Information for Patients**

1099 **Patients should be instructed to read the**
1100 **accompanying Medication Guide with each new**
1101 **prescription and refill.**

1102

1103 Patients being treated with SYMBICORT should receive
1104 the following information and instructions. This
1105 information is intended to aid the patient in the safe and
1106 effective use of the medication. It is not a disclosure of
1107 all possible adverse or intended effects.

1108

1109 It is important that patients understand how to use the
1110 SYMBICORT inhaler device appropriately and how
1111 SYMBICORT should be used in relation to other asthma
1112 medications they are taking.

1113

1113

1114 1. **Patients should be informed that long-acting**
1115 **beta₂-adrenergic agonists may increase the risk of**
1116 **asthma-related death.** Patients should also be
1117 informed that data are not adequate to determine
1118 whether the concurrent use of inhaled
1119 corticosteroids, such as budesonide, the other
1120 component of SYMBICORT, or other asthma-
1121 controller therapy modifies this risk.

1122 2. Patients should be instructed that the correct dose of
1123 SYMBICORT is 2 puffs inhaled twice daily of the
1124 appropriate dosage strength, 80/4.5 or 160/4.5. They
1125 should take 2 puffs of SYMBICORT in the morning
1126 and 2 puffs in the evening every day. The maximum
1127 daily recommended dose is 640/18 mcg
1128 budesonide/formoterol (given as two inhalations of
1129 SYMBICORT 160/4.5 twice daily). Do not use
1130 more than twice daily or use a higher number of
1131 inhalations (more than 2 inhalations twice daily) of
1132 the prescribed strength of SYMBICORT as this will
1133 result in a daily dose of formoterol in excess of the
1134 dose determined to be safe. **Patients should also be**
1135 **instructed not to take SYMBICORT more often**
1136 **or use more puffs than you have prescribed.** If
1137 they miss a dose, they should be instructed to take
1138 their next dose at the same time they normally do.

1139 3. **SYMBICORT is not meant to relieve acute**
1140 **asthma symptoms and extra doses should not be**
1141 **used for that purpose.** Acute symptoms should be
1142 treated with an inhaled, short-acting beta₂-agonist
1143 such as albuterol (the physician should provide the
1144 patient with such medication and instruct the patient
1145 on how it should be used).

1146 4. The physician should be notified immediately if any
1147 of the following situations occur, which may be a
1148 sign of seriously worsening asthma:

- 1149 • Decreasing effectiveness of inhaled, short-acting
1150 beta₂-agonists
- 1151 • Need for more inhalations than usual of inhaled,
1152 short-acting beta₂-agonists
- 1153 • Significant decrease in lung function as outlined
1154 by the physician
- 1155 • Marked change in symptoms

- 1156 5. When patients are prescribed SYMBICORT, other
1157 inhaled drugs and asthma medications should be
1158 used only as directed by a physician.
- 1159 6. Patients who are receiving SYMBICORT should not
1160 use formoterol or another long-acting inhaled beta₂-
1161 agonist for prevention of exercise-induced
1162 bronchospasm or maintenance treatment of asthma.
- 1163 7. Patients should not stop therapy with SYMBICORT
1164 without physician/provider guidance since
1165 symptoms may recur after discontinuation.
- 1166 8. Patients should be cautioned regarding common
1167 adverse effects associated with beta₂-agonists, such
1168 as palpitations, chest pain, rapid heart rate, tremor,
1169 or nervousness.
- 1170 9. Patients should be warned to avoid exposure to
1171 chicken pox or measles and if they are exposed, to
1172 consult their physicians without delay.
- 1173 10. Long-term use of inhaled corticosteroids, including
1174 budesonide, a component of SYMBICORT, may
1175 increase the risk of some eye problems (cataracts or
1176 glaucoma). Regular eye examinations should be
1177 considered.
- 1178 11. If the patient is pregnant or nursing, they should
1179 contact their physician about the use of
1180 SYMBICORT.
- 1181 12. Results of clinical trials indicate that in most
1182 patients, clinically significant improvement occurred
1183 within 15 minutes of beginning treatment with
1184 SYMBICORT. The maximum benefit may not be
1185 achieved for 2 weeks or longer after starting
1186 treatment. Individual patients may experience a
1187 variable time to onset and degree of symptom relief.
- 1188 13. The bronchodilation from a dose (2 inhalations) of
1189 SYMBICORT has been shown to last up to 12 hours
1190 or longer. The recommended dosage should not be
1191 exceeded.
- 1192 14. The following measures should be observed when
1193 using SYMBICORT:
- 1194 • Patients should not attempt to take the inhaler
1195 apart.
 - 1196 • SYMBICORT should be primed before using the
1197 first time and also when the inhaler has not been
1198 used for more than 7 days by releasing 2 test
1199 sprays into the air away from the face, shaking
1200 well for 5 seconds before each spray.

- 1201 • Patients should replace the mouthpiece cover
1202 after each use.
- 1203 • To remove any excess medication, patients
1204 should rinse their mouth with water after each
1205 dose (do not swallow) to decrease the risk of the
1206 development of oral candidiasis.
- 1207 • Patients should clean the inhaler every 7 days by
1208 wiping the mouthpiece with a dry cloth.
- 1209 • Use SYMBICORT only with the actuator
1210 supplied with the product. Discard the inhaler
1211 after 120 sprays have been used by the patient.
- 1212 • Store in a dry place at controlled room
1213 temperature 20°C to 25°C (68°F to 77°F) [see
1214 USP] and out of the reach of children.
- 1215

1216 **Drug Interactions**

1217 In clinical studies, concurrent administration of
1218 SYMBICORT and other drugs, such as short-acting
1219 beta₂-agonists, intranasal corticosteroids, and
1220 antihistamines/decongestants has not resulted in an
1221 increased frequency of adverse events. No formal drug
1222 interaction studies have been performed with
1223 SYMBICORT.

1224

1225 **Short-Acting Beta₂-Agonists:** In three 12-week,
1226 placebo-controlled US clinical studies, the mean daily
1227 need for albuterol rescue use in 401 adult and adolescent
1228 patients using SYMBICORT twice daily was
1229 approximately 0.8 inhalations/day, and ranged from 0 to
1230 14 inhalations/day. Approximately 2% (N= 8) of the
1231 SYMBICORT patients in these studies averaged 6 or
1232 more inhalations per day. No cardiac adverse events
1233 were reported in these patients.

1234

1235 **Methylxanthines and leukotriene modifying agents:**
1236 The concurrent use of intravenously or orally
1237 administered methylxanthines (e.g., aminophylline,
1238 theophylline) by patients receiving SYMBICORT has
1239 not been completely evaluated. In clinical trials with
1240 SYMBICORT, limited number of patients received
1241 concurrent methylxanthines or leukotriene modifying
1242 agents, and therefore no clinically meaningful
1243 conclusions on adverse events can be made.

1244

1244

1245 **Intranasal and systemic corticosteroids:**

1246 Among adult and adolescent patients participating in
1247 active- and placebo-controlled US clinical trials, twice
1248 daily SYMBICORT was used concurrently with
1249 intranasal budesonide in 105 patients and with any
1250 intranasal corticosteroids in 585 patients. Two hundred
1251 seventeen patients used courses of systemic
1252 corticosteroids while taking SYMBICORT. There were
1253 no important differences noted in the adverse event
1254 profiles between these groups.

1255

1256 **Monoamine Oxidase Inhibitors and Tricyclic**
1257 **Antidepressants:**

SYMBICORT should be
1258 administered with caution to patients being treated with
1259 monoamine oxidase inhibitors or tricyclic
1260 antidepressants, or within 2 weeks of discontinuation of
1261 such agents, because the action of formoterol, a
1262 component of SYMBICORT, on the vascular system
1263 may be potentiated by these agents. In clinical trials
1264 with SYMBICORT, a limited number of patients
1265 received tricyclic antidepressants and therefore no
1266 clinically meaningful conclusions on adverse events can
1267 be made.

1268

1269 **Beta-Adrenergic Receptor Blocking Agents:** Beta-
1270 blockers (including eye drops) may not only block the
1271 pulmonary effect of beta-agonists, such as formoterol, a
1272 component of SYMBICORT, but may produce severe
1273 bronchospasm in patients with asthma. Therefore,
1274 patients with asthma should not normally be treated with
1275 beta-blockers. However, under certain circumstances,
1276 there may be no acceptable alternatives to the use of
1277 beta-adrenergic blocking agents in patients with asthma.
1278 In this setting, cardioselective beta-blockers could be
1279 considered, although they should be administered with
1280 caution.

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1282 **Diuretics:** The ECG changes and/or hypokalemia that
1283 may result from the administration of nonpotassium-
1284 sparing diuretics (such as loop or thiazide diuretics) can
1285 be acutely worsened by beta-agonists, especially when
1286 the recommended dose of the beta-agonist is exceeded.
1287 Although the clinical significance of these effects is not
1288 known, caution is advised in the coadministration of
1289 SYMBICORT with nonpotassium-sparing diuretics.

1290

1291 **Ketoconazole and Other Inhibitors of Cytochrome**
1292 **p450:** The main route of metabolism of corticosteroids,
1293 including budesonide, a component of SYMBICORT, is
1294 via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4).
1295 After oral administration of ketoconazole, a potent
1296 inhibitor of CYP3A4, the mean plasma concentration of
1297 orally administered budesonide increased. Concomitant
1298 administration of other known inhibitors of CYP3A4
1299 (e.g., itraconazole, clarithromycin, erythromycin, etc.)
1300 may inhibit the metabolism of, and increase the systemic
1301 exposure to, budesonide. Caution should be exercised
1302 when considering the coadministration of SYMBICORT
1303 with long-term ketoconazole and other known potent
1304 CYP3A4 inhibitors.

1305

1306 **Varicella Vaccine:** An open-label non-randomized
1307 clinical study examined the immune responsiveness to
1308 varicella vaccine in 243 asthma patients 12 months to 8
1309 years of age who were treated with budesonide
1310 inhalation suspension 0.25 mg to 1 mg daily (n=151) or
1311 non-corticosteroid asthma therapy (n=92) (ie, beta₂-
1312 agonists, leukotriene receptor antagonists, cromones).
1313 The percentage of patients developing a seroprotective
1314 antibody titer of ≥ 5.0 (gpELISA value) in response to
1315 the vaccination was similar in patients treated with
1316 budesonide inhalation suspension (85%) compared to
1317 patients treated with non-corticosteroid asthma therapy
1318 (90%). No patient treated with budesonide inhalation
1319 suspension developed chickenpox as a result of
1320 vaccination.

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1322 **Carcinogenesis, Mutagenesis, Impairment of**
1323 **Fertility**

1324 **Budesonide**

1325 Long-term studies were conducted in rats and mice
1326 using oral administration to evaluate the carcinogenic
1327 potential of budesonide.

1328

1329 In a two-year study in Sprague-Dawley rats, budesonide
1330 caused a statistically significant increase in the incidence
1331 of gliomas in male rats at an oral dose of 50 mcg/kg
1332 (less than the maximum recommended human daily
1333 inhalation dose on a mcg/m² basis). No tumorigenicity
1334 was seen in male and female rats at respective oral doses
1335 up to 25 and 50 mcg/kg (less than the maximum
1336 recommended human daily inhalation dose on a mcg/m²
1337 basis). In two additional two-year studies in male
1338 Fischer and Sprague-Dawley rats, budesonide caused no
1339 gliomas at an oral dose of 50 mcg/kg (less than the
1340 maximum recommended human daily inhalation dose on
1341 a mcg/m² basis). However, in the male Sprague-Dawley
1342 rats, budesonide caused a statistically significant
1343 increase in the incidence of hepatocellular tumors at an
1344 oral dose of 50 mcg/kg (less than the maximum
1345 recommended human daily inhalation dose on a mcg/m²
1346 basis). The concurrent reference corticosteroids
1347 (prednisolone and triamcinolone acetonide) in these two
1348 studies showed similar findings.

1349

1350 In a 91-week study in mice, budesonide caused no
1351 treatment-related carcinogenicity at oral doses up to 200
1352 mcg/kg (approximately equal to the maximum
1353 recommended human daily inhalation dose on a mcg/m²
1354 basis).

1355

1356 Budesonide was not mutagenic or clastogenic in six
1357 different test systems: Ames *Salmonella*/microsome
1358 plate test, mouse micronucleus test, mouse lymphoma
1359 test, chromosome aberration test in human lymphocytes,
1360 sex-linked recessive lethal test in *Drosophila*
1361 *melanogaster*, and DNA repair analysis in rat hepatocyte
1362 culture.

1363

1364 In rats, budesonide had no effect on fertility at
1365 subcutaneous doses up to 80 mcg/kg (approximately
1366 equal to the maximum recommended human daily

1367 inhalation dose on a mcg/m² basis). However, it caused
1368 a decrease in prenatal viability and viability in the pups
1369 at birth and during lactation, along with a decrease in
1370 maternal body-weight gain, at subcutaneous doses of 20
1371 mcg/kg and above (less than the maximum
1372 recommended human daily inhalation dose on a mcg/m²
1373 basis). No such effects were noted at 5 mcg/kg (less
1374 than the maximum recommended human daily
1375 inhalation dose on a mcg/m² basis).

1376

1377 **Formoterol**

1378 Long-term studies were conducted in mice using oral
1379 administration and rats using inhalation administration
1380 to evaluate the carcinogenic potential of formoterol
1381 fumarate.

1382

1383 In a 24-month carcinogenicity study in CD-1 mice,
1384 formoterol at oral doses of 0.1 mg/kg and above
1385 (approximately 20 times the maximum recommended
1386 human daily inhalation dose on a mcg/m² basis) caused
1387 a dose-related increase in the incidence of uterine
1388 leiomyomas.

1389

1390 In a 24-month carcinogenicity study in Sprague-Dawley
1391 rats, an increased incidence of mesovarian leiomyoma
1392 and uterine leiomyosarcoma were observed at the
1393 inhaled dose of 130 mcg/kg (approximately 60 times the
1394 maximum recommended human daily inhalation dose on
1395 a mcg/m² basis). No tumors were seen at 22 mcg/kg
1396 (approximately 10 times the maximum recommended
1397 human daily inhalation dose on a mcg/m² basis).

1398

1399 Other beta-agonist drugs, have similarly demonstrated
1400 increases in leiomyomas of the genital tract in female
1401 rodents. The relevance of these findings to human use is
1402 unknown.

1403

1404 Formoterol was not mutagenic or clastogenic in Ames
1405 *Salmonella*/microsome plate test, mouse lymphoma test,
1406 chromosome aberration test in human lymphocytes, and
1407 rat micronucleus test.

1408

1409 A reduction in fertility and/or reproductive performance
1410 was identified in male rats treated with formoterol at an
1411 oral dose of 15 mg/kg (approximately 7000 times the

1412 maximum recommended human daily inhalation dose on
1413 a mcg/m² basis). In a separate study with male rats
1414 treated with an oral dose of 15 mg/kg (approximately
1415 7000 times the maximum recommended human daily
1416 inhalation dose on a mcg/m² basis), there were findings
1417 of testicular tubular atrophy and spermatogenic debris in the
1418 testes and oligospermia in the epididymides. No such
1419 effect was seen at 3 mg/kg (approximately 1400 times
1420 the maximum recommended human daily inhalation
1421 dose on a mcg/m² basis). No effect on fertility was
1422 detected in female rats at doses up to 15 mg/kg
1423 (approximately 7000 times the maximum recommended
1424 human daily inhalation dose on a mcg/m² basis).

1425

1426 **Pregnancy**

1427 **Symbicort**

1428 **Teratogenic Effects: Pregnancy Category C**

1429 SYMBICORT has been shown to be teratogenic and
1430 embryocidal in rats when given at inhalation doses of
1431 12/0.66 mcg/kg (budesonide/formoterol) and above (less
1432 than the maximum recommended human daily inhaled
1433 dose on a mcg/m² basis). Umbilical hernia, a
1434 malformation, was observed for fetuses at doses of
1435 12/0.66 mcg/kg and above (less than the maximum
1436 recommended human daily inhaled dose on a mcg/m²
1437 basis). No teratogenic or embryocidal effects were
1438 detected at 2.5/0.14 mcg/kg (less than the maximum
1439 recommended human daily inhaled dose on a mcg/m²
1440 basis). There are no adequate and well-controlled
1441 studies in pregnant women. SYMBICORT should be
1442 used during pregnancy only if the potential benefit
1443 justifies the potential risk to the fetus.

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1444

1445 **Budesonide**

1446 **Teratogenic Effects:**

1447 As with other corticosteroids, budesonide has been
1448 shown to be teratogenic and embryocidal in rabbits and
1449 rats. Budesonide produced fetal loss, decreased pup
1450 weight, and skeletal abnormalities at subcutaneous doses
1451 of 25 mcg/kg/day in rabbits (less than the maximum
1452 recommended human daily inhalation dose on a mcg/m²
1453 basis) and 500 mcg/kg/day in rats (approximately 6
1454 times the maximum recommended human daily
1455 inhalation dose on a mcg/m² basis). In another study in
1456 rats, no teratogenic or embryocidal effects were seen at
1457 inhalation doses up to 250 mcg/kg/day (approximately 3
1458 times the maximum recommended human daily
1459 inhalation dose on a mcg/m² basis).

1460

1461 Experience with oral corticosteroids since their
1462 introduction in pharmacologic as opposed to physiologic
1463 doses suggests that rodents are more prone to
1464 teratogenic effects from corticosteroids than humans.

1465

1466 Studies of pregnant women, however, have not shown
1467 that inhaled budesonide increases the risk of
1468 abnormalities when administered during pregnancy.
1469 The results from a large population-based prospective
1470 cohort epidemiological study reviewing data from three
1471 Swedish registries covering approximately 99% of the
1472 pregnancies from 1995-1997 (ie, Swedish Medical Birth
1473 Registry; Registry of Congenital Malformations; Child
1474 Cardiology Registry) indicate no increased risk for
1475 congenital malformations from the use of inhaled
1476 budesonide during early pregnancy. Congenital
1477 malformations were studied in 2014 infants born to
1478 mothers reporting the use of inhaled budesonide for
1479 asthma in early pregnancy (usually 10-12 weeks after
1480 the last menstrual period), the period when most major
1481 organ malformations occur. The rate of recorded
1482 congenital malformations was similar compared to the
1483 general population rate (3.8% vs. 3.5%, respectively).
1484 In addition, after exposure to inhaled budesonide, the
1485 number of infants born with orofacial clefts was similar
1486 to the expected number in the normal population (4
1487 children vs. 3.3, respectively).

1488

1489 These same data were utilized in a second study
1490 bringing the total to 2534 infants whose mothers were
1491 exposed to inhaled budesonide. In this study, the rate of
1492 congenital malformations among infants whose mothers
1493 were exposed to inhaled budesonide during early
1494 pregnancy was not different from the rate for all
1495 newborn babies during the same period (3.6%).

1496

1497 **Formoterol**

1498 **Teratogenic Effects:**

1499 Formoterol fumarate has been shown to be teratogenic,
1500 embryocidal, increase pup loss at birth and during
1501 lactation, and decreased pup weights in rats when given
1502 at oral doses of 3 mg/kg/day and above (approximately
1503 1400 times the maximum recommended human daily
1504 inhalation dose on a mcg/m² basis). Umbilical hernia, a
1505 malformation, was observed in rat fetuses at oral doses
1506 of 3 mg/kg/day and above (approximately 1400 times
1507 the maximum recommended human daily inhalation
1508 dose on a mcg/m² basis). Brachygnathia, a skeletal
1509 malformation, was observed for rat fetuses at an oral
1510 dose of 15 mg/kg/day (approximately 7000 times the
1511 maximum recommended human daily inhalation dose on
1512 a mcg/m² basis). Pregnancy was prolonged at an oral
1513 dose of 15 mg/kg/day (approximately 7000 times the
1514 maximum recommended human daily inhalation dose on
1515 a mcg/m² basis). In another study in rats, no teratogenic
1516 effects were seen at inhalation doses up to 1.2
1517 mg/kg/day (approximately 500 times the maximum
1518 recommended human daily inhalation dose on a mcg/m²
1519 basis).

1520

1521 Formoterol fumarate has been shown to be teratogenic
1522 in rabbits when given at an oral dose of 60 mg/kg
1523 (approximately 54,000 times the maximum
1524 recommended human daily inhalation dose on a mcg/m²
1525 basis). Subcapsular cysts on the liver were observed for
1526 rabbit fetuses at an oral dose of 60 mg/kg
1527 (approximately 54,000 times the maximum
1528 recommended human daily inhalation dose on a mcg/m²
1529 basis). No teratogenic effects were observed at oral
1530 doses up to 3.5 mg/kg (approximately 3200 times the
1531 maximum recommended human daily inhalation dose on
1532 a mcg/m² basis).

1533

1534 There are no adequate and well-controlled studies with
1535 formoterol in pregnant women.

1536

1537 **Nonteratogenic Effects**

1538 Hypoadrenalism may occur in infants born of mothers
1539 receiving corticosteroids during pregnancy. Such
1540 infants should be carefully observed.

1541

1542 **Use in Labor and Delivery**

1543 There are no well-controlled human studies that have
1544 investigated effects of SYMBICORT on preterm labor
1545 or labor at term. Because of the potential for beta-
1546 agonist interference with uterine contractility, use of
1547 SYMBICORT for management of asthma during labor
1548 should be restricted to those patients in whom the
1549 benefits clearly outweigh the risks.

1550

1551 **Nursing Mothers**

1552 Since there are no data from controlled trials on the use
1553 of SYMBICORT by nursing mothers, a decision should
1554 be made whether to discontinue nursing or to
1555 discontinue SYMBICORT, taking into account the
1556 importance of SYMBICORT to the mother.

1557

1558 It is not known whether budesonide, one of the main
1559 components of SYMBICORT, is excreted in human
1560 milk. Because other corticosteroids are excreted in
1561 human milk, caution should be exercised if budesonide
1562 is administered to nursing women.

1563

1564 In reproductive studies in rats, formoterol was excreted
1565 in the milk. It is not known whether formoterol is
1566 excreted in human milk. Because many drugs are
1567 excreted in human milk, caution should be exercised if
1568 formoterol is administered to nursing women.

1569

1570 **Pediatric Use**

1571 Safety and effectiveness of SYMBICORT in patients 12
1572 years of age and older have been established in studies
1573 up to 12 months. In the two 12-week, double-blind,
1574 placebo-controlled US pivotal studies 25 patients 12 to
1575 17 years of age were treated with SYMBICORT twice
1576 daily. Efficacy results in this age group were similar to
1577 those observed in patients 18 years and older. There
1578 were no obvious differences in the type or frequency of

1579 adverse events reported in this age group compared with
1580 patients 18 years of age and older.
1581
1582 The effectiveness of SYMBICORT in patients 6 to < 12
1583 years of age has not been established.
1584
1585 Overall 1447 patients 6 to <12 years of age participated
1586 in placebo- and active-controlled SYMBICORT studies.
1587 Of these 1447 patients, 539 received SYMBICORT
1588 twice daily. The overall safety profile of these patients
1589 was similar to that observed in patients ≥ 12 years of age
1590 who also received SYMBICORT twice daily in studies
1591 of similar design.
1592
1593 Controlled clinical studies have shown that orally
1594 inhaled corticosteroids including budesonide, a
1595 component of SYMBICORT, may cause a reduction in
1596 growth velocity in pediatric patients. This effect has
1597 been observed in the absence of laboratory evidence of
1598 HPA axis suppression, suggesting that growth velocity
1599 is a more sensitive indicator of systemic corticosteroid
1600 exposure in pediatric patients than some commonly used
1601 tests of HPA axis function. The long-term effect of this
1602 reduction in growth velocity associated with orally
1603 inhaled corticosteroids, including the impact on final
1604 height are unknown. The potential for “catch-up”
1605 growth following discontinuation of treatment with
1606 orally inhaled corticosteroids has not been adequately
1607 studied.
1608
1609 In a study of asthmatic children 5-12 years of age, those
1610 treated with budesonide DPI 200 mcg twice daily
1611 (n=311) had a 1.1-centimeter reduction in growth
1612 compared with those receiving placebo (n=418) at the
1613 end of one year; the difference between these two
1614 treatment groups did not increase further over three
1615 years of additional treatment. By the end of four years,
1616 children treated with budesonide DPI and children
1617 treated with placebo had similar growth velocities.
1618 Conclusions drawn from this study may be confounded
1619 by the unequal use of corticosteroids in the treatment
1620 groups and inclusion of data from patients attaining
1621 puberty during the course of the study.
1622

1623 The growth of pediatric patients receiving orally inhaled
1624 corticosteroids, including SYMBICORT, should be
1625 monitored. If a child or adolescent on any corticosteroid
1626 appears to have growth suppression, the possibility that
1627 he/she is particularly sensitive to this effect should be
1628 considered. The potential growth effects of prolonged
1629 treatment should be weighed against the clinical benefits
1630 obtained. To minimize the systemic effects of orally
1631 inhaled corticosteroids, including SYMBICORT, each
1632 patient should be titrated to the lowest strength that
1633 effectively controls his/her asthma (see **DOSAGE AND**
1634 **ADMINISTRATION**).

1635

1636 **Geriatric Use**

1637 In three 12-week, double-blind, placebo-controlled US
1638 clinical studies, 17 patients treated with SYMBICORT
1639 twice daily were 65 years of age or older, of whom 2
1640 were 75 years of age or older. Of the total number of
1641 patients in clinical studies treated with SYMBICORT
1642 twice daily, 149 were 65 years of age or older, of whom,
1643 25 were 75 years of age or older. No overall differences
1644 in safety were observed between these patients and
1645 younger patients. As with other products containing
1646 beta₂-agonists, special caution should be observed when
1647 using SYMBICORT in geriatric patients who have
1648 concomitant cardiovascular disease that could be
1649 adversely affected by beta₂-agonists. Based on available
1650 data for SYMBICORT or its active components, no
1651 adjustment of dosage of SYMBICORT in geriatric
1652 patients is warranted.

1653

1654

1655 **ADVERSE REACTIONS**

1656 Long-acting beta₂-adrenergic agonists may increase
1657 the risk of asthma-related death (See **Boxed**
1658 **WARNING, WARNINGS, AND PRECAUTIONS**
1659 sections).

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1661 The incidence of common adverse events in the table
 1662 below is based upon three 12-week, double-blind,
 1663 placebo-controlled US clinical studies in which 401
 1664 adult and adolescent patients (148 males and 253
 1665 females) age 12 years and older were treated twice daily
 1666 with 2 inhalations of SYMBICORT 80/4.5 or
 1667 SYMBICORT 160/4.5, budesonide HFA metered dose
 1668 inhaler (MDI) 80 or 160 mcg, formoterol dry powder
 1669 inhaler (DPI) 4.5 mcg, or placebos (MDI and DPI).

1670

1671 **Table 4 - Adverse Events (regardless of causality)**

1672 **Occurring at an Incidence of $\geq 3\%$ and more**

1673 **Commonly than Placebo in any SYMBICORT**

1674 **Group**

1675

Treatment*	SYMBICORT		Budesonide HFA MDI		Formoterol DPI	Placebo MDI and DPI
Adverse Event	80/4.5 mcg N=277 (%)	160/4.5 mcg N=124 (%)	80 mcg N=121 (%)	160 mcg N=109 (%)	4.5 mcg N=237 (%)	N=400 (%)
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngo- laryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9

1676

*All treatments were administered as two inhalations twice daily.

1677

1678 The table above includes all events (whether or not

1679 considered drug-related by the investigators) that

1680 occurred at an incidence of $\geq 3\%$ in any one
1681 SYMBICORT group and that were more common than
1682 in the placebo group with twice daily dosing. In
1683 considering these data, the increased average duration of
1684 exposure for SYMBICORT patients should be taken into
1685 account, as incidences are not adjusted for unequal
1686 treatment duration.

1687

1688 The following additional adverse events occurred in
1689 patients ≥ 12 years of age in the active and placebo-
1690 controlled clinical studies among 2344 patients treated
1691 with SYMBICORT twice daily with an incidence of
1692 $\geq 1\%$ to $< 3\%$ regardless of relationship to treatment, and
1693 are listed in decreasing order of incidence: asthma,
1694 nausea, dysphonia, pyrexia, sinus headache, diarrhea,
1695 pharyngitis, tremor, lower respiratory tract infection,
1696 muscle spasms, urinary tract infection, rhinitis,
1697 arthralgia, myalgia, dyspepsia, gastroenteritis viral,
1698 abdominal pain upper, dizziness, sinus congestion,
1699 rhinitis allergic, pain in extremity, palpitations,
1700 bronchitis acute, tension headache, migraine, post
1701 procedural pain. Additionally, the incidence of cough,
1702 bronchitis, and viral upper respiratory tract infection was
1703 $\geq 3\%$ (but each $< 4\%$) in this population but did not meet
1704 criteria for inclusion in the above table, as these data are
1705 not derived from placebo-controlled trials for subjects
1706 ≥ 12 years old.

1707

1708 The following adverse events occurred in this same
1709 population (patients ≥ 12 years of age) with an incidence
1710 $< 1\%$, and are listed because they have previously been
1711 reported during treatment with any formulation of
1712 inhaled SYMBICORT, budesonide and/or formoterol,
1713 regardless of the indication: immediate and delayed
1714 hypersensitivity reactions, e.g., rash, pruritus, urticaria,
1715 angioedema; cardiac events, e.g., tachycardia, coronary
1716 ischemia, atrial and ventricular tachyarrhythmias;
1717 variations in blood pressure, e.g., hypotension,
1718 hypertension, hypertensive crisis; hypokalemia;
1719 hyperglycemia; taste disturbance; psychiatric symptoms,
1720 e.g., irritability, anxiety, restlessness, nervousness,
1721 agitation, depression; skin bruising.

1722

1723 **Long-Term Safety:** Long-term safety studies in
1724 adolescent and adult patients 12 years of age and older,

1725 treated for up to one year at doses up to 1280/36
1726 mcg/day (640/18 mcg twice daily), revealed neither
1727 clinically important changes in the incidence nor new
1728 types of adverse events emerging after longer periods of
1729 treatment. Similarly, no significant or unexpected
1730 patterns of abnormalities were observed for up to one
1731 year in safety measures including chemistry,
1732 hematology, ECG, Holter monitor, and HPA axis
1733 assessments.

1734

1735 **Adverse Event Reports From Other Sources:** Other
1736 relevant rare adverse events reported in the published
1737 literature, clinical trials or from worldwide marketing
1738 experience with any formulation of inhaled
1739 SYMBICORT, budesonide and/or formoterol, regardless
1740 of the indication include: immediate hypersensitivity
1741 reactions, such as anaphylactic reaction and
1742 bronchospasm; symptoms of hypocorticism and
1743 hypercorticism; glaucoma, cataracts, psychiatric
1744 symptoms, including aggressive reactions, behavioral
1745 disturbances, psychosis.

1746

1747

1748 **OVERDOSAGE**

1749 **SYMBICORT:** SYMBICORT contains both
1750 budesonide and formoterol; therefore, the risks
1751 associated with overdose for the individual
1752 components described below apply to SYMBICORT. In
1753 pharmacokinetic studies, a total of 1920/54 mcg (12
1754 actuations of SYMBICORT 160/4.5) was administered
1755 as a single dose to both healthy subjects and patients
1756 with asthma and was well tolerated. In a long-term
1757 active-controlled safety study, SYMBICORT 160/4.5
1758 was well tolerated for up to 12 months at doses up to
1759 twice the highest recommended daily dose.

1760

1761 Clinical signs in dogs that received a single inhalation
1762 dose of SYMBICORT (a combination of budesonide
1763 and formoterol) in a dry powder included tremor,
1764 mucosal redness, nasal catarrh, redness of intact skin,
1765 abdominal respiration, vomiting, and salivation; in the
1766 rat, the only clinical sign observed was increased
1767 respiratory rate in the first hour after dosing. No deaths
1768 occurred in rats given a combination of budesonide and
1769 formoterol at acute inhalation dose of 97 and 3 mg/kg,

1770 respectively (approximately 1200 and 1350 times the
1771 maximum recommended human daily inhalation dose on
1772 a mcg/m² basis). No deaths occurred in dogs given a
1773 combination of budesonide and formoterol at the acute
1774 inhalation dose of 732 and 22 mcg/kg, respectively
1775 (approximately 30 times the maximum recommended
1776 human daily inhalation dose of budesonide and
1777 formoterol on a mcg/m² basis).

1778

1779 **Budesonide:** The potential for acute toxic effects
1780 following overdose of budesonide is low. If used at
1781 excessive doses for prolonged periods, systemic
1782 corticosteroid effects such as hypercorticism may occur
1783 (see **PRECAUTIONS**). Budesonide at five times the
1784 highest recommended dose (3200 mcg daily)
1785 administered to humans for 6 weeks caused a significant
1786 reduction (27%) in the plasma cortisol response to a 6-
1787 hour infusion of ACTH compared with placebo (+1%).
1788 The corresponding effect of 10 mg prednisone daily was
1789 a 35% reduction in the plasma cortisol response to
1790 ACTH.

1791

1792 In mice the minimal inhalation lethal dose was 100
1793 mg/kg (approximately 600 times the maximum
1794 recommended human daily inhalation dose on a mcg/m²
1795 basis). In rats there were no deaths following the
1796 administration of an inhalation dose of 68 mg/kg
1797 (approximately 900 times the maximum recommended
1798 human daily inhalation dose on a mcg/m² basis). The
1799 minimal oral lethal dose in mice was 200 mg/kg
1800 (approximately 1300 times the maximum recommended
1801 human daily inhalation dose on a mcg/m² basis) and less
1802 than 100 mg/kg in rats (approximately 1300 times the
1803 maximum recommended human daily inhalation dose on
1804 a mcg/m² basis).

1805

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1806 **Formoterol:** An overdose of formoterol would likely
1807 lead to an exaggeration of effects that are typical for
1808 beta₂-agonists; therefore, the following adverse
1809 experiences may occur: angina, hypertension or
1810 hypotension, palpitations, tachycardia, arrhythmia,
1811 prolonged QTc-interval, headache, tremor, nervousness,
1812 muscle cramps, dry mouth, insomnia, fatigue, malaise,
1813 seizures, metabolic acidosis, hypokalemia,
1814 hyperglycemia, nausea and vomiting. As with all
1815 sympathomimetic medications, cardiac arrest and even
1816 death may be associated with abuse of formoterol.
1817 Formoterol was well tolerated at a delivered dose of 90
1818 mcg/day over 3 hours in adult patients with acute
1819 bronchoconstriction and when given three times daily
1820 for a total dose of 54 mcg/day for 3 days to stable
1821 asthmatics.

1822
1823 Treatment of formoterol overdosage consists of
1824 discontinuation of the medication together with
1825 institution of appropriate symptomatic and/or supportive
1826 therapy. The judicious use of a cardioselective beta-
1827 receptor blocker may be considered, bearing in mind
1828 that such medication can produce bronchospasm. There
1829 is insufficient evidence to determine if dialysis is
1830 beneficial for overdosage of formoterol. Cardiac
1831 monitoring is recommended in cases of overdosage.

1832
1833 No deaths were seen in mice given formoterol at an
1834 inhalation dose of 276 mg/kg (more than 62,200 times
1835 the maximum recommended human daily inhalation
1836 dose on a mcg/m² basis). In rats the minimum lethal
1837 inhalation dose was 40 mg/kg (approximately 18,000
1838 times the maximum recommended human daily
1839 inhalation dose on a mcg/m² basis). No deaths were
1840 seen in mice that received an oral dose of 2000 mg/kg
1841 (more than 450,000 times the maximum recommended
1842 human daily inhalation dose on a mcg/m² basis).
1843 Maximum non-lethal oral doses were 252 mg/kg in
1844 young rats and 1500 mg/kg in adult rats (approximately
1845 114,000 times and 675,000 times the maximum
1846 recommended human inhalation dose on a mcg/m²
1847 basis).

1848
1849

1850 **DOSAGE AND ADMINISTRATION**

1851 SYMBICORT should be administered by the orally
1852 inhaled route in patients with asthma 12 years of age and
1853 older. SYMBICORT should not be used for transferring
1854 patients from systemic corticosteroid therapy.

1855

1856 Long-acting beta₂-adrenergic agonists may increase the
1857 risk of asthma-related death (see **WARNINGS**).
1858 Therefore, when treating patients with asthma,
1859 SYMBICORT should only be used for patients not
1860 adequately controlled on other asthma-controller
1861 medications (e.g., low-to medium-dose inhaled
1862 corticosteroids) or whose disease severity clearly
1863 warrants initiation of treatment with two maintenance
1864 therapies. SYMBICORT is not indicated for patients
1865 whose asthma can be successfully managed by inhaled
1866 corticosteroids or other controller medications along
1867 with occasional use of inhaled short-acting beta₂-
1868 agonists.

1869

1870 SYMBICORT is available in 2 strengths, SYMBICORT
1871 80/4.5 and SYMBICORT 160/4.5, containing 80 and
1872 160 mcg of budesonide, respectively, and 4.5 mcg of
1873 formoterol fumarate dihydrate per inhalation. Each dose
1874 is administered as 2 inhalations twice daily (in the
1875 morning and the evening) by the orally inhaled route
1876 only. Rinsing the mouth after every dose is advised.

1877

1878 For patients who are currently receiving medium to high
1879 doses of inhaled corticosteroid therapy, and whose
1880 disease severity clearly warrants treatment with two
1881 maintenance therapies, the recommended starting dose
1882 is SYMBICORT 160/4.5, 2 inhalations twice daily.

1883

1884 For patients who are currently receiving low to medium
1885 doses of inhaled corticosteroid therapy, and whose
1886 disease severity clearly warrants treatment with two
1887 maintenance therapies, the recommended starting dose is
1888 SYMBICORT 80/4.5, 2 inhalations twice daily.

1889

1890 For patients who are not currently receiving inhaled
1891 corticosteroid therapy, but whose disease severity
1892 clearly warrants initiation of treatment with two
1893 maintenance therapies, the recommended starting dose is

1894 SYMBICORT 80/4.5 or 160/4.5, 2 inhalations twice
1895 daily depending upon asthma severity.
1896
1897 If a previously effective dosage regimen of
1898 SYMBICORT fails to provide adequate control of
1899 asthma, the therapeutic regimen should be reevaluated
1900 and additional therapeutic options, e.g., replacing the
1901 current strength of SYMBICORT with a higher strength,
1902 adding additional inhaled corticosteroid, or initiating
1903 oral corticosteroids, should be considered.
1904
1905 The maximum daily recommended dose is 640/18 mcg
1906 budesonide/formoterol (given as two inhalations of
1907 SYMBICORT 160/4.5 twice daily) for patients 12 years
1908 of age and older. Do not use more than twice daily or
1909 use a higher number of inhalations (more than 2
1910 inhalations twice daily) of the prescribed strength of
1911 SYMBICORT as this will result in a daily dose of
1912 formoterol in excess of the dose determined to be safe.
1913 For all patients, consideration should be given to
1914 titrating to the lowest effective strength after adequate
1915 asthma stability has been achieved.
1916
1917 SYMBICORT is not approved for the treatment or
1918 prevention of exercise-induced bronchospasm. Patients
1919 who are receiving SYMBICORT twice daily should not
1920 use formoterol or other long-acting beta₂-agonists for
1921 prevention of exercise-induced bronchospasm, or for
1922 any other reason. If symptoms arise in the period
1923 between doses, an inhaled, short-acting beta₂-agonist
1924 should be taken for immediate relief.
1925
1926 In clinical studies, significant improvement in FEV₁
1927 occurred within 15 minutes of beginning treatment with
1928 SYMBICORT in most patients and improvement in
1929 asthma control (asthma symptoms, albuterol rescue use,
1930 PEF) occurred within one day. The maximum benefit
1931 may not be achieved for 2 weeks or longer after
1932 beginning treatment. Individual patients may experience
1933 a variable time to onset and degree of symptom relief.
1934
1935 For patients who do not respond adequately to the
1936 starting dose after 1-2 weeks of therapy with
1937 SYMBICORT 80/4.5, replacing the strength with

1938 SYMBICORT 160/4.5 may provide additional asthma
1939 control.

1940

1941 SYMBICORT should be primed before using for the
1942 first time by releasing 2 test sprays into the air away
1943 from the face, shaking well for 5 seconds before each
1944 spray. In cases where the inhaler has not been used for
1945 more than 7 days or when it has been dropped, prime the
1946 inhaler again by shaking well before each spray and
1947 releasing 2 test sprays into the air away from the face.

1948

1949 **Geriatric Use**

1950 In studies where geriatric patients (65 years of age or
1951 older, see **PRECAUTIONS, Geriatric Use**) have been
1952 treated with SYMBICORT, efficacy and safety did not
1953 differ from that in younger patients. Based on available
1954 data for SYMBICORT and its active components, no
1955 dosage adjustment is recommended.

1956

1957

1958 **HOW SUPPLIED**

1959 SYMBICORT is available in two strengths:

1960

1961 **SYMBICORT 80/4.5 (NDC 0186-0372-20)** and
1962 **SYMBICORT 160/4.5 (NDC 0186-0370-20)**. Each
1963 strength is supplied as a pressurized aluminum canister
1964 with a shield component, with a red plastic actuator
1965 body with white mouthpiece and attached gray dust cap.
1966 Each canister contains 120 inhalations and has a net fill
1967 weight of 10.2 grams. Each canister is packaged in a foil
1968 overwrap pouch with desiccant sachet and placed into a
1969 carton. Each carton contains one canister and a
1970 Medication Guide.

1971

1972 The SYMBICORT canister should only be used with the
1973 SYMBICORT actuator and the SYMBICORT actuator
1974 should not be used with any other inhalation drug
1975 product.

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1977 The correct amount of medication in each inhalation
1978 cannot be ensured after the labeled number of
1979 inhalations from the canister have been used, even
1980 though the inhaler may not feel completely empty and
1981 may continue to operate. The inhaler should be
1982 discarded when the labeled number of inhalations have
1983 been used or within 3 months after removal from the foil
1984 pouch. Never immerse the canister into water to
1985 determine the amount remaining in the canister ("float
1986 test").
1987
1988 Store at controlled room temperature 20°C to 25°C
1989 (68°F to 77°F) [see USP]. Store the inhaler with the
1990 mouthpiece down.
1991
1992 For best results, the canister should be at room
1993 temperature before use. Shake well for 5 seconds before
1994 using.
1995
1996 Keep out of the reach of children. Avoid spraying in
1997 eyes. Contents under pressure. Do not puncture or
1998 incinerate. Do not store near heat or open flame.
1999 Exposure to temperatures over 120°F may cause
2000 bursting. Never throw container into fire or incinerator.
2001
2002 SYMBICORT® is a registered trademark of the
2003 AstraZeneca group of companies
2004 ©AstraZeneca 2006. All rights reserved.
2005
2006 Manufactured for: AstraZeneca LP, Wilmington, DE
2007 19850
2008 By: AstraZeneca Dunkerque Production, Dunkerque,
2009 France
2010
2011 Product of France
2012 XXXXXX-00
2013
2014 Rev. 7/20/06
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MEDICATION GUIDE

SYMBICORT 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

Read the Medication Guide that comes with SYMBICORT before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMBICORT?

- SYMBICORT contains 2 medicines:
 - Budesonide (the same medicine found in PULMICORT TURBUHALER[®]) an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - Formoterol (the same medicine found in FORADIL[®] AEROLIZER[®]), a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.
- In patients with asthma, LABA medicines such as formoterol (one of the medicines in SYMBICORT) may increase the chance of death

45 from asthma problems. In a large asthma study,
46 more patients who used another LABA medicine,
47 died from asthma problems compared with patients
48 who did not use that LABA medicine. Talk with
49 your healthcare provider about this risk and the
50 benefits of treating your asthma with SYMBICORT.

51

52 • **SYMBICORT does not relieve sudden symptoms.**
53 **Always have an inhaled short-acting beta₂-**
54 **agonist medicine with you to treat sudden**
55 **symptoms. If you do not have this type of**
56 **medicine, contact your healthcare provider to**
57 **have one prescribed for you.**

58

59 • **Do not stop using SYMBICORT unless told to do**
60 **so by your healthcare provider because your**
61 **symptoms might get worse.**

62

63 • **SYMBICORT should be used only if your**
64 **healthcare provider decides that another asthma-**
65 **controller medicine alone does not control your**
66 **asthma or that you need 2 asthma-controller**
67 **medicines.**

68

69 • **Call your healthcare provider if breathing**
70 **problems worsen over time while using**
71 **SYMBICORT. You may need different**
72 **treatment.**

73

74 • **Get emergency medical care if:**
75 ○ **Breathing problems worsen quickly, and**
76 ○ **You use your short-acting beta₂-agonist**
77 **medicine, but it does not relieve your**
78 **breathing problems.**

79

80

81 **What is SYMBICORT?**

82 SYMBICORT combines an inhaled corticosteroid
83 medicine, budesonide (the same medicine found in
84 PULMICORT TURBUHALER), and a long-acting
85 beta₂-agonist medicine (LABA), formoterol (the same
86 medicine found in FORADIL AEROLIZER).

87

88 SYMBICORT is used long-term, twice a day, everyday
89 to control symptoms of asthma, and prevent symptoms
90 such as wheezing in patients 12 years of age and older.

91

92 **SYMBICORT contains formoterol (the same**
93 **medicine found in FORADIL AEROLIZER).**

94 **Because LABA medicines such as formoterol may**
95 **increase the chance of death from asthma problems,**
96 **SYMBICORT is not for patients with asthma who:**

- 97 ○ are well controlled with another asthma-
98 controller medicine such as a low to medium
99 dose of an inhaled corticosteroid medicine
- 100 ○ only need short-acting beta₂-agonist medicines
101 once in awhile

102

103

104 **What should I tell my healthcare provider**
105 **before using SYMBICORT?**

106 **Tell your healthcare provider about all of your**
107 **health conditions, including if you:**

- 108 ○ **have heart problems**
- 109 ○ **have high blood pressure**
- 110 ○ **have seizures**
- 111 ○ **have thyroid problems**
- 112 ○ **have diabetes**
- 113 ○ **have liver problems**
- 114 ○ **have osteoporosis**
- 115 ○ **have an immune system problem**
- 116 ○ **are pregnant or planning to become pregnant.** It
117 is not known if SYMBICORT may harm your
118 unborn baby.
- 119 ○ **are breastfeeding.** It is not known if SYMBICORT
120 passes into your milk and if it can harm your baby.
- 121 ○ **are allergic to SYMBICORT or any other**
122 **medicines**
- 123 ○ **are exposed to chickenpox or measles**

124

125 Tell your healthcare provider about all the medicines
126 you take including prescription and non-prescription
127 medicines, vitamins, and herbal supplements.
128 SYMBICORT and certain other medicines may interact
129 with each other. This may cause serious side effects.

130

131 Know all the medicines you take. Keep a list and show
132 it to your healthcare provider and pharmacist each time
133 you get a new medicine.

134

135

136 **How do I use SYMBICORT?**

137 See the step-by-step instructions for using
138 SYMBICORT at the end of this Medication Guide.

139 Do not use SYMBICORT unless your healthcare
140 provider has taught you and you understand everything.
141 Ask your healthcare provider or pharmacist if you have
142 any questions.

143

144 • Use SYMBICORT exactly as prescribed. **Do not**
145 **use SYMBICORT more often than prescribed.**
146 SYMBICORT comes in 2 strengths. Your
147 healthcare provider has prescribed the strength that
148 is best for you.

149

150 • SYMBICORT should be taken as 2 puffs in the
151 morning and 2 puffs in the evening every day. If
152 you miss a dose of SYMBICORT, you should take
153 your next dose at the same time you normally do.
154 Do not take SYMBICORT more often or use more
155 puffs than you have been prescribed.

156

157 • Rinse your mouth with water after each dose (2
158 puffs) of SYMBICORT.

159

160 • While you are using SYMBICORT twice a day,
161 do not use other medicines that contain a long-
162 acting beta₂-agonist (LABA) for any reason, such
163 as SEREVENT DISKUS (salmeterol xinafoate
164 inhalation powder), ADVAIR DISKUS or
165 ADVAIR HFA (fluticasone propionate and
166 salmeterol), or FORADIL AEROLIZER
167 (formoterol fumarate inhalation powder).

168

169 • Do not change or stop any of your medicines used to
170 control or treat your breathing problems. Your
171 healthcare provider will adjust your medicines as
172 needed.

173

174 • Make sure you always have a short-acting beta₂-
175 agonist medicine with you. Use your short-acting
176 beta₂-agonist medicine if you have breathing
177 problems between doses of SYMBICORT.

178

179 • **Call your healthcare provider or get medical care**
180 **right away if:**

- 181 ○ your breathing problems worsen with
182 SYMBICORT
- 183 ○ you need to use your short-acting beta₂-
184 agonist medicine more often than usual
- 185 ○ your short-acting beta₂-agonist medicine
186 does not work as well for you at relieving
187 symptoms
- 188 ○ you need to use 4 or more inhalations of your
189 short-acting beta₂-agonist medicine for 2 or
190 more days in a row
- 191 ○ you use 1 whole canister of your short-acting
192 beta₂-agonist medicine in 8 weeks' time
- 193 ○ your peak flow meter results decrease. Your
194 healthcare provider will tell you the numbers
195 that are right for you.
- 196 ○ your asthma symptoms do not improve after
197 using SYMBICORT regularly for 1 week.

198

199 **What are the possible side effects with**
200 **SYMBICORT?**

201 SYMBICORT contains formoterol. In patients with
202 asthma, LABA medicines such as formoterol may
203 increase the chance of death from asthma problems.
204 See "What is the most important information I should
205 know about SYMBICORT?"

206

207 Other possible side effects with SYMBICORT
208 include:

209

- 210 • serious allergic reactions including rash, hives,
211 swelling of the face, mouth, and tongue, and
212 breathing problems. Call your healthcare provider
213 or get emergency medical care if you get any
214 symptoms of a serious allergic reaction.

215

- 216 • chest pain

217

218 • increased blood pressure
219
220 • a fast and irregular heartbeat
221
222 • headache
223
224 • tremor
225
226 • nervousness
227
228 • immune system effects and a higher chance for
229 infections
230
231 • eye problems including glaucoma and cataracts.
232 Regular eye exams should be considered while using
233 SYMBICORT.
234
235 • lower bone mineral density. This may be a
236 problem for people who already have a higher
237 chance for low bone mineral density (osteoporosis).
238
239 • slowed growth in children. A child's growth
240 should be checked often.
241
242 • throat irritation.
243
244 Tell your healthcare provider about any side effect that
245 bothers you or that does not go away.
246
247 These are not all the side effects with SYMBICORT.
248 Ask your healthcare provider or pharmacist for more
249 information.
250
251
252 **How do I store SYMBICORT?**
253 • Store SYMBICORT at room temperature 68°F to
254 77°F (20°C to 25°C). Store with the mouthpiece
255 down.
256 • The contents of your SYMBICORT canister are
257 under pressure. Do not puncture or throw the
258 canister into a fire or incinerator. Do not use or store
259 it near heat or open flame. Storage above 120°F may
260 cause the canister to burst.
261

- 262 • **Keep SYMBICORT and all medicines out of the**
263 **reach of children.**
264

265
266 **General Information about SYMBICORT**

267 Medicines are sometimes prescribed for purposes not
268 mentioned in a Medication Guide. Do not use
269 SYMBICORT for a condition for which it was not
270 prescribed. Do not give your SYMBICORT to other
271 people, even if they have the same condition. It may
272 harm them.

273
274 This Medication Guide summarizes the most important
275 information about SYMBICORT. If you would like
276 more information, talk with your healthcare provider or
277 pharmacist. You can ask your healthcare provider or
278 pharmacist for information about SYMBICORT that
279 was written for healthcare professionals. You can also
280 contact the company that makes SYMBICORT (toll
281 free) at 1-800-236-9933 or visit our website at
282 www.symbicort-us.com.

283

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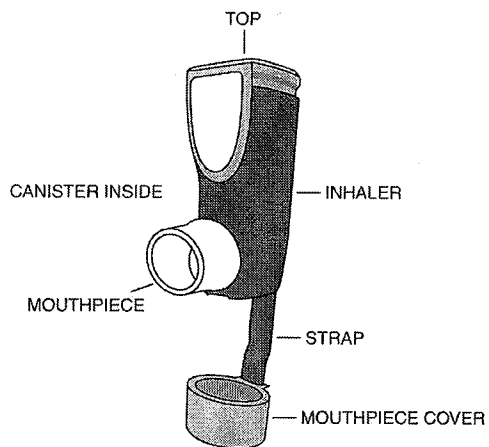


Figure 1

284

285

286

HOW TO USE SYMBICORT

287

288 Follow the instructions below for using SYMBICORT.

289 You will breathe-in (inhale) the medicine. If you have
290 any questions, ask your doctor or pharmacist.

291

292 PREPARING YOUR INHALER FOR USE

293

294

295 1. Take your SYMBICORT inhaler out of the
296 moisture-protective foil pouch before you use it
297 for the first time and throw the foil away. Write
298 the date that you open the foil pouch on the dose
299 tracker card that comes with your inhaler. You
300 should discard the inhaler when the labeled
301 number of inhalations have been used or within 3
302 months of opening the foil pouch.

303

304 2. Use the SYMBICORT canister only with the red
305 SYMBICORT inhaler supplied with the product.
306 Parts of the SYMBICORT inhaler should not be
307 used with parts from any other inhalation drug
308 product.

309

310 3. SHAKE THE INHALER WELL for 5 seconds
311 right before each use. Remove the mouthpiece
312 cover. Check the mouthpiece for foreign objects
prior to use.

313

314

315

316

317

318

319

320

321

322

323

324

325

4. SYMBICORT should be primed before using it for the first time and also when the inhaler has not been used for more than 7 days. Prime the inhaler by shaking the inhaler well for 5 seconds and then releasing a test spray. Then shake the inhaler again and release a second test spray. Your inhaler is now primed and ready for use.

Do not spray the medicine in your eyes during priming or use.

WAYS TO HOLD THE INHALER FOR USE

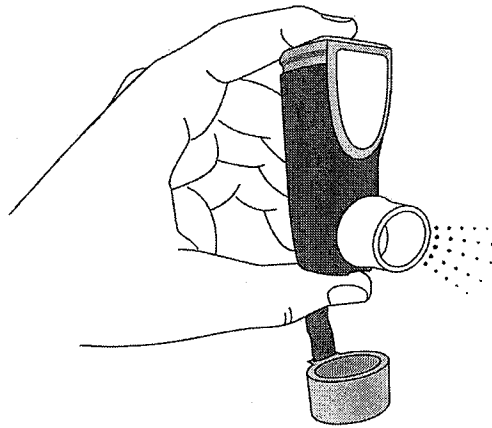


Figure 2

OR

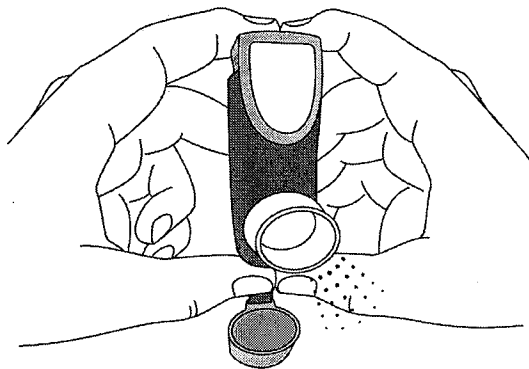


Figure 3

326
327

328

329
330 **USING YOUR SYMBICORT INHALER**
331

- 332 5. SHAKE THE INHALER WELL for 5 seconds.
333 Remove the mouthpiece cover. Check the
334 mouthpiece for foreign objects.
335
336 6. Breathe out fully (exhale). Raise the inhaler up
337 to your mouth. Place the white mouthpiece fully
338 into your mouth and close your lips around it.
339 Make sure that the inhaler is upright and that the
340 opening of the mouthpiece is pointing towards
341 the back of your throat (see Figure 4).
342
343



Figure 4

- 344
345
346 7. While breathing in deeply and slowly through
347 your mouth, press down firmly and fully on the
348 grey top of the inhaler to release the medicine
349 (see Figures 2 and 3).
350
351 8. Continue to breathe in and hold your breath for
352 about 10 seconds, or for as long as is
353 comfortable. Before breathing out, release your
354 finger from the grey top and remove the inhaler
355 from your mouth while keeping the inhaler
356 upright.
357

358 9. Shake the inhaler again for 5 seconds and repeat
359 steps 6 through 8.

360
361 **AFTER USING YOUR SYMBICORT INHALER**

362
363 10. Replace the mouthpiece cover after use.

364
365 11. After you finish taking this medicine (2 puffs),
366 rinse your mouth with water. Spit out the water.
367 Do not swallow it.

368
369 12. Use the enclosed dose tracker card to track the
370 number of puffs you have taken by marking off
371 or punching through each of your morning and
372 evening doses.

373
374 **OTHER IMPORTANT INFORMATION ABOUT**
375 **YOUR SYMBICORT INHALER**

376
377 It is very important that you keep track of the number of
378 inhalations (puffs) you have taken from your
379 SYMBICORT inhaler. Discard SYMBICORT after you
380 have used the number of inhalations on the product
381 label and box. Your inhaler may not feel empty, but you
382 will not get the right amount of medicine if you keep
383 using it.

384
385 SYMBICORT should also be discarded within 3 months
386 after it is taken out of its foil pouch.

- 387
388 • For best results, use and store at room temperature.
389 Avoid exposing product to extreme heat and cold.
390 Store with the mouthpiece down.

391
392 **HOW TO CLEAN YOUR SYMBICORT INHALER**

393 Clean the white mouthpiece of the inhaler every 7 days.

394 To clean the mouthpiece:

- 395
396 • Remove the grey mouthpiece cover
397 • Wipe the inside and outside of the white
398 mouthpiece opening with a clean, dry cloth
399 • Replace the mouthpiece cover
400 • **Do not put the inhaler into water**
401 • Do not try to take the inhaler apart

402

403

404 SYMBICORT® and PULMICORT TURBUHALER are
405 registered trademarks of the AstraZeneca group of
406 companies. ADVAIR DISKUS, ADVAIR HFA,
407 SEREVENT and DISKUS are registered trademarks of
408 GlaxoSmithKline. FORADIL AEROLIZER is a
409 registered trademark of Novartis Pharmaceuticals
410 Corporation.

411

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413

414 Manufactured for: AstraZeneca LP, Wilmington, DE
415 19850

416 By: AstraZeneca AB, Dunkerque, France

417

418 Product of France

419

420 XXXXXX-00

421 Rev 07/20/06

422

423 This Medication Guide has been approved by the U.S.

424 Food and Drug Administration.

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Badrul Chowdhury
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