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TABLETS
ATACAND HCT™ 16-12.5

(candesartan cilexetil –
hydrochlorothiazide)

ATACAND HCT™ 32-12.5

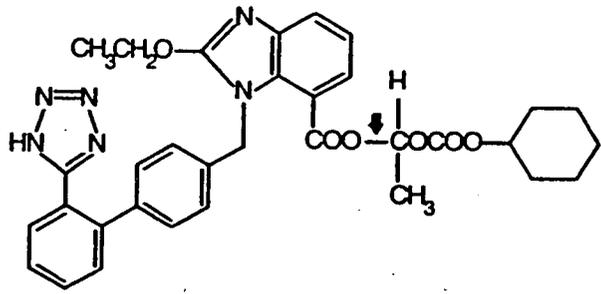
(candesartan cilexetil –
hydrochlorothiazide)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND HCT should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

ATACAND HCT* (candesartan cilexetil-hydrochlorothiazide) combines an angiotensin II receptor (type AT₁) antagonist and a diuretic, hydrochlorothiazide. Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-[[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate. Its empirical formula is C₃₃H₃₄N₆O₆, and its structural formula is



↓ site of ester hydrolysis.

31

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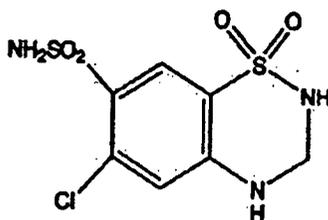
32

33 Candesartan cilexetil is a white to off-white powder with a
34 molecular weight of 610.67. It is practically insoluble in
35 water and sparingly soluble in methanol. Candesartan cilexetil
36 is a racemic mixture containing one chiral center at the
37 cyclohexyloxycarbonyloxy ethyl ester group. Following oral
38 administration, candesartan cilexetil undergoes hydrolysis at
39 the ester link to form the active drug, candesartan, which is
40 achiral.

41

42 Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-
43 benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical
44 formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is

45



46

47

48

49 Hydrochlorothiazide is a white, or practically white,
50 crystalline powder with a molecular weight of 297.72, which
51 is slightly soluble in water, but freely soluble in sodium
52 hydroxide solution.

53

54 ATACAND HCT is available for oral administration in two
55 tablet strengths of candesartan cilexetil and
56 hydrochlorothiazide.

57 ATACAND HCT 16-12.5 contains 16 mg of candesartan
58 cilexetil and 12.5 mg of hydrochlorothiazide. ATACAND
59 HCT 32-12.5 contains 32 mg of candesartan cilexetil and 12.5
60 mg of hydrochlorothiazide. The inactive ingredients of the
61 tablets are calcium carboxymethylcellulose, hydroxypropyl
62 cellulose, lactose monohydrate, magnesium stearate, corn
63 starch, polyethylene glycol 8000, and ferric oxide (yellow).
64 Ferric oxide (reddish brown) is also added to the 16-12.5 mg
65 tablet as colorant.

66

67 CLINICAL PHARMACOLOGY

68 Mechanism of Action

69 Angiotensin II is formed from angiotensin I in a reaction
70 catalyzed by angiotensin-converting enzyme (ACE, kininase
71 II). Angiotensin II is the principal pressor agent of the renin-
72 angiotensin system, with effects that include vasoconstriction,
73 stimulation of synthesis and release of aldosterone, cardiac
74 stimulation, and renal reabsorption of sodium. Candesartan
75 blocks the vasoconstrictor and aldosterone-secreting effects of
76 angiotensin II by selectively blocking the binding of
77 angiotensin II to the AT₁ receptor in many tissues, such as
78 vascular smooth muscle and the adrenal gland. Its action is,
79 therefore, independent of the pathways for angiotensin II
80 synthesis.

81
82 There is also an AT₂ receptor found in many tissues, but AT₂
83 is not known to be associated with cardiovascular
84 homeostasis. Candesartan has much greater affinity
85 (>10,000-fold) for the AT₁ receptor than for the AT₂ receptor.

86
87 Blockade of the renin-angiotensin system with ACE
88 inhibitors, which inhibit the biosynthesis of angiotensin II
89 from angiotensin I, is widely used in the treatment of
90 hypertension. ACE inhibitors also inhibit the degradation of
91 bradykinin, a reaction also catalyzed by ACE. Because
92 candesartan does not inhibit ACE (kininase II), it does not
93 affect the response to bradykinin. Whether this difference has
94 clinical relevance is not yet known. Candesartan does not
95 bind to or block other hormone receptors or ion channels
96 known to be important in cardiovascular regulation.

97
98 Blockade of the angiotensin II receptor inhibits the negative
99 regulatory feedback of angiotensin II on renin secretion, but
100 the resulting increased plasma renin activity and angiotensin
101 II circulating levels do not overcome the effect of candesartan
102 on blood pressure.

103

104 Hydrochlorothiazide is a thiazide diuretic. Thiazides affect
105 the renal tubular mechanisms of electrolyte reabsorption,
106 directly increasing excretion of sodium and chloride in
107 approximately equivalent amounts. Indirectly, the diuretic
108 action of hydrochlorothiazide reduces plasma volume, with
109 consequent increases in plasma renin activity, increases in
110 aldosterone secretion, increases in urinary potassium loss, and
111 decreases in serum potassium. The renin-aldosterone link is
112 mediated by angiotensin II, so coadministration of an
113 angiotensin II receptor antagonist tends to reverse the
114 potassium loss associated with these diuretics.

115

116 The mechanism of the antihypertensive effect of thiazides is
117 unknown.

118

119 **Pharmacokinetics**

120 *General*

121 *Candesartan Cilexetil*

122 Candesartan cilexetil is rapidly and completely bioactivated
123 by ester hydrolysis during absorption from the gastrointestinal
124 tract to candesartan, a selective AT₁ subtype angiotensin II
125 receptor antagonist. Candesartan is mainly excreted
126 unchanged in urine and feces (via bile). It undergoes minor
127 hepatic metabolism by O-deethylation to an inactive
128 metabolite. The elimination half-life of candesartan is
129 approximately 9 hours. After single and repeated
130 administration, the pharmacokinetics of candesartan are linear
131 for oral doses up to 32 mg of candesartan cilexetil.
132 Candesartan and its inactive metabolite do not accumulate in
133 serum upon repeated once-daily dosing.

134

135 Following administration of candesartan cilexetil, the absolute
136 bioavailability of candesartan was estimated to be 15%. After
137 tablet ingestion, the peak serum concentration (C_{max}) is
138 reached after 3 to 4 hours. Food with a high fat content does
139 not affect the bioavailability of candesartan after candesartan
140 cilexetil administration.

141

142 *Hydrochlorothiazide*

143 When plasma levels have been followed for at least 24 hours,
144 the plasma half-life has been observed to vary between 5.6
145 and 14.8 hours.

146

147

148

149

150 **Metabolism and Excretion**

151 *Candesartan Cilexetil*

152 Total plasma clearance of candesartan is 0.37 mL/min/kg,
153 with a renal clearance of 0.19 mL/min/kg. When candesartan
154 is administered orally, about 26% of the dose is excreted
155 unchanged in urine. Following an oral dose of ¹⁴C-labeled
156 candesartan cilexetil, approximately 33% of radioactivity is
157 recovered in urine and approximately 67% in feces.
158 Following an intravenous dose of ¹⁴C-labeled candesartan,
159 approximately 59% of radioactivity is recovered in urine and
160 approximately 36% in feces. Biliary excretion contributes to
161 the elimination of candesartan.

162

163 *Hydrochlorothiazide*

164 Hydrochlorothiazide is not metabolized but is eliminated
165 rapidly by the kidney. At least 61% of the oral dose is
166 eliminated unchanged within 24 hours.

167

168 **Distribution**

169 *Candesartan Cilexetil*

170 The volume of distribution of candesartan is 0.13 L/kg.
171 Candesartan is highly bound to plasma proteins (>99%) and
172 does not penetrate red blood cells. The protein binding is
173 constant at candesartan plasma concentrations well above the
174 range achieved with recommended doses. In rats, it has been
175 demonstrated that candesartan crosses the blood-brain barrier
176 poorly, if at all. It has also been demonstrated in rats that
177 candesartan passes across the placental barrier and is
178 distributed in the fetus.

179

180 *Hydrochlorothiazide*

181 Hydrochlorothiazide crosses the placental but not the blood-
182 brain barrier and is excreted in breast milk.

183

184 **Special Populations**

185 *Pediatric*

186 The pharmacokinetics of candesartan cilexetil have not been
187 investigated in patients <18 years of age.

188 *Geriatric*

189 The pharmacokinetics of candesartan have been studied in the
190 elderly (≥ 65 years). The plasma concentration of candesartan
191 was higher in the elderly (C_{max} was approximately 50%
192 higher, and AUC was approximately 80% higher) compared
193 to younger subjects administered the same dose. The
194 pharmacokinetics of candesartan were linear in the elderly,
195 and candesartan and its inactive metabolite did not
196 accumulate in the serum of these subjects upon repeated,
197 once-daily administration. No initial dosage adjustment is
198 necessary. (See DOSAGE AND ADMINISTRATION.)

199

200 *Gender*

201 There is no difference in the pharmacokinetics of candesartan
202 between male and female subjects.

203

204 *Renal Insufficiency*

205 In hypertensive patients with renal insufficiency, serum
206 concentrations of candesartan were elevated. After repeated
207 dosing, the AUC and C_{max} were approximately doubled in
208 patients with severe renal impairment (creatinine clearance
209 < 30 mL/min/1.73m²) compared to patients with normal
210 kidney function. The pharmacokinetics of candesartan in
211 hypertensive patients undergoing hemodialysis are similar to
212 those in hypertensive patients with severe renal impairment.
213 Candesartan cannot be removed by hemodialysis. No initial
214 dosage adjustment is necessary in patients with renal
215 insufficiency.

216

217 Thiazide diuretics are eliminated by the kidney, with a
218 terminal half-life of 5-15 hours. In a study of patients with
219 impaired renal function (mean creatinine clearance of 19
220 mL/min), the half-life of hydrochlorothiazide elimination was
221 lengthened to 21 hours. (See DOSAGE AND
222 ADMINISTRATION.)

223

224 *Hepatic Insufficiency*

225 No differences in the pharmacokinetics of candesartan were
226 observed in patients with mild to moderate chronic liver
227 disease. Thiazide diuretics should be used with caution in
228 patients with hepatic impairment. (See DOSAGE AND
229 ADMINISTRATION.)

230

231

232

233

234 **Pharmacodynamics**

235 *Candesartan Cilexetil*

236 Candesartan inhibits the pressor effects of angiotensin II
237 infusion in a dose-dependent manner. After 1 week of once-
238 daily dosing with 8-mg of candesartan cilexetil, the pressor
239 effect was inhibited by approximately 90% at peak with
240 approximately 50% inhibition persisting for 24 hours.

241

242 Plasma concentrations of angiotensin I and angiotensin II, and
243 plasma renin activity (PRA), increased in a dose-dependent
244 manner after single and repeated administration of
245 candesartan cilexetil to healthy subjects and hypertensive
246 patients. ACE activity was not altered in healthy subjects
247 after repeated candesartan cilexetil administration. The once-
248 daily administration of up to 16 mg of candesartan cilexetil to
249 healthy subjects did not influence plasma aldosterone
250 concentrations, but a decrease in the plasma concentration of
251 aldosterone was observed when 32 mg of candesartan cilexetil
252 was administered to hypertensive patients. In spite of the
253 effect of candesartan cilexetil on aldosterone secretion, very
254 little effect on serum potassium was observed.

255

256 In multiple-dose studies with hypertensive patients, there
257 were no clinically significant changes in metabolic function
258 including serum levels of total cholesterol, triglycerides,
259 glucose, or uric acid. In a 12-week study of 161 patients with
260 noninsulin-dependent (type 2) diabetes mellitus and
261 hypertension, there was no change in the level of HbA_{1c}.

262

263 *Hydrochlorothiazide*

264 After oral administration of hydrochlorothiazide, diuresis
265 begins within 2 hours, peaks in about 4 hours and lasts about
266 6 to 12 hours.

267

268 **Clinical Trials**

269 *Candesartan Cilexetil – Hydrochlorothiazide*

270 Of 12 controlled clinical trials involving 4588 patients, 5 were
271 double-blind, placebo controlled and evaluated the
272 antihypertensive effects of single entities vs the combination.
273 These 5 trials, of 8 to 12 weeks duration, randomized 3037
274 hypertensive patients. Doses ranged from 2 to 32 mg
275 candesartan cilexetil and from 6.25 to 25 mg
276 hydrochlorothiazide administered once daily in various
277 combinations.

278

279 The combination of candesartan cilexetil-hydrochlorothiazide
280 resulted in placebo-adjusted decreases in sitting systolic and
281 diastolic blood pressures of 14-18/8-11 mm Hg at doses of
282 16-12.5 mg and 32-12.5 mg. The combination of candesartan
283 cilexetil and hydrochlorothiazide 32-25 mg resulted in
284 placebo-adjusted decreases in sitting systolic and diastolic
285 blood pressures of 16-19/9-11 mm Hg. The placebo corrected
286 trough to peak ratio was evaluated in a study of candesartan
287 cilexetil-hydrochlorothiazide 32-12.5 mg and was 88%.

288

289 Most of the antihypertensive effect of the combination of
290 candesartan cilexetil and hydrochlorothiazide was seen in
291 1- to 2-weeks with the full effect observed within 4 weeks. In
292 long-term studies of up to 1 year, the blood pressure lowering
293 effect of the combination was maintained. The
294 antihypertensive effect was similar regardless of age or
295 gender, and overall response to the combination was similar
296 in black and non-black patients. No appreciable changes in
297 heart rate were observed with combination therapy in
298 controlled trials.

299

300 **INDICATIONS AND USAGE**

301 ATACAND HCT is indicated for the treatment of
302 hypertension. This fixed dose combination is not indicated
303 for initial therapy (see DOSAGE AND
304 ADMINISTRATION).

305

306 **CONTRAINDICATIONS**

307 ATACAND HCT is contraindicated in patients who are
308 hypersensitive to any component of this product.
309 Because of the hydrochlorothiazide component, this product
310 is contraindicated in patients with anuria or hypersensitivity to
311 other sulfonamide-derived drugs.

312

313 **WARNINGS**

314 **Fetal/Neonatal Morbidity and Mortality**

315 Drugs that act directly on the renin-angiotensin system can
316 cause fetal and neonatal morbidity and death when
317 administered to pregnant women. Several dozen cases have
318 been reported in the world literature in patients who were
319 taking angiotensin-converting enzyme inhibitors. When
320 pregnancy is detected, ATACAND HCT should be
321 discontinued as soon as possible.

322

323 The use of drugs that act directly on the renin-angiotensin
324 system during the second and third trimesters of pregnancy
325 has been associated with fetal and neonatal injury, including
326 hypotension, neonatal skull hypoplasia, anuria, reversible or
327 irreversible renal failure, and death. Oligohydramnios has
328 also been reported, presumably resulting from decreased fetal
329 renal function; oligohydramnios in this setting has been
330 associated with fetal limb contractures, craniofacial
331 deformation, and hypoplastic lung development. Prematurity,
332 intrauterine growth retardation, and patent ductus arteriosus
333 have also been reported, although it is not clear whether these
334 occurrences were due to exposure to the drug.

335
336 These adverse effects do not appear to have resulted from
337 intrauterine drug exposure that has been limited to the first
338 trimester. Mothers whose embryos and fetuses are exposed to
339 an angiotensin II receptor antagonist only during the first
340 trimester should be so informed. Nonetheless, when patients
341 become pregnant, physicians should have the patient
342 discontinue the use of ATACAND HCT as soon as possible.

343
344 Rarely (probably less often than once in every thousand
345 pregnancies), no alternative to a drug acting on the renin-
346 angiotensin system will be found. In these rare cases, the
347 mothers should be apprised of the potential hazards to their
348 fetuses, and serial ultrasound examinations should be
349 performed to assess the intra-amniotic environment.

350
351 If oligohydramnios is observed, ATACAND HCT should be
352 discontinued unless it is considered life saving for the mother.
353 Contraction stress testing (CST), a nonstress test (NST), or
354 biophysical profiling (BPP) may be appropriate, depending
355 upon the week of pregnancy. Patients and physicians should
356 be aware, however, that oligohydramnios may not appear
357 until after the fetus has sustained irreversible injury.

358
359 Infants with histories of *in utero* exposure to an angiotensin II
360 receptor antagonist should be closely observed for
361 hypotension, oliguria, and hyperkalemia. If oliguria occurs,
362 attention should be directed toward support of blood pressure
363 and renal perfusion. Exchange transfusion or dialysis may be
364 required as means of reversing hypotension and/or
365 substituting for disordered renal function.

366

367

368

369

370 *Candesartan Cilexetil-Hydrochlorothiazide*

371 There was no evidence of teratogenicity or other adverse
372 effects on embryo-fetal development when pregnant mice,
373 rats or rabbits were treated orally with candesartan cilexetil
374 alone or in combination with hydrochlorothiazide. For mice,
375 the maximum dose of candesartan cilexetil was 1000
376 mg/kg/day (about 150 times the maximum recommended
377 daily human dose [MRHD]*). For rats, the maximum dose of
378 candesartan cilexetil was 100 mg/kg/day (about 31 times the
379 MRHD*). For rabbits, the maximum dose of candesartan
380 cilexetil was 1 mg/kg/day (a maternally toxic dose that is
381 about half the MRHD*). In each of these studies,
382 hydrochlorothiazide was tested at the same dose level (10
383 mg/kg/day, about 4, 8, and 15 times the MRHD* in mouse,
384 rats, and rabbit, respectively). There was no evidence of harm
385 to the rat or mouse fetus or embryo in studies in which
386 hydrochlorothiazide was administered alone to the pregnant
387 rat or mouse at doses of up to 1000 and 3000 mg/kg/day,
388 respectively.

389

390 Thiazides cross the placental barrier and appear in cord blood.
391 There is a risk of fetal or neonatal jaundice,
392 thrombocytopenia, and possibly other adverse reactions that
393 have occurred in adults.

394

395 **Hypotension in Volume- and Salt-Depleted Patients**

396 Based on adverse events reported from all clinical trials of
397 ATACAND HCT, excessive reduction of blood pressure was
398 rarely seen in patients with uncomplicated hypertension
399 treated with candesartan cilexetil and hydrochlorothiazide
400 (0.4%). Initiation of antihypertensive therapy may cause
401 symptomatic hypotension in patients with intravascular
402 volume- or sodium- depletion, eg, in patients treated
403 vigorously with diuretics or in patients on dialysis. These
404 conditions should be corrected prior to administration of
405 ATACAND HCT, or the treatment should start under close
406 medical supervision (see DOSAGE AND
407 ADMINISTRATION).

408

409

410

411

412 * Doses compared on the basis of body surface area. MRHD
413 considered to be 32 mg for candesartan cilexetil and 12.5 mg for
414 hydrochlorothiazide.

415

416 If hypotension occurs, the patients should be placed in the
417 supine position and, if necessary, given an intravenous
418 infusion of normal saline. A transient hypotensive response is
419 not a contraindication to further treatment which usually can
420 be continued without difficulty once the blood pressure has
421 stabilized.

422

423 **Hydrochlorothiazide**

424 *Impaired Hepatic Function*

425 Thiazide diuretics should be used with caution in patients
426 with impaired hepatic function or progressive liver disease,
427 since minor alterations of fluid and electrolyte balance may
428 precipitate hepatic coma.

429

430 *Hypersensitivity Reaction*

431 Hypersensitivity reactions to hydrochlorothiazide may occur
432 in patients with or without a history of allergy or bronchial
433 asthma, but are more likely in patients with such a history.

434

435 *Systemic Lupus Erythematosus*

436 Thiazide diuretics have been reported to cause exacerbation or
437 activation of systemic lupus erythematosus.

438

439 *Lithium Interaction*

440 Lithium generally should not be given with thiazides (see
441 PRECAUTIONS, Drug Interactions, Hydrochlorothiazide,
442 Lithium).

443

444 **PRECAUTIONS**

445 **General**

446 *Candesartan Cilexetil – Hydrochlorothiazide*

447 In clinical trials of various doses of candesartan cilexetil and
448 hydrochlorothiazide, the incidence of hypertensive patients
449 who developed hypokalemia (serum potassium <3.5 mEq/L)
450 was 2.5% versus 2.1% for placebo; the incidence of
451 hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%
452 versus 1.0% for placebo. No patient receiving ATACAND
453 HCT 16-12.5 mg or 32-12.5 mg was discontinued due to
454 increases or decreases in serum potassium. Overall, the
455 combination of candesartan cilexetil and hydrochlorothiazide
456 had no clinically significant effect on serum potassium.

457

458

459

460
461 *Hydrochlorothiazide*
462 Periodic determination of serum electrolytes to detect possible
463 electrolyte imbalance should be performed at appropriate
464 intervals.
465
466 All patients receiving thiazide therapy should be observed for
467 clinical signs of fluid or electrolyte imbalance: namely,
468 hyponatremia, hypochloremic alkalosis, and hypokalemia.
469 Serum and urine electrolyte determinations are particularly
470 important when the patient is vomiting excessively or
471 receiving parenteral fluids. Warning signs or symptoms of
472 fluid and electrolyte imbalance, irrespective of cause, include
473 dryness of mouth, thirst, weakness, lethargy, drowsiness,
474 restlessness, confusion, seizures, muscle pains or cramps,
475 muscular fatigue, hypotension, oliguria, tachycardia, and
476 gastrointestinal disturbances such as nausea and vomiting.
477
478 Hypokalemia may develop, especially with brisk diuresis,
479 when severe cirrhosis is present, or after prolonged therapy.
480 Interference with adequate oral electrolyte intake will also
481 contribute to hypokalemia. Hypokalemia may cause cardiac
482 arrhythmia and may also sensitize or exaggerate the response
483 of the heart to the toxic effects of digitalis (eg, increased
484 ventricular irritability).
485
486 Although any chloride deficit is generally mild and usually
487 does not require specific treatment, except under
488 extraordinary circumstances (as in liver disease or renal
489 disease), chloride replacement may be required in the
490 treatment of metabolic alkalosis.
491
492 Dilutional hyponatremia may occur in edematous patients in
493 hot weather; appropriate therapy is water restriction, rather
494 than administration of salt, except in rare instances when the
495 hyponatremia is life-threatening. In actual salt depletion,
496 appropriate replacement is the therapy of choice.
497
498 Hyperuricemia may occur or acute gout may be precipitated
499 in certain patients receiving thiazide therapy.
500
501 In diabetic patients dosage adjustments of insulin or oral
502 hypoglycemic agents may be required. Hyperglycemia may
503 occur with thiazide diuretics. Thus latent diabetes mellitus
504 may become manifest during thiazide therapy.
505

506
507 The antihypertensive effects of the drug may be enhanced in
508 the post-sympathectomy patient.
509
510 If progressive renal impairment becomes evident consider
511 withholding or discontinuing diuretic therapy.
512
513 Thiazides have been shown to increase the urinary excretion
514 of magnesium; this may result in hypomagnesemia.
515
516 Thiazides may decrease urinary calcium excretion. Thiazides
517 may cause intermittent and slight elevation of serum calcium
518 in the absence of known disorders of calcium metabolism.
519 Marked hypercalcemia may be evidence of hidden
520 hyperparathyroidism. Thiazides should be discontinued
521 before carrying out tests for parathyroid function.
522
523 Increases in cholesterol and triglyceride levels may be
524 associated with thiazide diuretic therapy.
525
526 **Impaired Renal Function**
527 *Candesartan cilexetil*
528 As a consequence of inhibiting the renin-angiotensin-
529 aldosterone system, changes in renal function may be
530 anticipated in susceptible individuals treated with candesartan
531 cilexetil. In patients whose renal function may depend upon
532 the activity of the renin-angiotensin-aldosterone system (eg,
533 patients with severe congestive heart failure), treatment with
534 angiotensin-converting enzyme inhibitors and angiotensin
535 receptor antagonists has been associated with oliguria and/or
536 progressive azotemia and (rarely) with acute renal failure
537 and/or death. Similar results may be anticipated in patients
538 treated with candesartan cilexetil. (See CLINICAL
539 PHARMACOLOGY, Special Populations.)
540
541 In studies of ACE inhibitors in patients with unilateral or
542 bilateral renal artery stenosis, increases in serum creatinine or
543 blood urea nitrogen (BUN) have been reported. There has
544 been no long-term use of candesartan cilexetil in patients with
545 unilateral or bilateral renal artery stenosis, but similar results
546 may be expected.
547
548
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551

552 *Hydrochlorothiazide*

553 Thiazides should be used with caution in severe renal disease.
554 In patients with renal disease, thiazides may precipitate
555 azotemia. Cumulative effects of the drug may develop in
556 patients with impaired renal function.

557

558 **Information for Patients**

559 *Pregnancy*

560 Female patients of childbearing age should be told about the
561 consequences of second- and third- trimester exposure to
562 drugs that act on the renin-angiotensin system, and they
563 should also be told that these consequences do not appear to
564 have resulted from intrauterine drug exposure that has been
565 limited to the first trimester. These patients should be asked
566 to report pregnancies to their physicians as soon as possible.

567

568 *Symptomatic Hypotension*

569 A patient receiving ATACAND HCT should be cautioned
570 that lightheadedness can occur, especially during the first days
571 of therapy, and that it should be reported to the prescribing
572 physician. The patients should be told that if syncope occurs,
573 ATACAND HCT should be discontinued until the physician
574 has been consulted.

575

576 All patients should be cautioned that inadequate fluid intake,
577 excessive perspiration, diarrhea, or vomiting can lead to an
578 excessive fall in blood pressure, with the same consequences
579 of lightheadedness and possible syncope.

580

581 *Potassium Supplements*

582 A patient receiving ATACAND HCT should be told not to
583 use potassium supplements or salt substitutes containing
584 potassium without consulting the prescribing physician.

585

586 **Drug Interactions**

587 *Candesartan Cilexetil*

588 No significant drug interactions have been reported in studies
589 of candesartan cilexetil given with other drugs such as
590 glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide,
591 and oral contraceptives in healthy volunteers. Because
592 candesartan is not significantly metabolized by the
593 cytochrome P450 system and at therapeutic concentrations
594 has no effects on P450 enzymes, interactions with drugs that
595 inhibit or are metabolized by those enzymes would not be
596 expected.

597

598 *Hydrochlorothiazide*
599 When administered concurrently the following drugs may
600 interact with thiazide diuretics:
601 *Alcohol, barbiturates, or narcotics* – Potentiation of
602 orthostatic hypotension may occur.
603 *Antidiabetic drugs (oral agents and insulin)* – Dosage
604 adjustment of the antidiabetic drug may be required.
605 *Other antihypertensive drugs* – Additive effect or
606 potentiation.
607 *Cholestyramine and colestipol resins* – Absorption of
608 hydrochlorothiazide is impaired in the presence of anionic
609 exchange resins. Single doses of either cholestyramine or
610 colestipol resins bind the hydrochlorothiazide and reduce its
611 absorption from the gastrointestinal tract by up to 85 and 43
612 percent, respectively.
613 *Corticosteroids, ACTH* – Intensified electrolyte depletion,
614 particularly hypokalemia.
615 *Pressor amines (e.g., norepinephrine)* – Possible decreased
616 response to pressor amines but not sufficient to preclude their
617 use.
618 *Skeletal muscle relaxants, nondepolarizing (e.g.,*
619 *tubocurarine)* – Possible increased responsiveness to the
620 muscle relaxant.
621 *Lithium* – Generally should not be given with diuretics.
622 Diuretic agents reduce the renal clearance of lithium and add
623 a high risk of lithium toxicity. Refer to the package insert for
624 lithium preparations before use of such preparations with
625 ATACAND HCT.
626 *Non-steroidal Anti-inflammatory Drugs* – In some patients,
627 the administration of a non-steroidal anti-inflammatory agent
628 can reduce the diuretic, natriuretic, and antihypertensive
629 effects of loop, potassium-sparing and thiazide diuretics.
630 Therefore, when ATACAND HCT and non-steroidal anti-
631 inflammatory agents are used concomitantly, the patient
632 should be observed closely to determine if the desired effect
633 of the diuretic is obtained.
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644

645 **Carcinogenesis, Mutagenesis, Impairment of**
646 **Fertility**

647 *Candesartan Cilexetil – Hydrochlorothiazide*

648 No carcinogenicity studies have been conducted with the
649 combination of candesartan cilexetil and hydrochlorothiazide.
650 There was no evidence of carcinogenicity when candesartan
651 cilexetil was orally administered to mice and rats for up to
652 104 weeks at doses up to 100 and 1000 mg/kg/day,
653 respectively. Rats received the drug by gavage whereas mice
654 received the drug by dietary administration. These
655 (maximally-tolerated) doses of candesartan cilexetil provided
656 systemic exposures to candesartan (AUCs) that were, in mice,
657 approximately 7 times and, in rats, more than 70 times the
658 exposure in man at the maximum recommended daily human
659 dose (32 mg). Two-year feeding studies in mice and rats
660 conducted under the auspices of the National Toxicology
661 Program (NTP) uncovered no evidence of a carcinogenic
662 potential of hydrochlorothiazide in female mice (at doses of
663 up to approximately 600 mg/kg/day) or in male and female
664 rats (at doses of up to approximately 100 mg/kg/day). The
665 NTP, however, found equivocal evidence for
666 hepatocarcinogenicity in male mice.

667 Candesartan cilexetil, alone or in combination with
668 hydrochlorothiazide, tested negative for mutagenicity in
669 bacteria (Ames test), for unscheduled DNA synthesis in rat
670 liver, for chromosomal aberrations in rat bone marrow and for
671 micronuclei in mouse bone marrow. In addition, candesartan
672 (the active metabolite) was not genotoxic in the microbial
673 mutagenesis, mammalian cell mutagenesis, and *in vitro* and *in*
674 *vivo* chromosome aberration assays. In the *in vitro* Chinese
675 hamster lung cell chromosomal aberration and mouse
676 lymphoma assays, mutagenic effects were detected when
677 hydrochlorothiazide was tested in the presence of candesartan.
678 Hydrochlorothiazide was not genotoxic *in vitro* in the Ames
679 test for point mutations and the Chinese Hamster Ovary
680 (CHO) test for chromosomal aberrations, or *in vivo* in assays
681 using mouse germinal cell chromosomes, Chinese hamster
682 bone marrow chromosomes, and the *Drosophila* sex-linked
683 recessive lethal trait gene. Positive test results were obtained
684 for hydrochlorothiazide in the *in vitro* CHO Sister Chromatid
685 Exchange (clastogenicity) and in the Mouse Lymphoma Cell
686 (mutagenicity) assays and in the *Aspergillus nidulans* non-
687 disjunction assay.

688

689 No fertility studies have been conducted with the combination
690 of candesartan cilexetil and hydrochlorothiazide. Fertility and
691 reproductive performance were not affected in studies with
692 male and female rats given oral doses of up to 300 mg
693 candesartan cilexetil/kg/day (83-times the maximum daily
694 human dose of 32 mg on a body surface area basis).
695 Hydrochlorothiazide had no adverse effects on the fertility of
696 mice and rats of either sex in studies wherein these species
697 were exposed, via their diet, to doses of up to 100 and 4
698 mg/kg, respectively, prior to conception and throughout
699 gestation.

700

701 **Pregnancy**

702 *Pregnancy Categories C* (first trimester) *and D* (second and
703 third trimesters). See WARNINGS, Fetal/Neonatal Morbidity
704 and Mortality.

705

706 **Nursing Mothers**

707 It is not known whether candesartan is excreted in human
708 milk, but candesartan has been shown to be present in rat
709 milk. Thiazides appear in human milk. Because of the
710 potential for adverse effects on the nursing infant, a decision
711 should be made whether to discontinue nursing or discontinue
712 the drug, taking into account the importance of the drug to the
713 mother.

714

715 **Pediatric Use**

716 Safety and effectiveness in pediatric patients have not been
717 established.

718

719 **Geriatric Use**

720 Of the total number of subjects in all clinical studies of
721 ATACAND HCT (2831), 611 (22%) were 65 and over, while
722 94 (3%) were 75 and over. No overall differences in safety or
723 effectiveness were observed between these subjects and
724 younger subjects. Other reported clinical experience has not
725 identified differences in responses between the elderly and
726 younger patients, but greater sensitivity of some older
727 individuals cannot be ruled out.

728

729

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734

735 **ADVERSE REACTIONS**

736 *Candesartan Cilexetil-Hydrochlorothiazide*

737 ATACAND HCT has been evaluated for safety in more than
738 2800 patients treated for hypertension. More than 750 of
739 these patients were studied for at least six months and more
740 than 500 patients were treated for at least one year. Adverse
741 experiences have generally been mild and transient in nature
742 and have only infrequently required discontinuation of
743 therapy. The overall incidence of adverse events reported with
744 ATACAND HCT was comparable to placebo. The overall
745 frequency of adverse experiences was not related to dose, age,
746 gender, or race.

747

748 In placebo-controlled trials that included 1089 patients treated
749 with various combinations of candesartan cilexetil (doses of
750 2-32 mg) and hydrochlorothiazide (doses of 6.25-25 mg) and
751 592 patients treated with placebo, adverse events, whether or
752 not attributed to treatment, occurring in greater than 2% of
753 patients treated with ATACAND HCT and that were more
754 frequent for ATACAND HCT than placebo were: *Respiratory*
755 *System Disorder*: upper respiratory tract infection (3.6% vs
756 3.0%); *Body as a Whole*: back pain (3.3% vs 2.4%);
757 influenza-like symptoms (2.5% vs 1.9%); *Central/Peripheral*
758 *Nervous System*: dizziness (2.9% vs 1.2%).

759

760 The frequency of headache was greater than 2% (2.9%) in
761 patients treated with ATACAND HCT but was less frequent
762 than the rate in patients treated with placebo (5.2%).

763 Other adverse events that have been reported, whether or not
764 attributed to treatment, with an incidence of 0.5% or greater
765 from the more than 2800 patients worldwide treated with
766 ATACAND HCT included: *Body as a Whole*: inflicted
767 injury, fatigue, pain, chest pain, peripheral edema, asthenia;
768 *Central and Peripheral Nervous System*: vertigo, paresthesia,
769 hypesthesia; *Respiratory System Disorders*: bronchitis,
770 sinusitis, pharyngitis, coughing, rhinitis, dyspnea;
771 *Musculoskeletal System Disorders*: arthralgia, myalgia,
772 arthrosis, arthritis, leg cramps, sciatica; *Gastrointestinal*
773 *System Disorders*: nausea, abdominal pain, diarrhea,
774 dyspepsia, gastritis, gastroenteritis, vomiting; *Metabolic and*
775 *Nutritional Disorders*: hyperuricemia, hyperglycemia,
776 hypokalemia, increased BUN, creatine phosphokinase
777 increased; *Urinary System Disorders*: urinary tract infection,
778 hematuria, cystitis; *Liver/Biliary System Disorders*: hepatic
779 function abnormal, increased transaminase levels; *Heart Rate*
780 *and Rhythm Disorders*: tachycardia, palpitation,
781 extrasystoles, bradycardia; *Psychiatric Disorders*: depression,
782 insomnia, anxiety; *Cardiovascular Disorders*: ECG
783 abnormal; *Skin and Appendages Disorders*: eczema,
784 sweating increased, pruritus, dermatitis, rash;
785 *Platelet/Bleeding Clotting Disorders*: epistaxis; *Resistance*
786 *Mechanism Disorders*: infection, viral infection; *Vision*
787 *Disorders*: conjunctivitis; *Hearing and Vestibular Disorders*:
788 tinnitus.

789

790 Reported events seen less frequently than 0.5% included
791 angina pectoris, myocardial infarction and angioedema.

792

793 *Candesartan Cilexetil*

794 Other adverse experiences that have been reported with
795 candesartan cilexetil, without regard to causality, were: *Body*
796 *as a Whole*: fever; *Metabolic and Nutritional Disorders*:
797 hypertriglyceridemia; *Psychiatric Disorders*: somnolence;
798 *Urinary System Disorders*: albuminuria.

799

800 *Hydrochlorothiazide*

801 Other adverse experiences that have been reported with
802 hydrochlorothiazide, without regard to causality, are listed
803 below:

804

805 **Body As A Whole:** weakness; **Cardiovascular:** hypotension
806 including orthostatic hypotension (may be aggravated by
807 alcohol, barbiturates, narcotics or antihypertensive drugs);
808 **Digestive:** pancreatitis, jaundice (intrahepatic cholestatic
809 jaundice), sialadenitis, cramping, constipation, gastric
810 irritation, anorexia; **Hematologic:** aplastic anemia,
811 agranulocytosis, leukopenia, hemolytic anemia,
812 thrombocytopenia; **Hypersensitivity:** anaphylactic reactions,
813 necrotizing angiitis (vasculitis and cutaneous vasculitis),
814 respiratory distress including pneumonitis and pulmonary
815 edema, photosensitivity, urticaria, purpura; **Metabolic:**
816 electrolyte imbalance, glycosuria; **Musculoskeletal:** muscle
817 spasm; **Nervous System/Psychiatric:** restlessness; **Renal:**
818 renal failure, renal dysfunction, interstitial nephritis; **Skin:**
819 erythema multiforme including Stevens-Johnson syndrome,
820 exfoliative dermatitis including toxic epidermal necrolysis,
821 alopecia; **Special Senses:** transient blurred vision,
822 xanthopsia; **Urogenital:** impotence.

823

824 **Laboratory Test Findings**

825 In controlled clinical trials, clinically important changes in
826 standard laboratory parameters were rarely associated with the
827 administration of ATACAND HCT.

828 **Creatinine, Blood Urea Nitrogen**— Minor increases in blood
829 urea nitrogen (BUN) and serum creatinine were observed
830 infrequently. One patient was discontinued from ATACAND
831 HCT due to increased BUN. No patient was discontinued due
832 to an increase in serum creatinine.

833

834 **Hemoglobin and Hematocrit**— Small decreases in hemoglobin
835 and hematocrit (mean decreases of approximately 0.2 g/dL
836 and 0.4 volume percent, respectively) were observed in
837 patients treated with ATACAND HCT, but were rarely of
838 clinical importance.

839

840 **Potassium**— A small decrease (mean decrease of 0.1 mEq/L)
841 was observed in patients treated with ATACAND HCT. In
842 placebo-controlled trials, hypokalemia was reported in 0.4%
843 of patients treated with ATACAND HCT as compared to
844 1.0% of patients treated with hydrochlorothiazide or 0.2% of
845 patients treated with placebo.

846

847 **Liver Function Tests**— Occasional elevations of liver enzymes
848 and/or serum bilirubin have occurred.

849

850

851

852 **OVERDOSAGE**

853 *Candesartan Cilexetil – Hydrochlorothiazide*

854 No lethality was observed in acute toxicity studies in mice,
855 rats and dogs given single oral doses of up to 2000 mg/kg of
856 candesartan cilexetil or in rats given single oral doses of up to
857 2000 mg/kg of candesartan cilexetil in combination with 1000
858 mg/kg of hydrochlorothiazide. In mice given single oral
859 doses of the primary metabolite, candesartan, the minimum
860 lethal dose was greater than 1000 mg/kg but less than 2000
861 mg/kg.

862

863 Limited data are available in regard to overdosage with
864 candesartan cilexetil in humans. The most likely
865 manifestations of overdosage with candesartan cilexetil would
866 be hypotension, dizziness, and tachycardia; bradycardia could
867 occur from parasympathetic (vagal) stimulation. If
868 symptomatic hypotension should occur, supportive treatment
869 should be initiated. For hydrochlorothiazide, the most
870 common signs and symptoms observed are those caused by
871 electrolyte depletion (hypokalemia, hypochloremia,
872 hyponatremia) and dehydration resulting from excessive
873 diuresis. If digitalis has also been administered, hypokalemia
874 may accentuate cardiac arrhythmias.

875

876 Candesartan cannot be removed by hemodialysis. The degree
877 to which hydrochlorothiazide is removed by hemodialysis has
878 not been established.

879

880 *Treatment*

881 To obtain up-to-date information about the treatment of
882 overdose, consult your Regional Poison Control Center.
883 Telephone numbers of certified poison control centers are
884 listed in the Physicians' Desk Reference (PDR). In managing
885 overdose, consider the possibilities of multiple-drug
886 overdoses, drug-drug interactions, and altered
887 pharmacokinetics in your patient.

888

889 **DOSAGE AND ADMINISTRATION**

890 The usual recommended starting dose of candesartan cilexetil
891 is 16 mg once daily when it is used as monotherapy in
892 patients who are not volume depleted. ATACAND can be
893 administered once or twice daily with total daily doses
894 ranging from 8 mg to 32 mg. Patients requiring further
895 reduction in blood pressure should be titrated to 32 mg.
896 Doses larger than 32 mg do not appear to have a greater blood
897 pressure lowering effect.

898

899 Hydrochlorothiazide is effective in doses of 12.5 to 50 mg
900 once daily.

901

902 To minimize dose-independent side effects, it is usually
903 appropriate to begin combination therapy only after a patient
904 has failed to achieve the desired effect with monotherapy.

905

906 The side effects (See WARNINGS) of candesartan cilexetil
907 are generally rare and apparently independent of dose; those
908 of hydrochlorothiazide are a mixture of dose-dependent
909 phenomena (primarily hypokalemia) and dose-independent
910 phenomena (eg, pancreatitis), the former much more common
911 than the latter.

912 Therapy with any combination of candesartan cilexetil and
913 hydrochlorothiazide will be associated with both sets of dose-
914 independent side effects.

915

916 **Replacement Therapy:** The combination may be substituted
917 for the titrated components.

918

919 **Dose Titration by Clinical Effect:** A patient whose blood
920 pressure is not controlled on 25 mg of hydrochlorothiazide
921 once daily can expect an incremental effect from ATACAND
922 HCT 16-12.5 mg. A patient whose blood pressure is
923 controlled on 25 mg of hydrochlorothiazide but is
924 experiencing decreases in serum potassium can expect the
925 same or incremental blood pressure effects from ATACAND
926 HCT 16-12.5 mg and serum potassium may improve.

927 A patient whose blood pressure is not controlled on 32 mg of
928 ATACAND can expect incremental blood pressure effects
929 from ATACAND HCT 32-12.5 mg and then 32-25 mg. The
930 maximal antihypertensive effect of any dose of ATACAND
931 HCT can be expected within 4 weeks of initiating that dose.

932

933 **Patients with Renal Impairment:** The usual regimens of
934 therapy with ATACAND HCT may be followed as long as
935 the patient's creatinine clearance is > 30 mL/min. In patients
936 with more severe renal impairment, loop diuretics are
937 preferred to thiazides, so ATACAND HCT is not
938 recommended.

939

940 **Patients with Hepatic Impairment:** Thiazide diuretics
941 should be used with caution in patients with hepatic
942 impairment; therefore, care should be exercised with dosing
943 of ATACAND HCT.

944

945 ATACAND HCT may be administered with other
946 antihypertensive agents.

947

948 ATACAND HCT may be administered with or without food.

949

950 **HOW SUPPLIED**

951 No. 3825 — Tablets ATACAND HCT 16-12.5, are peach,
952 oval, biconvex, non-film-coated tablets, coded ACS on one
953 side and 162 on the other. They are supplied as follows:

954

955 NDC 0186-0162-28 unit dose packages of 100.

956 NDC 0186-0162-31 unit of use bottles of 30.

957 NDC 0186-0162-54 unit of use bottles of 90.

958 NDC 0186-0162-82 bottles of 1000.

959

960 No. 3826 — Tablets ATACAND HCT 32-12.5, are yellow,
961 oval, biconvex, non-film-coated tablets, coded ACJ on one
962 side and 322 on the other. They are supplied as follows:

963

964 NDC 0186-0322-28 unit dose packages of 100.

965 NDC 0186-0322-31 unit of use bottles of 30.

966 NDC 0186-0322-54 unit of use bottles of 90.

967 NDC 0186-0322-82 bottles of 1000.

968

969 **Storage**

970 Store at 25°C (77°F); excursions permitted to 15-30°C (59-
971 86°F) [see USP Controlled Room Temperature]. Keep
972 container tightly closed.

973

974 ATACAND HCT is a trademark of the AstraZeneca Group of
975 Companies

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977

978 Issued -date place here

979

980

981  Manufactured under the license
982 from Takeda Chemical Industries, Ltd.
983 by: AstraZeneca AB, S-151 85 Södertälje, Sweden
984 for: AstraZeneca LP, Wilmington, DE 19850

985

986 Made in Sweden

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