WARNING
FETAL TOXICITY

- **When pregnancy is detected, discontinue telmisartan as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus**

For the use of a Registered Medical Practitioner only

1. Generic Name and Brand Name

Telmisartan and Amlodipine Tablets I.P.
TELMITORVA® AM 40

2. Qualitative and Quantitative Composition

Each uncoated bilayered tablet contains:
Telmisartan I.P. 40 mg
Amlodipine Besilate IP eq. to Amlodipine 5 mg
Excipients: q.s.
Colour: Lake of Ponceau 4R
(In Amlodipine Besilate Layer)

3. Dosage Form & Strength

Refer section 1 & 2

4. Clinical Particulars

4.1.Therapeutic Indication

For the treatment of Essential Hypertension.

4.2.Posology and Method of Administration

One tablet once daily

4.3.Contraindications

Contraindicated in patients with

- Known hypersensitivity to Telmisartan, Amlodipine or any other component of this product
- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy
- Biliary obstructive disorders
- Severe hepatic impairment
- The concomitant use of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)
- Anuria
- Hypersensitivity to this product or other sulfonamide derived drugs.

4.4.Special Warnings and Precautions for Use

1. Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Discontinue Telmisartan tablets as soon as possible, when pregnancy is detected.

During the second and third trimesters of pregnancy, using drugs which act directly on the renin-angiotensin system has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function which have been associated with craniofacial deformation, fetal limb contractures, and hypoplastic lung development.
When patients become pregnant or are considering pregnancy, discontinue the use of Telmisartan as soon as possible.
If no alternative to angiotensin II receptor antagonist is found, mothers should be informed of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, telmisartan should be discontinued. Biophysical profiling (BPP), Contraction stress testing (CST), a non-stress test (NST), may be appropriate, depending upon the week of pregnancy.
Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely monitored for hypotension, oliguria, and hyperkalemia.
There are no adequate and well-controlled studies of amlodipine in pregnant women, hence, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. Hypotension

Symptomatic hypotension may occur after initiation of therapy with Telmisartan, in patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients. This condition should be treated prior to or at start of treatment with Telmisartan, under close medical supervision with a reduced dose.
If hypotension occurs, the patient should be placed in the supine position and, given an intravenous infusion of normal saline, if necessary.
Symptomatic hypotension with amlodipine is possible, especially in patients with severe aortic stenosis. As amlodipine has gradual onset of action, acute hypotension is unlikely.

3. Hyperkalemia

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

4. Impaired Hepatic Function

Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance, as the majority of telmisartan is eliminated by biliary excretion. Telmisartan should be initiated at low doses and titrated slowly in these patients.
In patients with impaired hepatic function, amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours. Hence, dose should be titrated slowly when administering amlodipine to patients with severe hepatic impairment.
Thiazides should be used with caution in patients with impaired hepatic function as they can precipitate hepatic coma in patients with severe liver disease.

5. Impaired Renal Function

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

Long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis has not been established, but an effect similar to that seen with ACE inhibitors can be anticipated.

6. Dual Blockade of the Renin-Angiotensin-Aldosterone System

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

Patients receiving the combination of Telmisartan and ramipril experienced an increased incidence of renal dysfunction (e.g., acute renal failure), hence concomitant use of these drugs is not recommended.

7. Increased Angina or Myocardial Infarction

After starting or increasing the dose of Amlodipine, worsening angina and acute myocardial infarction can develop, particularly in patients with severe obstructive coronary artery disease.

8. Beta-Blocker Withdrawal

As Amlodipine is not a beta-blocker it gives no protection against the dangers of abrupt beta-blocker withdrawal. Any withdrawal should be by gradual reduction of the dose of beta-blocker.

9. Diabetes and Hypoglycemia

Thiazide may cause manifestation of latent diabetes mellitus and these patients may require adjustment of their insulin dose.

10. Hyperuricemia

Certain patients receiving thiazide diuretics, may be precipitated Hyperuricemia or acute gout.

11. Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. No drug-related effects on the reproductive performance of male and female rats were noted.

No evidence of carcinogenic effect and mutagenicity effect of amlodipine was observed in animal studies. There was no effect on the fertility of rats treated orally with amlodipine maleate.

4.5. Drug Interactions

No.	Drug	Drug Interaction	Remark
1.	Digoxin	Median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed when Telmisartan and Digoxin are administered concomitantly.	Digoxin levels should be monitored when initiating, adjusting, and discontinuing telmisartan
2.	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity	Monitor serum lithium levels during concomitant use. Generally should not be given with diuretics

3.	Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)	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. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.	Monitor renal function periodically in patients receiving telmisartan and NSAID therapy concomitantly.
4.	Ramipril and Ramiprilat	Co-administration of telmisartan and ramipril to healthy subjects increases steady-state Cmax and AUC of ramipriland ramiprilat and decreases Cmax and AUC of telmisartan. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan.	Concomitant use of Telmisartan and ramipril is not recommended.
5.	Other Drugs: Acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen.	Co-administration of telmisartan did not result in a clinically significant interaction with these drugs	
6.	Drugs that inhibit cytochrome P450 enzymes	Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes	
7.	drugs metabolized by cytochrome P450 enzymes	Telmisartan does not interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.	
8.	Cimetidine	Co-administration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine.	

9.	Grapefruit Juice	Co-administration of grapefruit juice with a single oral dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.	
10.	Magnesium and Aluminum Hydroxide Antacid	Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of Amlodipine had no significant effect on the pharmacokinetics of Amlodipine	
11.	Sildenafil	Coadministration of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Amlodipine.	
12.	Atorvastatin	Co-administration of Amlodipine atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.	
13.	Digoxin	In normal volunteers, co-administration of Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance	
14.	Ethanol (Alcohol)	Amlodipine had no significant effect on the pharmacokinetics of ethanol.	
15.	Warfarin	Co-administration of Amlodipine with warfarin did not change the warfarin prothrombin response time.	
16.	CYP3A4 Inhibitors	Co-administration of diltiazem with amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.	Monitoring for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors should be carried out.
17.	CYP3A4 Inducers	No information is available on the quantitative effects of CYP3A4 inducers on amlodipine.	Monitor Blood pressure closely when Amlodipine is co-administered with CYP3A4 inducers
18.	Alcohol, barbiturates, or narcotics	Potentiation of orthostatic hypotension may occur with thiazides	

19.	Antidiabetic drugs (oral agents and insulin)		Dosage adjustment of the antidiabetic drug may be required when given concomitantly with thiazides

4.6.Use in Special Populations

It is unknown whether telmisartan and amlodipine are excreted in human milk. As there is potential for adverse effects on the nursing infant, it should be decided whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in effectiveness and safety of Telmisartan were observed in elderly patients compared to younger patients.

Pregnancy Category C:

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on patient weight of 50 kg.

4.7.Effects on Ability to Drive and Use Machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. When driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8.Undesirable Effects

Autonomic Nervous System: increased sweating, dry mouth, flushing, impotence,

Body as a Whole: allergy, leg pain, Weakness, hot flushes, pain, rigors, weight gain, weight decrease, malaise, fever, asthenia, back pain

Cardiovascular: palpitation, angina pectoris, tachycardia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, Hypotension including orthostatic hypotension, postural dizziness, postural hypotension, vasculitis, leg edema, abnormal ECG, dependent edema, arrhythmia (including ventricular tachycardia and atrial fibrillation)

CNS and PNS: insomnia, vertigo, paresthesia, neuropathy peripheral, tremor, involuntary muscle contractions, somnolence, migraine, hypoesthesia

Gastrointestinal: flatulence, constipation, anorexia, constipation, dyspepsia, dysphagia, diarrhea, pancreatitis, gingival hyperplasia, Pancreatitis, jaundice (intrahepatic cholestatic

jaundice), diarrhea, sialadenitis, cramping, nausea, anorexia, gastroesophageal reflux, toothache, gastritis, vomiting, dry mouth, haemorrhoids, gastroenteritis, enteritis, nonspecific gastrointestinal disorders, gingival hypertrophy.
Metabolic: gout, diabetes mellitus, hyperglycemia, Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia, thirst, hypercholesterolemia
Musculoskeletal: arthritis, arthralgia, arthrosis, Muscle spasm, muscle cramps, myalgia, leg cramps
Psychiatric: depression, sexual dysfunction (male and female), Vertigo, paresthesia, dizziness, headache, restlessness, insomnia, depression, abnormal dreams, depersonalization, anxiety, nervousness
Resistance Mechanism: infection, dyspnea, epistaxis, fungal infection, abscess, otitis media
Respiratory: asthma, dyspnea, epistaxis, bronchitis, rhinitis
Skin: dermatitis, angioedema, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, rash erythematous, rash maculopapular eczema, pruritus, rash, alopecia
Urinary: micturition frequency, micturition disorder, nocturia, cystitis
Vascular: cerebrovascular disorder
Special Senses: conjunctivitis, abnormal vision, Transient blurred vision, xanthopsia., diplopia, eye pain, tinnitus, earache.
Hemopoietic: leukopenia, thrombocytopenia, Aplastic anemia, agranulocytosis, Hemolytic anemia, purpura
Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), photosensitivity, fever, urticaria, rash, purpura, respiratory distress including pneumonitis and pulmonary edema.
Renal: Renal failure, interstitial nephritis, renal dysfunction
Urogenital*:* Impotence.

4.9.Overdose
Limited data is available with regard to overdosage in humans. The most likely manifestation of overdosage with telmisartan would be dizziness and tachycardia, hypotension; bradycardia could occur from parasympathetic stimulation. Supportive treatment should be instituted, if symptomatic hypotension should occur. Telmisartan is not removed by hemodialysis.
Amlodipine overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and also reflex tachycardia. Experience with intentional overdosage of Amlodipine is limited, in humans.
Initiate active cardiac and respiratory monitoring, if massive overdose with amlodipine should occur. Measure blood pressure frequently. If hypotension occurs, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be provided. If hypotension still pertains after these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. Hemodialysis is not likely to be of benefit, as Amlodipine is highly protein bound.

5. Pharmacological Properties
5.1.Mechanism of Action
Telmisartan:
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

Amlodipine:
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle

5.2.Pharmacodynamic Properties
Telmisartan
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.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.
Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure

5.3.Pharmacokinetic Properties

Parameters	Telmisartan	Amlodipine

Absorption	Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetic. Trough plasma concentrations of telmisartan with once daily dosing are about 10 to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0.	After oral administration of therapeutic doses of Amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose. Elderly patients and patients with hepatic insufficiency and patient with moderate to severe heart failure have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required.
Bioavailability	Food slightly reduces the bioavailability of telmisartan, with a reduction in the AUC of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. Absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively.	Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability is not altered by the presence of food
Distribution	Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution is approximately 500 liters indicating additional tissue binding.	Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
Plasma Protein Binding	Highly bound to plasma proteins (>99.5%) mainly albumin and α1 - acid glycoprotein	93% of the circulating drug is bound to plasma proteins in hypertensive patients.
Metabolism	Metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine.	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.
Excretion	Most of the administered dose (>97%) is eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine Total plasma clearance of telmisartan is >800 mL/min.	Elimination from the plasma is biphasic.

Half-life	Terminal elimination half-life of approximately 24 hours.	Terminal elimination half-life of about 30–50 hours

6. Nonclinical Particulars

6.1.Animal Toxicology or Pharmacology

Telmisartan:

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Amlodipine:

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m2 basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.). Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m2 basis).

7. Description

TELMITORVA AM 40 is supplied for oral administration, as an uncoated bilayered tablet of Telmisartan & Amlodipine Besylate. Each uncoated bilayered tablet of TELMITORVA AM 40 contains Telmisartan 40 mg & Amlodipine Besylate equivalent to Amlodipine 5 mg.

8. Pharmaceutical Particulars

8.1.Incompatibilities

Not applicable

8.2.Shelf-Life

Refer Pack

8.3.Packaging Information

Refer Pack

8.4.Storage and Handling Instructions

Refer Pack

9. Patient Counselling Information

Instruct patients on the risk of foetal harm when this drug is used in pregnancy [see Warnings and Precautions and Use in Specific Populations]. Advise patients to immediately contact their healthcare provider if they develop rash or with the use of any other prescription or non-prescription medication or herbal products along with this drug.

10. Details of Manufacturer

Refer Pack for manufacturer details.

Marketed By:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

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11. Details of Permission or Licence Number with Date

Refer Pack for Permission/License details.

12. Date of Revision

Version: 1.0, dated 20-Jan-26

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com