



4546

PRODUCT NAME	: Amlopidine, Valsartan and Hydrochlorothiazide Tablets, USP	COUNTRY : US	LOCATION : -	Supersedes A/W No.:
ITEM / PACK	: Outset	NO. OF COLORS: 1	REMARK :	
DESIGN STYLE	: Front Side	PANTONE SHADE NOS.:	SUBSTRATE : 40 gm/2 Bible Paper	
CODE	: 8079271		Activities	Department
DIMENSIONS (MM)	: 560 x 375		Prepared By	Pkg.Dev
ART WORK SIZE	: S/S	Black	Reviewed By	Pkg.Dev
DATE	: 02-09-2020	Font Size 6 pt Med, 10 pt	Approved By	Quality

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet. These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **AMLOPIDINE, VALSARTAN and HYDROCHLOROTHIAZIDE TABLETS** safely and effectively. See full prescribing information for **AMLOPIDINE, VALSARTAN and HYDROCHLOROTHIAZIDE TABLETS**.

AMLOPIDINE, VALSARTAN and HYDROCHLOROTHIAZIDE tablets, for oral use
Initial U.S. Approval: 2009

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

When pregnancy is detected, discontinue **amlopidine, valsartan and hydrochlorothiazide tablets as soon as possible**. (5.1)
• **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.** (5.1)

INDICATIONS AND USAGE

Amlopidine, valsartan and hydrochlorothiazide tablets are a combination tablet of amlopidine, a dihydropyridine calcium channel blocker (DHP CCB), valsartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a thiazide diuretic. Amlopidine, valsartan and hydrochlorothiazide tablets are indicated for the treatment of hypertension to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

Limitation of Use
Amlopidine, valsartan and hydrochlorothiazide tablets are not indicated for initial treatment of hypertension.

DOSE AND ADMINISTRATION

• Dose once-daily. Titrate up to a maximum dose of 10 mg/320 mg/25 mg.

Amlopidine, valsartan and hydrochlorothiazide tablets may be used as add-on/switch therapy for patients not adequately controlled on any two of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics.

Amlopidine, valsartan and hydrochlorothiazide tablets may be substituted for its individual components.

DOSE FORMS AND STRENGTHS

Tablets: (amlopidine/valsartan/hydrochlorothiazide mg) 5/160/12.5, 5/160/25, 10/160/25, 10/320/25 (3)

CONTRAINDICATIONS

• Anuria (4)
• Hypersensitivity to sulfonamide-derived drugs (4)
• Known hypersensitivity to any component (4)
• Do not coadminister aliskiren with amlopidine, valsartan and hydrochlorothiazide in patients with diabetes (4)

WARNINGS AND PRECAUTIONS

• Hypotension: Correct volume depletion prior to initiation (5.2)
• Increased angina and/or myocardial infarction (5.3)
• Monitor renal function and potassium in susceptible patients (5.4, 5.5)
• Exacerbation or activation of systemic lupus erythematosus (5.7)
• Observe for signs of fluid or electrolyte imbalance (5.9)
• Acute angle-closure glaucoma (5.10)

Most common adverse events (≥ 2% incidence) are dizziness, peripheral edema, headache, dyspepsia, fatigue, muscle spasms, back pain, nausea, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Pharma Inc. at 1-800-912-9561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• If simvastatin is coadministered with amlopidine, do not exceed doses greater than 20 mg daily of simvastatin (7)
• Antidiabetic drugs: Dosage adjustment of antidiabetic may be required (7)
• Oral contraceptives and colestipol: Reduced absorption of thiazides (12.3)
• Lithium: Increased risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use. (7)
• Non-Steroidal Anti-inflammatory Drug (NSAID) use may lead to increased risk of renal impairment and loss of antihypertensive effect (8.7)
• Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7)

USE IN SPECIFIC POPULATIONS
Lactation: Breastfeeding is not recommended (8.2)
Geriatric Patients: Not recommended for initial therapy (8.5)
Hepatic Impairment: Not recommended for initial therapy (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: September 2020

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

2 **DOSE AND ADMINISTRATION**

3 **DOSE FORMS AND STRENGTHS**

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 **ADVERSE REACTIONS**

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9 DESCRIPTION

10 OVERDOSAGE

11 CLINICAL PHARMACOLOGY

12 MECHANISM OF ACTION

13 NONCLINICAL TOXICOLOGY

14 HOW SUPPLIED/STORAGE AND HANDLING

15 PATIENT COUNSELING INFORMATION

16 REFERENCES

17 PATIENT COUNSELING INFORMATION

18 SUPPLEMENTAL INFORMATION

19 OTHER INFORMATION

20 REFERENCES

21 OTHER INFORMATION

22 REFERENCES

23 OTHER INFORMATION

24 REFERENCES

25 OTHER INFORMATION

26 REFERENCES

27 OTHER INFORMATION

28 REFERENCES

29 OTHER INFORMATION

30 REFERENCES

31 OTHER INFORMATION

32 REFERENCES

33 OTHER INFORMATION

34 REFERENCES

35 OTHER INFORMATION

36 REFERENCES

37 OTHER INFORMATION

38 REFERENCES

39 OTHER INFORMATION

40 REFERENCES

41 OTHER INFORMATION

42 REFERENCES

43 OTHER INFORMATION

44 REFERENCES

45 OTHER INFORMATION

46 REFERENCES

47 OTHER INFORMATION

48 REFERENCES

49 OTHER INFORMATION

50 REFERENCES

51 OTHER INFORMATION

52 REFERENCES

53 OTHER INFORMATION

54 REFERENCES

55 OTHER INFORMATION

56 REFERENCES

57 OTHER INFORMATION

58 REFERENCES

59 OTHER INFORMATION

60 REFERENCES

61 OTHER INFORMATION

62 REFERENCES

63 OTHER INFORMATION

64 REFERENCES

65 OTHER INFORMATION

66 REFERENCES

67 OTHER INFORMATION

68 REFERENCES

69 OTHER INFORMATION

70 REFERENCES

71 OTHER INFORMATION

72 REFERENCES

73 OTHER INFORMATION

74 REFERENCES

75 OTHER INFORMATION

76 REFERENCES

77 OTHER INFORMATION

78 REFERENCES

79 OTHER INFORMATION

80 REFERENCES

81 OTHER INFORMATION

82 REFERENCES

83 OTHER INFORMATION

84 REFERENCES

85 OTHER INFORMATION

86 REFERENCES

87 OTHER INFORMATION

88 REFERENCES

89 OTHER INFORMATION

90 REFERENCES

91 OTHER INFORMATION

92 REFERENCES

93 OTHER INFORMATION

94 REFERENCES

95 OTHER INFORMATION

96 REFERENCES

97 OTHER INFORMATION

98 REFERENCES

99 OTHER INFORMATION

100 REFERENCES

101 OTHER INFORMATION

102 REFERENCES

103 OTHER INFORMATION

104 REFERENCES

105 OTHER INFORMATION

106 REFERENCES

107 OTHER INFORMATION

108 REFERENCES

109 OTHER INFORMATION

110 REFERENCES

111 OTHER INFORMATION

112 REFERENCES

113 OTHER INFORMATION

114 REFERENCES

115 OTHER INFORMATION

116 REFERENCES

117 OTHER INFORMATION

118 REFERENCES

119 OTHER INFORMATION

120 REFERENCES

121 OTHER INFORMATION

122 REFERENCES

123 OTHER INFORMATION

124 REFERENCES

125 OTHER INFORMATION

126 REFERENCES

127 OTHER INFORMATION

128 REFERENCES

129 OTHER INFORMATION

130 REFERENCES

131 OTHER INFORMATION

132 REFERENCES

133 OTHER INFORMATION

134 REFERENCES

135 OTHER INFORMATION

136 REFERENCES

137 OTHER INFORMATION

138 REFERENCES

139 OTHER INFORMATION

140 REFERENCES

141 OTHER INFORMATION

142 REFERENCES

143 OTHER INFORMATION

144 REFERENCES

145 OTHER INFORMATION

146 REFERENCES

147 OTHER INFORMATION

148 REFERENCES

149 OTHER INFORMATION

150 REFERENCES

151 OTHER INFORMATION

152 REFERENCES

153 OTHER INFORMATION

154 REFERENCES

155 OTHER INFORMATION

156 REFERENCES

157 OTHER INFORMATION

158 REFERENCES

159 OTHER INFORMATION

160 REFERENCES

161 OTHER INFORMATION

162 REFERENCES

163 OTHER INFORMATION

164 REFERENCES

165 OTHER INFORMATION

166 REFERENCES

167 OTHER INFORMATION

168 REFERENCES

169 OTHER INFORMATION

170 REFERENCES

171 OTHER INFORMATION

172 REFERENCES

173 OTHER INFORMATION

174 REFERENCES

175 OTHER INFORMATION

176 REFERENCES

177 OTHER INFORMATION

178 REFERENCES

179 OTHER INFORMATION

180 REFERENCES

181 OTHER INFORMATION

182 REFERENCES

183 OTHER INFORMATION

184 REFERENCES

185 OTHER INFORMATION

186 REFERENCES

187 OTHER INFORMATION

188 REFERENCES

189 OTHER INFORMATION

190 REFERENCES

191 OTHER INFORMATION

192 REFERENCES

193 OTHER INFORMATION

194 REFERENCES

195 OTHER INFORMATION

196 REFERENCES

197 OTHER INFORMATION

198 REFERENCES

199 OTHER INFORMATION

200 REFERENCES

201 OTHER INFORMATION

202 REFERENCES

203 OTHER INFORMATION

204 REFERENCES

205 OTHER INFORMATION

206 REFERENCES

207 OTHER INFORMATION

208 REFERENCES

209 OTHER INFORMATION

210 REFERENCES

211 OTHER INFORMATION

212 REFERENCES

213 OTHER INFORMATION

214 REFERENCES

215 OTHER INFORMATION

216 REFERENCES

217 OTHER INFORMATION

218 REFERENCES

219 OTHER INFORMATION

220 REFERENCES

221 OTHER INFORMATION

222 REFERENCES

223 OTHER INFORMATION

224 REFERENCES

225 OTHER INFORMATION

226 REFERENCES

227 OTHER INFORMATION

228 REFERENCES

229 OTHER INFORMATION

230 REFERENCES

231 OTHER INFORMATION

232 REFERENCES

233 OTHER INFORMATION

234 REFERENCES

235 OTHER INFORMATION

236 REFERENCES

237 OTHER INFORMATION

238 REFERENCES

239 OTHER INFORMATION

240 REFERENCES

241 OTHER INFORMATION

242 REFERENCES

PRODUCT NAME :	Amlodipine, Valsartan and Hydrochlorothiazide Tablets, USP	COUNTRY : US	LOCATION : -		Supersedes A/W No.:		
ITEM / PACK :	Outsert	NO. OF COLORS: 1	REMARK :				
DESIGN STYLE :	Back Side	PANTONE SHADE NOS.:	SUBSTRATE : 40 g/m ² Bible Paper				
CODE :	8079271		Activities	Department	Name	Signature	Date
DIMENSIONS (MM) :	560 x 375		Prepared By	Pkg.Dev			
ART WORK SIZE :	S/S	Black	Reviewed By	Pkg.Dev			
DATE :	02-09-2020	Font Size 6 pt Medi_10_pt	Approved By	Quality			

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet.
These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.



Valsartan
 No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.
 Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
Hydrochlorothiazide:
Drugs that alter gastrointestinal motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g., atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

Cholestyramine: In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine resulted in 35% reduction in exposure to hydrochlorothiazide.
Antimetoplastic agents (e.g., cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.
Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.
Skeletal muscle relaxants: Possible increased responsiveness to muscle relaxants such as curare derivatives.
Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 Studies with amlodipine/valsartan/hydrochlorothiazide: No carcinogenicity, mutagenicity, or fertility studies have been conducted with this combination. However, these studies have been conducted for amlodipine, valsartan and hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic studies, there is no indication of any toxicologically significant adverse interaction between these components.
 Studies with amlodipine: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m² basis, about 2.5 times the MRHD. (Calculations based on a 60 kg patient.)
 Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.
 There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m² basis).

Studies with valsartan: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m² basis (Calculations based on a 60 kg patient).
 Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli*, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the MRHD on a mg/m² basis.
 Studies with hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella Typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and Mouse Lymphoma Cell (mutagenicity) assays and in the Aspergillus Nidulans non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed via diet at doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats are 19 and 1.5 times, respectively, the MRHD on a mg/m² basis (Calculations assume an oral dose of 25 mg/day and a 60-kg patient).

14 CLINICAL STUDIES
 Amlodipine, valsartan and hydrochlorothiazide tablets were studied in a double-blind, active controlled study in hypertensive patients. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/HCTZ 10 mg/320 mg/25 mg, valsartan/HCTZ 200 mg/25 mg, amlodipine/valsartan 10 mg/320 mg, or HCTZ/amlodipine 25 mg/10 mg. At study initiation, patients assigned to the 2-component arms received lower doses of their treatment combination while patients assigned to the amlodipine, valsartan and hydrochlorothiazide tablets arm received 160 mg/12.5 mg valsartan/hydrochlorothiazide. After 1 week, amlodipine, valsartan and hydrochlorothiazide tablets patients were titrated to 5 mg/160 mg/12.5 mg amlodipine/valsartan/hydrochlorothiazide, while all other patients continued receiving their initial doses. After 2 weeks, all patients were titrated to their full treatment dose. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian, and 17% were black.
 At Week 8, the triple combination therapy produced greater reductions in blood pressure than each of the 3 dual combination treatments (p < 0.0001 for both diastolic and systolic blood pressures reductions). The reductions in systolic/diastolic blood pressure with amlodipine, valsartan and hydrochlorothiazide tablets were 7.6/5.0 mmHg greater than with valsartan/HCTZ, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/6.3 mmHg greater than with amlodipine/HCTZ (see Figure 1). The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of amlodipine, valsartan and hydrochlorothiazide tablets (see Figure 2 and Figure 3). As the pivotal study was an active-controlled trial, the treatment effects shown in Figures 1, 2, and 3 include a placebo effect of unknown size.

Figure 1: Reduction in Mean Blood Pressure at Endpoint

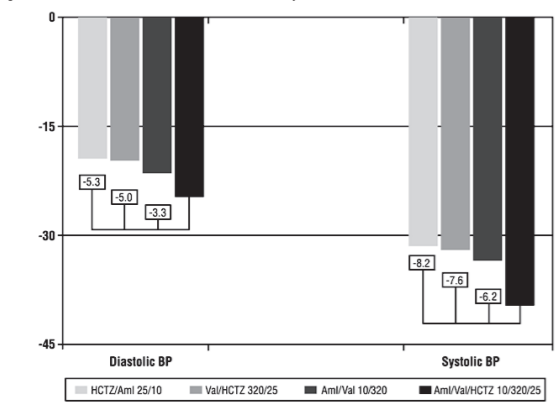


Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

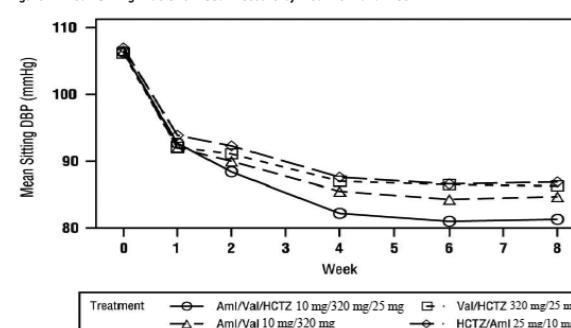
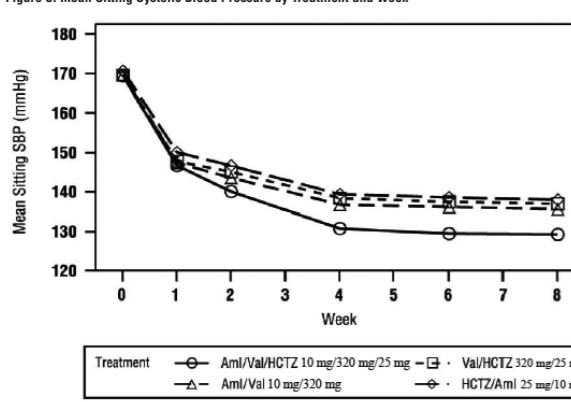


Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week



A subgroup of 283 patients was studied with ambulatory blood pressure monitoring. The blood pressure lowering effect in the triple therapy group was maintained throughout the 24-hour period (see Figure 4 and Figure 5).

Figure 4: Mean Ambulatory Diastolic Blood Pressure at Endpoint by Treatment and Hour

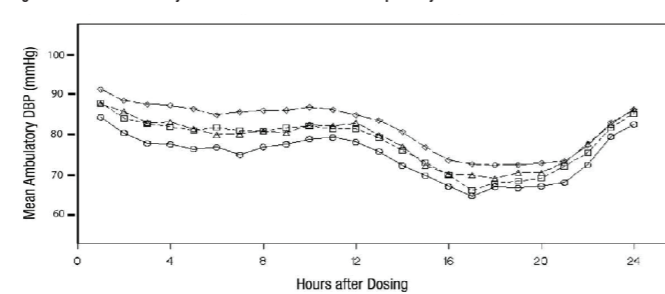
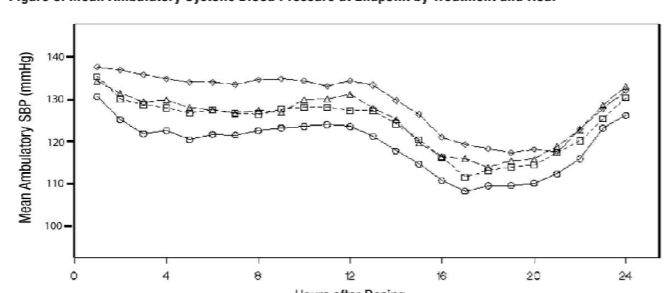


Figure 5: Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Hour



There are no trials of the amlodipine, valsartan and hydrochlorothiazide combination tablets demonstrating reductions in cardiovascular risk in patients with hypertension, but both the amlodipine and hydrochlorothiazide components and several ARBs, which are the same pharmacological class as the valsartan component, have demonstrated such benefits.

16 HOW SUPPLIED/STORAGE AND HANDLING
 Amlodipine, valsartan and hydrochlorothiazide tablets, USP are available as film-coated tablets containing amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg, and hydrochlorothiazide 12.5 mg or 25 mg, providing for the following available combinations: 5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25 mg, and 10 mg/320 mg/25 mg. All strengths are packaged in bottles of 30, 100, 500 tablets and Carton of 100 tablets (10X10 unit-dose).

5 mg amlodipine/160 mg valsartan/12.5 mg hydrochlorothiazide Tablets, USP- White to off-white colored, oval shaped, biconvex, film coated tablets debossed with "1525" on one side and plain on other side.
 Bottles of 30 NDC 13668-326-30
 Bottles of 100 NDC 13668-326-01
 Bottles of 500 NDC 13668-326-05
 Carton of 100 tablets (10 x 10 unit-dose) NDC 13668-326-74

5 mg amlodipine/160 mg valsartan/25 mg hydrochlorothiazide Tablets, USP- Yellow colored, capsule shaped, biconvex, film coated tablets debossed with "1329" on one side and plain on other side.
 Bottles of 30 NDC 13668-329-30
 Bottles of 100 NDC 13668-329-01
 Bottles of 500 NDC 13668-329-05
 Carton of 100 tablets (10 x 10 unit-dose) NDC 13668-329-74

10 mg amlodipine/160 mg valsartan/12.5 mg hydrochlorothiazide Tablets, USP- Pale yellow colored, oval shaped, biconvex, film coated tablets debossed with "1527" on one side and plain on other side.
 Bottles of 30 NDC 13668-327-30
 Bottles of 100 NDC 13668-327-01
 Bottles of 500 NDC 13668-327-05
 Carton of 100 tablets (10 x 10 unit-dose) NDC 13668-327-74

10 mg amlodipine/160 mg valsartan/25 mg hydrochlorothiazide Tablets, USP- Brown-yellow colored, capsule shaped, biconvex, film coated tablets debossed with "1328" on one side and plain on other side.
 Bottles of 30 NDC 13668-328-30
 Bottles of 100 NDC 13668-328-01
 Bottles of 500 NDC 13668-328-05
 Carton of 100 tablets (10 x 10 unit-dose) NDC 13668-328-74

10 mg amlodipine/320 mg valsartan/25 mg hydrochlorothiazide Tablets, USP- Brown-yellow colored, capsule shaped, biconvex, film coated tablets debossed with "1525" on one side and plain on other side.
 Bottles of 30 NDC 13668-325-30
 Bottles of 100 NDC 13668-325-01
 Bottles of 500 NDC 13668-325-05
 Carton of 100 tablets (10 x 10 unit-dose) NDC 13668-325-74

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
 Protect from moisture.
 Dispense in a tight container as defined in the USP.

17 PATIENT COUNSELING INFORMATION
 Advise the patient to read the FDA-approved patient labeling (Patient Information).
Pregnancy: Advise female patients of childbearing age about the consequences of exposure to amlodipine, valsartan and hydrochlorothiazide tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].
Lactation: Advise women not to breastfeed during treatment with amlodipine, valsartan and hydrochlorothiazide tablet [see Use in Specific Populations (8.2)].
Symptomatic Hypotension: Advise patients that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to their healthcare provider. Tell patients that if syncope occurs to discontinue amlodipine, valsartan and hydrochlorothiazide tablets until the physician has been consulted. Caution all patients 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 [see Warnings and Precautions (5.2)].
Potassium Supplements: Advise patients not to use salt substitutes without consulting their healthcare provider [see Drug Interactions (7)].
Non-melanoma Skin Cancer: Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

Information for Patients
Patient Information
Amlodipine, Valsartan and Hydrochlorothiazide (am-LOE-di-peen, val-SAR-tan and hye-droe klor-oh-THYE-a-zide) Tablets, USP
 Read the Patient Information that comes with amlodipine, valsartan and hydrochlorothiazide tablets before you start taking them and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.
What is the most important information I should know about amlodipine, valsartan and hydrochlorothiazide tablets?
 • Amlodipine, valsartan and hydrochlorothiazide tablets can cause harm or death to an unborn baby.
 • Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
 If you get pregnant while taking amlodipine, valsartan and hydrochlorothiazide tablets, tell your doctor right away.
What are amlodipine, valsartan and hydrochlorothiazide tablets?
 Amlodipine, valsartan and hydrochlorothiazide tablets contain 3 prescription medicines:
 1. amlodipine, a calcium channel blocker
 2. valsartan, an angiotensin receptor blocker, and
 3. hydrochlorothiazide, a diuretic (water pill)

Amlodipine, valsartan and hydrochlorothiazide tablets may be used to

lower blood pressure in adults when 2 medicines to lower your high blood pressure are not enough.

Amlodipine, valsartan and hydrochlorothiazide tablets have not been studied in children under 18 years of age.

Who should not take amlodipine, valsartan and hydrochlorothiazide tablets?

Do not take amlodipine, valsartan and hydrochlorothiazide tablets if you have low or no urine output (anuria).

What should I tell my doctor before taking amlodipine, valsartan and hydrochlorothiazide tablets?

Tell your doctor about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. See “What is the most important information I should know about amlodipine, valsartan and hydrochlorothiazide tablets?”
- are breastfeeding or plan to breastfeed. Amlodipine, valsartan and hydrochlorothiazide are present in human milk. It is not known whether amlodipine, valsartan and hydrochlorothiazide affects your breastfed baby or milk production. Do not breastfeed while you are taking amlodipine, valsartan and hydrochlorothiazide tablets.
- are allergic to any of the ingredients in amlodipine, valsartan and hydrochlorothiazide tablets. See the end of this leaflet for a list of the ingredients in amlodipine, valsartan and hydrochlorothiazide tablets.
- have heart problems
- have liver problems
- have kidney problems
- are vomiting or having a lot of diarrhea
- have or had gallstones
- have Lupus
- have low levels of potassium (with or without symptoms such as muscle weakness, muscle spasms, abnormal heart rhythm) or magnesium in your blood
- have high levels of calcium in your blood (with or without symptoms such as nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness, and twitching).
- have high levels of uric acid in the blood.
- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue, and may cause difficulty breathing.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines and amlodipine, valsartan and hydrochlorothiazide tablets could affect each other, causing serious side effects.

Especially tell your doctor if you take:

- simvastatin or other cholesterol-lowering medicine
- other medicines for high blood pressure or a heart problem
- water pills (“diuretics”)
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- salt substitute containing potassium. Your doctor may check the amount of potassium in your blood periodically.
- diabetes medicine including insulin
- narctic pain medicines
- sleeping pills and antiseizure medicines called barbiturates
- lithium, a medicine used to treat some types of depression
- aspirin or other medicines called nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen or naproxen
- steroids
- alcohol
- digoxin or other digitalis glycosides (a heart medicine)
- muscle relaxants (medicines used during operations)
- certain cancer medicines, like cyclophosphamide or methotrexate
- medicines used to prevent and treat fungal infections (such as ketoconazole, itraconazole)
- medicines used to treat bacterial infections (such as clarithromycin, telithromycin)
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

Know the medicines you take. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new medicine.

How should I take amlodipine, valsartan and hydrochlorothiazide tablets?

- Take amlodipine, valsartan and hydrochlorothiazide tablets exactly as your doctor tells you.
- Take amlodipine, valsartan and hydrochlorothiazide tablets one time each day.
- Amlodipine, valsartan and hydrochlorothiazide tablets can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at the regular time.
- If you take too many amlodipine, valsartan and hydrochlorothiazide tablets, call your doctor or Poison Control Center, or go to the emergency room.
- Tell all your doctors and dentist you are taking amlodipine, valsartan and hydrochlorothiazide tablets. This is especially important if you:

- are going to have surgery
- go for kidney dialysis

What are the possible side effects of amlodipine, valsartan and hydrochlorothiazide tablets?

Amlodipine, valsartan and hydrochlorothiazide tablets may cause serious side effects including:

- harm to an unborn baby causing injury or death. See “What is the most important information I should know about amlodipine, valsartan and hydrochlorothiazide tablets?”
- low blood pressure (hypotension). Low blood pressure is most likely to happen if you:
 - take water pills
 - are on a low-salt diet
 - have heart problems
 - get dialysis treatments
 - get sick with vomiting or diarrhea
 - drink alcohol

Lie down if you feel faint or dizzy. If you faint (lose consciousness), stop taking amlodipine, valsartan and hydrochlorothiazide tablets. Call your doctor right away.

- Get emergency help if you get worse chest pain or chest pain that does not go away.
- kidney problems. Kidney problems may become worse in people that already have kidney disease. Some people will have changes in blood tests for kidney function and may need a lower dose of amlodipine, valsartan and hydrochlorothiazide tablets. Call your doctor if you have swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing amlodipine, valsartan and hydrochlorothiazide tablets.

laboratory blood test changes in people with heart failure. Some people with heart failure who take valsartan, one of the medicines in amlodipine, valsartan and hydrochlorothiazide tablets, have changes in blood tests including increased potassium and decreased kidney function.

- allergic reactions**
- skin rash.** Call your doctor right away if you get an unusual skin rash.
- eye problems.** One of the medicines in amlodipine, valsartan and hydrochlorothiazide tablets can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting amlodipine, valsartan and hydrochlorothiazide tablets.

Tell your doctor right away if you have:

- decrease in vision
- eye pain

The most common side effects of amlodipine, valsartan and hydrochlorothiazide tablets include:

- dizziness
- swelling (edema) of the hands, ankles, or feet
- headache
- indigestion
- tiredness
- muscle spasms
- back pain
- nausea

Protect your skin from the sun and undergo regular skin cancer screening, as one of the medicines in amlodipine, valsartan and hydrochlorothiazide may cause non-melanoma skin cancer.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of amlodipine, valsartan and hydrochlorothiazide tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store amlodipine, valsartan and hydrochlorothiazide tablets?

- Store amlodipine, valsartan, and hydrochlorothiazide tablets at room temperature between 59°F and 86°F (15°C and 30°C).
- Keep amlodipine, valsartan and hydrochlorothiazide tablets dry (protect it from moisture).

Keep amlodipine, valsartan and hydrochlorothiazide tablets and all medicines out of the reach of children.

General Information about amlodipine, valsartan and hydrochlorothiazide tablets

Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use amlodipine, valsartan and hydrochlorothiazide tablets for a condition for which it was not prescribed. Do not give amlodipine, valsartan and hydrochlorothiazide tablets to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about amlodipine, valsartan and hydrochlorothiazide tablets. If you would like more information about amlodipine, valsartan and hydrochlorothiazide tablets, talk with your doctor. You can ask your doctor or pharmacist for information about amlodipine, valsartan and hydrochlorothiazide tablets that is written for health professionals. For

more information, call at 1-800-912-9561.

What are the ingredients in amlodipine, valsartan and hydrochlorothiazide tablets?

Active ingredients: amlodipine besylate, USP, vals