Tri-Redupres ٹرائی-ریڈوپریس ٹیبلیٹس

(ایملوڈیپین/ویلسارٹن/ہائیڈروکلوروتھایازائیڈ)

(Amlodipine / Valsartan / Hydrochlorothiazide) Tablets, USP

COMPOSITION:

Tri-Redupres 5mg/160mg/12.5mg Tablets
Each film coated tablet contains:
Amlodipine besylate eq. to Amlodipine ... 5mg
Valsartan 160mg
Hydrochlorothiazide 12.5mg
[USP Specs.]

Tri-Redupres 10mg/160mg/12.5mg Tablets
Each film coated tablet contains:
Amlodipine besylate eq. to Amlodipine ... 10mg
Valsartan 160mg
Hydrochlorothiazide 12.5mg
[USP Specs.]

Tri-Redupres 5mg/160mg/25mg Tablets
Each film coated tablet contains:
Amlodipine besylate eq. to Amlodipine ... 5mg
Valsartan 160mg
Hydrochlorothiazide 25mg
[USP Specs.]

Tri-Redupres 10mg/320mg/25mg Tablets
Each film coated tablet contains:
Amlodipine besylate eq. to Amlodipine ... 10mg
Valsartan 320mg
Hydrochlorothiazide 25mg
[USP Specs.]

DESCRIPTION: Tri-Redupres is a fixed combination of amlodipine, valsartan and hydrochlorothiazide. **Tri-Redupres** contains the besylate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB). Amlodipine besylate's chemical name is 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4 (o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate. Valsartan, USP is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan's chemical name is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4 yl]methyl]-L-valine. Hydrochlorothiazide is a thiazide diuretic. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide.

INDICATIONS: Tri-Redupres is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension.

DOSAGE AND ADMINISTRATION: General Considerations: Dose once-daily. The dosage may be increased after two weeks of therapy. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of **Tri-Redupres**. The maximum recommended dose of **Tri-Redupres** is 10/320/25mg. No initial dosage adjustment is required for elderly patients.
Renal impairment: The usual regimens of therapy with **Tri-Redupres** may be followed if the patient's creatinine clearance is >30ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so avoid use of **Tri-Redupres**.
Hepatic impairment: Avoid **Tri-Redupres** in patients with severe hepatic impairment. In patients with lesser degrees of hepatic impairment, monitor for worsening of hepatic or renal function and adverse reactions.
Add-on / Switch Therapy: Tri-Redupres may be used for patients not adequately controlled on any two of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of **Tri-Redupres** may be switched to **Tri-Redupres** containing a lower dose of that component to achieve similar blood pressure reductions.
Replacement Therapy: Tri-Redupres may be substituted for the individually titrated components.
Method of Administration: Tri-Redupres may be administered with or without food.

CLINICAL PHARMACOLOGY: Mechanism of Action: The active ingredients of **Tri-Redupres** target three separate mechanisms involved in blood pressure regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; valsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume. A more detailed description of the mechanism of action of each individual component follows.

Pharmacokinetics: Following oral administration of **Tri-Redupres** in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and Hydrochlorothiazide are reached in about 6 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and Hydrochlorothiazide from **Tri-Redupres** are the same as when administered as individual dosage forms.
Amlodipine: Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.
Distribution: Volume of distribution is approximately 21 l/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.
Metabolism: Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.
Elimination: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.
Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94-97%), mainly serum albumin.
Valsartan: Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23%.
Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94-97%), mainly serum albumin.
Metabolism: Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.
Elimination: Valsartan shows multiexponential decay kinetics ($t_{½}\ \alpha$ <1 h and $t_{½}\ \beta$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose),

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mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.
Hydrochlorothiazide: Absorption: The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 hours). The increase in mean AUC is linear and dose proportional in the therapeutic range.
Distribution: The apparent volume of distribution is 4-8 l/kg. Circulating Hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.
Metabolism: Hydrochlorothiazide is eliminated predominantly as unchanged compound.
Elimination: Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase.

CONTRAINDICATIONS: Because of the hydrochlorothiazide component, **Tri-Redupres** is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality: Tri-Redupres can cause harm to the fetus when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Hypotension in Volume- or Salt-Depleted Patients: Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with the maximum dose of **Tri-Redupres** (10/320/25mg) compared to 1.8% of valsartan/Hydrochlorothiazide (320/25mg) patients, 0.4% of amlodipine/valsartan (10/320mg) patients, and 0.2% of Hydrochlorothiazide/amlodipine (25/10mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.
Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction upon starting calcium channel blocker therapy or at the time of dosage increase.
Impaired Hepatic Function: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{½}$) is 56 hours in patients with impaired hepatic function.
Heart Failure: Tri-Redupres has not been studied in patients with heart failure.

SIDE EFFECTS: The following are the side effects as described below: Dizziness, Swelling (edema) of the hands, ankles, or feet, Headache, Indigestion, Tiredness, Muscle Spasms, Back Pain, Nausea & Skin Rash.

DRUG INTERACTIONS: No drug interaction studies have been conducted with **Tri-Redupres** and other drugs, although studies have been conducted with the individual components. A pharmacokinetic drug-drug interaction study has been conducted to address the potential for pharmacokinetic interaction between the triple combination, **Tri-Redupres** and the corresponding three double combinations. No clinically relevant interaction was observed.
Amlodipine: In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
Grapefruit juice: Co-administration of 240ml of grapefruit juice with a single oral dose of amlodipine 10mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
Magnesium and aluminum hydroxide (antacid): Co-administration of the magnesium and aluminum hydroxide antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.
Sildenafil: A single 100mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.
Atorvastatin: Co-administration of multiple 10mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
Simvastatin: Co-administration of multiple doses of 10mg of amlodipine with 80mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20mg daily.
Valsartan: No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered 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.
Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics.
Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.
Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

OVERDOSE: Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

INSTRUCTIONS: Store below 30° C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION:
Tri-Redupres 5mg/160mg/12.5mg Tablets are available in pack size of 28's.
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ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
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PHARMA
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