

## **11. Recommendations**

### **Valsartan plus HCTZ**

Valsartan plus HCTZ is safe and tolerable for long term usage in the therapy of hypertension. The combination product's development program did not uncover safety concerns that might mitigate against approval. Valsartan plus HCTZ should be approved as an alternative for the treatment of hypertension only in patients not responding to other forms of antihypertensive monotherapies, particularly valsartan monotherapy, and such approval should be subject to suggested amendments in the label contained in the marked-up draft in this review. This approval need not be predicated upon the sponsor's commitment to any post-marketing studies.

The narratives of deaths in the clinical trials are summarized below in Appendix Table 1  
**Appendix Table 1 : Narratives of patient deaths**

Protocol/Age/ Sex/Race/Drug	Narrative of events
012/509/ 11E1/62/M/W/ V80/HCTZ/ 12.5mg	<p><b>Arteriosclerotic heart disease/Death</b></p> <p>The patient was last seen by the investigator on 5/11/94 when he came in for an unscheduled visit for blood pressure monitoring post-initiation of HCTZ. At that time his blood pressure was 133/75 mmHg. On 6/23/94, the study coordinator received a voice mail message from a family member of the patient's indicating that he had died on 6/22/94. The patient was scheduled for an interim visit on 6/23/94, and the study coordinator had spoken to him on 6/21/94, confirming his appointment. The patient had experienced chest pain during the week, which he attributed to indigestion and did not seek medical intervention. At 2:00 A.M. on 6/22/94, the patient experienced an acute episode of chest pains and expired. No autopsy was performed. The investigator indicated that when the patient was last seen, he was in good condition and that he had a heart attack while sleeping. The investigator felt that this event was not related to trial drug. Throughout the study, the patient experienced the following adverse events: gastrointestinal flu (10/03/93 - 10/10/93), abdominal pain right upper quadrant (12/13/93 - 12/15/93), cold and sinusitis (03/30/94 - 04/10/94). All were considered not related or unlikely related to trial drug. An autopsy was not performed. Investigator considered cause of death to be arteriosclerotic heart disease and unrelated to trial medication. Duration to death-102 days.</p>
757/1031/28E/71/ M/Oth. 80/HCTZ25mg	<p><b>Cholecystitis/Death</b></p> <p>The patient was enrolled in the trial in June 1994 and entered the extension phase on 05-Jun-95. He was receiving valsartan 80 mg o.d. and hydrochlorothiazide 25 mg o.d. (Level E). The patient had a medical history of diverticular disease of the bowel and peptic ulcer (and a recent episode of cholecystitis) and was treated for these conditions with dicycloverine hydrochloride 10 mg qd and lansoprazole 30 mg qd. On 20-Oct-95, the patient experienced recurrent right-sided abdominal pain with nausea but no vomiting. On 22-Oct-95, diverticulitis was diagnosed and the patient was admitted to hospital. Further information indicated a misdiagnosis. An abdominal ultrasound was carried out on 26-Oct-95, which confirmed cholecystitis and was the reason for hospitalisation. This was unrelated to study medication. The patient recovered from the acute attack, but still had infected gallbladder and was scheduled for a cholecystectomy at a later date. The patient was discharged from the hospital on 30-Oct-95. Study medication was continued during hospitalisation and in addition the patient received Cefadroxil 500 mg b.i.d. and aporex 2 tablets t.i.d. The patient was again admitted to hospital on 6-Jan-96 and on 13-Feb-96 following another attack of cholecystitis. On 19-Feb-96, a cholecystectomy was performed. The patient's condition deteriorated post-operatively and he died of bronchopneumonia, renal failure and cardiac failure on 28-Feb-96. There is no evidence of death due to any medication. It is presumed that the patient continued study medication until the time of death. In the investigator's opinion this adverse experience had no causal relationship with the trial drug. Duration to death-577</p>
1082/62/ 28/68/M /W V80/HCTZ25mg	<p><b>Sudden Cardiac Arrest/Death</b></p> <p>The patient was a 68 year old male with hypertension. The patient's history was notable for below knee amputation of the left leg in 1983 and chronic obstructive airways since 1994. The patient was included in the trial on June 6, 1994. He was titrated to valsartan 80 mg and hydrochlorothiazide 25 mg over a period of 4 months. After 2 months of treatment with this combination, he was discontinued from the trial on December 12, 1994, for unsatisfactory therapeutic effect of trial drug on his blood pressure. The patient was then prescribed captopril 25 mg twice daily and bendrofluazide 2.5 mg once daily for hypertension. Sudden death occurred on March 23, 1995, around three months post trial participation. At autopsy the pathologist discovered signs of acute left ventricular failure as well as ventricular ischemia secondary to coronary artery atheroma. Duration to death -</p>

<p>010/510/ 11E2/50/M/W V40mg</p>	<p><b>Accidental drowning/Death</b> This 50 year old male patient with a 15 year history of hypertension died due to accidental drowning approximately 90 weeks after beginning treatment with valsartan in the open-label extension phase. The patient had been fishing on a boat with relatives when the boat sank. The patient never made it to shore. His body was later recovered by divers. An autopsy was performed confirming that the death was accidental. The investigator considered the event unrelated to trial medication.</p>
<p>421/1563/28/71/ M /W/ V40mg</p>	<p><b>Astrocytoma /Death</b> The patient was a 71 year old male. He began the double-blind phase of the trial on 11/05/94 and progressed to valsartan 80 mg on 25/05/94. He had no significant medical history of note and was not taking any concurrent medication. On 28/04/95, 338 days after starting valsartan 80 mg, he was hospitalized due to headaches, unsteady gait, difficulty in communicating and urinary incontinence. A diagnosis of astrocytoma was made and the patient started treatment with dexamethasone 30 mg daily on 30/04/95. The investigator considered that there was no relationship to study medication. Follow up information indicates that the patient died 6 months after trial participation on October 25, 1995.</p>
<p>1282/28/88/M/W/ V40mg</p>	<p><b>Bronchopneumonia/Death</b> This patient began the double-blind phase of the trial on 03/05/94, and progressed to Level B (valsartan 80 mg) medication on 16/05/94. He had a previous history of chronic bronchitis, but was not taking any medication. On 04/01/95 he became unconscious and was admitted to hospital where a diagnosis of bronchopneumonia was made. Trial medication was discontinued. The adverse experience commenced 246 days after starting Level B (valsartan 80 mg) medication. The patient died 5 days later on 09/01/95. In the investigator's opinion there was no relationship between the trial medication and the adverse experience.</p>
<p>1214/28/70/M /W/V40mg</p>	<p><b>Carcinoma of kidney / Death</b> This patient began the double-blind phase of the trial on 05/04/94, and progressed to Level B (valsartan 80 mg) medication on 19/04/94 and Level C (valsartan 80 mg) medication on 03/05/94. He had no previous history of urinary problems. On 15/09/94 he was admitted to hospital with bilateral groin pain, and was subsequently diagnosed as having chronic urinary retention secondary to prostatic enlargement, along with a urinary tract infection. This adverse experience began 149 days after starting Level C medication. Treatment with trial medication was stopped. He was discharged two days later on 17/09/94, having been prescribed trimethoprim. He was re-admitted on 01/10/94, after a blood urea sample taken during his follow-up out-patient clinic visit was found to be high. He was subsequently referred to an oncologist, who diagnosed kidney carcinoma. He was then referred for bilateral nephrostomy and radiotherapy treatment. This patient died on 22/10/94. In the investigator's opinion there was no relationship between the trial medication and the adverse experience.</p>
<p>011/511/ 11E2/49/M /W/ V20mg</p>	<p><b>Cardiac arrest / Death (Renal carcinoma)</b> This 49 year old male patient with a 6 year history of hypertension presented in an emergency room with chest pain approximately 85 weeks after beginning treatment with valsartan in the open-label extension phase. Laboratory evaluations and ECG were normal. The patient was diagnosed with esophagitis, treated with cisapride, scheduled for a GI consultation and discharged. The patient was last seen by the investigator approximately 9 weeks prior to the onset of the chest pain for a routine trial visit. Physical examination at that time was unremarkable and the patient was without complaints. Eight days following the chest pain episode, the patient was reported to have complained to his spouse of difficulty breathing while sitting in a chair. The patient's wife called for an ambulance and on returning to the room found the patient blue and gurgling. The patient was transported to the emergency room and pronounced dead on arrival. Preliminary autopsy revealed severe gastroenteritis and 90% occlusion of the left anterior descending coronary artery. Final autopsy results revealed findings of CAD with 90% narrowing of the left anterior descending coronary artery and passive congestion of the liver and spleen with hemosiderin laden macrophages consistent with CHF. Autopsy results also revealed the patient had early renal cell carcinoma.</p>

	<p>Cause of death was determined to be sudden cardiac arrest most likely due to arrhythmia. The investigator considered the relationship of this event to trial medication as unlikely. Duration to death - 636 days</p>
1189/20/71/F/W/ V80mg	<p><b>Cardiac arrest / Death</b> After 15 days of exposure to the trial medication, the patient was found dead at home one morning. The investigator had seen her a few days before and no medical problem had been noticed. Her previous medical history included a depression since 1980, hypothyroidism since 1985 and a gastric ulcer in 1988. She was treated by levothyroxine, metanizole caffeine, paracetamol and iron sulfate. No autopsy was performed, causality of death was cardiac arrest. The investigator did not assess the relationship between treatment and adverse event because of the insufficiency of data. Duration to death - 31.</p>
016/515/11E/74/F /W/ V20mg	<p><b>Cardiovascular collapse/Death</b> The patient entered the open-label treatment period on 8/17/93. The patient lived alone and was last seen on 2/20/94. When the neighbors did not see her on 2/21/94, they had the maintenance man check on her. She was found unresponsive in her apartment. The rescue company was called and she was declared dead on arrival at the hospital. The actual date of death (2/20 or 2/21) has not been determined. The family did not want an autopsy to be performed. The death was ruled due to cardiovascular collapse. The patient had a history of hypertension since 1986.</p>
1184/28/ 82/F/W/ V80mg	<p><b>Myocardial infarction/Death</b> This patient began the double-blind phase of the trial on 09/06/94, and progressed to Level B (valsartan 80 mg) medication on 08/09/94. She had a previous history of mild angina of effort, but was not taking any medication. On 17/09/94 she was hospitalized with chest pains, and a diagnosis of myocardial infarction was made. This adverse experience occurred 9 days after beginning Level B (valsartan 80 mg) medication. This patient died one day later on 18/09/94. In the investigator's opinion there was no relationship between the trial medication and the adverse experience. Duration to death 101 days.</p>
1338/28/66/M/W / Lisinopril 2.5mg	<p><b>Bronchopneumonia/Death</b> The patient began the double blind phase of the trial on 03/05/94. He had a -previous history of cervical spondylosis and cervical decompression, and had suffered a brainstem infarct. On 23/11/94 the patient was diagnosed as having a chest infection, and was admitted to hospital on 29/11/94. He died in hospital of bronchopneumonia on 30/11/94. The bronchopneumonia began 204 days after the start of treatment. In the investigators opinion there was no relationship between the trial medication and the adverse experience.</p>
1889/28/75/F/W/ Lisinopril 20mg	<p><b>Cerebrovascul accident/Death</b> This patient began the double-blind phase of the trial on 10/15/94, and progressed to level B (lisinopril 10mg) medication on 26/05/94 and level C (lisinopril 20mg) medication on 10/06/94. She had a previous history of CVA, having had an attack in 1991, and concomitant medications included omeprazole 20mg daily, metoclopramide 10mg tds and isosorbide mononitrate 60mg daily. She also had a history of esophagitis treated with antacids. On 01/09/94 the patient stopped taking her trial medication because of dizziness. On 05/09/94 she attended her GP and confirmed this. Later that day, she died of a CVA. The CVA occurred 118 days after beginning treatment with level C (lisinopril 20mg) medication. In the investigator's opinion there was no relationship between the trial medication and the adverse experience. Duration to death - 119 days.</p>
628/1810/ 20 / M / W/ Lisinopril 2.5mg/HCTZ	<p><b>Fractured neck of femur/Death</b> This patient was enrolled in the trial, with hypertension, on 07-Jun-94, and entered the extension phase on 15-Jun-95. On 03-Sep-95, about 8.5 months after starting treatment with Level E (lisinopril 20 mg q.d. and hydrochlorothiazide 25 mg q.d.), the patient fractured her femur after a fall and was admitted to hospital the same day. The anesthetist requested codebreak due to the patient's fracture of the hip and trial medication was permanently discontinued. The patient died on 17-Sep-95, not having been discharged from hospital. The death was due to natural causes, CHF and left ventricular hypertrophy, which was confirmed by autopsy. In the investigator's opinion this adverse experience had no causal relationship with the trial drug.</p>

**Appendix Table 2: SAEs in cardiovascular and neurological systems in all clinical trials**

Protocol/Subject/ Age/Sex/Days/ Treatment	Diagnosis, History, and Relationship to Trial Drug
<b>Double Blind and open label phases (U=Unlikely; N=Not related; PR=Probable;PO=Possible)</b>	
28/1673/68 /M/13/80/12.5	<p><b>CEREBROVASCULAR ACCIDENT (U)</b></p> <p>This patient began the double-blind phase of the trial on 12/03/94 and progressed to Level B (valsartan 80 mg), C (valsartan 80 mg) and D (valsartan 80 mg + hydrochlorothiazide 12.5 mg) medication on 25/03/94, 11/04/94 and 03/05/94, respectively. He had a medical history of cervical disc degeneration (1978), headaches (1978), acute myocardial infarction (1989), insomnia (1990), chilblains (1993) and dizziness due to mild CVA (1993). He took paracetamol for headache and nitrazepam for insomnia throughout the study. In addition, in January 1994, a CT scan had revealed an infarct (lacunar) in the right basal ganglion region. On 16/05/94, 13 days after starting treatment at Level D (valsartan 80 mg + hydrochlorothiazide 12.5 mg), he reported a cerebrovascular accident and the trial drug was discontinued. In the investigator's opinion there was an unlikely relationship between the trial medication and the adverse experience.</p>
11E/025/518 69/M/350/80/12.5	<p><b>CEREBROVASCULAR ACCIDENT (N)</b></p> <p>Approximately 50 weeks after beginning treatment with valsartan 80 mg + HCTZ 25 mg in the open-label extension phase, this 69 year old male patient fell when arising and experienced left sided weakness of the upper and lower extremities along with left sided facial drooping. The patient was hospitalized with a tentative diagnosis of cerebrovascular accident (CVA). Eight days after admission the patient was discharged; final diagnosis was right pontine lacunar infarct. The CVA symptoms have subsequently resolved and the patient continued in the trial on a dose of valsartan 80 mg and HCTZ 12.5 mg. According to the investigator, the patient's blood pressure was well controlled throughout the trial. Blood pressure measurement at the last trial visit prior to the event was 147/89 mmHg.</p> <p>The investigator considered the event unrelated to trial medication</p>
11E/2003/501/ 65/M ?? 80.25	<p><b>CORONARY ARTERY DISEASE (U)</b></p> <p>The medical problems experienced by this patient are discussed under Body as a Whole.</p>
28E/200/674/89/F /448/80/12.5	<p><b>CEREBROVASCULAR ACCIDENT (U)</b></p> <p>This patient was enrolled into the trial on 21-Apr-94 with a diagnosis of hypertension and entered the extension period on 20-Apr-95. Prior to dosing, the patient's significant medical history included a transient cerebral ischaemic episode (29-Jul-86), for which she was treated with 75 mg acetylsalicylic acid (p.o., q.d) since 17-Jan-91. On 13-Jun-95, approximately 14 _ months after randomization and while receiving valsartan 80 mg + hydrochlorothiazide 25 mg (Level E), the patient experienced a mild cerebrovascular accident with a weakness of the right side (mainly right arm) and vertigo. On 14-Jun-95, she was revisited and the decision was made to transfer her to the hospital. The patient remained on study medication and had completely recovered on 01-Sep-95. In the investigator's opinion this adverse experience was unlikely to be related to the trial drug.</p>
28/1705/68/M/ 17/80/12.5	<p><b>MYOCARDIAL INFARCTION (U)</b></p> <p>This patient began the double-blind phase of the trial on 03/03/94 and progressed to Level B (valsartan 80 mg) medication on 17/03/94, Level C (valsartan 80 mg) medication on 07/04/94 and Level D (valsartan 80 mg + hydrochlorothiazide 12.5 mg) medication on 05/05/94. He had a previous history of angina (1979), myocardial infarction (1979) and osteoarthritis (1990). At the start of the trial, the patient was receiving codeine phosphate and paracetamol for joint pain. On 22/05/94, the patient complained of chest pain and was admitted to the Medical Unit. A diagnosis of inferior myocardial infarction was made. This experience was noted 17 days after starting medication at Level D (valsartan 80 mg + hydrochlorothiazide 12.5 mg). The patient completely recovered. In the investigator's opinion, there was an unlikely relationship between the trial medication and the adverse experience.</p>
19/406/5634, C/52/M/19/80/25	<p><b>MYOCARDIAL INFARCTION (N)</b></p> <p>On Trial Day 19, this 52 year old male with a history of hypertension and obesity was</p>

	<p>hospitalized with complaints of severe aching discomfort in both upper arms radiating transversely across the anterior chest along with slight difficulty in breathing and nausea. Initial ECG showed sinus tachycardia, lateral and possible inferior mild ST segment elevation along with questionable changes in V2 lead. Blood pressure was 183/122 at admission and dropped to 170/110 after treatment with metoprolol IV. A coronary angiogram revealed multivessel coronary artery disease with a clot in a branch of the left circumflex. Patient opted for medical treatment at this time and was discharged 7 days later on captopril, metoprolol, coumadin, and nitroglycerin prn. The patient was prematurely discontinued from the trial. The adverse experience was considered not related to trial medication by the investigator. A follow-up report from the investigator 2 months after the patient discontinued from the trial informed Ciba that the patient was involved in an airplane crash while trying to land his plane in bad weather. The patient died and his body was recovered.</p>
<p>301/687/3617 56/F/13/160/25</p>	<p><b>ORTHOSTATIC HYPOTENSION (PR)</b>  This patient had a history of ringing in ears for two years which started shortly after she began treatment with her pre-trial antihypertensive medication, terazosin, and was active at the initial visit. She had a three year history of hypertension, and the initial visit ECG and x-ray were within normal limits. Four days post the initial visit, the patient experienced mild vertigo, lasting 11 days (ending at the randomization visit). At randomization, her average sitting blood pressure was 163/95 mmHg, and standing was 132/98 mmHg, and her laboratory results were within normal limits. One day post-randomization, the patient began experiencing severe fatigue, and three days later she began having mild shortness of breath. Twelve days post-randomization, the patient reported a severe headache and severe vomiting lasting 24 hours, moderate increased thirst, nausea, stomach cramps, sweating, increased ringing in ears, and mild chest pain and diarrhea. On day thirteen post-randomization, the patient went to investigator's office, as a result of these symptoms, and was subsequently admitted to the hospital for observation. Initial exam upon admission revealed a blood pressure of 161/81 mmHg dropping to 106/66 mmHg upon standing, heart rate was 65, increasing to 104 upon standing. Examination revealed she was dehydrated, had a ketotic odor, and slightly decreased skin turgor. Hospital laboratory results indicated a slightly low sodium at 129 mEq/L, with the remainder of electrolytes normal. Her last day of trial medication was 12 days post-randomization. The patient was treated with intravenous normal saline and discharged the following day with a diagnosis of orthostatic hypotension, hyponatremia, and dehydration. Laboratory results during the trial indicated a change from randomization to final visit for sodium of 141 to 127 mEq/L, chloride of 107 to 85 mEq/L, and total bilirubin of 0.5 to 1.2 mg/dL, all other values remained within normal limits. The investigator reported seeing the patient for follow-up the day after discharge when she had a mild orthostatic blood pressure drop from 150/80 mmHg while sitting to a standing of 120/68 mmHg. Subsequent visits indicated the patient completely recovered and resumed treatment with terazosin. The investigator considered the relationship to trial medication as highly probable.</p>
<p>301/803/3723 61/F/7/80/25</p>	<p><b>PALPITATIONS (PO)</b>  This patient had a 42 year history of smoking and history of hypertension for 5 years. At randomization the patient's average sitting blood pressure was 153/95 mmHg. Four days post-randomization, the patient began experiencing mild palpitations and insomnia. Seven days post-randomization the patient stopped trial medication, and the symptoms resolved the following day. At the final visit the patient's average sitting blood pressure was 157/83 mmHg. The investigator considered both events to be possibly related to trial medication.</p>
<p>31E/429/5286/ 72/F/84/160/25</p>	<p><b>PAROXYSMAL ATRIAL TACHYCARDIA (PO)</b>  This patient had normal screening ECG results and a normal ECG at the end of the core phase of the trial and she had a history of hypertension for 30 years. Her MSBP upon entering the open-label extension was 157/101mmHg (standing 164/100mmHg). Two weeks after taking valsartan in the extension, the patient experienced "heart racing". The patient reported to an emergency facility, however, the symptoms had resolved before she arrived and an ECG was normal. Approximately two weeks after this episode, a Holter monitor examination revealed "some run of tachycardia". A few days later the patient complained of 2 episodes of mild chest tightness each</p>

	<p>lasting 1 day. The patient's potassium was 3.4meq/L (normal range 3.5-5.3meq/L) and she was started on potassium supplements. Approximately, 3 _ months after treatment with valsartan (including HCTZ 25mg for 2 _ months) in the extension, the patient developed a rapid heart rate and was taken to an emergency facility where an ECG revealed paroxysmal atrial tachycardia. Conversion was accomplished with intravenous adenosine and the patient was given nitroglycerine and diltiazem and released. The patient was seen at the site the following day and was discontinued from the trial. At final visit, her one sitting blood pressure was 140/80mmHg (standing 138/88mmHg). The investigator considered the adverse experience to be possibly related to trial drug. This patient had hypokalemia as well as the cardiac arrhythmia but the relationship between the two adverse events was not commented upon prior to discontinuation.</p>
<p>301/176/3159 54/F/18/160/25</p>	<p><b>PREMATURE VENTRICULAR TACHYCARDIA COMPLEX COUPLETS (N)</b> This patient had no relevant past medical history, except for a recent diagnosis of hypertension four months prior to the initial visit. The initial visit ECG finding of non-specific ST-T wave changes was considered clinically insignificant by the investigator. At randomization, the patient's average sitting blood pressure was 143/98 mmHg, sitting pulse was 80 beats/minutes, and standing blood pressure was 148/102 mmHg. Eighteen days post-randomization, the patient was seen for her scheduled protocol visit and at that time reported experiencing "skipped heart beats." An ECG was performed and revealed frequent multi-focal premature ventricular contraction (PVC) couplets. The investigator continued the patient in the trial, and she was scheduled for a 24-hour Holter and echocardiogram by her cardiologist. The Holter revealed frequent ventricular premature contraction couplets, marked ST segment depression with periods of tachycardia, and the echocardiogram was within normal limits with the exception of marked left ventricular hypertrophy. On day thirty-two post-randomization the patient discontinued trial medication due to PVC's. At the onset of the adverse event, the investigator considered the event possibly related to trial drug. At the terminal visit, the patient's average sitting blood pressure was 159/86 mmHg. It is unknown whether any additional medication therapy was added. Approximately two months after study drug was stopped, the adverse event was still present and unchanged; however, at that time the investigator considered the event unrelated to trial medication</p>
<p>11E/1007/506 /54/M/84/80/12.5</p>	<p><b>PULMONARY EMBOLISM (U)</b> This 54 year old male patient with a 4 year history of hypertension was seen in a hospital emergency room approximately three months after entering the open-label extension phase of the trial with complaints of severe leg and lung pain. The patient was admitted with a diagnosis of pulmonary embolism and thrombophlebitis and treated with i.v. heparin. Trial medication was discontinued. While hospitalized, an MRI of the brain was obtained. The patient had a history of an abnormal MRI scan approximately 15 months prior to admission, reportedly revealing a small mass. The MRI obtained during hospitalization revealed a brain mass. A biopsy was conducted approximately 4 weeks later and a pathology exam revealed an astrocytoma. The patient was treated with s.c. heparin and discharged. Approximately 6 weeks after the initial hospitalization, the patient was readmitted to the hospital with severe leg pain and difficulty breathing. He was treated with heparin i.v. and bed rest for a reoccurrence of the pulmonary embolism. The patient was scheduled to begin 6 weeks of radiation therapy following discharge from the hospital. The investigator considered the relationship of these events to trial medication as unlikely.</p>
<p>11E/1017/511 43/M/161/80/25</p>	<p><b>LEFT COMMON ILIAC STENOSIS (N)</b> This 43 year old male patient with a history of left calf deklaudication, gout and hyperlipidemia, complained of right leg discomfort in the femoral area, approximately 23 weeks after beginning treatment in the open-label extension. Trial medication was discontinued at the patient's request because of unsatisfactory therapeutic response and the patient began treatment with benazepril. Four weeks after the onset of the pain, the patient underwent angioplasty. An abdominal aortogram revealed a 95% stenosis of the left common iliac vessel. A balloon angioplasty was performed; however, when the balloon was deflated, the vessel restenosed. A 3 cm palmaz stent was placed in the stenosed area. The patient remained hospitalized overnight for observation. The investigator considered this event to be unrelated to trial medication.</p>

302128/N-S/ 26/M/<1/160/ 12.5	<p><b>*SYNCOPE (U)</b></p> <p>This 26 year old male subject experienced a moderate syncope secondary to blood draw approximately 1.5 hours following dosing with initial treatment sequence (Valsartan 160 mg + HCTZ 12.5 mg). His blood pressure at the time of this event was 100/80 mmHg. The investigator decided to discontinue the subject from the trial because he thought the subject would not tolerate the multiple blood draw. He was monitored for 24 hours; the adverse experience resolved, and the subject was discharged. The investigator felt that this event was unlikely related to the trial drug.</p>
31E/429/5286 75?M/84/160/25	<p><b>SYNCOPE (U)</b></p> <p>This patient had a history of bradycardia and dyspnea on exertion. His screening ECG result showed sinus bradycardia and incomplete right bundle branch block and his ECG at the end of the core revealed sinus bradycardia and right ventricular conduction delay. Approximately 3_ months after treatment with valsartan (including HCTZ 25mg for 1 month) in the open-label extension, the patient reported lightheadedness, shortness of breath, and syncope prior to falling down a flight of stairs. It is unknown how long the patient was unconscious. He was taken to the hospital where he was admitted and treated for a right shoulder abrasion and received sutures for a left hand abrasion. It was determined that the patient lost consciousness due to bradycardia, a pacemaker was inserted and the patient was discharged from the hospital. The patient's MSBP at the two visits prior to the syncopal episode were 148/90mmHg (standing 146/90mmHg) and 151/95mmHg (standing 158/90mmHg). The patient continued in the trial and investigator considered the event to be unlikely related to trial drug.</p>
31E899/5763 74/F/112/160/25	<p><b>SYNCOPE (PO)</b></p> <p>Approximately 4 months after treatment with valsartan (including HCTZ 25mg for 4 months) in the open-label extension, this patient experienced a syncopal episode. Three weeks later she experienced another episode. After the second episode, she was discontinued from the trial and the investigator indicated that the patient had been recently diagnosed with hyperglycemia and had been placed on glyburide 2.5mg OD and that low blood sugar was noted at the time of each episode (exact values unavailable). Throughout the extension, the patient's serum glucose was in the range of 126-144 mg/dL (normal range 65 - 115mg/dL) and her mean sitting blood pressure was in the range of 143/84-156/95mmHg. Her ECG results while in the core phase of the trial showed questionable old inferior myocardial infarction and left axis deviation. The investigator considered the adverse experience to be possibly related to trial drug.</p>
11E/2016/516 59/M/567/80/25	<p><b>TRANSIENT ISCHEMIC ATTACK (N)</b></p> <p>This 59 year old male patient with an 18 month history of hypertension was enrolled in the open-label extension after completing the double-blind treatment phase uneventfully. Prior treatment for hypertension included guanfacine. Approximately 81 weeks after beginning open-label treatment with valsartan, the patient was hospitalized following the sudden onset of right arm and leg weakness and an inability to speak intelligible words. Blood pressure on admission was 176/110 mmHg. CAT scan of the brain was suggestive of an aneurysm or a communicating hydrocephalus; however, an MRI with contrast showed no evidence of an aneurysm or hydrocephalus. Small lacunar infarcts were seen in the right basal ganglia and other changes likely of chronic ischemic changes. A carotid ultrasound was unremarkable. The patient was treated with nifedipine and improved significantly within 24 hours. He was then managed on only aspirin. The patient was discharged 3 days after admission. Discharge diagnosis was acute cerebrovascular accident with partial paralysis right arm and leg, and left occipital lobe defect, probably representing a small acute infarct.</p> <p>The patient was seen by the investigator 9 weeks after the event occurred. Based on physical examination at that time and review of the attending physician's report, the investigator determined that the patient had experienced a transient ischemic attack rather than an acute CVA. The investigator considered the event to be unrelated to trial medication.</p>

All subjects were discontinued prematurely except one patient with syncope\*.

**Appendix Table 3: Adverse events considered plausibly drug related-19/301**

Prot No.	Subject ID	Drug		Last Visit Week	Reasons for discontinuation
		mg	mcg LZ		
<b>***"Highly probable" - drug related</b>					
19	1072/5739	80	25	2	Dizziness
19	297/5196	80	12.5	4	Fatigue
19	438/5292	80	12.5	4	Headache
301	42/3039	80	25	8	Dizziness
301	42/3039	80	25	8	Dizziness
301	42/3039	80	25	8	Dizziness
301	175/3158	160	12.5	8	Rash
301	175/3158	160	12.5	8	Dizziness
301	175/3158	160	12.5	8	Paresthesia
301	175/3158	160	12.5	8	Hypoesthesia
301	998/3889	80	25	8	Nausea
301	998/3889	80	25	2	Fatigue
301	31/3028	160	25	4	Impotence
301	35/3032	80	0	5	Headache
301	397/3355	0	12.5	2	Hypokalemia
301	621/3559	0	0	8	Headache
301	812/3732	0	12.5	4	Hypokalemia
301	729/3654	160	0	4	Headache
301	734/3658	160	25	4	Dehydration
301	734/3658	160	25	4	Hypokalemia
<b>***"Probable"</b>					
19	75067	80	25	2	Ankle edema
19	75067	80	25	2	Urinary frequency
19	75739	80	25	2	Nausea
19	75739	80	25	0	Dizziness
19	5027	0	0	4	Tiredness
19	5031	80	12.5	4	Coughing
19	5031	80	12.5	0	Headaches
19	5305	0	0	0	Diarrhea
19	5305	0	0	0	Cramps in Stomach
19	5305	0	0	0	Tingling sensation face
19	5305	0	0	2	Headache
19	5306	80	25	0	Episodes of lightheaded feeling
19	5310	0	0	4	Pungent and increased flatulence
19	5310	80	12.5	8	Cramps in feet
19	5310	80	12.5	2	Cramps in feet
19	5798	80	12.5	4	Urinary frequency
19	5077	80	25	4	Palpitations
19	5077	80	25	2	Shortness of breath
19	5244	80	0	2	Blackout and falling to the floor
19	5244	80	0	2	Recumbent dizziness
19	5373	160	0	2	Diarrhea

19	5373	160	0	4	Abdominal Pain
19	5083979	80	12.5	8	Coughing
19	5011	160	0	0	Vertigo
19	5488	0	0	2	Fatigue
19	5488	80	25	0	Fatigue
19	3844	80	25	0	Nausea
301	3844	80	25	2	Dizziness and lightheadedness
301	3844	80	25	2	Visual disturbances
301	3844	80	25	2	Headache
301	3844	80	25	2	Urinary frequency
301	3847	0	25	8	Hypokalemia
301	3077	160	12.5	4	Fatigue
301	3158	160	12.5	4	Dizziness
301	3158	80	25	2	Dizziness
301	3180				Dizziness
***Possibly drug related AE - present and unchanged at end of trial					
301	4039	80	0	2	Bilateral pedal edema
301	4039	80	0	4	Palpitations
301	3007	160	12.5	8	Nausea
301	3212	0	25	4	Rash on legs /arms
301	3524	0	0	0	Headache
301	3030	80	12.5	2	Impotence
301	3032	80	0	2	Headache
301	3857	0	25	2	Hypokalemia
301	3857	0	25	2	Urinary frequency
301	38571973	0	0	8	Urinary frequency
301	3999	0	0	2	Persistent frontal headaches
301	3514	0	0	2	Postural lightheadedness
301	3517	0	25	2	Postural dizziness
301	3344	0	0	4	Postural lightheadedness
301	3552	0	0	2	Hypokalemia
301	3553	80	25	2	Urinary frequency
301	3559	160	0	8	Diarrhea
301	3915	0	0	2	Tachycardia
301	3615	80	12.5	8	Rash
301	3615	0	12.5	2	Lightheadedness
301	3615	0	12.5	2	Headache
301	3615	0	12.5	2	Pressure sensation in the chest
301	3617	0	12.5	2	Vomiting
301	3617	160	25	2	Severe fatigue
301	3617	160	25	2	Cramps in stomach
301	3617	160	25	2	Headache
301	3617	160	25	2	Shortness of breath
301	3668	160	25	2	Lightheadedness
301	3768	80	25	2	Intermittent lightheadedness
301	3786	0	25	4	Lightheadedness
301	3786	0	25	8	Lightheadedness
301	3786	0	25	2	Impotence
301	36342753	160	25	2	Dizziness
301	3644	0	0	0	Dizziness
301	3640	0	25	2	Dizziness
301	3646	0	0	0	Dizziness

301	3646	0	12.5	2	Postural Hypotension
301	3646	0	12.5	2	Dizziness
301	3652	160	12.5	4	Dizziness
301	3658	160	25	4	Muscle weakness
301	3662	80	12.5	2	dehydration
301	36642832	160	0	8	Impotence
V= Valsartan ; H = HCTZ; ** Sponsors classification in electronic submission					

**Appendix Table 4: All discontinuations due to adverse experiences by treatment groups - Valsartan 80mg and Placebo - Protocol 301**

Protocol	Subject ID/Age/Sex/Race	Treatment Group (V and Placebo)	Duration of Therapy (days)	Reasons for discontinuation
301	686/40/M/W	80mg	14	Asthenia
301	958/49/M/W	80mg	1	Dizziness
301	42/55/M/W	80mg	42	Dizziness
301	42/55/M/W	80mg	42	Dizziness
301	998/64/F/W	80mg	38	Fatigue
301	686/40/M/W	80mg	14	Flushing
301	958/49/M/W	80mg	1	Headache
301	165/42/F/W	80mg	28	Headache
301	803/61/F/W	80mg	7	Insomnia
301	958/49/M/W	80mg	1	Nausea
301	998/64/F/W	80mg	38	Nausea
301	803/61/F/W	80mg	7	Palpitation
301	1023/36/M/W	80mg	38	Rash
301	958/49/M/W	80mg	1	Abnormal Vision
<b>Placebo group</b>				
301	692/50/M/W	Placebo	30	Amnesia
301	692/50/M/W	Placebo	30	Confusion
301	692/50/M/W	Placebo	30	Dizziness
301	735/52/F/W	Placebo	36	Epistaxis
301	905/58/M/W	Placebo	49	Headache
301	735/52/F/W	Placebo	39	Headache
301	557/48/M/W	Placebo	44	Impotence
301	692/50/M/W	Placebo	8	Abnormal thinking

**Appendix Table 5: All discontinuations due to adverse experiences by treatment group - HCTZ - Protocol 301**

Protocol	Subject/ID Age/Sex/Race	Treatment Group HCTZ mg	Duration of Therapy	Reasons for discontinuation
301	1079/69/F/W	25	5	Depression
301	882/56/F/W	25	32	Dizziness
301	1047/55/M/BLK	25	49	Tuberculosis
301	449/51/M/W	12.5	14	CVA
301	835/69/M/W	12.5	22	Coughing
301	1006/80/F/W	12.5	14	Dizziness
301	684/43/F/W	12.5	2	Dizziness
301	720/64/M/W	12.5	12	Dizziness
301	449/51/M/W	12.5	14	Dysphagia
301	691/56/F/W	12.5	3	Dyspnea
301	1006/80/F/W	12.5	14	Fatigue
301	691/56/F/W	12.5	3	Fatigue
301	691/56/F/W	12.5	3	Flushing
301	784/65/F/W	12.5	10	Headache
301	630/35/M/W	12.5	24	Headache
301	684/43/F/W	12.5	2	Headache
301	691/56/F/W	12.5	3	Headache
301	784/65/F/W	12.5	10	Hypesthesia
301	720/64/M/W	12.5	12	Postural hypotension
301	784/65/F/W	12.5	10	Nausea
301	684/43/F/W	12.5	2	Chest pain
301	449/51/M/W	12.5	14	Paralysis
301	784/65/F/W	12.5	10	Tachycardia
301	784/65/F/W	12.5	10	Visual field defect

**Appendix Table 6: All discontinuations due to adverse experiences by treatment group - Valsartan 160mg + HCTZ - Protocol 301**

Protocol	Subject/ID Age/Sex/Race	Treatment Group	Duration of Therapy	Reasons for discontinuation
301	687/56/F/W	160+HCTZ	13	Asthenia
301	734/53/F/W	160+HCTZ	27	Leg cramps
301	687/56/F/W	160+HCTZ	13	Dehydration
301	734/53/F/W	160+HCTZ	27	Dehydration
301	687/56/F/W	160+HCTZ	13	Diarrhea
301	175/65/M/W	160+HCTZ	29	Dizziness
301	585/62/M/OR	160+HCTZ	3	Dizziness
301	585/62/M/OR	160+HCTZ	3	Dizziness
301	749/49/M/W	160+HCTZ	3	Dizziness
301	687/56/F/W	160+HCTZ	15	Dyspnea
301	176/54/F/W	160+HCTZ	29	Ventricular Extrasystole
301	715/45/M/W	160+HCTZ	32	Atrial fibrillation
301	151/60/M/W	160+HCTZ	4	Gout
301	535/34/F/W	160+HCTZ	4	Headache
301	687/56/F/W	160+HCTZ	13	Headache

301	749/49/M/W	160+HCTZ	3	Headache
301	175/65/M/W	160+HCTZ	29	Hypoesthesia
301	734/53/F/W	160+HCTZ	27	Hypokalemia
301	749/49/M/W	160+HCTZ	3	Malaise
301	734/53/F/W	160+HCTZ	27	Muscle weakness
301	687/56/F/W	160+HCTZ	13	Nausea
301	687/56/F/W	160+HCTZ	13	Abdominal pain
301	687/56/F/W	160+HCTZ	13	Chest pain
301	715/45/M/W	160+HCTZ	32	Chest pain
301	175/65/M/W	160+HCTZ	29	Paresthesia
301	175/65/M/W	160+HCTZ	29	Rash
301	1235/66/M/W	160+HCTZ	14	Rash
301	687/56/F/W	160+HCTZ	13	Increased sweating
301	749/49/M/W	160+HCTZ	3	Increased sweating
301	687/56/F/W	160+HCTZ	13	Tachycardia
301	687/56/F/W	160+HCTZ	13	Thirst
301	687/56/F/W	160+HCTZ	13	Tinnitus
301	687/56/F/W	160+HCTZ	13	Vomiting

**Appendix Table 7: All discontinuations due to adverse experiences by treatment groups - Valsartan 160 mg and 80 mg - Protocol 19**

Protocol	Subject/ID Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
19	1057/50/M/OTH	V160	35	CVA
19	299/32/M/W	V160	9	Diarrhea
19	568/39/F/BLK	V160	15	Headache
19	476/51/F/W	V160	28	Hepatic cirrhosis
19	1027/46/M/BLK	V160	28	Myocardial infarction
19	299/32/M/W	V160	9	Abdominal pain
19	1037/60/F/BLK	V160	14	Paralysis
19	1037/60/F/BLK	V160	14	Ptosis
19	1231/51/M/W	V160	32	Sprains
Protocol	Subject/ID Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
19	234/47/M/W	V80	15	Bronchitis
19	314/51/F/W	V80	35	Dermatitis
19	157/60/F/W	V80	22	Fatigue
19	668/42/F/W	V80	7	Fatigue
19	451/48/F/W	V80	28	Headache
19	1097/59/F/W	V80	14	Infectious hepatitis

**Appendix Table 8: All discontinuations due to adverse experiences by treatment group - Valsartan 80 mg + HCTZ - Protocol 19**

Protocol	Subject ID/Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
19	722/51/M/W	V80+HCTZ	24	Aneurysm
19	43/66/F/W	V80	28	Coughing
19	1072/46/F/W	V80	26	Dizziness
19	748/53/M/BLK	V80	14	Dyspnea
19	297/74/F/W	V80	7	Fatigue
19	683/66/M/W	V80	3	Fatigue
19	43/66/F/W	V80	28	Headache
19	406/52/M/W	V80	19	Myocardial Infarction
19	1069/41/M/W	V80	52	Abdominal pain
19	748/53/M/BLK	V80	14	Chest pain
19	180/75/M/W	V80	36	Rash
19	722/51/M/W	V80	24	Subarachnoid Hemorrhage

**Appendix Table 9: All discontinuations due to adverse experiences by treatment groups and protocol - Valsartan 160 mg - Protocol 31E**

Protocol	Subject ID/Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
31	615/47/M/W	V160	21	Arrhythmia
31	214/67/M/W	V160	50	Bilirubinemia
31	192/55/M/W	V160	159	Bronchospasm
31	225/65/M/W	V160	293	Bronchospasm
31	72/40/M/W	V160	284	Coughing
31	225/65/M/W	V160	293	Coughing
31	287/72/F/W	V160	61	Coughing
31	767/65/F/W	V160	94	Diverticulosis
31	179/63/F/W	V160	58	Dizziness
31	287/72/F/W	V160	61	Dysphonia
31	225/65/M/W	V160	293	Dependent edema
31	225/65/M/W	V160	293	Peripheral edema
31	133/43/M/W	V160	6	Fatigue
31	813/63/F/W	V160	271	Gastrointestinal disorder
31	173/56/M/W	V160	224	Impotence
31	173/56/M/W	V160	224	Decreased libido
31	214/67/M/W	V160	50	Frequency of micturition
31	168/40/M/W	V160	7	Nausea
31	168/40/M/W	V160	7	Nervousness
31	168/40/M/W	V160	7	Chest pain
31	119/61/F/W	V160	75	Chest pain
31	113/39/M/W	V160	25	Palpitation
31	173/56/M/W	V160	224	Penis disorder
31	225/65/M/W	V160	293	Pneumonia
31	701/41/M/W	V160	56	Prostatic disorder
31	468/50/F/W	V160	18	Urticaria
31	306/43/F/W	V160	17	Uterine hemorrhage
31	198/47/F/W	V160	8	Vertigo

31	209/45/F/W	V160	57	Vertigo
31	618/49/M/W	V160	51	Diarrhea
31	856/71/M/W	V160	10	Dizziness
31	729/37/M/OTH	V160	14	Headache
31	670/58/F/W	V160	14	Abdominal pain
31	556/47/M/W	V160	1	Chest pain
31	685/50/M/W	V160	14	Syncope
<b>Valsartan 80 mg treatment group</b>				
31	880/66/M/W	V80	30	Dizziness
31	688/50/M/W	V80	15	Peripheral edema
31	1071/55/M/W	V80	14	Palpitation

**Appendix Table 10: All discontinuations due to adverse experiences by treatment group and protocol - Valsartan 160 mg + HCTZ - Protocol 31**

Protocol	Subject ID/ Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
31E	286/49/F/BLK	V160+HCTZ	99	Arthralgia
31E	297/34/M/W	V160+HCTZ	14	Diarrhea
31E	314/53/M/W	V160+HCTZ	31	Dizziness
31E	696/56/F/W	V160+HCTZ	1	Dyspepsia
31E	286/49/F/BLK	V160+HCTZ	99	Fatigue
31E	297/34/M/W	V160+HCTZ	14	Fatigue
31E	115/56/M/W	V160+HCTZ	89	Hypokalemia
31E	115/56/M/W	V160+HCTZ	89	Hyponatremia
31E	605/48/F/W	V160+HCTZ	79	Breast Cancer
31E	11/42/M/W	V160+HCTZ	182	Pain
31E	300/67/M/OTH	V160+HCTZ	75	Chest pain
31E	314/53/M/W	V160+HCTZ	31	Paresthesia
31E	291/70/F/W	V160+HCTZ	252	Rash
31E	899/73/F/W	V160+HCTZ	135	Syncope
31E	429/72/F/W	V160+HCTZ	73	Supraventricular Tachycardia
31E	696/56/F/W	V160+HCTZ	1	Weight increase

**Appendix Table 11: All discontinuations due to adverse experiences by treatment group and protocol - Valsartan 80 mg - Protocol 28**

Protocol	Subject ID/ Age/Sex/Race	Treatment Group (mg)	Duration of Therapy	Reason for discontinuation
28	1481/73/M/W	V80	137	Aneurysm
28	1079/85/F/W	V80	321	Angina Pectoris
28	1559/79/F/W	V80	157	Angina Pectoris
28	1214/69/M/W	V80	163	Renal Carcinoma
28	1021/75/F/W	V80	207	Dizziness
28	1379/76/F/W	V80	290	Dizziness
28	1537/66/F/W	V80	85	Dizziness
28	1513/67/M/W	V80	65	Dyspnea
28	1011/79/F/W	V80	111	Dependent edema
28	1014/69/F/W	V80	78	Dependent edema
28	1379/76/F/W	V80	290	Atrial fibrillation
28	1522/73/M/W	V80	233	Atrial fibrillation

28	1563/70/M/W	V80	353	Glioma
28	1006/69/M/W	V80	141	Myocardial infarction
28	1513/67/M/W	V80	65	Chest pain
28	1021/75/F/W	V80	207	Leg pain
28	1513/67/M/W	V80	65	Rash
28	1021/75/F/W	V80	207	Upper Resp T Infection
28	1021/75/F/W	V80	207	Upper Resp T Infection
28	1556/85/F/W	V40	68	Arthralgia
28	1811/71/F/W	V40	147	CVA
28	1856/69/M/W	V40	179	Colon carcinoma
28	1013/73/F/W	V40	2	Confusion
28	1756/73/M/W	V40	202	Coughing
28	1473/71/F/W	V40	182	Coughing
28	1556/83/F/W	V40	68	Coughing
28	1348/66/F/W	V40	18	Depression
28	1804/75/F/W	V40	12	Diarrhea
28	1636/84/F/W	V40	309	Diarrhea
28	1538/71/F/W	V40	13	Dizziness
28	1556/83/F/W	V40	68	Dizziness
28	1265/69/M/W	V40	14	Fatigue
28	1556/83/F/W	V40	68	Fatigue
28	1556/83/F/W	V40	68	Abnormal gait
28	1265/69/M/W	V40	14	Headache
28	1396/65/F/W	V40	2	Headache
28	1538/71/F/W	V40	13	Malaise
28	1235/73/F/W	V40	28	Frequency of micturition
28	1013/73/F/W	V40	2	Muscle weakness
28	1396/65/F/W	V40	2	Nausea
28	1396/65/F/W	V40	2	Pain arm
28	1538/71/F/W	V40	13	Pain arm
28	1556/83/F/W	V40	68	Chest pain
28	1928/74/F/W	V40	27	Leg pain
28	1556/83/F/W	V40	68	Increased sweating
28	1753/68/F/W	V40	66	Vertigo
28	1396/65/F/W	V40	2	Abnormal vision
28	1556/83/F/W	V40	68	Abnormal vision
28	1636/84/F/W	V40	309	Vomiting

**Appendix Table 12: All discontinuations due to adverse experiences by treatment group and protocol - Valsartan 80 mg + HCTZ -Protocol 28**

Protocol	Subject ID/ Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
28E	1324/86/F/W	V80+HCTZ	4	Anxiety
28	1673/67/M/W	V80+HCTZ	14	CVA
28	1921/67/F/W	V80+HCTZ	369	Leg cramps
28	1586/81/M/W	V80+HCTZ	245	Diarrhea
28	1025/79/F/W	V80+HCTZ	18	Dizziness
28	1573/73/F/W	V80+HCTZ	88	Dizziness
28	1921/67/F/W	V80+HCTZ	369	Ear disorder
28	1321/79/F/W	V80+HCTZ	91	Edema face
28	1334/72/M/W	V80+HCTZ	349	Gout
28	1025/79/F/W	V80+HCTZ	18	Headache
28	1705/67/M/W	V80+HCTZ	18	Myocardial Infarction
28	1113/72/F/W	V80+HCTZ	86	Nausea

**Appendix Table 13: All discontinuations due to adverse experiences by treatment group and protocol - Valsartan 80 mg - Protocol 11**

Protocol	Subject ID/ Age/Sex/Race	Treatment Group	Duration of Therapy	Reason for discontinuation
11E	19/57/M/W	V80	165	Alopecia
11	14/31/M/W	V80	437	Anxiety
11	32/59/F/W	V80	105	Arthralgia
11	32/59/F/W	V80	103	Arthrosis
11	15/71/M/W	V80	29	Dizziness
11	15/71/M/W	V80	29	Dyspepsia
11	32/59/F/W	V80	103	Peripheral edema
11	32/59F/W	V80	103	Peripheral edema
11	32/59/F/W	V80	103	Peripheral edema
11	19/57/M/W	V80	165	Fatigue
11	15/71/M/W	V80	29	Headache
11	16/72/M/W	V80	178	Heart block
11	13/67/M/W	V80	102	Leukemia
11	14/31/M/W	V80	437	Migraine
11	16/72/M/W	V80	178	Myocardial Infarction
11	19/57/M/W	V80	165	Nail disorder
11	15/59/M/W	V80	265	Nerve root lesion
11	32/59/F/W	V80	103	Pain arm
11	32/59/F/W	V80	103	Pain arm
11	32/59/F/W	V80	103	Pain arm
11	15/59/F/W	V80	265	Pain arm
11	15/71/M/W	V80	29	Pain back
11	17/62/M/W	V80	306	Pain back
11	32/59/F/W	V80	103	Pain leg
11	18/60/M/W	V80	226	Weight increase
11	9/44/M/W	V40	27	Agitation
11	5/65/M/W	V40	29	Atherosclerosis
11	5/65/M/W	V40	29	Atherosclerosis
11	13/55/M/W	V40	267	CVA

11	13/55/M/W	V40	267	Confusion
11	2/76/M/W	V40	239	Diarrhea
11	26/55/F/W	V40	70	Dizziness
11	9/44/M/W	V40	27	Eye abnormality
11	29/48/F/W	V40	42	Headache
11	9/44/M/W	V40	27	Headache
11	20/48/M/W	V40	42	Headache
11	2/35/M/W	V40	18	Headache
11	9/48/M/W	V40	61	Hypotension
11	16/71/M/W	V40	293	Impotence
11	9/44/M/W	V40	27	Decreased libido
11	9/44/M/W	V40	27	Dry mouth
11	9/44/M/W	V40	27	Muscle contractions
11	9/44/M/W	V40	27	Nervousness
11	20/48/M/W	V40	42	Sexual problems
11	17/71/F/W	V20	24	Abdomen enlarged
11	24/67/M/W	V20	310	Cardiomyopathy
11	6/65/M/W	V20	435	Cerebrovascular disorder
11	15/59/F/W	V20	604	Coronary artery disease
11	4/63/M/W	V20	42	Diarrhea
11	1/47/M/W	V20	27	Dyspepsia
11	1/47/M/W	V20	27	Dyspepsia
11	5/64/M/W	V20	27	Dyspepsia
11	7/50/M/W	V20	173	Edema legs
11	7/50/M/W	V20	173	Peripheral edema
11	5/64/M/W	V20	27	Eye complaints
11	11/66/F/W	V20	414	Fatigue
11	5/64/M/W	V20	27	Headache
11	8/55/F/W	V20	8	Headache
11	19/66/M/W	V20	6	Headache
11	4/58/M/W	V20	218	Hypoesthesia
11	4/58/M/W	V20	218	Hypoesthesia
11	7/44/M/W	V20	218	Impotence
11	4/58/M/W	V20	42	Impotence
11	16/56/M/W	V20	421	Impotence
11	4/58/M/W	V20	218	Back pain
11	25/35/M/W	V20	273	Back pain
11	13/46/M/W	V20	2	Chest pain
11	4/58/M/W	V20	216	Paroniria
11	5/64/M/W	V20	27	Rhinitis
11	11/66/F/M	V20	414	Somnolence
11	30/49/F/W	V20	401	Syncope
11	6/49/F/W	V20	367	Syncope
11	5/64/M/W	V20	27	Tremor
11	14/58/F/W	V20	622	Urticaria
11	8/55/F/W	V20	8	Abnormal vision

**Appendix Table 14: All discontinuations due to adverse experiences by treatment group and protocol - Valsartan 80 mg +HCTZ - Protocol 11**

Protocol	Subject ID / Age / Sex / Race	Treatment Group	Duration of Therapy	Reason for discontinuation
11	7/56/M/W	V80+HCTZ	288	Bone disorder
11	17/49/M/W	V80	171	Bronchospasm
11	8/67/F/W	V80	390	Carcinoma colon
11	17/49/M/W	V80	171	Coughing
11	11/73/M/W	V80	873	Dementia
11	12/46/M/W	V80	124	Diarrhea
11	12/46/M/W	V80	124	Dysuria
11	7/54/M/W	V80	57	Pulmonary embolism
11	12/46/M/W	V80	124	Fatigue
11	1/46/M/W	V80	69	Fracture
11	4/50/M/W	V80	156	Impotence
11	8/54/M/W	V80	749	Lymphatic leukemia
11	18/38/M/W	V80	478	Decreased libido
11	22/59/M/W	V80	21	Decreased libido
11	12/72/M/W	V80	21	Melena
11	7/68/F/W	V80	87	Myalgia
11	8/67/F/W	V80	390	GI benign neoplasm
11	2/65/M/W	V80	191	Cancer larynx
11	7/56/M/W	V80	288	Back pain
11	3/54/M/W	V80	521	Chest pain
11	10/47/M/W	V80	743	Leg pain
11	26/47/M/W	V80	814	Palpitation
11	21/57/F/W	V80	81	Pruritus

**Appendix Table 15: All discontinuations due to adverse experiences by treatment group and protocol - Valsartan 80 mg - Protocol 20**

Protocol	Subject ID / Age / Sex / Race	Treatment Group	Duration of Therapy	Reason for discontinuation
20	1269/62/F/W	V80	63	Coughing
20	1199/78/F/W	V80	74	Musculo-skeletal procedure

**Appendix Table 16**

This appendix tabulates data on 5 patients and also narratives related to the data.

**Patient 29-Laboratory data showing laboratory error**

Patient	Protocol	Visit	Treatment (mg)	Lab Date	WBC Count (T/mm <sup>3</sup> )	Absolute Neutrophils (T/mm <sup>3</sup> )	Absolute Lymphocytes T/mm <sup>3</sup> )
291	31	1		04-26-94	8.3	5.06	2.32
		B2	Valsartan 320	05-10-94	8.4	4.45	3.02
		4	Valsartan 320	07-05-94	8.1	4.86	2.27
		6	Valsartan 160	08-04-94	7.4	4.14	2.22
		8	V 160/HCTZ 25	10-27-94	7.9	0.00	2.37
		11	V160/HCTZ 12.5	04-13-95	8.0	5.52	2.08
		Normal range			3.7 - 10.5	1.48 - 7.77	0.52 - 4.83

*This 70 year old female patient received double-blind valsartan 320 mg for 70 days before entering the extension and receiving valsartan 160 mg monotherapy for 27 days at which point HCTZ 25 mg was added. The patient received valsartan 160 mg/HCTZ 25 mg for the remaining 242 days of the trial. At Visit 8 in the extension an absolute neutrophil value of 0.00 T/mm<sup>3</sup> was obtained. No adverse experiences or concomitant medications were reported for this patient with the exception of a moderate rash which started 91 days after Visit 8. The investigator noted that the neutrophil result of 0.00 T/mm<sup>3</sup> was probably due to a laboratory error. The final visit result was within normal range.*

**Patient 64 - Neutropenia**

Patient	Protocol	Visit	Treatment	Lab Date	WBC Count (T/mm <sup>3</sup> )	Absolute Neutrophils (T/mm <sup>3</sup> )	Absolute Lymphocytes (T/mm <sup>3</sup> )
64	301	1		04-13-95	3.3	0.96	1.95
		B2	Valsartan80/HCTZ12.5	04-27-95	4.4	1.23	2.73
		5		06-21-95	3.2	0.83	1.92
		normal range			3.7 - 10.5	1.48 - 7.77	0.52 - 4.83

*This 53 year old female patient received double-blind valsartan 80 mg/HCTZ 12.5 mg for 55 days. At the final visit an absolute neutrophil value of 0.83 T/mm<sup>3</sup> was obtained; this represented a 32% decrease from baseline but only a 13% decrease from the Visit 1 laboratory value. The patient experienced abdominal pain, diarrhea, vertigo, and vomiting for which she took nizatidine, diazepam, and promethazine in addition to her daily estrogen regimen. However, all symptoms resolved 37 days before the date of the final study visit. No comment was made by the investigator regarding the low absolute neutrophil count, but this probably represented normal fluctuation around a low baseline value (1.23 T/mm<sup>3</sup>) for this patient..*

**Patient 50 - Laboratory error of entering data**

Patient	Protocol	Visit	Treatment	Lab Date	WBC Count (T/mm <sup>3</sup> )	Absolute Neutrophils (T/mm <sup>3</sup> )	Absolute Lymphocytes (T/mm <sup>3</sup> )
50	301	1		06-02-95	6.6	4.16	1.72
		B2	Valsartan80/HCTZ12.5	06-16-95	6.7	4.22	1.81
		5		08-11-95	7.1	0.00	1.35
		normal range			3.7 - 10.5	1.48 - 7.77	0.52 - 4.83

This 42 year old male patient received double-blind valsartan 80 mg/HCTZ 12.5 mg for 57 days. The patient reported no adverse experiences or use of concomitant medications during the trial. At the final visit of the trial, a value for absolute neutrophils of 4.97 T/mm<sup>3</sup> was obtained; however, a value of 0.00 was entered into the database in error. This was found during review of data for this Integrated Summary of Safety submission.

#### Patient 929-Neutropenia

Patient	Protocol	Visits	Treatment	Lab Date	WBC Count (T/mm <sup>3</sup> )	Absolute Neutrophils (T/mm <sup>3</sup> )	Absolute Lymphocytes (T/mm <sup>3</sup> )
929	19	1		10-05-94	4.0	1.52	1.96
		B3	Valsartan80 HCTZ12.5	11-21-94	5.0	2.40	1.95
		6		01-13-95	3.5	0.88	2.17
		normal range			3.7 - 10.5	1.48 - 7.77	0.52 - 4.83

This 50 year old male patient received valsartan 80 mg for 48 days then was randomized to valsartan 80 mg/HCTZ 25 mg for 54 days. At the final visit of the trial, an absolute neutrophil value of 0.88 T/mm<sup>3</sup> was obtained with a corresponding shift in absolute lymphocytes. The patient reported no adverse experiences or use of concomitant medications during the trial. The investigator commented the WBC, neutrophil, and lymphocyte counts obtained at the final visit were not clinically significant. It is possible that the shift observed in neutrophils and lymphocytes represents a subclinical infection.

#### Patient 34-Neutropenia

Patient	Protocol	Visit week	Treatment	Lab Date	WBC Count (T/mm <sup>3</sup> )	Absolute Neutrophils (T/mm <sup>3</sup> )	Absolute Lymphocytes (T/mm <sup>3</sup> )
34	301	1		05-08-95	5.3	2.60	2.17
		B2	Valsartan160 HCTZ12.5	05-24-95	3.3	0.86	2.01
		3		06-06-95	3.0	0.69	1.92
		5		07-18-95	3.3	0.99	1.91
		normal range			3.7 - 10.5	1.48 - 7.77	0.52 - 4.83

This 62 year old female patient received double-blind valsartan 160 mg/HCTZ 12.5 mg for 55 days. The patient had absolute neutrophil values below 1.0 T/mm<sup>3</sup> at baseline and at each subsequent visit during the trial. All absolute neutrophil values post-baseline represented a <20% change from the baseline value. The patient entered the trial taking only acetaminophen for arthritis and reported no other adverse experiences or use of concomitant medications during the trial. It is most likely the absolute neutrophil values obtained during this trial represent a normal fluctuation around a low baseline value (0.86 T/mm<sup>3</sup>) for this patient.

**Appendix 1**  
**References**

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## APPENDIX 2

### Proposed labeling

#### ADVERSE REACTIONS

Diovan HCT has been evaluated for safety in more than 1,300 patients, including over 360 treated for over 6 months, and 170 for over 1 year.<sup>i</sup> Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan HCT was comparable to placebo.

Dose-related orthostatic effects were seen in less than 1% of patients. A dose-related increase in the incidence of dizziness was observed in patients treated with Diovan HCT from 80/12.5 mg (6%) to 160/25 mg (16%).

The side effects (see WARNINGS) of valsartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age or race. In controlled clinical trials, discontinuation of therapy due to side effects was required in 3.6% of valsartan-hydrochlorothiazide patients and 4.5% of placebo patients.<sup>ii</sup> The most common reasons for discontinuation of therapy with Diovan HCT were headache, fatigue and dizziness.

The adverse experiences that occurred in controlled clinical trials in at least 2% of patients treated with Diovan HCT and at a higher incidence in valsartan-hydrochlorothiazide (n=730) than placebo (n=93) patients included dizziness (9% vs. 7%), viral infection (3% vs. 1%), fatigue (5% vs. 1%), pharyngitis (3% vs. 1%), coughing (3% vs. 0%) and diarrhea (3% vs. 0%). These differences were not statistically significant.<sup>iii</sup> using a threshold of >2%.

Headache, upper respiratory infection, sinusitis, back pain and chest pain occurred at a more than 2% rate but at about the same incidence in placebo and valsartan-hydrochlorothiazide patients.

Other adverse experiences that have been reported with valsartan-hydrochlorothiazide (>0.2% of valsartan-hydrochlorothiazide patients in controlled clinical trials) without regard to causality, are listed below:

**Body as a Whole:** Allergic reaction, anaphylaxis, asthenia, and dependent edema. **fatigue**

**Cardiovascular:** Palpitations, syncope, and tachycardia.

**Dermatologic:** Flushing, rash, sunburn, and increased sweating.

**Digestive:** Increased appetite, constipation, dyspepsia, flatulence, dry mouth, nausea, abdominal pain, **stomach cramps** and vomiting.

**Metabolic:** Dehydration and gout.

**Musculoskeletal:** Arthralgia, muscle cramps, muscle weakness, arm pain, and leg pain.

**Neurologic and Psychiatric :** Anxiety, depression, insomnia, decreased libido, paresthesia, and somnolence.

**Respiratory:** Bronchospasm, dyspnea,

**Special Senses:** Tinnitus, vertigo, and abnormal vision.

**Urogenital:** Dysuria, impotence, micturition frequency, and urinary tract infection.<sup>iv</sup>

#### Valsartan

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received

ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, 69% respectively ( $p < 0.001$ ).

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema  
Hydrochlorothiazide.

Hydrochlorothiazide has been extensively prescribed for many years, but there has not been enough systematic collection of data to support an estimate of the frequency of the observed adverse reactions. Within organ-system groups, the reported reactions are listed here in decreasing order of severity, without regard to frequency.

Prescribing Information

## **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, Diovan HCT should be discontinued as soon as possible.

## **WARNINGS**

### **Fetal/Neonatal Morbidity and Mortality**

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

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

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

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

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

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

## **PRECAUTIONS**

### **General**

#### **Valsartan - Hydrochlorothiazide**

In the controlled trials of various doses of the combination of valsartan and hydrochlorothiazide the mean change in serum potassium was a decrease of 0.15 mEq/L<sup>vi</sup>; 3.2% of patients developed a greater than 20% increase in serum potassium and 3.9% of patients developed a greater than 20% decrease in serum potassium, compared to baseline (pretreatment) levels.<sup>vi</sup> Two patients discontinued from a trial for decreases in serum potassium

In these same trials, 4.7% of patients receiving valsartan monotherapy developed a greater than 20% increase in serum potassium compared to baseline levels and 8.7% of patients receiving hydrochlorothiazide alone developed a greater than 20% decrease in serum potassium compared to baseline

#### **To be deleted:**

“The opposite effects of valsartan and hydrochlorothiazide on serum potassium will approximately balance each other in many patients, so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant.

Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals”.

#### **Hydrochlorothiazide**

Treatment with thiazide diuretics has been associated with hypokalemia, hyponatremia, and hypochloremic alkalosis. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

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

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

### **Valsartan**

*Impaired Hepatic Function:* As the majority of valsartan is eliminated in the bile, patients with mild to moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.

*Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Valsartan would be expected to behave similarly.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

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

### **Information for Patients**

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

**Symptomatic Hypotension:** A patient receiving Diovan HCT should be cautioned that lightheadedness can occur, especially during the first days or weeks of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Diovan HCT should be discontinued until the physician has been consulted.

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

**Potassium Supplements:** A patient receiving Diovan HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

### **Clinical Laboratory Test Findings**

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan HCT.

**Creatinine:** Minor elevations in creatinine occurred in 1.4% of patients taking Diovan HCT and 1.1% given placebo in controlled clinical trials.

**Hemoglobin and Hematocrit:** Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.1% and 1.0%, respectively, of Diovan HCT -treated patients, compared with 0.0% in placebo-treated patients.

**Liver function tests:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan HCT-treated.

**Neutropenia:** Neutropenia was observed in 0.6% of patients treated with Diovan HCT-treated patients compared to 0.0% of patients treated with placebo.

## **OVERDOSAGE**

### **Valsartan - Hydrochlorothiazide**

In rats and marmosets single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 23 and 14 times the maximum recommended human dose (MRHD) of valsartan and 193 and 116 times the MRHD of hydrochlorothiazide on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 160 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

### **Valsartan**

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Valsartan is not removed from the plasma by dialysis.<sup>vii</sup>

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (31 and 18 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis). (Calculations assume an oral dose of 160 mg/day and a 60-kg patient.)

### **Hydrochlorothiazide**

The oral LD<sub>50</sub> of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, which represents 2027 and 4054 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

## **DOSAGE AND ADMINISTRATION**

The recommended starting dose of valsartan is 80 mg once daily when used as monotherapy in patients who are not volume depleted. Valsartan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day. Hydrochlorothiazide is effective in doses of 12.5 to 100 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects (see WARNINGS) of valsartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of valsartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects, but regimens in which valsartan is combined with low doses of hydrochlorothiazide produce minimal effects on serum potassium.

In controlled clinical trials of Diovan HCT, the average change in serum potassium was near zero in subjects who received Diovan HCT 80/12.5 mg or 160/12.5 mg, but the majority of average subject who received Diovan HCT 80/25 mg or 160/25 mg experienced a mild reduction in serum potassium, similar to that experienced by the average subject receiving the same dose of hydrochlorothiazide monotherapy.

**Special populations**

**Pediatric:** The pharmacokinetics of valsartan have not been investigated in patients < 18 years of age.

**Geriatric:** Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

**Gender:** Pharmacokinetics of valsartan does not differ significantly between males and females.

**To be added to label:**

**Renal Insufficiency:** There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment.

Consequently, dose adjustment is not required in patients with renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min) or patients undergoing dialysis. Valsartan is not removed from the plasma by dialysis. In the case of severe renal disease exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

### Appendix 3

#### Administrative History

Two trials, Protocols 11 Extension and 28, pool data collected under various trial phases and amendments. Protocol 11 Extension consisted of an open-label 98 week phase in which patients took valsartan monotherapy and could have HCTZ added on for blood pressure control if needed. An amendment to the protocol allowed patients who had been receiving valsartan/HCTZ for at least one year at the time of the amendment to continue for another year on the combination. These phases are described under 'Protocol 11 Extension' which incorporates 3 years of data.

Protocol 28 consisted of a double-blind core portion which was 52 weeks in duration. Patients could have open-label HCTZ added on for blood pressure control if needed. An amendment to the protocol allowed patients who had been receiving valsartan/HCTZ for at least one year at the time of the amendment to continue for another year on the combination. These phases are described under 'Protocol 28' and incorporates 2 years of data.

Three trials, Protocols 20, 24, and 28 were controlled for valsartan monotherapy but were not controlled for valsartan/HCTZ. Protocols 20 and 28 allowed HCTZ to be added in an open-label fashion onto the double-blind regimen as needed for blood pressure control. Protocol 24 was a single-dose three-way crossover trial on a background of open-label hydrochlorothiazide/amiloride .

During the trial the following administrative changes occurred: Dr. William Hilty had 13 randomized patients return for Visit 5 two weeks after Visit 4 instead of 4 weeks per the protocol. Dr. Andrew Lewin, Dr. Thomas Littlejohn, and Dr. Abraham Waks had single-blind and/or double-blind numbers assigned out of sequence as patients were screened. Dr. J. D. Smucker relocated and Dr. Douglas Schumacher replaced him as principal investigator. Dr. Michael Weber relocated and Dr. David Smith replaced him as principal investigator. Dr. Rodney Berger (original principal investigator Seth Tannenbaum, M.D.) was initiated but did not enroll any patients into the trial. Dr. Charles Singleton was initiated but did not enroll any patients into the trial.

In June of 1995.

changed their name to

The following amendments were made to the Clinical Trial Report for Valsartan Protocol 19 :Clinical Trial Report Summary: Clinical Trial Summary, item Test product, dose and mode of administration, batch and formulation nos. The incorrect reference was given.

It is amended to read: See CTR Section 15. Clinical Trial Report: Module I, Section 4.2. Quality assurance page 16. Additional information was made available after the report was written. The last paragraph is amended to read: A Clinical Research Quality Assurance (QA) Program operates within Ciba and conducts audits, as required, of clinical trials performed by the Clinical Research areas. Dr. Neutel's site in Orange CA was audited by the Ciba Regulatory Compliance group on March 8-9, 1995. Clinical Trial Report: Module IV, Table 8.1:1 Summary Statistics for blood pressure, pulses, and body weight by center, treatment group, and visit (all randomized patients) pages 2116 - 2239. The title of the row was incorrect. It is amended to read: Standing systolic blood pressure. Clinical Trial Report: Module V, Ethical and regulatory issues, Title Page, page 2612. Additional information was made available after the report was written. The title page is amended to read Dr. Neutel's Site in Orange, CA was audited on March 8-9, 1995.

## Appendix 4

### Definitions of Adverse Events

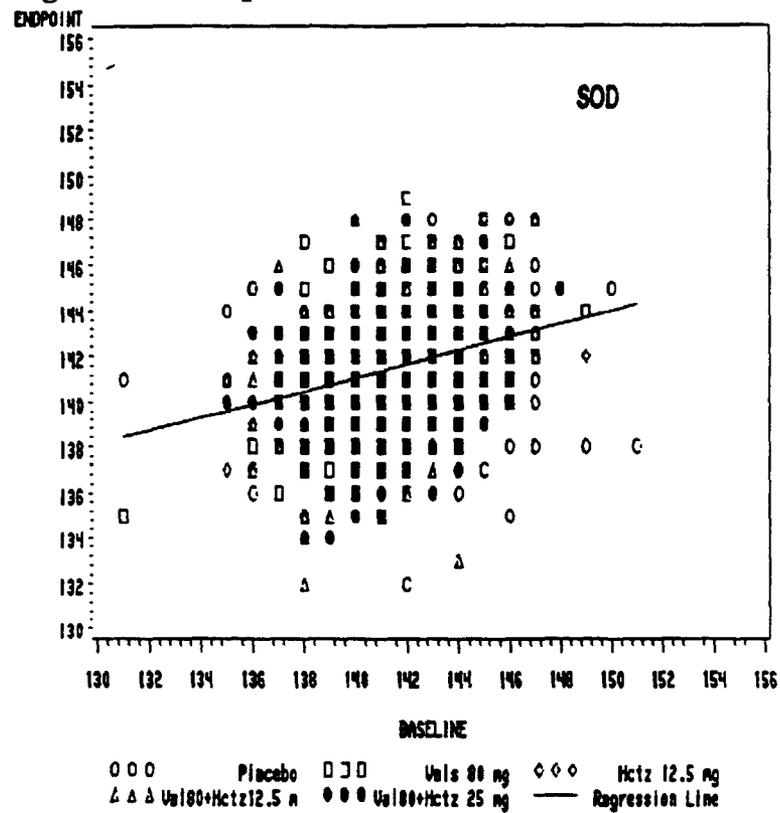
The definition of a serious adverse experience (SAE) is as follows:

A serious adverse experience is considered to be any experience that suggests a significant hazard, contraindication, side effect, or precaution. In that regard, medical judgment is required in the evaluation of incoming information. As a rule, a serious adverse experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient or prolonged hospitalization, or is a congenital anomaly, cancer, or a drug overdose. The patient/subject must be followed carefully until the condition disappears and/or the etiology is identified. Trial drug relationship for each adverse experience should be determined by the investigator using the following explanations: **Not related** The experience is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject. **Unlikely** The experience was most likely produced by other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject, and does not follow a known response pattern to the trial drug. **Possible** The experience follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the trial drug, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject

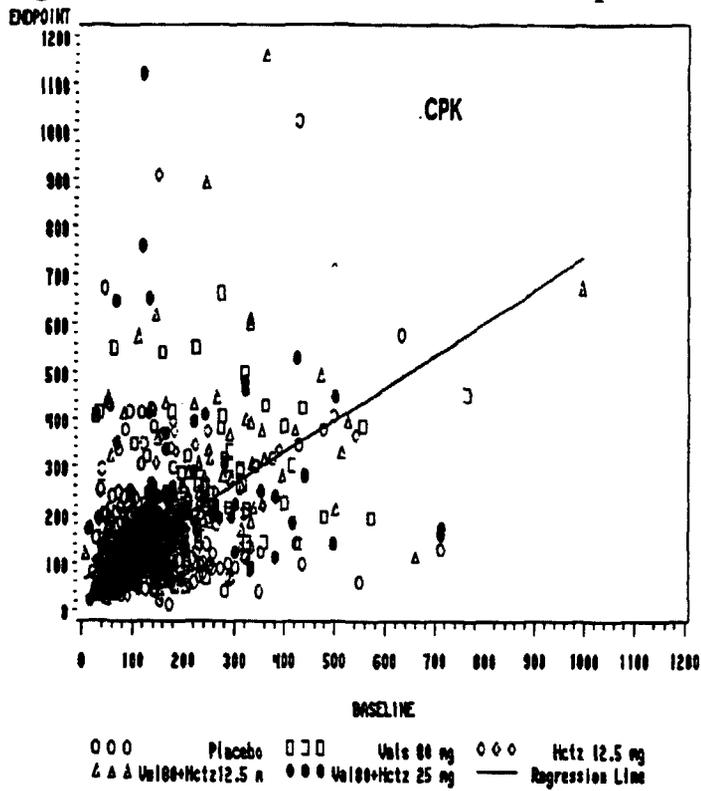
**Probable** The experience follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the trial drug, and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject.

**Highly probable** The experience follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the trial drug, and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject, and either occurs immediately following trial drug administration, or improves on stopping the drug, or reappears on repeat exposure, or there is a positive reaction at the application site.

**Appendix Figure 1**  
**Figures show regression lines**  
**Figure 1a: Graph of serum sodium on Protocols 19/301**



**Figure 1b: CPK level - baseline to endpoint and outliers**



**Figure 1c: CPK level-baseline to endpoint and outlier**

