Normisar *Plus* Tablets

(TELMISARTAN/HYDROCHLOROTHIAZIDE)

COMPOSITION:
Each film coated tablet contains:
Telmisartan ..... 40mg.
Hydrochlorothiazide USP ...12.5mg.
NQ's Specs.

MECHANISM OF ACTION: Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibits the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because Telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of Telmisartan on blood pressure. Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of Hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

PHARMACOKINETICS: Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% following a 40mg dose and 58% following a 160mg dose. Peak plasma concentrations of Telmisartan are reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the faeces via bile, mainly as unchanged drug. The terminal elimination half life of Telmisartan is about 24 hours. Hydrochlorothiazide is fairly rapidly absorbed from gastrointestinal tract. It is reported to have a bioavailability of about 65% to 70%. It has been estimated to have a plasma half life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

INDICATIONS AND USAGE: Normisar Plus is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

DOSAGE AND ADMINISTRATION: The usual initial dosage is one tablet of **Normisar Plus** daily. A patient whose blood pressure is not adequately controlled with Telmisartan monotherapy 40mg Normisar may be switched to **Normisar Plus**. The dose may be increased, if necessary, to two tablets of **Normisar Plus** daily. **Normisar Plus** may be administered with other antihypertensive agents. It may be administered with or without food. The combination may be substituted for the titrated components.
Patients with Renal Impairment: The usual regimens of therapy with **Normisar Plus** may be followed as long as the patient's creatinine clearance is >30ml/min. In patients with more severe renal impairment, **Normisar Plus** is not recommended.
Patients with Hepatic Impairment: Normisar Plus is not recommended for patients with severe hepatic impairment, patients with biliary obstructive disorders or hepatic impairment.

CONTRA-INDICATIONS: Hypersensitivity to any component of this product; Anuria; Hypersensitivity to other sulfonamide derived drugs.

WARNINGS AND PRECAUTIONS:
Drug Interactions:
Digoxin: When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Monitoring of digoxin levels is recommended when initiating, adjusting and discontinuing **Normisar Plus** to avoid possible over- or under-digitalization.
Warfarin: Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration without a change in International Normalized Ratio (INR).
Other Drugs: Co-administration of **Normisar Plus** did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. 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. **Normisar Plus** is not expected to interact with drugs that inhibit or are metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.
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.
Other Antihypertensive Drugs: Additive effect or potentiation.

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Cholestyramine and Colestipol Resins: Absorption of **Normisar Plus** is impaired in the presence of anionic exchange resins.
Single doses of either cholestyramine or colestipol resins bind the Hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.
Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.
Pressor Amines (eg, Norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal Muscle Relaxants, NonDepolarizing (eg, Tubocurarine): Possible increased responsiveness to the muscle relaxant.
Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): In some patients, the administration of a NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when **Normisar Plus** and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Hypotension in volume depleted patients: Initiation of antihypertensive therapy in patients with activated renin angiotensin system, such as patients who are intravascular volume or sodium depleted, eg, in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of **Normisar Plus.** Treatment should be started under close medical supervision.
Hypersensitivity Reaction: Hypersensitivity reactions to **Normisar Plus** may occur in patients with or without a history of allergy or bronchial asthma to Hydrochlorothiazide. **Systemic Lupus Erythematosus:** Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
Electrolytes: Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

PREGNANCY: Telmisartan have been found to cause fetal and neonatal toxicity and death when taken by pregnant women. Pregnant mothers should discontinue use of Telmisartan as soon as they know they are pregnant. Thiazides cross the placental barrier and appear in cord blood. They may cause foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia of foetal or neonatal jaundice have been reported with maternal thiazide therapy.

NURSING MOTHERS: It is not known if Telmisartan is secreted into milk. Since most medicines are secreted into breast milk, potential risks and benefits need to be assessed in women who are nursing to determine if breast feeding or Telmisartan need to be discontinued.

UNDESIRABLE EFFECTS: The combination of Telmisartan and Hydrochlorothiazide is generally well tolerated. The most frequent clinical adverse effects in patients treated with this combination are fatigue, dizziness, diarrhea, nausea, back pain, dyspepsia, vomiting, hypokalemia, bronchitis, rash and postural hypotension.

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

AVAILABILITY: Normisar Plus tablets are available in 2x7's Pack.

نورمی سار پلس گولیاں

(ٹیلمیسارٹن / ہائیڈروکلوروتھایازائیڈ)

اجزائے ترکیب: نورمی سار پلس کی ہر فلم بند گولی میں ۴۰ ملی گرام ٹیلمیسارٹن اور ۱۲٫۵ ملی گرام ہائیڈروکلوروتھایازائیڈ موجود ہے۔

علامات: نورمی سار پلس گولیاں (ٹیلمیسارٹن اور ہائیڈروکلوروتھایازائیڈ) بلند فشارِ خون میں استعمال کی جاتی ہے۔

یہ متعین خوراک کا مرکب بلند فشارِ خون میں ابتدائی علاج کے طور پر استعمال نہیں کیا جاتا ہے۔

خوراک: عمومی ابتدائی خوراک روزانہ ایک نورمی سار پلس کی گولی ہے۔ وہ مریض جن کا بلند فشارِ خون مجرد علاج ٹیلمیسارٹن گولی سے اختیار میں نہیں ہے ان مریضوں کو نورمی سار پلس دی جاتی ہے۔ بہ ضرورت نورمی سار پلس گولی کی خوراک کو بڑھا کر روزانہ دو گولی کیا جا سکتا ہے۔

دورانِ حمل اور رضاعت: دورانِ حمل نورمی سار پلس گولیاں تجویز نہیں کی جاتی۔ دودھ پلانے والی مائیں دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ بچوں میں دوا کا استعمال ممنوع ہے۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

طریقہ فراہمی: نورمی سار پلس گولیاں 2x7's کے پیک میں دستیاب ہیں۔

Manufactured by:
NABIQASIM INDUSTRIES (Pvt) LTD.
17/24, Korangi Industrial Area, Karachi-Pakistan.
PHARMA
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