

1 **PRESCRIBING INFORMATION**

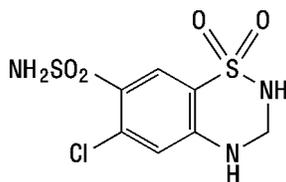
2 **DYAZIDE[®]**
3 **(hydrochlorothiazide/triamterene)**
4 **Capsules**

5 **DESCRIPTION**

6 Each capsule of DYAZIDE (hydrochlorothiazide and triamterene) for oral use, with opaque
7 red cap and opaque white body, contains hydrochlorothiazide 25 mg and triamterene 37.5 mg,
8 and is imprinted with the product name DYAZIDE and SB. Hydrochlorothiazide is a
9 diuretic/antihypertensive agent and triamterene is an antikaliuretic agent.

10 Hydrochlorothiazide is slightly soluble in water. It is soluble in dilute ammonia, dilute
11 aqueous sodium hydroxide, and dimethylformamide. It is sparingly soluble in methanol.

12 Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1,1-
13 dioxide, and its structural formula is:

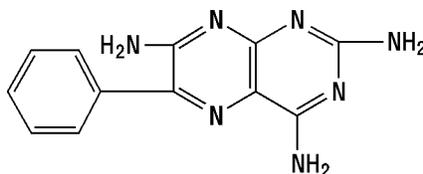


15

16

17 At 50°C, triamterene is practically insoluble in water (less than 0.1%). It is soluble in formic
18 acid, sparingly soluble in methoxyethanol, and very slightly soluble in alcohol.

19 Triamterene is 2, 4, 7-triamino-6-phenylpteridine and its structural formula is:



21

22

23 Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C Red No. 33,
24 FD&C Yellow No. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose,
25 povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other
26 inactive ingredients.

27 Capsules of DYAZIDE meet Drug Release Test 3 as published in the current USP monograph
28 for Triamterene and Hydrochlorothiazide Capsules.

29 **CLINICAL PHARMACOLOGY**

30 DYAZIDE is a diuretic/antihypertensive drug product that combines natriuretic and
31 antikaliuretic effects. Each component complements the action of the other. The
32 hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby

33 increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A
 34 portion of the additional sodium presented to the distal tubule is exchanged there for potassium
 35 and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium,
 36 compensatory mechanisms tend to increase this exchange and may produce excessive loss of
 37 potassium, hydrogen, and chloride ions. Hydrochlorothiazide also decreases the excretion of
 38 calcium and uric acid, may increase the excretion of iodide, and may reduce glomerular filtration
 39 rate. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

40 The triamterene component of DYZAZIDE exerts its diuretic effect on the distal renal tubule to
 41 inhibit the reabsorption of sodium in exchange for potassium and hydrogen ions. Its natriuretic
 42 activity is limited by the amount of sodium reaching its site of action. Although it blocks the
 43 increase in this exchange that is stimulated by mineralocorticoids (chiefly aldosterone), it is not a
 44 competitive antagonist of aldosterone and its activity can be demonstrated in adrenalectomized
 45 rats and patients with Addison's disease. As a result, the dose of triamterene required is not
 46 proportionally related to the level of mineralocorticoid activity, but is dictated by the response of
 47 the individual patients, and the kaliuretic effect of concomitantly administered drugs. By
 48 inhibiting the distal tubular exchange mechanism, triamterene maintains or increases the sodium
 49 excretion and reduces the excess loss of potassium, hydrogen and chloride ions induced by
 50 hydrochlorothiazide. As with hydrochlorothiazide, triamterene may reduce glomerular filtration
 51 and renal plasma flow. Via this mechanism it may reduce uric acid excretion although it has no
 52 tubular effect on uric acid reabsorption or secretion. Triamterene does not affect calcium
 53 excretion. No predictable antihypertensive effect has been demonstrated for triamterene.

54 Duration of diuretic activity and effective dosage range of the hydrochlorothiazide and
 55 triamterene components of DYZAZIDE are similar. Onset of diuresis with DYZAZIDE takes place
 56 within 1 hour, peaks at 2 to 3 hours and tapers off during the subsequent 7 to 9 hours.

57 DYZAZIDE is well absorbed.

58 Upon administration of a single oral dose to fasted normal male volunteers, the following
 59 mean pharmacokinetic parameters were determined:

	AUC₍₀₋₄₈₎ ng*hrs/mL (± SD)	C_{max} ng/mL (± SD)	Median T_{max} Hrs	Ae Mg (± SD)
Triamterene	148.7 (87.9)	46.4 (29.4)	1.1	2.7 (1.4)
hydroxytriamterene sulfate	1,865 (471)	720 (364)	1.3	19.7 (6.1)
hydrochlorothiazide	834 (177)	135.1 (35.7)	2.0	14.3 (3.8)

60 where AUC₍₀₋₄₈₎, C_{max}, T_{max} and Ae represent area under the plasma concentration versus time
 61 plot, maximum plasma concentration, time to reach C_{max}, and amount excreted in urine over
 62 48 hours.

63 A capsule of DYZAZIDE is bioequivalent to a single-entity 25 mg hydrochlorothiazide tablet
64 and 37.5 mg triamterene capsule used in the double-blind clinical trial below (see Clinical
65 Trials).

66 In a limited study involving 12 subjects, coadministration of DYZAZIDE with a high-fat meal
67 resulted in: (1) an increase in the mean bioavailability of triamterene by about 67% (90%
68 confidence interval = 0.99, 1.90), p-hydroxytriamterene sulfate by about 50% (90% confidence
69 interval = 1.06, 1.77), hydrochlorothiazide by about 17% (90% confidence interval = 0.90, 1.34);
70 (2) increases in the peak concentrations of triamterene and p-hydroxytriamterene; and (3) a delay
71 of up to 2 hours in the absorption of the active constituents.

72 **CLINICAL TRIALS**

73 A placebo-controlled, double-blind trial was conducted to evaluate the efficacy of DYZAZIDE.
74 This trial demonstrated that DYZAZIDE (25 mg hydrochlorothiazide/37.5 mg triamterene) was
75 effective in controlling blood pressure while reducing the incidence of
76 hydrochlorothiazide-induced hypokalemia. This trial involved 636 patients with mild to
77 moderate hypertension controlled by hydrochlorothiazide 25 mg daily and who had hypokalemia
78 (serum potassium <3.5 mEq/L) secondary to the hydrochlorothiazide. Patients were randomly
79 assigned to 4 weeks' treatment with once-daily regimens of 25 mg hydrochlorothiazide plus
80 placebo, or 25 mg hydrochlorothiazide combined with one of the following doses of triamterene:
81 25 mg, 37.5 mg, 50 mg, or 75 mg.

82 Blood pressure and serum potassium were monitored at baseline and throughout the trial. All
83 five treatment groups had similar mean blood pressure and serum potassium concentrations at
84 baseline (mean systolic blood pressure range: 137±14 mmHg to 140±16 mmHg; mean diastolic
85 blood pressure range: 86±9 mmHg to 88±8 mmHg; mean serum potassium range: 2.3 to
86 3.4 mEq/L with the majority of patients having values between 3.1 and 3.4 mEq/L).

87 While all triamterene regimens reversed hypokalemia, at week 4 the 37.5 mg regimen proved
88 optimal compared with the other tested regimens. On this regimen, 81% of the patients had a
89 significant ($p < 0.05$) reversal of hypokalemia vs. 59% of patients on the
90 placebo/hydrochlorothiazide regimen. The mean serum potassium concentration on 37.5 mg
91 triamterene went from 3.2±0.2 mEq/L at baseline to 3.7±0.3 mEq/L at week 4, a significantly
92 greater ($p < 0.05$) improvement than that achieved with placebo/hydrochlorothiazide (i.e.,
93 3.2±0.2 mEq/L at baseline and 3.5±0.4 mEq/L at week 4). Also, 51% of patients in the 37.5 mg
94 triamterene group had an increase in serum potassium of ≥ 0.5 mEq/L at week 4 vs. 33% in the
95 placebo group. The 37.5 mg triamterene/25 mg hydrochlorothiazide regimen also maintained
96 control of blood pressure; mean supine systolic blood pressure at week 4 was 138±21 mmHg
97 while mean supine diastolic blood pressure was 87±13 mmHg.

98 **INDICATIONS AND USAGE**

99 **This fixed combination drug is not indicated for the initial therapy of edema or**
100 **hypertension except in individuals in whom the development of hypokalemia cannot be**
101 **risked.**

102 DYZAZIDE is indicated for the treatment of hypertension or edema in patients who develop
103 hypokalemia on hydrochlorothiazide alone.

104 DYZAZIDE is also indicated for those patients who require a thiazide diuretic and in whom the
105 development of hypokalemia cannot be risked.

106 DYZAZIDE may be used alone or as an adjunct to other antihypertensive drugs, such as
107 beta-blockers. Since DYZAZIDE may enhance the action of these agents, dosage adjustments may
108 be necessary.

109 **Usage in Pregnancy:** The routine use of diuretics in an otherwise healthy woman is
110 inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent
111 development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful
112 in the treatment of developed toxemia.

113 Edema during pregnancy may arise from pathological causes or from the physiologic and
114 mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due
115 to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in
116 pregnancy resulting from restriction of venous return by the expanded uterus is properly treated
117 through elevation of the lower extremities and use of support hose; use of diuretics to lower
118 intravascular volume in this case is illogical and unnecessary. There is hypervolemia during
119 normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of
120 cardiovascular disease), but which is associated with edema, including generalized edema in the
121 majority of pregnant women. If this edema produces discomfort, increased recumbency will
122 often provide relief. In rare instances this edema may cause extreme discomfort which is not
123 relieved by rest. In these cases a short course of diuretics may provide relief and may be
124 appropriate.

125 **CONTRAINDICATIONS**

126 **Antikaliuretic Therapy and Potassium Supplementation:** DYZAZIDE should not be
127 given to patients receiving other potassium-sparing agents such as spironolactone, amiloride, or
128 other formulations containing triamterene. Concomitant potassium-containing salt substitutes
129 should also not be used.

130 Potassium supplementation should not be used with DYZAZIDE except in severe cases of
131 hypokalemia. Such concomitant therapy can be associated with rapid increases in serum
132 potassium levels. If potassium supplementation is used, careful monitoring of the serum
133 potassium level is necessary.

134 **Impaired Renal Function:** DYZAZIDE is contraindicated in patients with anuria, acute and
135 chronic renal insufficiency or significant renal impairment.

136 **Hypersensitivity:** Hypersensitivity to either drug in the preparation or to other
137 sulfonamide-derived drugs is a contraindication.

138 **Hyperkalemia:** DYZAZIDE should not be used in patients with preexisting elevated serum
139 potassium.

140 **WARNINGS**

141 **Hyperkalemia:** Abnormal elevation of serum potassium levels (greater than or equal to
142 5.5 mEq/liter) can occur with all potassium-sparing diuretic combinations, including DYZAZIDE.
143 Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even
144 without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected
145 hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals
146 especially in patients first receiving DYZAZIDE, when dosages are changed or with any illness
147 that may influence renal function.

148 If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue,
149 flaccid paralysis of the extremities, bradycardia, and shock), an electrocardiogram (ECG) should
150 be obtained. However, it is important to monitor serum potassium levels because hyperkalemia
151 may not be associated with ECG changes.

152 If hyperkalemia is present, DYZAZIDE should be discontinued immediately and a thiazide
153 alone should be substituted. If the serum potassium exceeds 6.5 mEq/liter more vigorous therapy
154 is required. The clinical situation dictates the procedures to be employed. These include the
155 intravenous administration of calcium chloride solution, sodium bicarbonate solution, and/or the
156 oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic
157 exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered.
158 Persistent hyperkalemia may require dialysis.

159 The development of hyperkalemia associated with potassium-sparing diuretics is accentuated
160 in the presence of renal impairment (see CONTRAINDICATIONS section). Patients with mild
161 renal functional impairment should not receive this drug without frequent and continuing
162 monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with
163 impaired renal function. The renal clearances of hydrochlorothiazide and the pharmacologically
164 active metabolite of triamterene, the sulfate ester of hydroxytriamterene, have been shown to be
165 reduced and the plasma levels increased following administration of DYZAZIDE to elderly
166 patients and patients with impaired renal function.

167 Hyperkalemia has been reported in diabetic patients with the use of potassium-sparing agents
168 even in the absence of apparent renal impairment. Accordingly, serum electrolytes must be
169 frequently monitored if DYZAZIDE is used in diabetic patients.

170 **Metabolic or Respiratory Acidosis:** Potassium-sparing therapy should also be avoided in
171 severely ill patients in whom respiratory or metabolic acidosis may occur. Acidosis may be
172 associated with rapid elevations in serum potassium levels. If DYZAZIDE is employed, frequent
173 evaluations of acid/base balance and serum electrolytes are necessary.

174 **Acute Myopia and Secondary Angle-Closure Glaucoma:** Hydrochlorothiazide, a
175 sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute
176 angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain
177 and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure
178 glaucoma can lead to permanent vision loss. The primary treatment is to discontinue
179 hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be

180 considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute
181 angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

182 **PRECAUTIONS**

183 **Diabetes:** Caution should be exercised when administering DYZAZIDE to patients with
184 diabetes, since thiazides may cause hyperglycemia, glycosuria, and alter insulin requirements in
185 diabetes. Also, diabetes mellitus may become manifest during thiazide administration.

186 **Impaired Hepatic Function:** Thiazides should be used with caution in patients with impaired
187 hepatic function. They can precipitate hepatic coma in patients with severe liver disease.

188 Potassium depletion induced by the thiazide may be important in this connection. Administer
189 DYZAZIDE cautiously and be alert for such early signs of impending coma as confusion,
190 drowsiness, and tremor; if mental confusion increases discontinue DYZAZIDE for a few days.

191 Attention must be given to other factors that may precipitate hepatic coma, such as blood in the
192 gastrointestinal tract or preexisting potassium depletion.

193 **Hypokalemia:** Hypokalemia is uncommon with DYZAZIDE; but, should it develop, corrective
194 measures should be taken such as potassium supplementation or increased intake of
195 potassium-rich foods. Institute such measures cautiously with frequent determinations of serum
196 potassium levels, especially in patients receiving digitalis or with a history of cardiac
197 arrhythmias. If serious hypokalemia (serum potassium less than 3.0 mEq/L) is demonstrated by
198 repeat serum potassium determinations, DYZAZIDE should be discontinued and potassium
199 chloride supplementation initiated. Less serious hypokalemia should be evaluated with regard to
200 other coexisting conditions and treated accordingly.

201 **Electrolyte Imbalance:** Electrolyte imbalance, often encountered in such conditions as heart
202 failure, renal disease or cirrhosis of the liver, may also be aggravated by diuretics and should be
203 considered during therapy with DYZAZIDE when using high doses for prolonged periods or in
204 patients on a salt-restricted diet. Serum determinations of electrolytes should be performed, and
205 are particularly important if the patient is vomiting excessively or receiving fluids parenterally.
206 Possible fluid and electrolyte imbalance may be indicated by such warning signs as: dry mouth,
207 thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue,
208 hypotension, oliguria, tachycardia, and gastrointestinal symptoms.

209 **Hypochloremia:** Although any chloride deficit is generally mild and usually does not require
210 specific treatment except under extraordinary circumstances (as in liver disease or renal disease),
211 chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional
212 hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water
213 restriction, rather than administration of salt, except in rare instances when the hyponatremia is
214 life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

215 **Renal Stones:** Triamterene has been found in renal stones in association with the other usual
216 calculus components. DYZAZIDE should be used with caution in patients with a history of renal
217 stones.

218 **Laboratory Tests: Serum Potassium:** The normal adult range of serum potassium is 3.5 to
219 5.0 mEq per liter with 4.5 mEq often being used for a reference point. If hypokalemia should
220 develop, corrective measures should be taken such as potassium supplementation or increased
221 dietary intake of potassium-rich foods.

222 Institute such measures cautiously with frequent determinations of serum potassium levels.
223 Potassium levels persistently above 6 mEq per liter require careful observation and treatment.
224 Serum potassium levels do not necessarily indicate true body potassium concentration. A rise in
225 plasma pH may cause a decrease in plasma potassium concentration and an increase in the
226 intracellular potassium concentration. Discontinue corrective measures for hypokalemia
227 immediately if laboratory determinations reveal an abnormal elevation of serum potassium.

228 Discontinue DYZAZIDE and substitute a thiazide diuretic alone until potassium levels return to
229 normal.

230 **Serum Creatinine and BUN:** DYZAZIDE may produce an elevated blood urea nitrogen
231 level, creatinine level or both. This apparently is secondary to a reversible reduction of
232 glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia) rather
233 than renal toxicity; levels usually return to normal when DYZAZIDE is discontinued. If azotemia
234 increases, discontinue DYZAZIDE. Periodic BUN or serum creatinine determinations should be
235 made, especially in elderly patients and in patients with suspected or confirmed renal
236 insufficiency.

237 **Serum PBI:** Thiazide may decrease serum PBI levels without sign of thyroid disturbance.

238 **Parathyroid Function:** Thiazides should be discontinued before carrying out tests for
239 parathyroid function. Calcium excretion is decreased by thiazides. Pathologic changes in the
240 parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few
241 patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such
242 as bone resorption and peptic ulceration have not been seen.

243 **Drug Interactions: Angiotensin-converting Enzyme Inhibitors:** Potassium-sparing
244 agents should be used with caution in conjunction with angiotensin-converting enzyme (ACE)
245 inhibitors due to an increased risk of hyperkalemia.

246 **Oral Hypoglycemic Drugs:** Concurrent use with chlorpropamide may increase the risk of
247 severe hyponatremia.

248 **Nonsteroidal Anti-inflammatory Drugs:** A possible interaction resulting in acute renal
249 failure has been reported in a few patients on DYZAZIDE when treated with indomethacin, a
250 nonsteroidal anti-inflammatory agent. Caution is advised in administering nonsteroidal
251 anti-inflammatory agents with DYZAZIDE.

252 **Lithium:** Lithium generally should not be given with diuretics because they reduce its renal
253 clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before
254 use of such concomitant therapy with DYZAZIDE.

255 **Surgical Considerations:** Thiazides have been shown to decrease arterial responsiveness
256 to norepinephrine (an effect attributed to loss of sodium). This diminution is not sufficient to
257 preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown

258 to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine (an
259 effect attributed to potassium loss); consequently caution should be observed in patients
260 undergoing surgery.

261 **Other Considerations:** Concurrent use of hydrochlorothiazide with amphotericin B or
262 corticosteroids or corticotropin (ACTH) may intensify electrolyte imbalance, particularly
263 hypokalemia, although the presence of triamterene minimizes the hypokalemic effect.

264 Thiazides may add to or potentiate the action of other antihypertensive drugs. See
265 INDICATIONS AND USAGE for concomitant use with other antihypertensive drugs.

266 The effect of oral anticoagulants may be decreased when used concurrently with
267 hydrochlorothiazide; dosage adjustments may be necessary.

268 DYZAZIDE may raise the level of blood uric acid; dosage adjustments of antigout medication
269 may be necessary to control hyperuricemia and gout.

270 The following agents given together with triamterene may promote serum potassium
271 accumulation and possibly result in hyperkalemia because of the potassium-sparing nature of
272 triamterene, especially in patients with renal insufficiency: blood from blood bank (may contain
273 up to 30 mEq of potassium per liter of plasma or up to 65 mEq per liter of whole blood when
274 stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter);
275 potassium-containing medications (such as parenteral penicillin G potassium); salt substitutes
276 (most contain substantial amounts of potassium).

277 Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or
278 rectally, reduce serum potassium levels by sodium replacement of the potassium; fluid retention
279 may occur in some patients because of the increased sodium intake.

280 Chronic or overuse of laxatives may reduce serum potassium levels by promoting excessive
281 potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining
282 effects of triamterene.

283 The effectiveness of methenamine may be decreased when used concurrently with
284 hydrochlorothiazide because of alkalization of the urine.

285 **Drug/Laboratory Test Interactions:** Triamterene and quinidine have similar fluorescence
286 spectra; thus, DYZAZIDE will interfere with the fluorescent measurement of quinidine.

287 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Long-term
288 studies have not been conducted with DYZAZIDE (the triamterene/hydrochlorothiazide
289 combination), or with triamterene alone.

290 **Hydrochlorothiazide:** Two-year feeding studies in mice and rats, conducted under the
291 auspices of the National Toxicology Program (NTP), treated mice and rats with doses of
292 hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body-weight basis, these
293 doses are 600 times (in mice) and 100 times (in rats) the Maximum Recommended Human Dose
294 (MRHD) for the hydrochlorothiazide component of DYZAZIDE at 50 mg/day (or 1.0 mg/kg/day
295 based on 50 kg individuals). On the basis of body-surface area, these doses are 56 times (in
296 mice) and 21 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic

297 potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of
298 hepatocarcinogenicity in male mice.

299 **Mutagenesis:** Studies of the mutagenic potential of DYZAZIDE (the
300 triamterene/hydrochlorothiazide combination), or of triamterene alone have not been performed.

301 **Hydrochlorothiazide:** Hydrochlorothiazide was not genotoxic in in vitro assays using
302 strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames
303 test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in in vivo
304 assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes,
305 and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in
306 the in vitro CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma
307 Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL.
308 Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an
309 unspecified concentration of hydrochlorothiazide.

310 **Impairment of Fertility:** Studies of the effects of DYZAZIDE (the
311 triamterene/hydrochlorothiazide combination), or of triamterene alone on animal reproductive
312 function have not been conducted.

313 **Hydrochlorothiazide:** Hydrochlorothiazide had no adverse effects on the fertility of mice
314 and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up
315 to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding
316 multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice)
317 and 0.8 (rats) on the basis of body-surface area.

318 **Pregnancy: Category C: Teratogenic Effects: DYZAZIDE:** Animal reproduction studies to
319 determine the potential for fetal harm by DYZAZIDE have not been conducted. However, a One
320 Generation Study in the rat approximated composition of DYZAZIDE by using a 1:1 ratio of
321 triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at
322 those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and
323 on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

324 The safe use of DYZAZIDE in pregnancy has not been established since there are no adequate
325 and well-controlled studies with DYZAZIDE in pregnant women. DYZAZIDE should be used
326 during pregnancy only if the potential benefit justifies the risk to the fetus.

327 **Triamterene:** Reproduction studies have been performed in rats at doses as high as 20 times
328 the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface
329 area without evidence of harm to the fetus due to triamterene.

330 Because animal reproduction studies are not always predictive of human response, this drug
331 should be used during pregnancy only if clearly needed.

332 **Hydrochlorothiazide:** Hydrochlorothiazide was orally administered to pregnant mice and
333 rats during respective periods of major organogenesis at doses up to 3,000 and 1,000 mg/kg/day,
334 respectively. At these doses, which are multiples of the MRHD equal to 3,000 for mice and
335 1,000 for rats, based on body-weight, and equal to 282 for mice and 206 for rats, based on
336 body-surface area, there was no evidence of harm to the fetus.

337 There are, however, no adequate and well-controlled studies in pregnant women. Because
338 animal reproduction studies are not always predictive of human response, this drug should be
339 used during pregnancy only if clearly needed.

340 **Nonteratogenic Effects:** Thiazides and triamterene have been shown to cross the placental
341 barrier and appear in cord blood. The use of thiazides and triamterene in pregnant women
342 requires that the anticipated benefit be weighed against possible hazards to the fetus. These
343 hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possible other
344 adverse reactions which have occurred in the adult.

345 **Nursing Mothers:** Thiazides and triamterene in combination have not been studied in nursing
346 mothers. Triamterene appears in animal milk; this may occur in humans. Thiazides are excreted
347 in human breast milk. If use of the combination drug product is deemed essential, the patient
348 should stop nursing.

349 **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

350 **ADVERSE REACTIONS**

351 Adverse effects are listed in decreasing order of severity.

352 **Hypersensitivity:** Anaphylaxis, rash, urticaria, subacute cutaneous lupus erythematosus-like
353 reactions, photosensitivity.

354 **Cardiovascular:** Arrhythmia, postural hypotension.

355 **Metabolic:** Diabetes mellitus, hyperkalemia, hypokalemia, hyponatremia, acidosis,
356 hypercalcemia, hyperglycemia, glycosuria, hyperuricemia, hypochloremia.

357 **Gastrointestinal:** Jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and
358 vomiting, diarrhea, constipation, abdominal pain.

359 **Renal:** Acute renal failure (one case of irreversible renal failure has been reported), interstitial
360 nephritis, renal stones composed primarily of triamterene, elevated BUN, and serum creatinine,
361 abnormal urinary sediment.

362 **Hematologic:** Leukopenia, thrombocytopenia and purpura, megaloblastic anemia.

363 **Musculoskeletal:** Muscle cramps.

364 **Central Nervous System:** Weakness, fatigue, dizziness, headache, dry mouth.

365 **Miscellaneous:** Impotence, sialadenitis.

366 Thiazides alone have been shown to cause the following additional adverse reactions:

367 **Central Nervous System:** Paresthesias, vertigo.

368 **Ophthalmic:** Xanthopsia, transient blurred vision.

369 **Respiratory:** Allergic pneumonitis, pulmonary edema, respiratory distress.

370 **Other:** Necrotizing vasculitis, exacerbation of lupus.

371 **Hematologic:** Aplastic anemia, agranulocytosis, hemolytic anemia.

372 **Neonate and infancy:** Thrombocytopenia and pancreatitis—rarely, in newborns whose
373 mothers have received thiazides during pregnancy.

374 **Skin:** Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis
375 including toxic epidermal necrolysis.

376 **DOSAGE AND ADMINISTRATION**

377 **The usual dose of DYZAZIDE is one or two capsules given once daily, with appropriate**
378 **monitoring of serum potassium and of the clinical effect (see WARNINGS, Hyperkalemia).**

379 **OVERDOSAGE**

380 Electrolyte imbalance is the major concern (see WARNINGS section). Symptoms reported
381 include: polyuria, nausea, vomiting, weakness, lassitude, fever, flushed face, and hyperactive
382 deep tendon reflexes. If hypotension occurs, it may be treated with pressor agents such as
383 levarterenol to maintain blood pressure. Carefully evaluate the electrolyte pattern and fluid
384 balance. Induce immediate evacuation of the stomach through emesis or gastric lavage. There is
385 no specific antidote.

386 Reversible acute renal failure following ingestion of 50 tablets of a product containing a
387 combination of 50 mg triamterene and 25 mg hydrochlorothiazide has been reported.
388 Although triamterene is largely protein-bound (approximately 67%), there may be some benefit
389 to dialysis in cases of overdosage.

390 **HOW SUPPLIED**

391 Capsules containing 25 mg hydrochlorothiazide and 37.5 mg triamterene, in bottles of
392 1,000 capsules; in Patient-Pak™ unit-of-use bottles of 100.

393 They are supplied as follows:

394 NDC 0007-3650-22—in Patient-Pak™ unit-of-use bottles of 100.

395 NDC 0007-3650-30—bottles of 1,000.

396 Store at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15°
397 to 30°C (59° to 86°F). Protect from light. Dispense in a tight, light-resistant container.

398



GlaxoSmithKline

399

400 GlaxoSmithKline

401 Research Triangle Park, NC 27709

402

403 DYZAZIDE is a registered trademark of GlaxoSmithKline.

404 ©2011, GlaxoSmithKline. All rights reserved.

405

406 February 2011

407 DYZ:74PI