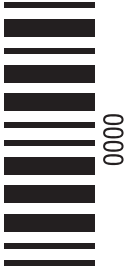


hovid

ITEM CODE



hovid-Telmisartan Tablet

DESCRIPTION
hovid-Telmisartan Tablet 40 mg: White to off white, capsule shaped tablets debossed with "H" on one side and plain on the other side.
hovid-Telmisartan Tablet 80 mg: White to off white, oval shaped tablets debossed with "D" on one side and plain on the other side.

COMPOSITION
hovid-Telmisartan Tablet 40mg: Each tablet contains Telmisartan Ph.Eur. 40 mg.
hovid-Telmisartan Tablet 80mg: Each tablet contains Telmisartan Ph.Eur. 80 mg.

ACTIONS AND PHARMACOLOGY
Telmisartan is an orally active and specific angiotensin II receptor (type AT₁) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT₁ receptor. Telmisartan selectively binds the AT₁ receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT₂ and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects.

In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Treatment of essential hypertension
After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

Cardiovascular prevention
Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

PHARMACOKINETICS
Absorption
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50%. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC_{0-∞}) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Distribution
Telmisartan is largely bound to plasma protein (>99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{ss}) is approximately 500 l.

Biotransformation
Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination
Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}), and to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose.

There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Special Populations
Paediatric population
The pharmacokinetics of children under 12 years of age are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max}.

Gender
Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly
The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years.

Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is not changed in patients with hepatic impairment.

INDICATION
Hypertension
Treatment of essential hypertension.

Cardiovascular prevention
Telmisartan is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors. High risk of cardiovascular events can be evidenced by history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin-dependent or non-insulin dependent) with evidence of end-organ damage.

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Telmisartan can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy). Consider using the ACE inhibitor first, and, if it is stopped for cough only, consider re-trying the ACE inhibitor after the cough resolves.

Use of telmisartan with an ACE inhibitor is not recommended.

CONTRAINDICATION

- Hypersensitivity to the active substance or to any excipients used.
- Second and third trimesters of pregnancy
- Biliary obstructive disorders
- Severe hepatic impairment
- Concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m²).
- Telmisartan is contraindicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.

WARNINGS AND PRECAUTIONS
Pregnancy
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment
Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system (RAAS).

Renal impairment and kidney transplantation
When telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan in patients with recent kidney transplantation.

Intravascular hypovolaemia
Symptomatic hypotension, especially after the first dose of telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting. Such conditions should be corrected before the administration of telmisartan. Volume and/or sodium depletion should be corrected prior to administration of telmisartan.

Dual blockade of the RAAS
There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the RAAS
In patients whose vascular tone and renal function depend predominantly on the activity of the RAAS (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the RAAS. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Diabetic patients treated with insulin or antidiabetics
In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia
The use of medicinal products that affect the RAAS may cause hyperkalaemia. The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the RAAS and / or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Before considering the concomitant use of medicinal products that affect the RAAS, the benefit risk ratio should be evaluated. Close monitoring of serum potassium in at risk patients is recommended.

Other
As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

PREGNANCY AND LACTATION
Pregnancy
The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.



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The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Angiotensin II receptor antagonists exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

Lactation
Telmisartan is contraindicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.

DRUG INTERACTIONS
Digoxin
When initiating, adjusting, and discontinuing telmisartan, digoxin levels should be monitored in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the RAAS, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended:
Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution:
Non-steroidal anti-inflammatory medicinal products
NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use:
Other antihypertensive agents
The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Effects on ability to drive and use machines
When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as telmisartan.

MAIN SIDE EFFECTS / ADVERSE EFFECTS
Infections and infestations: Urinary tract infections (including cystitis), upper respiratory tract infections, sepsis including fatal outcome

Blood and lymphatic system disorders: Anaemia, eosinophilia, thrombocytopenia

Immune system disorders: Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders: Hyperkalaemia, hypoglycaemia (in diabetic patients)

Psychiatric disorders: Insomnia, depression, anxiety

Nervous system disorders: Syncope (faint)

Eye disorders: Visual disturbance

Ear and labyrinth disorders: Vertigo

Cardiac disorders: Bradycardia, tachycardia

Vascular disorders: Hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders: Dyspnoea

Gastro-intestinal disorders: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth, stomach discomfort

Hepatobiliary disorders: Hepatic function abnormal / liver disorder*
*Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.

Skin and subcutaneous tissue disorders: Pruritus, hyperhidrosis, rash, angioedema (with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders: Back pain, muscle spasms (cramps in legs), myalgia, arthralgia, pain in extremity (leg pain), tendon pain (tendinitis like symptoms)

Renal and urinary disorders: Renal impairment including acute renal failure (see Special precautions and warnings)

General disorders and administration site conditions: Chest pain, asthenia (weakness), influenza-like illness

Investigations: Blood creatinine increased, haemoglobin decreased, blood uric acid increased, hepatic enzymes increased, blood creatine phosphokinase (CPK) increased

OVERDOSE AND TREATMENT
There is limited information available with regard to overdose in humans.

Symptoms
The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Treatment
Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

DOSAGE AND ADMINISTRATION
Telmisartan tablets are for once-daily oral administration and should be taken with liquid. Telmisartan may be taken with or without food. Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

Treatment of Essential Hypertension
The recommended dose is 40 mg once daily. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four - eight weeks after the start of treatment.

In patients with severe hypertension treatment with telmisartan at doses up to 160 mg alone and in combination with hydrochlorothiazide 12.5 - 25 mg daily was well tolerated and effective.

Cardiovascular Risk Reduction
The recommended dose of Telmisartan Tablets is 80mg once a day and can be administered with or without food. It is not known whether doses lower than 80mg of telmisartan are effective in reducing the risk of cardiovascular morbidity and mortality.

When initiating Telmisartan therapy for cardiovascular risk reduction, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Renal impairment
No posology adjustment is required for patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by hemofiltration.

Hepatic impairment
In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily.

Elderly
No dosing adjustment is necessary.

Children and adolescents
The safety and efficacy of Telmisartan for use in children below 18 years have not been established.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Storage : Store below 30°C. Protect from moisture.

Presentation/Packaging : Blister pack of 3 x 10's.

Product Registration Holder : **HOVID Bhd.**
121, Jalan Tunku Abdul Rahman
(Jalan Kuala Kangsar),
30010 Ipoh, Perak, Malaysia.

Manufactured by : Jubilant Generics Ltd.
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Uttarakhand-247661 India.

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