JOSWE

dubara®

Amlodipine / Atorvastatin

COMPOSITION

JOSWE Dubara caplets **5/10**: Film-coated caplets containing 5mg amlodipine and 10mg atorvastatin.
JOSWE Dubara caplets **5/20**: Film-coated caplets containing 5mg amlodipine and 20mg atorvastatin.
JOSWE Dubara caplets **5/40**: Film-coated caplets containing 5mg amlodipine and 40mg atorvastatin.
JOSWE Dubara caplets **5/80**: Film-coated caplets containing 5mg amlodipine and 80mg atorvastatin.
JOSWE Dubara caplets **10/10**: Film-coated caplets containing 10mg amlodipine and 10mg atorvastatin.
JOSWE Dubara caplets **10/20**: Film-coated caplets containing 10mg amlodipine and 20mg atorvastatin.
JOSWE Dubara caplets **10/40**: Film-coated caplets containing 10mg amlodipine and 40mg atorvastatin.
JOSWE Dubara caplets **10/80**: Film-coated caplets containing 10mg amlodipine and 80mg atorvastatin.

INDICATION AND USAGE

JOSWE Dubara caplets (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine

1. Hypertension: amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents;

2. Coronary artery disease (CAD):

Chronic stable angina: amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antihypertensive agents;

Vasopastic angina (Prinzmetal's or Variant angina): amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.

Angiographically documented CAD: in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, amlodipine is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of coronary vascularization procedure.

A N D

Atorvastatin

1. Prevention of cardiovascular disease: in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk of revascularization and angina

In patients with type 2 diabetes and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, Atorvastatin is indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke.
- Reduce the risk of revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

2. Heterozygous familial and nonfamilial hypercholesterolemia: atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb);

3. Elevated serum TG levels: atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);

4. Primary dysbetalipoproteinemia: atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet;

5. Homozygous familial hypercholesterolemia: atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatment (e.g. LDL apheresis) or if such treatments are unavailable;

6. Pediatric patients: atorvastatin is indicated as an adjunct to diet to reduce total-C , LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥190 mg/dL or
b. LDL-C remains ≥ 160 mg/dL and:
- There is a positive family history of premature cardiovascular disease or
- Two or more other CVD risk factors are present in the pediatric patients.

Therapy with lipid-altering agents should be a component of multiple-risk factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other non pharmacological measures has been inadequate (see national cholesterol education program (NCEP) guidelines, summarized in table 1).

Table 1. NCEP treatment guidelines: LDL-C goats and cutpoints for therapeutic lifestyle changes and drug therapy in different risk categories

Risk Category	LDL-C Goal (mg/dL)	LDL-C level at which to initiate therapeutic lifestyle changes (mg/dL)	LDL-C level at which to consider drug therapy (mg/dL)
CHD[a] or CHD risk equivalents (10- year risk > 20%)	< 100	≥ 100	≥ 130 (100-129: drug optional)[b]
2+ Risk factors (10-year risk ≤ 20%)	< 130	≥ 130	10 -year risk 10% -20%: ≥130 10 -year risk <10 % :≥160
0-1 Risk Factor [c]	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease
[b] some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
[c] almost all people with 0-1 risk factor have 10-year risk < 10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG still ≥ 200 mg/dL, non-HDL-C (total C-minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolemia (e.g. poorly controlled diabetes mellitus, hypothyroidism , nephritic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, TG. For patients with TG < 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C – (0.20 X [TG]+ HDL-C). For TG levels > 400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. The antidyslipidemic component of Amlodipine and atorvastatin combination caplets has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson type I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Table 2. NCEP classification of cholesterol levels in pediatric patients

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	< 170	< 110
Borderline	170-199	110-129
High	≥ 200	≥ 130

CONTRAINDICATIONS

JOSWE Dubara caplets contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. Amlodipine and atorvastatin combination caplets is contraindicated in patients with hypersensitivity to atorvastatin and amlodipine.

Pregnancy and lactation:

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membrane). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. Amlodipine and atorvastatin combination caplets , WHICH INCLUDES ATORVASTATIN, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED THE POTENTIAL HAZARDS.

If the patients become pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Increased angina and/or myocardial infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Liver dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin In clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40 and 80 mg, respectively.

In clinical trials in patients taking atorvastatin the following has been observed. One patient in clinical trials developed jaundice. Increase in liver function test (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms.

Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients, with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatine. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or Ast of >3 times ULN persist, reduction of dose or withdrawal of Amlodipine and atorvastatin combination caplets is recommended.

Amlodipine and atorvastatin combination caplets should be used with caution in patients who consume substantial quantities of alcohol and\or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of amlodipine and atorvastatin combination caplets (see **CONTRAINDICATIONS**).

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglodinuria have been reported with the atrovastatine component and other drugs in the HMG-CoA reductase inhibitor class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTION). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creation phosphokinase (CPK) values.10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and\or marked elevation of CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in the HMG-CoA reductase inhibitor class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, combination of ritonavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with Amlodipine and atorvastatin combination caplets and fibric derivatives, erythromycin, clarithromycin, combination of ritonavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential banafits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance dose of atrovastatine should be considered when taken concomitantly with the aforementioned drugs (See **DRUG INTERACTION**).

Periodic creation phosphokinase (CPK) determinations may be considered in such situations, but there is no assurances that such monitoring will prevent the occurrence of sever myopathy. In patients taking Amlodipine and atorvastatin combination, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sever acute infiction, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Since the vasodilation induced by the amlodipine component of Amlodipine and atorvastatin combination caplets is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administrating Amlodipine and atorvastatin combination caplets as with any other peripheral vasodilator particularly in Patients with severe aortic stenosis.

Before instituting therapy with Amlodipine and atorvastatin combination caplets, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**).

Use in patients with congestive heart failure

In General, calcium channel blockers should be used in caution in patients with heart failure.

The amlodipine component of Amlodipine and atorvastatin combination caplets (5-10 mg per day) has been studied in placebo-controlled trial of 1153 Patients with NYHA class 111 or 1V heart failure (~~see CLINICAL PHARMACOLOGY~~) on stable dose of ACE inhibitor, digoxin, and diuretics. Follow up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity

(as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patient's withNYHA class 1I/111 heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal

The amlodipine component of Amlodipine and atorvastatin combination caplets is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta blocker.

Endocrine function

HMG-CoA reductase inhibitors, such as the atrovastatin component of Amlodipine and atorvastatin combination caplets interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atrovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administrated concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolacton, and cimetidine.

CNS Toxicity

Studies with atorvastatin: Brain hemorrhage was seen in a female dog treated with atorvastatin calcium for 3 months at a dose equivalent to 120 mg atorvastatin /kg/day. Brain Hemorrhage and optic nerve vacuolation were seen in anther female dog that was sacrificed in moribund condition after 11 weeks of escalating doses of atorvastatin calcium equivalent to 280 mg atorvastatin/kg/day. The 120 mg/kg dose of atorvastatin resulted in a systemic exposure approximately 16 times the human plasma area-under-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg\day. A single tonic convulsion was seen in each of 2 male dogs (one treated with atorvastatin calcium at a dose equivalent to 10 mg atorvastatin/kg/day and one at a dose equivalent to 120 mg atorvastatin/kg/day) in a 2 year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses of atorvastatin Calcium equivalent to up tp 400 mg Atorvastatin/kg/day or in rats at doses equivalent to up to 100 mg atorvastatin/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg atorvastatin/day.

CNS vascular lesions, Characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of prevascular spaces, have been observed in dogs treated with other members of the HMG-CoA reductase class, A Chemically similar drug in this class product optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Information for patients

Due to the risk of myopathy with drugs of the HMG-CoA reductase class, to which the atorvastatin component of Amlodipine and atorvastatin combination caplets belongs, patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by a malaise or fever.

Drug interaction

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are coadministered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the Cmax; 91%(90% confidential interval: 80 to 103%), but the AUC of Atorvastatin increased by 18% (90% confidential interval:109 to 127%) in the presence of amlodipine.

No drug interaction studies have been conducted with Amlodipine and atorvastatin combination caplets and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Studies with amlodipine:

In vetro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytion, warafarin, and indomethacin).

Cimetidine: Co-administration of the amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Maalox® (antacid): co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetics of parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warferin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long action nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Studies with atorvastatin:

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. Cyclosporine, erythromycin, and azole antifungals)(see WARNINGS, Skeletal Muscle).

Inhibitors of cytochrom P450 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of Cytochrome P450 3A4 can lead to increase in plasma concentrations of atorvastatin. The extnt of interaction and potentiation of effect depends on the variability of effect on cytochrome P450 3A4.

Clarithromycin: Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atrovastatin AUC (saa WARNINGS, Skeletal muscle, and DOSAGE AND ADMINISTRAYION).

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochromo P450 3A4 (see WARNINGS, Skeletal muscle).

Combination of Protease inhibitors: Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC.

Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400mg+ 100mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC (see WARNINGS, Skeletal Muscle, and DOSAGE AND ADMINISTARTION).

Itraconazole: Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with a 2.5-3.3-fold increase in atorvastatin AUC.

Diltiazem hydrochloride: Co-administration of atorvastatin (40 mg)with diltiazem(240 mg) was associated with higher plasma concentration of atorvastatin.

Cimetidine: Atorvastatine plasma concentration and LDL-C reduction were not altered by co-administration of cimetidine.

Grapefruit juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially excessive grapefruit juice consumption (>1.2 liter per day).

Cyclosporine: Atorvastatin and atorvastatine-metabolites are substrates of the OATP1B1 trans-porter. Inhibitors of the OATP1B1 (e.g. Cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and Cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC. In case where co-administration of atorvastatin with Cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg (see WARNINGS, Skeletal muscle).

Inducers of cytochrome P450 3A4: concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampin) can lead to variable reduction in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacid: when atorvastatin and Maalox TC suspension were co-administrated, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozmes are not expected.

Colestipol: Plasma concentration of atorvastatin decreased approximately 25% when colestipol and atorvastatin were co-administrated however; LDL-C reduction was greater when atorvastatin and colestipol were co-administrated than when either drug was given alone.

Digoxin: when multiple doses of atorvastatin and digoxin were co-administrated, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral contraceptives: co-administrated of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinly etradiol by approximately 30% and 20%. These increases should be considered when selecting oral contraceptives for a women taking Amlodipine and atorvastatin combination caplets.

Warfarin: atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Amlodipine: in a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18%increas in exposure to atorvastatin which was not clinically meaningful.

Drug/Laboratory test interactions:

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 maximum recommended human dose of 10 mg amlodipine/day*. For the rat the highest dose level was, on a mg/m2 basis, about twice the maximum recommended human dose*.

Mutagenicity studies conducted with amlodipine maleate revealed no drug relates effects at either the gene or chromosome levels.

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 dose up to 10 mg amlodipine/kg/day (8 times*maximum recommended human dose of 10mg/day on a mg\m2 basis).

Studies with atorvastatin: In a 2-year carcinogenicity study with atorvastatin calcium in rates at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabomyasarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC(0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvatatin/kr/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvatatin was negative in the in vivo mouse micronucleus test.

There were no effect on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin\kg\day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 to 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin\kg\day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg\kg\day and epididymal weight was lower at 100 mg\kg\day. Male rats given the equivalent to 100 mg atorvastatin\kg\day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40 or 120 mg atorvastatin\kg\day for two years. (* based on patients weight of 50 kg).

Pregnanacy

Pregnancy category X (see Contraindications)

Safety in pregnant women has not been established with Amlodipine and atorvastatin combination caplets. Amlodipine and atorvastatin combination caplets should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Amlodipine and atorvastatin combination caplets,

JOSWE® medical	Packaging Material Artwork Design		Page 1 of 1
Prepared by Designer:	Reviewed by Registration:	Reviewed by QC:	Approved by QA:
Signature:	Signature:	Signature:	Signature:
Date:	Date:	Date:	Date:

Product: Dubara	Lebanon
Size: L * W 21 * 29.7cm 2 Face	
Color: - Pantone	Black
Code No.: P765R0	

it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Studies with amlodipine: No evidence of teratogenicity or other embryo/fatal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine at doses up to 10mg amlodipine/Kg/day(respectively 8* time and 23* times the maximum recommended human dose of 10mg/day on a mg/m2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine at 10mg amlodipine/Kg/day for 14 days before mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well controlled studies in pregnant women.

*Based on patient weight of 50 kg.

Studies with atorvastatin: atorvaststin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvaststin equivalent to up to 300 mg atorvastatin/Kg/day or in rabbit at doses of atorvaststin equivalent to up to 100 mg atorvastatin/Kg/day. These doses resulted in multiples of about 30 times (rats) or 20 times (rabbits) the human exposure based on surface area (mg/m2).

in a study in rats given atorvastatin calcium equivalent to 20, 100 or 225 mg atorvastatin/Kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth , neonate, weaning and maturity for pups of mothers dosed with 225 mg /Kg/day. Body weight was decreased on days 4 and 21 for mothers dosed with 100 mg /Kg/day; pup body weight was decreased on days 4, 21 and 91 at 225 mg /Kg/day. Pup development was delayed (rotord performance at 100 mg /Kg/day and acoustic startle at 225 mg /Kg/day; pinnae detachment and eye opening at 225 mg /Kg/day). these doses of atorvastatin correspond to 6 times (100mg/Kg) and 22 times (225mg/Kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intra-uterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, trachea-esophageal fistula, and anal atresia (Va ter association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy.

Labor and Delivery

No studies have been conducted in pregnant women on the effect of Amlodipine and atorvastatin combination caplets , amlodipine or atorvastain on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats.

Nursing Mothers

It is not known wether the amlodipine component of Amlodipine and atorvastatin combination caplets is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Amlodipine and atorvastatin combination caplets should not breast feed (see **Contraindications**).

Pediatric use

There have been no studies conducted to determine the safety or effectiveness of Amlodipine and atorvastatin combination caplets in pediatric populations.

Studies with amlodipine: The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Studies with atorvastatin: Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20mg have not been studies in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. see **clinical pharmacology, clinical studies section**; **adverse reactions**, pediatric patients; dosage and administration, pediatric patients(10-17 years of age) with heterozygous familial Hypercholesterolemia. Adolescent females should be counseled on appropriate contraceptive methods, while on atorvastatin therapy (see **Contraindications and precautions, pregnancy**). **Atorvastatin has not been studied in controlled in clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses of atorvastatin up to 80mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See **clinical pharmacology, clinical studies**, atorvastatin effects in homozygous Familial hypercholesterolemia.

Geriatric use

There have been no studies conducted to determine the safety or effectiveness of Amlodipine and atorvastatin combination caplets in geriatric populations.

In studies with amlodipine: Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection of the amlodipine component of Amlodipine and atorvastatin combination caplets for an elderly patients should be cautious , usually starting at the low end of the dosing range, reflecting the grater frequency of decreased hepatic , renal or cardiac function and of concimittent disease or other drug therapy. Eldrly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required. (See **Dosage and Administration**).

In studies with atorvastatin: The safety and efficacy of atorvastatin (10-80mg) in the geriatric population (> 65 years of age) was evaluated in Access study. In this 54 week open label trial 1,958 patients initiated therapy with atorvastatin calcium 10mg. Of these, 853 were elderly (> 65 years of age) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6-weeks of treatment with atorvastatin calcium 10mg was 38.2% in the elderly patients versus 34.6% I the non-elderly group.

The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the two age groups.

ADVERSE REACTION

Amlodipine and atorvastatin combination caplets

(amlodipine besylate/ atorvastatin calcium) has been evaluated for safety in 1092 patients in double-blind placebo controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with Amlodipine and atorvastatin combination caplets was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with Amlodipine and atorvastatin combination caplets , no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity and frequency to those reported previously with amlodipine and atorvastatin.

The following information is based on the clinical experience with amlodipine and atorvastatin.

The Amlodipine component of the combination

Amlodipine has been evaluated for safety in more than 11,000 patients in U. S and foreign clinical trials. In general treatment with amlodipine was well tolerated at doses up to 10mg daily. Most adverse reactions reported during therapy with amlodipine were of mild to moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effect which occurred in a dose related manner is as follows:

Adverse Event	Amlodipine			
	2.5mg *N=275*	**5.0 mg** *N=296*	**10.0mg** *N=268*	**Placebo** *N=520*
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-controlled studies:

Adverse Event	Amlodipine (%) *N=1730*	Placebo (%) *N=1250*
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Adverse Event	Amlodipine		Placebo	
	M=% *N=1218*	**F=%** *N=512*	**M=%** *N=914*	**F=%** *N=336*
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in ≤ 1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials o marketing experience where a casual relationship is uncertain; they are listed to alert the physician to possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and peripheral nervous system: hypoesthesia, neuropathy peripheral, paraestheia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis vomiting, gingival hyperplasia.

General: allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal system: arthralgia, arthrosis, muscle cramps, myalgia.

Psychiatric: sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory system: dyspnea, **epistaxis.

Skin and appendages: angioedema, eryhema multiforme, pruritis, rash, rash erythromatous, rash maculopapular.

** These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Special senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary system: micturition frequency, micutrition disorder, nocturia.

Metabolic and nutritional: hyperglycemia, thirst.

Hemopoietic: leucopenia, putpura, thrombocytopenia.

the following events occurred in <0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience; cardiac failure, pulse irregularity, extrasystoles, skin discoloration urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stool, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual, accommodation and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine.

In the Camelot and prevent studies (see **clinical pharmacology clinical studies, clinical studies with** amlodipine) the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.

The following post marketing event has been reported infrequently with amlodipine treatment where a casual relationship in uncertain: gynecomastia. In post marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus and abnormal lipid profiles.

The Atorvastatin component of the combination Atorvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In controlled clinical trials of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse event s thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia and abdominal pain.

Clinical adverse experiences Adverse experiences reported in > 2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of casualty assessment, are shown in table below.

Body system/ Adverse event body as a whole	Placebo *N=270*	10mg *N=863*	20mg *N=36*	40mg *N=79*	80mg *N=94*
Body as a whole Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental injury	3.7	4.2	0.0	1.3	3.2
Flu syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal pain	0.7	2.8	0.0	3.8	1.1
Back pain	3.0	2.8	0.0	3.8	1.1
Allergic reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
Digestive system Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
Respiratory system Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
Skin and appendages Rash	0.7	3.9	2.8	3.8	1.1
Musculoskeletal system Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac outcomes trial (ASCOT)

In ASCOT (see **clinical pharmacology clinical studies, clinical studies with atorvastatin**) involving 10,305 participants treated with atorvastatin 10mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)

In CARDS (see **clinical pharmacology clinical studies, clinical studies with atorvastatin**) involving 2838 subjects with type 2 diabetes treated with atorvastatin 10mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow up of 3.9 tears. No cases of rhabdomyolysis were reported.

Treating to new targets study (TNT)

In TNT (see clinical PHARMACOLOGY, Clinical studies), involving 10,001 subjects with clinically evident CHD treated with atorvastatin 10 mg daily (n=5006) or atorvastatin 80 mg daily (n=4995), there were more serious adverse events and discontinuation due to adverse events in the high dose atorvastatin group (92, 1.8%, 479, 9.9%, respectively) as compared to the low dose group (69, 1.4%, 404, 8.1% respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 * ULN twice within 4-10 days) occurred in 62 (1.3%) individuals with atorvastatin and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥10* ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL) in IDEAL (See CLINICAL PHARMACOLOGT, Clinical studies) involving 8,888 subjects treated with atorvastatin 80 mg/day (n=4439) or simvastatin 20-40 mg daily (n=4449), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 4.8 years.

The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction generalized edema.

Digestive system: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagities, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory system: Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis.

Nervous system: Insomnia, dizziness, peresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, Peripheral neuropathy, torticollis, facial paralysis, hyperkinesias, depression, hypesthesia, hypertonia.

Musculoskeletal system: Arthritis, leg cramps, bursitis, tenosynovities, myasthenia, tendinuos contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital system: Urinary tract infection, hematuria, albuminuria, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special senses: amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosimia, taste loss, taste prevention.

Cardiovascular system: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional disorders: Peripheral edema, hyperglycemia, Creatine phosphokainase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic system: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction reports with Atorvastatin

Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, anagioneurotic edema, bullous rashes (including erythema multiforme, Stevns-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue and tendon rupture.

Pediatric patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 gm daily was generally similar to that of placebo (See CLINICAL PHARMACOLOGY, Clinical studies section and precautions, pediatric use).

OVERDOSAGE

There is no information on overdosage with Amlodipine and atorvastatin combination caplets in human.

Information on amlodipine Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with international overdosage of amlodipine is limited. Reports of international overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Information on atorvastatin There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atrovastatin clearance.

DOSAGE AND ADMINISTRATION

Dosage of **JOSWE Dubara caplets** must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

Amlodipine (Hypertension or angina)

Adults: the usual initial antihypertensive oral dose of amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy. Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently. The recommended dose of amlodipine for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See adverse reactions section for information related to dosage and side effects. The recommended dose range of amlodipine for patients with coronary artery disease is 5-10 mg once daily. In clinical studies the majority of patients required 10 mg (see clinical pharmacology, clinical studies).

Children: the effective antihypertensive oral dose of amlodipine in pediatric patients ages 6-17 years is 2.5 mg – 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See clinical pharmacology.

Atorvastatin (Hyperlipidemia)

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

Hypercholesterolemia (Heterozygous familial and nonfamilial) and Mixed Dyslipidemia (Fredrickson types IIa and IIb).

The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response (see NCEP guidelines). After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels to be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous familial hypercholesterolemia in pediatric patients (10-17 years of age)

The recommended starting dose of atorvastatin is 10 mg/day, the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP pediatric Panel guidelines, clinical pharmacology, and indications and usage). Adjustments should be made at intervals of 4 weeks or more.

Homozygous familial hypercholesterolemia

The dosage of atorvastatin in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable. Note: a 2.5/80 mg (Amlodipine and atorvastatin combination caplets is not available. Management of patients needing a 2.5/80 mg combination requires individual assessment of dyslipidemia and therapy with the individual components as a 2.5/80 mg Amlodipine and atorvastatin combination caplets is not available.

Concomitant lipid lowering therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally avoided (see warnings, skeletal muscle and precautions, drug interactions for other drug-drug intractions).

Dosage in patients with renal insufficiency

Renal disease does not affect the plasma concentrations nor LDL-Creduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see clinical pharmacology, pharmacokinetics).

Dosage in patients taking cyclosporine, clarithromycin or a combination of ritonavir plus saquinavir or lopinavir plus ritonavir.

In patients taking cyclosporine, therapy should be limited to atorvastatin 10 mg once daily. In patients taking clarithromycin or in patients with HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of atorvastatin exceeding 20 mg appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed (see warnings, skeletal muscle, and precautions, drug interactions).

JOSWE Dubara caplets

JOSWE Dubara caplets may be substituted for its individually titrated component. Patients may be given the equivalent dose of **JOSWE Dubara caplets** with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, blood pressure lowering, or lipid lowering effect.

JOSWE Dubara caplets may be used to provide additional therapy for patients already on one of its components.

As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of **JOSWE Dubara caplets** should be selected based on the continuation of the component being used and the recommended starting dose for the added monotherapy.

JOSWE Dubara caplets may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of **JOSWE Dubara caplets** should be based on appropriate combination of recommendations for the monotherapies. The maximum dose of the amlodipine component of **JOSWE Dubara caplets** is 10 mg once daily. The maximum dose of the atorvastatin component of **JOSWE Dubara caplets** is 80 mg once daily.

See above for detailed information related to the dosing and administration of amlodipine and atorvastatin.

STORAGE CONDITIONS

Store below 30°C

PRESENTATION

JOSWE Dubara caplets **5/10**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **5/20**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **5/40**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **5/80**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **10/10**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **10/20**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **10/40**: Each pack contains **30** film-coated caplets.
JOSWE Dubara caplets **10/80**: Each pack contains **30** film-coated caplets.

IN ACTIVE INGREDIENTS

Hydroxypropylcellulose, Microcrystalline Cellulose, Lactose, Croscarmellose, Calcium carbonate, Magnesium Stearate, HPMC, Titanium Dioxide,Polyethylene glycol & (Joswe Dubara 10/10 & 10/80:FD&C Blue # 2 Lake).

- A medicament is a product that affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTRIES
UNION OF ARAB PHARMACISTS

Produced by:
JOSWE® medical
Jordan Sweden Medical and Sterilization Co.
Na'ur - Jordan
الأردنية السويدية للمنتجات الطبية والتعقيم م.م. ناعور - الأردن
www.joswe.com

(P765/22-07-2012/R0)