# Misar H™

(Telmisartan + Hydrochlorothiazide)

Highnoon

**COMPOSITION**

**Misar H 40mg/12.5mg Tablet:** Each tablet contains:
Telmisartan 40mg
Hydrochlorothiazide 12.5mg
**Misar H 80mg/12.5mg Tablet:** Each tablet contains:
Telmisartan 80mg
Hydrochlorothiazide 12.5mg
**Misar H 80mg/25mg Tablet:** Each tablet contains:
Telmisartan 80mg
Hydrochlorothiazide 25mg

**DESCRIPTION**

**Misar H** (Telmisartan and Hydrochlorothiazide) tablets are a combination of telmisartan, an orally active angiotensin II antagonist acting on the AT1 receptor subtype, and hydrochlorothiazide, a thiazide diuretic.

**MECHANISM OF ACTION**

**Telmisartan:** Angiotensin II is formed from angiotensin I in a reaction catalysed 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, 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. 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 inhibit 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 catalysed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin.

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:** 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 ARB tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood.

**PHARMACOKINETICS**

**Telmisartan:** Telmisartan is rapidly absorbed from the gastrointestinal tract. The absolute bioavailability is dose dependent and is about 42% after a 40 mg dose and 58% after a 160 mg dose. Peak plasma concentration of telmisartan 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 is about 24 hours.

**Hydrochlorothiazide:** Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

**INDICATIONS AND USAGE**

- It is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- It may be used alone or in combination with other antihypertensive agents.
- It is not indicated for initial therapy for the treatment of hypertension.

**DOSAGE AND ADMINISTRATION**

- Initiate a patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg on Misar H, 80mg/12.5 mg once daily. Dose can be titrated up to 160 mg/25 mg after 2 to 4 weeks, if necessary.

  Initiate a patient whose blood pressure is not adequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen (Telmisartan 80 mg and Hydrochlorothiazide 12.5 mg) once daily. Dose can be titrated up to 160 mg/25 mg after 2 to 4 weeks, if necessary.

  Patients titrated to the individual components (telmisartan and hydrochlorothiazide) may instead receive the corresponding dose of Misar H.
  It may be administered with other antihypertensive drugs.
- Initiate patients with biliary obstructive disorders or hepatic insufficiency under close medical supervision using the 40 mg/12.5 mg combination. This combination (telmisartan and Hydrochlorothiazide) tablets are not recommended for patients with severe hepatic impairment.

**ADVERSE REACTIONS**

The reported adverse events are hypotension, renal impairment, electrolyte and metabolic disorder, upper respiratory tract infection, back pain, sinusitis, diarrhoea, pharyngitis, influenza-like symptoms, dyspepsia, erythema, bronchitis and abdominal pain.

**Telmisartan:** The reported adverse events are headache, dizziness, pain, fatigue, hypertension, chest pain, nausea, cough, peripheral edema, impotence, increased sweating, flushing, allergy, fever, leg pain, pain in extremity, malaise, palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG, insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia, flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroesophageal reflux, toothache, gout, hypercholesterolemia, diabetes mellitus, arthritis, arthralgia, leg cramps, anxiety, depression, nervousness, increase risk infection, myalgia, abscess, otitis media, asthma, rhinitis, dyspnea, epistaxis, dermatitis, rash, eczema, pruritus, micturition frequency, cystitis, cerebrovascular disorder, abnormal vision, conjunctivitis, tinnitus and earache.

**Hydrochlorothiazide:** The reported adverse events are weakness, pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, aplastic anaemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions, hyperglycemia, glycosuria
*Musculoskeletal:* muscle spasm, restlessness, interstitial nephritis, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, transient blurred vision and xanthopsia.

The additional reported events are asthenia, edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, atrial fibrillation, congestive heart failure, myocardial infarction, hypertension aggravated, orthostatic hypotension, hyperkalemia, syncope, tachycardia, urinary tract infection, erectile dysfunction, muscle cramps, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anaemia, and increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (e.g., toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), angioedema (with fatal outcome), decrease in haemoglobin, increase serum creatinine, increase BUN, elevations of liver chemistries, intermittent claudication, sciatica, arrhythmias, gastrointestinal discomfort, interstitial lung disease, drowsiness, sepsis, taste altered, visual impairment and skin ulcer. In rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan and occasional elevations of liver chemistries occurred in patients treated with telmisartan.

**DRUG INTERACTIONS**

- **Agents Increasing Serum Potassium:** Co-administration of telmisartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.
- **Aliskiren:** Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min).
- **Digoxin:** Monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.
- **Lithium:** Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.
- **Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):**

  **Telmisartan:** In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

  **Hydrochlorothiazide:** Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. Therefore, when (Temisartan and hydrochlorothiazide) and non-steroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.
- **Antidiabetic Drugs (Oral Agents and Insulin):** Dosage adjustment of antidiabetic drugs may be required when coadministered with hydrochlorothiazide.
- **Cholestyramine and Colestipol Resins:** Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

**CONTRAINDICATIONS**

- In patients who are hypersensitive to any component of this product.
- In patients with anuria.
- For co-administration with aliskiren in patients with diabetes.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

***Telmisartan:*** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue medicine as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue medicine (Telmisartan and Hydrochlorothiazide), unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to this combination (Telmisartan and hydrochlorothiazide) for hypotension, oliguria, and hyperkalemia.

***Hydrochlorothiazide:*** Thiazides cross the placenta and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in adults.

**Nursing Mothers**

Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with it.

**Paediatric Use**

Safety and effectiveness of telmisartan in paediatric patients have not been established. If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

**Geriatric Use**

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

**Hepatic Impairment**

Patients with biliary obstructive disorders or hepatic insufficiency should initiate treatment under close medical supervision using the 40 mg/12.5 mg combination.
***Telmisartan:*** As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance and higher blood levels.
***Hydrochlorothiazide:*** Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

**Renal Impairment**

Safety and effectiveness of (Telmisartan and hydrochlorothiazide) in patients with severe renal impairment (CrCl ≤30 mL/min) have not been established. In patients with severe renal impairment, it is not recommended. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

**WARNINGS AND PRECAUTIONS**

**Fetal Toxicity**

***Telmisartan***

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible.

***Hydrochlorothiazide***

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia.

**Hypotension in Volume-or Salt-Depleted Patients**

In patients with an activated renin-angiotensin system, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initialization of treatment with (Telmisartan and hydrochlorothiazide). Correct volume or salt depletion prior to administration of this combination (Telmisartan and hydrochlorothiazide).
If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

**Hyperkalemia**

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

**Impaired Hepatic Function**

Caution should be exercised in hepatic impairment patients. Titrate slowly in hepatic impairment patients. As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance.

**Impaired Renal Function**

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia, or acute renal failure on (Telmisartan and hydrochlorothiazide). Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on this combination (Telmisartan and hydrochlorothiazide).

**Dual Blockade of the Renin-Angiotensin-Aldosterone System**

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients taking Telmisartan and other agents that affect the RAS.
Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m ).

**Electrolytes and Metabolic Disorders**

Drugs, including telmisartan, that inhibit the renin-angiotensin system can cause hyperkalemia, particularly in patients with renal insufficiency, diabetes, or combination use with other angiotensin receptor blockers or ACE inhibitors and the concomitant use of other drugs that raise serum potassium levels.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because telmisartan decreases uric acid, telmisartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

**Hypersensitivity Reaction**

***Hydrochlorothiazide***

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma but are more likely in patients with such a history.

**Acute Myopia and Secondary Angle-Closure Glaucoma**

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

**Systemic Lupus Erythematosus**

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

**Postsympathectomy Patients**

The antihypertensive effects of hydrochlorothiazide may be enhanced in the postsympathectomy patient.

**OVERDOSAGE**

***Telmisartan:*** 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. Telmisartan is not removed by hemodialysis.

***Hydrochlorothiazide:*** The most common signs and symptoms observed in patients with a hydrochlorothiazide overdose are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

**DOSAGE AND INSTRUCTIONS**

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

**PRESENTATION**

**Misar H 40mg/12.5mg Tablets:** Alu. Alu. Blister Pack of 2 x 7's.
**Misar H 80mg/12.5mg Tablets:** Alu. Alu. Blister Pack of 2 x 7's.
**Misar H 80mg/25mg Tablets:** Alu. Alu. Blister Pack of 2 x 7's.

# مِسار ایچ™

(ٹیلمی سارٹن + ہائیڈروکلوروتھائیزائیڈ)

## خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔

بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔

خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

**Manufactured by**
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