NADSAR®-A

(Telmisartan/Amlodipine)

Tablets U.S.P.

40mg/5mg, 40mg/10mg
80mg/5mg, 80mg/10mg

ناڈسار-اے

ٹیبلٹس یو۔ایس۔پی۔

(ٹیلمیسارٹن/ ایملوڈیپائین)

۴۰ ملی گرام/۵ ملی گرام ۴۰ ملی گرام/۱۰ ملی گرام
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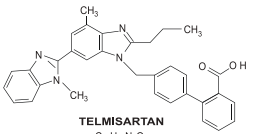
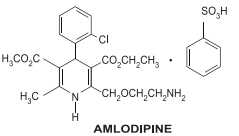
DESCRIPTION: NADSAR®A is a fixed dose combination of Telmisartan and Amlodipine.



TELMISARTAN

$C_{33}H_{30}N_4O_2$



AMLODIPINE

$C_{20}H_{25}ClN_2O_5 \cdot C_6H_5O_3S$

QUALITATIVE AND QUANTITATIVE COMPOSITION

NADSAR® A 40mg/5mg Tablets U.S.P.
Each bilayer tablet contains:
Telmisartan U.S.P. 40mg
Amlodipine as Besilate U.S. P. 5mg

NADSAR®A 40mg/10mg Tablets U.S.P.
Each bilayer tablet contains:
Telmisartan U.S.P. 40mg
Amlodipine as Besilate U.S. P. 10mg

NADSAR®A 80mg/5mg Tablets U.S.P.
Each bilayer tablet contains:
Telmisartan U.S.P. 80mg
Amlodipine as Besilate U.S. P 5mg

NADSAR®A 80mg/10mg Tablets U.S.P.
Each bilayer tablet contains:
Telmisartan U.S.P. 80mg
Amlodipine as Besilate U.S. P 10mg

WARNING: Fetal Toxicity
- When pregnancy is detected, discontinue NADSAR®A as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

CLINICAL PHARMACOLOGY: Mechanism of Action: Telmisartan: Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin by selectively blocking the binding of angiotensin to the AT1, receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin synthesis. **Amlodipine:** Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions by binding to both dihydropyridine and nondihydropyridine sites into vascular smooth muscle and cardiac muscle.

Pharmacokinetics: Telmisartan: Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. **Amlodipine:** Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached after 7-8 days of consecutive daily dosing. **Distribution: Telmisartan:** Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding. **Amlodipine:** The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Metabolism And Elimination: Telmisartan: Most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan. Total plasma clearance of Telmisartan is > 800 mL/min. Terminal half-life and total clearance appears to be independent of dose. **Amlodipine:** Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

RENAL INSUFFICIENCY: Telmisartan: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration. **Amlodipine:** The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.
HEPATIC INSUFFICIENCY: Telmisartan: In patients with hepatic insufficiency, plasma concentrations of Telmisartan are increased, and absolute bioavailability approaches 100%. **Amlodipine:** Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of amlodipine.
GERIATRIC PATIENTS: Telmisartan: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years. **Amlodipine:** Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of amlodipine

INDICATION: NADSAR®A (Telmisartan/Amlodipine) tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents.NADSAR®A tablets may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure

goals. Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure) kidney failure, and vision problems, so prompt treatment is clinically relevant.

DOSAGE ADMINISTRATION: NADSAR®A is an effective treatment of hypertension in once daily doses. The usual starting dose of NADSAR®A is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on NADSAR®A 80/5 mg once daily. Initial therapy with NADSAR®A is not recommended in patients ≥ 75 years old. **Dosing in Specific Populations Renal Impairment:** No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment. Hepatic Impairment: In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients with hepatic impairment. Patients 75 Years of Age & Older: In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients 75 years of age and older.

SIDE EFFECTS: TELMISARTAN: Adverse events that occurred in >0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are, Autonomic Nervous System: impotence, increased sweating, flushing; Body as a Whole: allergy, fever, leg pain, malaise; Cardiovascular: Palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal. ECG; CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders; Metabolic: gout, hypercholesterolemia, diabetes mellitus; Musculoskeletal: arthritis, arthralgia, leg cramps; Psychiatric: anxiety, depression, nervousness; Resistance Mechanism: infection, fungal infection, abscess, otitis media; Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis; Skin: dermatitis, rash, eczema, pruritus; Urinary: micturition frequency, cystitis; Vascular: cerebrovascular disorder; and Special Senses: abnormal vision, conjunctivitis, tinnitus, earache. **AMLODIPINE:** The following events occurred in >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience. **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, paresthesia, tremor, vertigo; Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change of bowel habit; 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 & female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change; Respiratory System: dyspnea, epistaxis; Skin & Appendages: angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular; Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; Urinary System: micturition frequency, micturition disorder, nocturia; Autonomic Nervous System: Dry mouth, sweating increased; Metabolic and Nutritional: hyperglycemia, thirst; Hemopoietic: leukopenia, purpura, thrombocytopenia. **DRUG INTERACTION:** No drug interaction studies have been conducted with telmisartan/amlodipine and other drugs, although studies have been conducted with the individual Telmisartan & amlodipine components. **TELMISARTAN:** Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19. However Telmisartan was found to be interaction with Digoxin, Lithium, Ramipril and Ramiprilat by increasing or decreasing the concentration. **AMLODIPINE:** Amlodipine was not found to be interact with any drug. In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin

PRECAUTIONS: Pregnancy: Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue telmisartan/amlodipine combination as soon as possible. **NURSING MOTHERS: Telmisartan:** It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Amlodipine: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered. Pediatric Use: Safety and effectiveness of telmisartan/amlodipine in pediatric patients have not been established.

OVER DOSAGE: Telmisartan: Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. **Amlodipine:** In humans, experience with intentional overdosage of amlodipine is limited. Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in caused a marked peripheral vasodilation and hypotension.

CONTRAINDICATION: None.

INSTRUCTIONS: Dosage as directed by the physician. Store at 20°C-25°C, Excursions permitted to 15°C to 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
NADSAR®A 40mg/5mg tablets U.S.P. are available in Alu-Alu blister pack of 1x14's.
NADSAR®A 40mg/10mg tablets U.S.P. are available in Alu-Alu blister pack of 1x14's.
NADSAR®A 80mg/5mg tablets U.S.P. are available in Alu-Alu blister pack of 1x10's.
NADSAR®A 80mg/10mg tablets U.S.P. are available in Alu-Alu blister pack of 2x7's.

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ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۲۰ سے ۲۵ ڈگری سینٹی گریڈ پر محفوظ رکھیں،
محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔