PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] RIVA-TELMISARTAN/AMLODIPINE

Telmisartan and Amlodipine (as Amlodipine Besylate) Tablets, Mfr. Std.

Tablets, 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg, Oral

Angiotensin II AT1 Receptor Blocker / Calcium Channel Blocker

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Date of Initial Authorization:
JUL 31, 2025

Submission Control Number: 267902

RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RIVA-TELMISARTAN/AMLODIPINE (telmisartan/amlodipine besylate) is indicated for:

- treatment of mild to moderate essential hypertension for whom combination therapy with telmisartan and amlodipine is appropriate.

RIVA-TELMISARTAN/AMLODIPINE is not indicated for initial therapy (see 4 DOSAGE AND ADMINISTRATION).

1.1 Pediatrics

- **Pediatrics (<18 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of telmisartan/amlodipine besylate in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- **Geriatrics (> 65 years of age):** No dose adjustment is necessary for geriatric patients. It should be recognized, however, that greater sensitivity in some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

RIVA-TELMISARTAN/AMLODIPINE (telmisartan/amlodipine besylate) is contraindicated in:

- Concomitant use of angiotensin receptor blockers (ARBs) –including the telmisartan component of RIVA-TELMISARTAN/AMLODIPINE- with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m2) is contraindicated (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs).
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients with a hypersensitivity to dihydropyridine derivatives.
- Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs (see 7 WARNINGS AND PRECAUTIONS, General).
- Pregnant women (see 7.1.1 Pregnant Women)
    - When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, RIVA-TELMISARTAN/AMLODIPINE should be discontinued as soon as possible.
- Breast-feeding women (see 7.1.2 Breast-feeding).
- Patients with biliary obstructive disorders.
- Patients with severe hepatic impairment.

- Patients with shock including cardiogenic shock.
- Severe hypotension (less than 90 mmHg systolic).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Patients with rare hereditary conditions that may be incompatible with an excipient of the product.
- Patients with the rare hereditary condition of fructose intolerance (HFI)
    - Mannitol: Mannitol is a source of fructose. RIVA-TELMISARTAN/AMLODIPINE tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain 98.505 mg, 98.36 mg, 197.01 mg, 196.72 mg of mannitol in each tablet respectively.
    - Meglumine: Meglumine is a source of fructose. RIVA-TELMISARTAN/AMLODIPINE tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain 5.40 mg, 5.40 mg, 10.80 mg and 10.80 mg of meglumine in each tablet respectively.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, RIVA-TELMISARTAN/AMLODIPINE should be discontinued as soon as possible (see 7.1 Special Populations).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients should be titrated on individual drugs. If the fixed dose combination represents the dose and dosing frequency determined by this titration, the use of RIVA-TELMISARTAN/AMLODIPINE may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

4.2 Recommended Dose and Dosage Adjustment

- RIVA-TELMISARTAN/AMLODIPINE should be taken once daily.
- If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

Replacement Therapy

- Patients receiving telmisartan and amlodipine from separate tablets can instead receive RIVA-TELMISARTAN/AMLODIPINE containing the same component doses in one tablet once daily, e.g. to enhance convenience.

Special populations

Renal impairment

No dosage adjustment is required for patients with renal impairment, including those on haemodialysis.

Hepatic impairment

In patients with mild to moderate hepatic impairment RIVA-TELMISARTAN/AMLODIPINE should be administered with caution. For telmisartan the dosage should not exceed 40 mg once daily as hepatic impairment increases bioavailability (see Special Populations and Conditions - Hepatic insufficiency).

Amlodipine dosage requirement have not been established in patients with impaired hepatic function. When amlodipine is used in these patients, it should be initiated at the lower end of the dosing range and the dosage should be carefully and gradually adjusted depending on the patient's tolerance and response.

Geriatrics (> 65 years of age)

No dose adjustment is necessary for elderly patients. It should be recognized, however, that greater sensitivity in some older individuals cannot be ruled out. If required, increase in the dose should be done gradually and with caution (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

Pediatric population (<18 years of age)

RIVA-TELMISARTAN/AMLODIPINE is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Drug discontinuation

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, RIVA-TELMISARTAN/AMLODIPINE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears.

When pregnancy is detected, RIVA-TELMISARTAN/AMLODIPINE should be discontinued as soon as possible.

4.4 Administration

Tablet for oral administration

RIVA-TELMISARTAN/AMLODIPINE should be taken consistently with or without food. RIVA-TELMISARTAN/AMLODIPINE tablets are for once-daily oral administration and should be swallowed whole with liquid.

4.5 Missed Dose

If a dose is missed during the day, the next dose should be continued at the usual time. Do not double dose.

5 OVERDOSAGE

Symptoms

Telmisartan/amlodipine tablets: Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.

Telmisartan: Limited data are available with regard to telmisartan overdosage in humans. The most prominent manifestations of overdosage were hypotension and/or tachycardia; bradycardia also occurred.

It is not known if telmisartan can be removed from the body by hemodialysis.

Amlodipine: Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome may occur.

A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Therapy

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function.

There is no experience of overdose with Telmisartan/amlodipine tablets.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg telmisartan/amlodipine	Colloidal anhydrous silica, crospovidone, iron oxide red (E172) (40/5 mg and 80/5 mg), iron oxide yellow (E172) (40/10 mg and 80/10 mg), magnesium stearate, maize starch, mannitol, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide.

RIVA-TELMISARTAN/AMLODIPINE 40/5 mg is available as bilayer tablets, white to off-white on one side and pink on the other side, acceptable slight speckles on the pink side, oblong, biconvex.

RIVA-TELMISARTAN/AMLODIPINE 40/10 mg is available as bilayer tablets, white to off-white on one side and yellow on the other side, acceptable slight speckles on the yellow side, oblong, biconvex.

RIVA-TELMISARTAN/AMLODIPINE 80/5 mg is available as bilayer tablets, white to off-white on one side and pink on the other side, acceptable slight speckles on the pink side, oblong, biconvex.

RIVA-TELMISARTAN/AMLODIPINE 80/10 mg is available as bilayer tablets, white to off-white on one side and yellow on the other side, acceptable slight speckles on the yellow side, oblong, biconvex.

Non-medicinal ingredients (in alphabetical order): Colloidal anhydrous silica, crospovidone, iron oxide red (E172) (40/5 mg and 80/5 mg), iron oxide yellow (E172) (40/10 mg and 80/10 mg), magnesium stearate, maize starch, mannitol, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide.

RIVA-TELMISARTAN/AMLODIPINE tablets are packed in aluminium/aluminium blister cards in cartons of 30 tablets as 2 cards containing 15 tablets each.

Mannitol

Mannitol is a source of fructose.

RIVA-TELMISARTAN/AMLODIPINE tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain 98.505 mg, 98.36 mg, 197.01 mg, 196.72 mg of mannitol in each tablet respectively and are contraindicated in patients with hereditary fructose intolerance (HFI) (see 2 CONTRAINDICATIONS).

Meglumine

Meglumine is a source of fructose.

RIVA-TELMISARTAN/AMLODIPINE tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain 5.40 mg, 5.40 mg, 10.80 mg and 10.80 mg of meglumine in each tablet respectively and are contraindicated in patients with hereditary fructose intolerance (HFI) (see 2 CONTRAINDICATIONS).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

A case of rare but fatal angioedema had occurred in a patient who had been medicated for about 6 months with telmisartan, one of the active components of telmisartan/amlodipine besylate. The Autopsy Report described evidence of edema of the laryngeal mucosa, with terminal respiratory and circulatory failure. This is in the context of approximately 5.2 million patient-years exposure to telmisartan annually.

In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 ml of subcutaneous epinephrine solution 1:1000) should be administered promptly (see 8.5 Post Market Adverse Drug Reactions; Telmisartan).

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be treated with RIVA-TELMISARTAN/AMLODIPINE (see 8.2 Clinical Trial Adverse Reactions - Unknown Frequencies, Immune System Disorders, Angioedema and 8.5 Post Market Adverse Drug Reactions; Telmisartan).

Beta-blocker withdrawal: RIVA-TELMISARTAN/AMLODIPINE gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Concomitant Use with Strong Inhibitors of CYP 3A4

Use of telmisartan/amlodipine besylate with drugs that result in strong inhibition of CYP 3A4, such as ketoconazole, clarithromycin, ritonavir, may lead to increased plasma levels of amlodipine and associated serious adverse events (see 9 DRUG INTERACTIONS). Such concomitant use should be avoided.

An observational study demonstrated an increased risk of hospitalisation with acute kidney injury when amlodipine was used concomitantly with clarithromycin in elderly patients (>65 years of age) compared to when it was used concomitantly with azithromycin, odds ratio [amlodipine: l.61 (95% C.I. 1.29 - 2.02)].

Cardiovascular

Ischaemic heart disease

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

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. These patients are at risk of decreased coronary perfusion resulting from a cardiac output that is limited by a fixed cardiac vascular obstruction.

Unstable Angina Pectoris, Acute Myocardial Infarction

There are no data to support the use of telmisartan/amlodipine besylate in unstable angina pectoris and during or within one month of a myocardial infarction. Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Patients with Cardiac Failure

In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Volume and/or sodium depleted patients

In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy. Such conditions should be corrected before the administration of RIVA-TELMISARTAN/AMLODIPINE.

Peripheral Edema

Peripheral edema is a recognised dose dependent side effect of amlodipine. In a single double blind, randomised, factorial clinical trial of eight weeks duration, edema was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor blockers (ARBs), such as the telmisartan component of telmisartan/amlodipine besylate, or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m2).

Therefore, the use of RIVA-TELMISARTAN/AMLODIPINE in combination with aliskiren-containing drugs is contraindicated in these patients.

Further, co-administration of ARBs, including the telmisartan component of telmisartan/amlodipine besylate, with other agents blocking the RAS, such as ACE inhibitors or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Diabetic Patients

In diabetic patients with undiagnosed coronary artery disease (CAD) on blood pressure lowering therapy, the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased. In patients with diabetes mellitus, CAD may be asymptomatic and therefore undiagnosed. These patients should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating blood pressure lowering treatment with RIVA-TELMISARTAN/AMLODIPINE.

Driving and Operating Machinery

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that dizziness, syncope or vertigo may occasionally occur when taking antihypertensive therapy.

If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Endocrine and Metabolism

Hyperkalaemia

Drugs such as RIVA-TELMISARTAN/AMLODIPINE that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of drugs that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or medicinal products that may increase potassium levels (heparin, etc.) may lead to a greater risk of an increase in serum potassium and should therefore be co-administered cautiously with telmisartan.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

As the majority of telmisartan is eliminated by biliary excretion, patients with cholestasis, biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan leading to increased systemic exposure. Three to four fold increases in Cmax and AUC of telmisartan were observed in patients with liver impairment as compared to healthy subjects. The half-life of amlodipine is prolonged to 56 h and AUC values are 40-60% higher in patients with impaired liver function (see 10.3 Pharmacokinetics). Amlodipine should therefore be initiated at the lower end of the dosing range and titration should be slow, with careful monitoring throughout. RIVA-TELMISARTAN/AMLODIPINE should be used with caution in these patients.

Use in patients with severe hepatic impairment is contraindicated (see 2 CONTRAINDICATIONS).

Monitoring and Laboratory Tests

For specific monitoring and laboratory tests, see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Endocrine and Metabolism, Hepatic, and Renal and 9 DRUG INTERACTIONS sections.

Renal

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.

Renal Impairment and Kidney Transplant

When RIVA-TELMISARTAN/AMLODIPINE is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan/amlodipine besylate in patients with a recent kidney transplant. Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

Blockade of the Renin-Angiotensin-Aldosterone System

In patients whose renal function may depend on the activity of the renin-angiotensin- aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, dual blockade (e.g. concomitant use of an angiotensin II receptor blocker with an ACE inhibitor or the direct renin- inhibitor aliskiren) or treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. Upon treatment in such cases, renal function should be closely monitored. However, RIVA-TELMISARTAN/AMLODIPINE can be administered with other antihypertensive drugs.

Primary Aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of RIVA-TELMISARTAN/AMLODIPINE is not recommended.

Renal Impairment

The use of ARBs – including the telmisartan component of RIVA-TELMISARTAN/AMLODIPINE – or of ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). (See 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Reproductive Health: Female and Male Potential

- **Fertility**

  No studies on fertility in humans with the fixed dose combination or with the individual components have been performed. Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted (See 16 NON-CLINICAL TOXICOLOGY, Telmisartan, Amlodipine).

  In some patients treated by calcium channel blockers, reversible biochemical changes in the head of spermatozoa have been reported.

  Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (See 16 NON-CLINICAL TOXICOLOGY, Telmisartan, Amlodipine)

7.1 Special Populations

7.1.1 Pregnant Women

RIVA-TELMISARTAN/AMLODIPINE

While the effects of telmisartan/amlodipine besylate during pregnancy are not known, treatment should be discontinued as soon as a pregnancy is detected due to the telmisartan component of this combination drug (see 2 CONTRAINDICATIONS).

Telmisartan

Drugs that act directly on the renin-angiotensin-aldosterone-system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women.

The use of angiotensin receptor (AT1) blockers (ARBs) is not recommended during pregnancy and should not be initiated during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

The use of ARBs 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, hyperkalemia).

Infants with a history of in utero exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypotension and/or substituting for disordered renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day with saline supplementation. In rabbits, fetotoxicity (total resorptions) associated with maternal toxicity (reduced body weight gain, mortality) was observed at the highest dose level (45 mg/kg/day). In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 50 mg/kg/day in late gestation and during lactation were observed to produce adverse effects in rat fetuses and neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain (see 16 NON-CLINICAL TOXICOLOGY, Telmisartan, Reproduction). Significant levels of telmisartan were present in rat milk and rat fetuses' blood during late gestation.

Amlodipine

Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with amlodipine in pregnant women

7.1.2 Breast-feeding

RIVA-TELMISARTAN/AMLODIPINE is contraindicated during breast feeding. It is not known whether telmisartan is excreted in human milk but significant levels have been found in the milk of lactating rats (see 2 CONTRAINDICATIONS).

Amlodipine is transferred into human breast milk and therefore its use is contraindicated during breast feeding. The minimum proportion of the maternal dose received by the infant has been estimated to be between 3 and 15% and this might vary according to breastmilk composition.

A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): RIVA-TELMISARTAN/AMLODIPINE is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): In geriatric patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC (see 10.3 Pharmacokinetics). In clinical trials for amlodipine, the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. RIVA-TELMISARTAN/AMLODIPINE should be used cautiously in elderly patients.

The increase of the amlodipine dosage should take place with care in the elderly patients (see sections 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Summary of the safety profile

The safety and tolerability of telmisartan/amlodipine besylate has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

No additional adverse reactions were identified in clinical trials with the combination telmisartan plus amlodipine compared to the adverse reactions of the monocomponents. Peripheral oedema, a recognized dose dependent adverse reaction of the monocomponent amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

Adverse reactions previously reported with one of the monocomponents (telmisartan or amlodipine) may be potential adverse reactions with telmisartan/amlodipine besylate as well, even if not observed in clinical trials or during the post-marketing period. Therefore, in addition to the reported adverse reactions during the telmisartan/amlodipine besylate development program all adverse reactions reported in patients who received telmisartan or amlodipine monotherapy, have been listed for telmisartan/amlodipine besylate.

Combination therapy showed a favourable safety profile, with lower edema rates than amlodipine monotherapies, especially when comparing amlodipine full -dose monotherapy with amlodipine low-dose combinations, which showed at least comparable or better efficacy

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse events potentially related to BP lowering (e.g. hypotension, orthostatic hypotension, syncope) were rare throughout the double-blind treatment period of a randomized, double- dummy, placebo-controlled 4 x 4 factorial design trial, including the initial 2 weeks of first-line combination therapy. There were no serious cases. Almost all of the events were of mild or moderate intensity, and the majority of patients continued treatment and recovered without requiring therapy.

In a single, randomized double-blind placebo controlled, 8-week factorial design comparing free dose combination telmisartan/amlodipine to monotherapy (telmisartan or amlodipine) and placebo, adverse events (AEs) occurred with similar frequency across the treatment groups, with the highest frequency in the telmisartan 80mg/amlodipine 5 mg (T80/A5) group but the incidence of all AEs, in all groups was within 4% of the placebo group. Three serious adverse events occurred in the T80/A5 group, none of which were felt to be drug related. The three serious adverse events occurred in 3 different patients and included multiple fractures, deep venous thrombosis, and chest pain (see Table 2).

Table 2: Summary of adverse events by overall treatment groups in the factorial study.

	T40/A5	T40/A10	T80/A5	T80/A10	T40	T80	A5	A10	Placebo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Incidence over entire study: No. treated	143	129	146	142	130	135	140	129	46
Any adverse event (AE)	47 (32.9)	48 (37.2)	54 (37.0)	62 (43.7)	47 (36.2)	47 (34.8)	50 (35.7)	51 (39.5)	18 (39.1)
Severe AEs	3 (2.1)	2 (1.6)	4 (2.7)	5 (3.5)	2 (1.5)	3 (2.2)	7 (5.0)	2 (1.6)	0 (0.0)
AEs considered drug-related	19 (13.3)	16 (12.4)	17 (11.6)	27 (19.0)	11 (8.5)	7 (5.2)	12 (8.6)	22 (17.1)	6 (13.0)
Other significant AEs[1]	0 (0.0)	5 (3.9)	3 (2.1)	6 (4.2)	2 (1.5)	3 (2.2)	3 (2.1)	3 (2.3)	2 (4.3)
AEs leading to discontinuation of study drug	0 (0.0)	5 (3.9)	4 (2.7)	6 (4.2)	2 (1.5)	4 (3.0)	3 (2.1)	3 (2.3)	2 (4.3)
Serious AEs [2]	0 (0.0)	0 (0.0)	3 (2.1)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Immediately life−threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Caused disability or incapacity	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	T40/A5	T40/A10	T80/A5	T80/A10	T40	T80	A5	A10	Placebo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Required hospitalization	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)

[1] Marked laboratory abnormalities or AEs leading to intervention, other than those considered serious
[2] A patient may be counted in more than one seriousness criterion
T = Telmisartan 40 or 80 mg; A = amlodipine 5 or 10 mg.

In the single, randomized double-blind placebo controlled, 8-week factorial design comparing free dose combination telmisartan (T, 40 or 80 mg) and amlodipine (A, 5 or 10 mg) to monotherapy (telmisartan or amlodipine) and placebo, adverse events (AEs) occurred with similar frequency across the treatment groups, the most frequent AE overall, peripheral edema, was reported for higher percentages of patients in treatment groups containing A10 than in the other groups, with lower frequencies in the A10 combination groups (T40/A10 6.2%, T80/A10 11.3%) than in the A10 monotherapy group (17.8%). Patient frequencies of some common AEs were higher in some combination groups than in the respective component monotherapy groups, but no consistent patterns were apparent (see Table 3). Other than these events (i.e. peripheral edema, headache and fatigue), all drug-related AEs were reported by <1% of patients in any treatment group.

Additional data on long term safety was based on an open-label, limited study, of 6 month up to 8 months duration and no new safety signals were noted.

Table 3: Adverse events with reported incidence ≥2% than in the placebo group of patients (N=46) in the factorial study

MedDRA system organ class	T40/A5 (N=143)	T40/A10 (N=129)	T80/A5 (N=146)	T80/A10 (N=142)	T40 (N=130)	T80 (N=135)	A5 (N=140)	A10 (N=129)
Preferred term	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Total with any adverse events	33	38	37	44	36	35	36	40
Gastrointestinal disorders								
Nausea	0	0	1	0	0	1	3	1
General disorders and administration site conditions								
Chest discomfort/ Chest pain	1	1	1	2	2	0	1	1
Fatigue	2	0	1	1	2	3	1	1
Edema	0	3	1	2	0	0	1	2
Edema peripheral	1	6	2	11	1	1	1	18
Infections and infestations								
Influenza	1	1	3	2	0	0	1	2
Upper respiratory tract infection	1	1	2	1	1	2	1	2

MedDRA system organ class	T40/A5 (N=143)	T40/A10 (N=129)	T80/A5 (N=146)	T80/A10 (N=142)	T40 (N=130)	T80 (N=135)	A5 (N=140)	A10 (N=129)
Preferred term	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Metabolism and nutrition disorders								
Hypokalemia*	0	0	0	0	0	2	0	0
Musculoskeletal and connective tissue disorders								
Back pain	3	3	1	2	0	2	4	1
Muscle spasms	0	1	0	2	2	0	1	1
Myalgia	0	1	0	1	0	2	2	0
Nervous system disorders								
Dizziness	5	2	4	1	1	1	3	0

T = Telmisartan 40 or 80 mg
A = amlodipine 5 or 10 mg
* Coincidental

Common Clinical Trial Adverse Drug Reactions- telmisartan and amlodipine combination therapy (> 1%)

General Disorders: edema peripheral

Nervous System Disorders: dizziness

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (<1%) for telmisartan and amlodipine combination therapy

Blood and the Lymphatic System Disorders: anemia, eosinophilia, thrombocytopenia

Cardiac Disorders: bradycardia, palpitations, tachycardia

Ear and Labyrinth Disorders: vertigo

Eye Disorders: visual impairment

Gastrointestinal Disorders: abdominal pain, diarrhea, vomiting, nausea, gingival hypertrophy, dyspepsia, dry mouth, flatulence, abdominal discomfort

General Disorders: asthenia (weakness), chest pain, fatigue, edema, malaise, influenza like illness

Hepato-Biliary Disorders: hepatic function abnormal, liver disorder

Immune System Disorders: hypersensitivity, anaphylactic reaction

Infections and Infestations: cystitis, sepsis including fatal outcome, urinary tract infections, upper respiratory tract infections

Investigations: hepatic enzyme increased, blood uric acid increased, hemoglobin decreased, blood creatinine increased, blood creatinine phosphokinase (CPK) increased

Metabolism and Nutrition Disorders: hyperkalemia, hypoglycemia (in diabetic patients)

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle spasms (cramps in leg), myalgia, pain in extremity (leg pain), tendon pain (tendinitis like symptoms)

Nervous System Disorders: syncope (faint), somnolence, migraine, headache, neuropathy peripheral, paraesthesia, hypoaesthesia, dysgeusia, tremor

Psychiatric disorders: depression, anxiety, insomnia

Renal and Urinary Disorders: nocturia, renal impairment (including acute kidney injury)

Reproductive System and Breast Disorders: erectile dysfunction,

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea

Skin and Subcutaneous Tissue Disorders: eczema, erythema, rash, pruritus, drug eruption, toxic skin eruption, hyperhidrosis, urticaria, angioedema

Vascular Disorders: hypotension, orthostatic hypotension, flushing

Less Common Clinical Trial Adverse Drug Reactions (<1%) for Telmisartan

The following adverse reactions may be expected based on experience with telmisartan as monocomponent, but not yet observed with this fixed dose combination:

Body as a Whole: abdomen enlarged, allergy, cyst nos, fall, fever, rigors.

Cardiovascular Disorders, General: hypotension, hypotension-postural, leg edema.

Central & Peripheral Nervous System Disorder: hypertonia, migraine-aggravated, muscle contraction-involuntary.

Gastrointestinal System Disorders: anorexia, appetite increased, gastrointestinal disorder nos, gastroenteritis, gastroesophageal reflux, melena, mouth dry.

Heart Rate & Rhythm Disorders: arrhythmia.

Metabolic & Nutritional Disorders: diabetes mellitus, hypokalaemia.

Musculoskeletal System Disorders: arthritis, arthritis aggravated, arthrosis, bursitis, fascitis plantar.

Myo Endo Pericardial & Valve Disorders: myocardial infarction.

Psychiatric Disorders: nervousness.

Reproductive Disorders, Female: vaginitis.

Resistance Mechanism Disorders: abscess, infection, bacterial, moniliasis genital, otitis media.

Respiratory System Disorders: bronchospasm, epistaxis, pneumonia, bronchitis.

Skin & Appendage Disorders: skin dry.

Urinary System Disorders: Dysuria, hematuria.

Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.

Vision Disorders: vision abnormal.

Less Common Clinical Trial Adverse Drug Reactions (<1%) for Amlodipine

The following adverse reactions may be expected based on experience with amlodipine, but not yet observed with this fixed dose combination:

Autonomic Nervous System : dry mouth, hyperhidrosis

Cardiovascular: myocardial infarction, arrhythmia (including ventricular tachycardia and atrial fibrillation), hypotension, peripheral ischemia, syncope, postural dizziness, postural hypotension, vasculitis, chest pain

Central and Peripheral Nervous System: hypaoesthesia/paraesthesia, neuropathy peripheral, tremor, vertigo

Gastrointestinal: anorexia, change of bowel habits, constipation, dysphagia, vomiting, gingival hyperplasia, dyspepsia

General: allergic reaction, asthenia+, back pain, pain, weight increased/decreased, rigors, hot flushes, malaise

Hemopoietic: leukopenia, purapura, thrombocytopenia

Metabolism and Nutritional: hyperglycemia, thirst

Musculoskeletal System: arthralgia, arthrosis, myalgia, muscle cramps

Psychiatric: sexual dysfunction (male+ and female), insomnia, mood altered, nervousness, depression, abnormal dreams, anxiety, depersonalization

Reproductive System and Breast Disorders: gynecomastia, erectile dysfunction

Respiratory System: dyspnoea, epistaxis

Skin and Appendages: pruritus, erythema multiforme, rash erythematous, rash maculopapular

Special Senses: conjunctivitis, diplopia, eye pain, visual impairment, tinnitus

Urinary System: pollakiuria, micronutrition disorder, nocturia

+These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤ 0.1% of patients: cardiac failure, skin discoloration*, urticaria*, skin dryness, Stevens-Johnson syndrome, alopecia*, twitching, ataxia, hypertonia*, migraine, apathy, amnesia, gastritis*, pancreatitis*, increased appetite, coughing*, rhinitis*, parosmia, taste perversion*, and xerophthalmia.

* these events were observed in marketing experience as well.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In placebo-controlled clinical trials involving 1041 patients treated with MICARDIS monotherapy, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS.

Creatinine, Blood Urea Nitrogen:

Increases in BUN (>11.2 mg/dl) and creatinine (>0.5 mg/dl) were observed in 1.5% and 0.6% of MICARDIS-treated patients; the corresponding incidence was 0.3% each for placebo-treated patients. These increases occurred primarily with MICARDIS in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Hemoglobin, Hemotocrit:

Clinically significant changes in hemoglobin and hematocrit (<10g/dl and <30%, respectively) were rarely observed with MICARDIS treatment and did not differ from rates in placebo-treated patients. No patients discontinued therapy due to anemia.

Serum Uric Acid:

An increase in serum uric acid (>2.7 mg/dl) was reported in 1.7% of patients treated with MICARDIS and in 0.0% of patients treated with placebo. Clinically significant hyperuricemia (>10mEq/L) was observed in 2.3% of patients with MICARDIS, with 0.4% reported in patients at baseline. Increases in serum uric acid were primarily observed in patients who received MICARDIS in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia.

Liver Function Tests:

Clinically significant elevations in AST and ALT (>3 times the upper limit of normal) occurred in 0.1% and 0.5%, respectively of patients treated with MICARDIS compared to 0.8% and 1.7% of patients receiving placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Serum Potassium:

Marked laboratory changes in serum potassium (>+/- 1.4 mEq/L) occurred rarely and with a lower frequency in MICARDIS-treated patients (0.3%, 0.1%, respectively) than in placebo patients (0.6%, 0.3%, respectively). Clinically significant changes in potassium (that exceeded 3 mEq/L) were found in 0.6% of MICARDIS-treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.

Cholesterol:

In placebo-controlled trials, marked increases in serum cholesterol were reported in a total of 6 telmisartan-treated patients (0.4%) and no placebo patients. Two of these patients were followed over time, in both cases cholesterol values reverted to baseline levels.

Serum elevations in cholesterol were reported as adverse events in 11 of 3445 patients (0.3%) in all clinical trials. There were no reported cases of hypercholesterolemia in telmisartan-treated patients in placebo-controlled trials.

8.5 Post-Market Adverse Reactions

Post-market adverse drug reactions are listed below for the respective monotherapies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Telmisartan

Since the introduction of telmisartan in the market, cases of anxiety, dizziness, vision trouble, vertigo, abdominal distension, abdominal pain, retching, hyperhidrosis, arthralgia, myalgia, muscle spasm, back

pain, asthenia, pain in extremity, fatigue, chest pain, blood creatinine increased, erythema, pruritus, syncope/faint, insomnia, depression, abdominal discomfort, vomiting, hypotension (including orthostatic hypotension), bradycardia, tachycardia, abnormal hepatic function/liver disorder, renal impairment including acute kidney injury, hyperkalemia, dyspnoea, anaemia, eosinophilia, thrombocytopenia, hyponatraemia and weakness have been reported. The frequency of these effects is unknown. As with other angiotensin II blockers, rare cases of angioedema (including fatal outcome), pruritus, rash and urticaria have been reported.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

In addition, since the introduction of telmisartan in the market, cases with increased blood creatinine phosphokinase (CPK) have been reported.

Amlodipine

In post marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Post marketing reporting has also revealed cases of extrapyramidal disorders induced by amlodipine.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of angiotensin receptor blockers (ARBs) –including the telmisartan component of RIVA-TELMISARTAN/AMLODIPINE- with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m2) is contraindicated (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs).
- Concomitant treatment of amlodipine with strong inhibitors of CYP 3A4 (see 9.4 Drug-Drug Interactions).

9.2 Drug Interactions Overview

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

No new drug interaction studies have been performed with telmisartan/amlodipine besylate and other medicinal products.

Amlodipine

Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.

9.3 Drug-Behavioural Interactions

Interactions with lifestyle have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Coadministration of telmisartan also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, or hydrochlorothiazide.

Table 4: Established or Potential Drug-Drug Interactions in telmisartan + amlodipine

Telmisartan + Amlodipine	Source of Evidence	Effect	Clinical comment
Other antihypertensive agents	T	The blood pressure lowering effect of telmisartan/amlodipine besylate can be increased by concomitant use of other antihypertensive medicinal products.	To be taken into account with concomitant use
Agents with blood pressure lowering potential	T	Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan/amlodipine besylate, e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.	To be taken into account with concomitant use
Corticosteroids (systemic route)	T	Reduction of the antihypertensive effect.	To be taken into account with concomitant use

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Table 5: Established or Potential Drug-Drug Interactions in telmisartan

Telmisartan	Source of Evidence	Effect	Clinical comment
Agents increasing serum potassium	T	Telmisartan component oftelmisartan/amlodipine besylate reduces the production of aldosterone.	Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that telmisartan may have on serum potassium.

Telmisartan	Source of Evidence	Effect	Clinical comment
Digoxin	CT	When telmisartan was co-administered with digoxin, mean increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed.	It is recommended that digoxin levels be monitored with appropriate dose adjustments when initiating, adjusting or discontinuing RIVA-TELMISARTAN/AMLODIPINE, to maintain appropriate plasma digoxin concentrations.
Diuretics	Hydrochlor-othiazide (CT)	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with telmisartan.	The possibility of symptomatic hypotension with the use of telmisartan can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of telmisartan. No drug interaction of clinical significance has been identified with thiazide diuretics.
Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs	T	The treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	Dual Blockade of the renin-angiotensin system (RAS) with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS).
Lithium salts	CT	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor blockers including telmisartan.	Serum lithium level monitoring is advisable during concomitant use.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	Combinations of angiotensin-II blockers (telmisartan) and NSAIDs (including ASA and COX-2 inhibitors) might have an increased risk for acute renal failure and hyperkalemia. NSAIDs (including ASA and COX-2 inhibitors) and angiotensin-II receptor blockers exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment, this may lead to acute renal failure.	Blood pressure and kidney function should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure. Monitoring of renal function at the beginning and during the course of the treatment should be recommended. Co-administration of telmisartan did not result in a clinically significant interaction with ibuprofen.

Telmisartan	Source of Evidence	Effect	Clinical comment
Ramipril	CT	In one study, the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat.	The clinical relevance of this observation is not known.
Warfarin	CT	Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration.	The decrease in the mean warfarin trough plasma concentration did not result in a change in the International Normalized Ratio (INR).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Table 6: Established or Potential Drug-Drug Interactions in amlodipine

Amlodipine	Source of Evidence	Effect	Clinical comment
Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, azole antifungals, quinidine, terfenadine and warfarin)	CT T	Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers (18 to 43 years of age) increased the systemic exposure of amlodipine by 22%.	Concomitant use requiring caution. Clinical monitoring and dose adjustment may be required. These pharmacokinetic changes may be more pronounced in the elderly.
Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir)	T	May significantly increase the plasma concentrations of amlodipine to a greater extent than diltiazem.	RIVA-TELMISARTAN/AMLODIPINE should be used with caution together with CYP3A4 inhibitors and monitoring of therapy is required. Appropriate dosage adjustment of RIVA-TELMISARTAN/AMLODIPINE may be necessary when used with CYP3A4 inhibitors. Patients should be advised to seek medical attention if they experience edema or swelling of the lower extremities; sudden, unexplained weight gain; difficulty breathing; chest pain or tightness; or hypotension as indicated by dizziness, fainting, or orthostasis. Avoid concomitant administration of RIVA-TELMISARTAN/AMLODIPINE with strong CYP3A4 inhibitors. (see 7 WARNINGS AND PRECAUTIONS)
Clarithromycin	CT	In elderly patients (>65 years of age), concomitant use of amlodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury.	

Amlodipine	Source of Evidence	Effect	Clinical comment
CYP3A4 inducers (e.g., phenobarbital, phenytoin, rifampin)	T	There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects.	Concomitant use requiring caution RIVA-TELMISARTAN/AMLODIPINE should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Blood pressure should be monitored and dose adjustment considered both during and after concomitant administration, particularly with strong CYP3A4 inducers (e.g., rifampicin, hypericum perforatum). Hence, monitoring of therapy is required.
Cimetidine, warfarin, digoxin	CT	Not Applicable.	Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated that cimetidine did not alter the pharmacokinetics of amlodipine and that amlodipine did not change warfarin-induced prothrombin response time nor did it change serum digoxin levels or digoxin renal clearance in normal volunteers.
Antacids	CT	Not Applicable.	Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.
Beta-blockers	T	Blood pressure lowering effect of beta-blockers may be increased by amlodipine.	When beta-adrenergic receptor blocking drugs are administered concomitantly with RIVA-TELMISARTAN/AMLODIPINE, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.
Sildenafil	CT	A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on AUC or Cmax of amlodipine. When sildenafil (100 mg) was co-administered with amlodipine, 5 or 10 mg in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.	Monitoring blood pressure is recommended and antihypertensive therapy may be adjusted.

Amlodipine	Source of Evidence	Effect	Clinical comment
Atorvastatin	CT	In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no clinical significant change in the AUC (average of 18% increase) or Cmax or Tmax of atorvastatin.	Close monitoring is required.
Simvastatin	CT	Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80 mg resulted in a 77% increase in simvastatin exposure compared to simvastatin exposure when used alone.	Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
Immunosuppressants Cyclosporine Tacrolimus	 CT C	Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients. A prospective study in hypertensive renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine. There is a risk of increased tacrolimus blood levels when co-administered with amlodipine.	Frequent monitoring of trough blood levels of cyclosporine and tacrolimus and dose adjustment when appropriate is recommended.
Mechanistic Target of Rapamycin (mTOR) Inhibitors	CT T	mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.	Caution is advised
Dantrolene	T	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene.	Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system (e.g., benzodiazepines, flecainide, imipramine, propafenone, theophylline).

9.5 Drug-Food Interactions

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) 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 (see 10.3 Pharmacokinetics, Distribution).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

Telmisartan/Amlodipine fixed-dose combination:

A bioavailability study was conducted to determine the effect of food on the pharmacokinetics of telmisartan and amlodipine when they are combined together in a fixed dose combination tablet. The bioavailability and pharmacokinetics of the highest dose strength of the fixed dose combination to be marketed (T80/A10) were investigated in the fasting state in 39 subjects (20 men and 19 women) and then after administration of a standardised high fat, high caloric meal, for the purpose of comparison. There was an approximately 25% reduction in the concentration of telmisartan after a high-fat meal, compared to the concentration in the fasting state. The telmisartan concentration reduction was greater in women than men. Under the same conditions, the amlodipine concentration was minimally increased after the high-fat meal. The terminal half-lives of both telmisartan and amlodipine were unchanged, irrespective of the fasting or high-fat fed state. The results of this study are more conclusive for amlodipine than telmisartan, as the pre-specified confidence interval for the assessment of telmisartan bioavailability was exceeded. Therefore, a lack of food effect on pharmacokinetics can be concluded for amlodipine but not for telmisartan.

9.6 Drug-Herb Interactions

St-John's Wort is an inducer of CYP3A4. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects. Amlodipine should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Telmisartan

Telmisartan is an orally active angiotensin II AT_1 receptor blocker. By selectively blocking the binding of angiotensin II to the AT_1 receptors telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptors and has essentially no affinity for the AT_2 receptors. AT_2 receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. In vitro binding studies indicate that telmisartan has no relevant affinity for other receptors nor does it inhibit human plasma renin.

Telmisartan does not inhibit angiotensin converting enzyme, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other

hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostasis.

In hypertensive patients blockade of angiotensin II AT_1 receptors results in two to three fold increase in plasma renin and angiotensin II plasma concentrations. Long term effects of increased AT_2 receptor stimulation by angiotensin II are unknown.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound and its kinetic interaction with the calcium channel receptor is characterized by the gradual association and dissociation with the receptor binding site.

10.2 Pharmacodynamics

Pharmacotherapeutic group: angiotensin II blockers, plain (telmisartan), combinations with dihydropyridine derivatives (amlodipine), ATC Code: C09DB04.

Telmisartan/amlodipine besylate combines two antihypertensive compounds with different mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor blocker, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Telmisartan/amlodipine besylate once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Diabetic Patients: Multiple exploratory post hoc analyses were carried out on the three cardiovascular (CV) outcome trials (ONTARGET, TRANSCEND and PRoFESS). In TRANSCEND and PRoFESS, an increased risk of unexpected CV death was seen with telmisartan versus placebo in diabetics without previously diagnosed coronary artery disease (CAD) but not in those with a documented history of CAD. No such increased risk was demonstrated in ONTARGET for telmisartan versus ramipril in diabetes patients without previously diagnosed CAD.

These findings in diabetics with added cardiovascular risk, could be related to a pre-existing but asymptomatic or silent CAD. Diabetics with undiagnosed and therefore untreated CAD may be at increased risk when lowering blood pressure too far, e.g. when initiating antihypertensive therapy, due to a further reduction of perfusion in an already narrowed coronary artery.

Telmisartan

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak with approximately 40% inhibition persisting for 24 hours.

In hypertensive patients with normal renal function, no clinically significant effects on renal plasma flow, filtration fraction, or glomerular filtration rate were observed. In multiple dose studies in hypertensive patients, telmisartan had no adverse effect on renal function as measured by serum creatinine or blood urea nitrogen.

The antihypertensive effects of telmisartan were demonstrated in six placebo-controlled clinical trials, in a total of 1773 patients, 1031 of whom were treated with telmisartan. Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose and there was a gradual increase in the antihypertensive effect during continued treatment for up to 12 weeks, with most of the increase occurring during the first month. Onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. The antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. The magnitude of blood pressure reduction from baseline, after placebo subtraction, was on average (SBP/DBP) -11.3/-7.3 mmHg for telmisartan 40 mg once daily, and -13.7/-8.1 mmHg for telmisartan 80 mg once daily. Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returned to baseline values over a period of several days. During long term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year.

For those patients treated with telmisartan 80 mg once daily who required additional blood pressure reduction, addition of a low dose of hydrochlorothiazide (12.5 mg) resulted in incremental blood pressure reductions of -9.4/-7.0 mmHg.

The antihypertensive effect of once-daily telmisartan (40-80 mg) was similar to that of once-daily amlodipine (5-10 mg), atenolol (50-100 mg), enalapril (5-20 mg) and lisinopril (10-40 mg).

There was essentially no change in heart rate in telmisartan-treated patients in controlled trials.

In clinical trials with post-dose in-clinic monitoring no excessive blood pressure lowering peak effect was observed even after the first dose, and the incidence of symptomatic orthostasis was very low (0.04%). With automated ambulatory blood pressure monitoring, the 24-hour trough-to-peak ratio for telmisartan was determined to be at least 80% for both systolic and diastolic blood pressure.

The antihypertensive effect of telmisartan is not influenced by patient age, weight or body mass index.

Amlodipine

Hemodynamics: Following administration of recommended doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by any significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration (5 and 10 mg once daily), antihypertensive effectiveness is maintained throughout the 24 hours dose interval with minimal peak to trough differences in plasma concentration. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine.

Negative inotropic effects have not been observed when amlodipine was administered at the recommended doses to man, but has been demonstrated in animal models.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals, or man. In clinical studies in which amlodipine was administered in

combination with beta-blockers to patients with hypertension, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

10.3 Pharmacokinetics

Table 7: Summary of telmisartan pharmacokinetic parameters (arithmetic means, CV%) in healthy volunteers, male, range: 20-47 years

Administration	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng h/mL)	CL (mL/min)	Vz/f (L)
40 mg, single dose, tablet	32.1 (44.9)	1.75 (27.9)	19.6 (36.8)	360 (61.5)	2670 (61.4)	4490 (84.9)

Administration	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng h/mL)	CL (mL/min)	Vz/f (L)
80 mg, single dose, tablet	245 (69.4)	1.00 (0.5-2.00)	27.29 (37.28)	1280 (91.71)	1766 (68.68)	3890 (95.49)

* Median

Pharmacokinetics of the co-administration of telmisartan and amlodipine as a free combination, were evaluated in two studies:

In one study pharmacokinetics of repeated oral doses of 10 mg amlodipine daily and of 10 mg amlodipine and 120 mg telmisartan daily were evaluated in a cross-over randomised open label study in healthy subjects. For this study, the reference treatment was amlodipine, 10 mg a day. Amlodipine 10 mg, or amlodipine 10 mg administered with telmisartan monotherapy were administered for 9 days, with a 13 to 15 day washout period between the two treatment periods.

The geometric mean ratios and 90% confidence intervals of $AUC_{\tau,ss}$ and $C_{max,ss}$ for amlodipine with (T) and without telmisartan (R) were as follows:

Parameter	T/R ratio	90% CI	
N=36		Lower limit	Upper limit
	[%]	[%]	[%]
$AUC_{\tau,ss}$	106	98	116
$C_{max,ss}$	106	97	114

The confidence interval for the $AUC_{\tau,ss}$ ratio was within the prespecified bioequivalence limits of 80 – 125%, and the confidence interval for the $C_{max,ss}$ ratio was within the prespecified bioequivalence limits of 80-125%. Based on the primary endpoints, $AUC_{\tau,ss}$ and $C_{max,ss}$, amlodipine bioequivalence was demonstrated and it was concluded that there was no drug interaction between amlodipine and telmisartan.

Pharmacokinetics of repeated oral doses of telmisartan 80 mg at steady state alone and in combination with repeated oral doses of amlodipine 10 mg were studied at steady state in a two-way crossover, open, randomised design study. The reference treatment was telmisartan, 80 mg a day, administered alone, for 9 days. The test treatment was telmisartan, 80 mg a day, co-administered with amlodipine, 10 mg a day, for 9 additional days. There was a 15 day washout between test periods.

The geometric mean ratios and 90% confidence intervals of $AUC_{\tau,ss}$ and $C_{max,ss}$ for telmisartan with (T) and without amlodipine (R) were as follows:

Parameter	T/R ratio	90% CI	
N=36		Lower limit	Upper limit
	[%]	[%]	[%]
AUCτ,ss	98	89	107
$C_{max,ss}$	89	76	104

The confidence interval for the $AUC_{\tau,ss}$ ratio was within the prespecified bioequivalence limits of 80 – 125%, and the confidence interval for the $C_{max,ss}$ ratio was within the prespecified bioequivalence limits of 75 – 133%. The latter were defined to be wider than for $AUC_{\tau,ss}$ because telmisartan is known to be a highly variable drug with respect to intrasubject variability of C_{max}, but also has a wide therapeutic window. It was concluded that there is no clinically significant change in systemic exposure to telmisartan 80 mg on coadministration of amlodipine 10 mg after dosing both medications to steady state and that there is no relevant drug-drug interaction with regard to the effect of amlodipine on telmisartan.

Pharmacokinetics of the Fixed Dose Combination

The rate and extent of absorption of telmisartan/amlodipine besylate are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetic of the Single Components

Absorption

Telmisartan: Following oral administration, telmisartan is well absorbed, with a mean absolute bioavailability of about 50%. Mean peak concentrations of telmisartan are reached in 0.5-1 hour after dosing.

The pharmacokinetic profile is characterized by greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses greater than 40 mg. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours, and does not accumulate in plasma upon repeated once-daily dosing.

Amlodipine: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution:

Telmisartan: Telmisartan is >99.5% bound to plasma protein, mainly albumin and alpha1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with therapeutic doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding sites.

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from approximately 6% (40 mg) to approximately 19% (160 mg), and the reduction in Cmax varies from approximately 26% (40 mg) to 56% (160 mg). However, three hours after administration, plasma concentrations are similar whether telmisartan is taken with or without food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy (see 9 DRUG INTERACTIONS, 9.5 Drug-Food Interactions).

Amlodipine: The volume of distribution of amlodipine is approximately 21 L/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism:

Telmisartan: Telmisartan is metabolized by conjugation with glucuronic acid to form an acylglucuronide of telmisartan. This glucuronide is the only metabolite which has been identified in human plasma and urine. Following both oral dosing and intravenous administration of radiolabeled telmisartan, the parent compound represented approximately 85% and the glucuronide approximately 11% of total radioactivity in plasma. No pharmacological activity has been shown for the glucuronide conjugate.

The CYP 450 isoenzymes are not responsible for telmisartan metabolism.

Amlodipine: Amlodipine is extensively (approximately 90%) metabolised by the liver to inactive metabolites.

Elimination

Telmisartan: Total plasma clearance of telmisartan is > 800 mL/min. Half-life and total clearance appear to be independent of dose. Biliary excretion is the main route of elimination of telmisartan and its metabolite. Following intravenous and oral administration of C14 labelled telmisartan 0.91% and 0.49% of administered dose were found in the urine as glucuronide, respectively. Most of the oral and intravenous dose, >97%, was excreted in feces as the parent compound.

Amlodipine: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Special Populations and Conditions

- **Pediatrics (age below 18 years):** Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.
- **Geriatrics**

  Telmisartan: The pharmacokinetics of telmisartan do not differ between the geriatric and those younger than 65 years (see 4 DOSAGE AND ADMINISTRATION).

  Amlodipine: Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) of about 60% and elimination half-life.
- **Sex:** Plasma concentrations of telmisartan are generally 2-3 fold higher in females than in males. No dosage adjustment is necessary. Women have a lower telmisartan clearance and have a greater systolic blood pressure response at trough than men.

- **Genetic Polymorphism:** *Telmisartan:* No studies were conducted to evaluate the influence of genetic polymorphisms on the pharmacokinetics or pharmacodynamics of telmisartan.
- **Ethnic Origin:** The effectiveness of telmisartan/amlodipine besylate in black patients (usually a low-renin population) was not significantly different than observed in other patients.

  However, in the Pivotal Study, since the majority of patients within each treatment group were non-black comparison across race is difficult. Baseline values were generally similar for the two race categories. In the combination treatment groups, diastolic blood pressure reductions observed with the combination therapy were numerically smaller in blacks than non-blacks, with the exception of T40+A10 treatment group. This finding is not unexpected in this population that is generally recognized as having low renin levels. However, based on the achieved blood pressure reductions, the T+A combination can be considered effective in black patients as well.
- **Hepatic Insufficiency:** *Telmisartan:* In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. The maximum dose in these patients is 40 mg (see 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION).

  Amlodipine: Patients with mid-moderate hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. This was presumably due to a reduction in clearance of amlodipine as the terminal elimination half-life was prolonged from 34 hrs in young normal subjects to 56 hrs in the elderly patients with hepatic insufficiency. Dosage requirement have not been established in patients with impaired hepatic function. When amlodipine is used in these patients the dosage should be carefully and gradually adjusted depending on patients tolerance and response. A lower starting dose should be considered (see 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION).
- **Renal Insufficiency:** *Telmisartan:* Renal excretion of telmisartan is negligible. No dosage adjustment is necessary in patients with renal insufficiency. In patients on haemodialysis both C_{max} and AUC of telmisartan were markedly reduced as compared to healthy volunteers. Telmisartan is not removed by haemodialysis (see 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION).

  Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. The recommended initial dose is 5 mg once daily. If required, increasing the dose should be done gradually and with caution (see 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store at 15-30°C.

Store in the original package in order to protect from light and moisture.

Due to the hygroscopic property of the tablets, they should be taken out of the sealed blister shortly before administration.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance – Telmisartan

Proper name: telmisartan

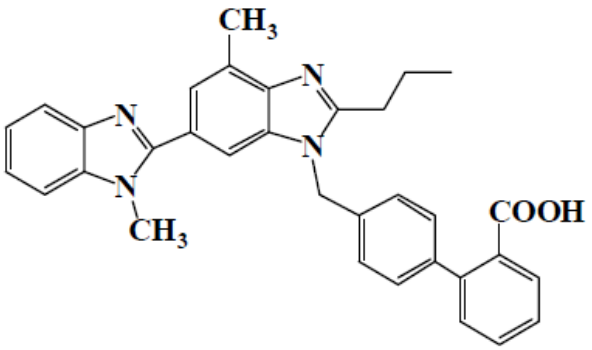
Chemical name: 4'-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2yl)-2-propyl-1H-benzimidazol-1-yl]methyl][1,1-biphenyl-2-carboxylic acid.

4'-[(1,4'-Dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl][1,1'-biphenyl]-2-carboxylic acid.

4'-[[4-methyl-6-(1-methyl-2-benzimidazolyl]-2-propyl-1-benzimidazolyl]methyl]-2-biphenyl carboxylic acid.

Molecular formula and molecular mass: $C_{33}H_{30}N_4O_2$, 514.6

Structural formula:



Physicochemical properties:

Description:

Telmisartan is a white or slightly yellowish, crystalline powder. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except HCl) and soluble in strong base.

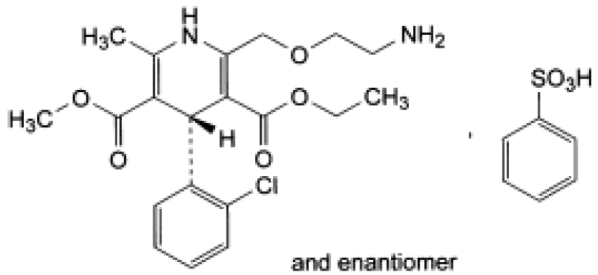
Polymorphism:

Telmisartan produced by the manufacturer is crystalline form-A polymorph.

Drug Substance – Amlodipine

Proper name:	amlodipine besylate
Chemical name:	3-Ethyl 5-methyl (4RS)-2[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate 3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy) methyl]- 4-(ochlorophenyl)-1,4 -dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzenesulphonate 3,5-pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate
Molecular formula and molecular mass:	$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$, 567.1

Structural formula:



Physicochemical properties:

Physical Form:

Amlodipine besylate is a white or almost white powder.

Solubility:

Amlodipine besylate is freely soluble in methanol, sparingly soluble in alcohol and slightly soluble in water and 2-propanol.

pKa = 8.14

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

INDICATION 1

Treatment of mild to moderate essential hypertension for whom combination therapy with telmisartan and amlodipine is appropriate.

Table 9: Summary of patient demographics for clinical trials in treatment of mild to moderate essential hypertension for whom combination therapy is appropriate

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
1235-0001	randomised, double-blind, placebo-controlled, parallel group factorial study	oral	1461	53.1 years	50.4 % male, 49.6% female

Study # 1235-0001

In a single 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study, 1461 patients with mean seated diastolic blood pressure ≥95 and <119 mmHg in which subjects were treated with combination doses of telmisartan/amlodipine besylate (telmisartan [T] and amlodipine [A] or its monotherapy components, including T/A doses of T40+A5, T40+A10, T80+A5, and T80+A10 mg), the combination treatments showed significant dose related reductions in systolic and diastolic blood pressure from baseline values. Limited data was available in subjects with severe hypertension.

Study demographics and trial design

Overall, 737 (50.4%) patients were male; 1160 (79.4%) Caucasian, 237 (16.2%) black, and 64 (4.4%) Asian. The overall mean age was 53.1 years with 205 (14.0%) of patients ≥65 years old. The majority of patients had a duration of hypertension >5 years [<1 year: 206 (14.1%), 1-5 years: 446 (30.5%), >5 years: 806 (55.2%), missing: 3 (0.2%)] with 307 (21.0%) not being previously prescribed antihypertensive medication, 531 (36.3%) previously treated with antihypertensive monotherapy, and 623 (42.6%) previously treated with combination therapy of ≥2 antihypertensive medications. The overall mean body mass index (BMI) was 31.3 kg/m2 with 238 (16.3%) of patients being diabetic and 12 (0.8%) with renal impairment.

Study Results

The primary endpoint of this study was the change from baseline in the in-clinic seated trough cuff diastolic blood pressure (DBP) after 8 weeks of treatment.

Treatment with each combination dose of telmisartan/amlodipine besylate resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components. The telmisartan/amlodipine combinations showed dose-related reductions in systolic/diastolic blood pressure (SBP/DBP) across the therapeutic dose range versus telmisartan monotherapy or amlodipine monotherapy:

Table 10: The Effect of Telmisartan/Amlodipine Combination in Reduction of Systolic/Diastolic Blood Pressure versus Telmisartan Monotherapy or Amlodipine Monotherapy

	Telmisartan/Amlodipine Dose							
	40/5 mg*	**80/5 mg***	**40/10 mg***	**80/10 mg***	**40/0 mg**	**80/0 mg**	**0/5 mg**	**0/10 mg**
Systolic BP (mmHg)	-21.8	-22.1	-24.7	-26.4	-14.6	-14.3	-15.4	-20.7
Diastolic BP (mmHg)	-16.5	-18.2	-20.2	-20.1	-13.4	-14.0	-13.4	-17.1

* $p < 0.05$ versus telmisartan monotherapy or amlodipine monotherapy

The greatest overall reduction in blood pressure was observed with telmisartan 80 mg plus amlodipine 10 mg combination (mean reduction in SBP/DBP; -26.4/-20.1 mmHg; $p < 0.05$ vs. both monotherapies).

The proportions of patients reaching DBP <90 mmHg with a telmisartan/amlodipine combination were:

71.6% with 40/5 mg,
74.8% with 80/5 mg,
82.1% with 40/10 mg, and
85.3% with 80/10 mg.

A subset of 1050 patients in the factorial design study had moderate to severe hypertension (DBP ≥100 mmHg). In these patients, the observed mean changes in SBP/DBP with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40/5 mg; -22.5/-19.1 mmHg with 80/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg). Additionally, combination therapy showed notably lower edema rates (1.4% with 40/5 mg; 0.5% with 80/5 mg; 17.6% with amlodipine 10 mg).

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic SBP and DBP reductions consistently over the entire 24-hours dosing period.

There was a significant difference in the change from baseline in seated trough cuff DBP among dosages of telmisartan (T: $p<0.0001$) and among dosages of amlodipine (A: $p<0.0001$), with no significant ($p=0.1777$) T-by-A interaction when excluding placebo patients, concluding that combination therapy with T+A is superior to either monotherapy in lowering seated trough cuff DBP in patients with Stage I or II hypertension.

The antihypertensive effect of telmisartan/amlodipine besylate was similar irrespective of age and gender, and was similar in patients with and without diabetes.

RIVA-TELMISARTAN/AMLODIPINE has not been studied in any patient population other than essential hypertension.

14.2 Comparative Bioavailability Studies

Bioequivalence was demonstrated between telmisartan/amlodipine besylate fixed dose combination tablets and the co-administration of the mono-component Canadian products MICARDIS (telmisartan) and NORVASC (amlodipine besylate) tablets based on comparative bioavailability data from open label, single-dose, two-period crossover studies conducted in healthy volunteers, under fasted conditions. The comparative bioavailability data is summarized below:

Table 11: Results for Telmisartan

Telmisartan (1 x 80 mg as either telmisartan/amlodipine besylate or MICARDIS) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng.h/mL)	1115 (79%) 922	1128 (88%) 898	103	98 - 108
C_{max} (ng/mL)	281 (110%) 205	278 (121%) 188	109	98 - 120

* Telmisartan/amlodipine besylate 80/10 mg combination tablet, by Boehringer Ingelheim (Canada) Ltd/Ltee.
† MICARDIS (telmisartan) 80 mg tablet, by Boehringer Ingelheim (Canada) Ltd/Ltee.

Table 12: Results for Amlodipine

Amlodipine (1 x 10 mg as either telmisartan/amlodipine besylate or NORVASC) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference€**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng.h/mL)	263.4 (23%) 255	275.6 (24%) 269	95	92 - 98
C_{max} (ng/mL)	6.81 (20%) 6.6	7.25 (22%) 7.0	94	91 - 98

* Telmisartan/amlodipine besylate 80/10 mg combination tablet, by Boehringer Ingelheim (Canada) Ltd/Ltee.
€ NORVASC (amlodipine besylate) 10 mg tablet, by Pfizer Canada Inc.

Fasting Study

A randomized, double blind, two-way, single dose crossover, comparative oral bioavailability study of PrRIVA-TELMISARTAN/AMLIDIPINE 80 mg/10 mg tablets (Laboratoire Riva Inc.) and PrTWYNSTA® 80 mg/10 mg tablets (Boehringer Ingelheim (Canada) Ltd.) was conducted in 26 healthy, adult, Caucasian male (12) and female (14) subjects under fasting conditions. Comparative bioavailability data from all 26 subjects were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Telmisartan (1 x 80 mg telmisartan/10 mg amlodipine) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-72h} (ng·h/mL)	1641.37 1924.95 (71.81)	1747.30 2078.97 (72.65)	93.9	87.6 – 100.7
C_{max} (ng/mL)	238.44 318.83 (85.11)	250.01 327.14 (72.03)	95.4	80.5 – 112.9
T_{max}[3] (h)	1.13 (0.50 – 2.50)	1.25 (0.67 – 3.00)		

[1] RIVA-AMLODIPINE/TELMISARTAN (telmisartan and amlodipine as amlodipine besylate) Tablets, 80/10 mg (Laboratoire RIVA Inc.)
[2] TWYNSTA (telmisartan and amlodipine as amlodipine besylate) Tablets, 80/10 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the median (range) only
Due to the long elimination half-life of telmisartan, AUC_I and $T_{½}$ could not be accurately calculated from the data obtained in this study.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amlodipine (1 x 80 mg telmisartan/10 mg amlodipine) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-72h} (ng·h/mL)	230.52 235.86 (21.64)	233.20 239.56 (24.14)	98.9	95.6 – 102.2
C_{max} (ng/mL)	5.67 5.78 (19.65)	5.84 5.95 (19.92)	97.1	93.6 – 100.8
T_{max}[3] (h)	8.00 (3.00 – 12.00)	8.00 (6.00 – 12.02)		

[1] RIVA-AMLODIPINE/TELMISARTAN (telmisartan and amlodipine as amlodipine besylate) Tablets, 80/10 mg (Laboratoire RIVA Inc.)
[2] TWYNSTA (telmisartan and amlodipine as amlodipine besylate) Tablets, 80/10 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as arithmetic means (CV%) only.
Due to the long elimination half-life of amlodipine, AUC_I and $T_{½}$ could not be accurately calculated from the data obtained in this study.

Fed Study

A randomized, double blind, two-way, single dose crossover, comparative oral bioavailability study of [Pr]RIVA-TELMISARTAN/AMLIDIPINE 80 mg/10 mg tablets (Laboratoire Riva Inc.) and [Pr]TWYNSTA® 80 mg/10 mg tablets (Boehringer Ingelheim (Canada) Ltd.) was conducted in 30 healthy, adult, Asian male subjects under high fat, high calorie fed conditions. Comparative bioavailability data from the 28 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Telmisartan (1 x 80 mg telmisartan/10 mg amlodipine) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-72h} (ng·h/mL)	1422.04 1898.67 (83.40)	1461.86 2018.50 (97.44)	97.3	92.3 – 102.7
C_{max} (ng/mL)	149.53 173.47 (59.03)	145.20 187.95 (89.08)	103.0	93.1 – 114.0
T_{max}[3] (h)	4.50 (1.00 - 6.02)	4.50 (2.00 - 7.00)		

[1] RIVA-AMLODIPINE/TELMISARTAN (telmisartan and amlodipine as amlodipine besylate) Tablets, 80 mg/10 mg (Laboratoire Riva Inc.)
[2] TWYNSTA (telmisartan and amlodipine as amlodipine besylate) Tablets, 80 mg/10 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the median (range) only
Due to the long elimination half-life of telmisartan, AUC_I and $T_{½}$ could not be accurately calculated from the data obtained in this study.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amlodipine (1 x 80 mg telmisartan/10 mg amlodipine) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-72h} (ng·h/mL)	262.32 268.87 (22.4)	265.92 273.36 (23.2)	98.6	94.9 – 102.6
C_{max} (ng/mL)	6.74 6.92 (24.3)	7.00 7.18 (23.3)	96.2	92.8 – 99.7
T_{max}[3] (h)	8.00 (4.00 - 12.00)	8.00 (6.00 - 12.00)		

[1] RIVA-AMLODIPINE/TELMISARTAN (telmisartan and amlodipine as amlodipine besylate) Tablets, 80 mg/10 mg (Laboratoire Riva Inc.)
[2] TWYNSTA (telmisartan and amlodipine as amlodipine besylate) Tablets, 80 mg/10 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the median (range) only
Due to the long elimination half-life of amlodipine, AUC_I and $T_{½}$ could not be accurately calculated from the data obtained in this study

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination.

This has been shown in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested. In this study, no additive or greater than additive adverse effects of amlodipine and telmisartan in combination as well as no change of the toxicity profile with regard to target organs were observed.

With respect to telmisartan/amlodipine (RIVA-TELMISARTAN/AMLODIPINE), separate reproductive toxicity studies assessing the potential effects of telmisartan and amlodipine on male or female fertility when both compounds are given in combination, have not been conducted.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan

General Toxicology:

Acute Toxicity:

In acute oral toxicity studies no deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest oral dose tested. The i.v. LD50 in rats was 150-200 mg/kg in males and 200-250 mg/kg in females.

Chronic Toxicity

Chronic oral toxicity of telmisartan was evaluated in studies following administration of doses ≤ 500 mg/kg for ≤ 26 weeks in rats, and ≤ 1 year in dogs. Chronic intravenous toxicity was evaluated in studies of ≤ 4 weeks at doses ≤ 20 mg/kg in rats and ≤ 50 mg/kg in dogs.

Repeated dose administration of telmisartan resulted in marked and long lasting hypotension, hyperplasia of juxtaglomerular apparatus and lesions of the gastrointestinal tract. Further effects were reduced body weight gain, heart weight and red blood cell indices, increased potassium and AST and ALT, the latter in the absence of morphological evidence of toxicity. No effect doses were not identified for decreased erythroid indices, increased BUN and juxtaglomerular hypertrophy/hyperplasia in rats and dogs.

Gastrointestinal Tract

Gastric and/or duodenal mucosal erosions and ulcers were seen in rats given ≥4 mg/kg orally or ≥2 mg/kg i.v. and in dogs given ≥40 mg/kg orally. Most lesions were small, focal or multifocal in distribution and limited to the mucosa and submucosa. Ulcers and erosions healed rapidly after drug withdrawal.

Urinary Tract and Electrolytes

Hypertrophy of the juxtaglomerular apparatus and increased granularity of renin-producing cells of the juxtaglomerular apparatus, afferent arterioles and interlobular arteries of the kidney were observed in rats at doses of ≥ 1 mg/kg and in dogs at ≥ 5 mg/kg. In rats and dogs subjected to long term treatment with telmisartan, plasma renin activity returned to normal levels after 26 to 52 weeks of treatment. Reversible slight to mild increases in serum potassium levels occurred in rats at oral doses of ≥ 4 mg/kg. In dogs, non-progressive increases in serum potassium levels were noted at 50 and 500 mg/kg in the 52 week oral study. Minimal to mild, reversible increases in blood urea nitrogen and creatinine were evident at oral doses of ≥ 4 mg/kg in rats and ≥ 5 mg/kg in dogs.

Haematology

Slight to mild reversible reductions of red blood cell count, hematocrit, and/or haemoglobin were observed after repeated oral dosing with telmisartan ≥50 mg/kg in the rat and ≥5 mg/kg in the dog.

Carcinogenicity:

The carcinogenic potential of telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg and in rats at 3, 15 and 100 mg/kg. Drug administration did not affect survival time in either study and also tumour mortality was not increased. Incidence and time to appearance of palpable masses showed no treatment influence in mice and rats. No increases were observed in overall tumour incidence, incidence of benign and malignant tumours or tumour multiplicity.

Genotoxicity:

Mutagenicity

Telmisartan was not mutagenic at a concentration range of 10 to 2500 µg/plate in the bacterial reverse mutation assay, with or without metabolic activation. No potential for chromosomal damage was found in the mouse micronucleus test at a dose range of 250 to 1000 mg/kg. No forward mutations at the HPRT locus in V79 cells were induced at a concentration range of 10 to 100 µg/ml, with or without metabolic activation. No chromosomal aberrations were induced in human peripheral lymphocytes in vitro at concentrations ≤ 100 µg/ml without metabolic activation and concentrations ≤ 200 µg/ml with metabolic activation.

Reproductive and Developmental Toxicology:

Reproduction

In studies on fertility and reproductive performance in male and female rats no effect on mating performance, reproductive organs, or fertility in either sex, or on litter parameters was observed with telmisartan doses of 5-100 mg/kg. No teratogenic or embryotoxic potential in rats was observed at doses up to 50 mg/kg administered from day 7 through day 16 of pregnancy. However, at toxic dose levels, non-clinical studies indicated some hazardous potential of telmisartan to fetal development (increased number of late resorptions in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality.

Telmisartan was detectable in the placenta, fetus and amniotic fluid of rats after single oral doses of 1 mg/kg.

Amlodipine

Carcinogenicity:

Carcinogenesis, mutagenesis

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 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*. For the rat, the highest dose was, on a mg/m2 basis, about twice the maximum recommended human dose*.

Mutagenicity studies revealed no drug-related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

Reproductive and Developmental Toxicology:

Reproductive toxicology

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 (approximately

10 and 20 times the maximum recommended human dose based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, 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.

Impairment of fertility

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 ≤ 10 mg amlodipine/kg/day (about 8 times the maximum recommended human dose of 10 mg/day on a mg/m2 basis, for a 50 kg human).

In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

17 SUPPORTING PRODUCT MONOGRAPHS

1. TWYNSTA (Telmisartan / Amlodipine (as Amlodipine Besylate) Tablets, 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg), submission control 287674, Product Monograph, Boehringer Ingelheim (Canada) Ltd. NOV 28, 2024

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] RIVA-TELMISARTAN/AMLODIPINE

Telmisartan/Amlodipine (as Amlodipine Besylate) Tablets, Mfr. Std.

Read this carefully before you start taking **RIVA-TELMISARTAN/AMLODIPINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RIVA-TELMISARTAN/AMLODIPINE**.

Serious Warnings and Precautions

- **RIVA-TELMISARTAN/AMLODIPINE should not be used during pregnancy. Taking RIVA-TELMISARTAN/AMLODIPINE during pregnancy can cause injury or even death to your baby.**
- **If you discover that you are pregnant while taking RIVA-TELMISARTAN/AMLODIPINE, stop the medication and talk to your healthcare professional as soon as possible.**

What is RIVA-TELMISARTAN/AMLODIPINE used for?

- RIVA-TELMISARTAN/AMLODIPINE is used in adults to treat mild to moderate **high blood pressure.**

How does RIVA-TELMISARTAN/AMLODIPINE work?

RIVA-TELMISARTAN/AMLODIPINE contains 2 medicines, telmisartan and amlodipine. They work together to control your blood pressure:

- Telmisartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "**-SARTAN**".
- Amlodipine is a calcium channel blocker.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking RIVA-TELMISARTAN/AMLODIPINE regularly even if you feel fine. Do not stop taking your medicine without talking to your healthcare professional.

What are the ingredients in RIVA-TELMISARTAN/AMLODIPINE?

Medicinal ingredients: Telmisartan and amlodipine (as amlodipine besylate)

Non-medicinal ingredients: Colloidal anhydrous silica, crospovidone, iron oxide red (E172) (40/5 mg and 80/5 mg), iron oxide yellow (E172) (40/10 mg and 80/10 mg), magnesium stearate, maize starch, mannitol, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide.

RIVA-TELMISARTAN/AMLODIPINE comes in the following dosage forms:

Tablets: 40 mg / 5 mg, 40 mg / 10 mg, 80 mg / 5 mg, 80 mg / 10 mg

Do not use RIVA-TELMISARTAN/AMLODIPINE if:

- you are allergic to:
    - telmisartan;
    - amlodipine;
    - medicines of the dihydropyridine type (a type of calcium channel blocker);
    - other ARBs;
    - any non-medicinal ingredient in RIVA-TELMISARTAN/AMLODIPINE (see **What are the ingredients in RIVA-TELMISARTAN/AMLODIPINE?**).
- you have had an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ARB.
- you are pregnant or planning to become pregnant. Taking RIVA-TELMISARTAN/AMLODIPINE during pregnancy can cause injury and even death to your baby.
- you are breastfeeding. RIVA-TELMISARTAN/AMLODIPINE passes into breast milk.
- have been diagnosed with hereditary fructose intolerance, a rare genetic disorder where you cannot break down fructose. RIVA-TELMISARTAN/AMLODIPINE tablets contain similar types of sugar called mannitol and meglumine. RIVA-TELMISARTAN/AMLODIPINE tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain 98.505 mg, 98.36 mg, 197.01 mg, 196.72 mg of a similar type of sugar called mannitol in each tablet respectively. RIVA-TELMISARTAN/AMLODIPINE tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain 5.40 mg, 5.40 mg, 10.80 mg and 10.80 mg of a similar type of sugar called meglumine in each tablet respectively.
- you have severe liver problems or problems with drainage of the bile from the liver and gallbladder (biliary obstruction).
- you have a serious heart problem, such as:
    - cardiac shock, where your heart cannot pump enough blood to your brain and organs;
    - aortic stenosis, a narrowing of the aortic heart valve;
    - problems with the heart muscle (hypertrophic cardiomyopathy);
    - unstable heart failure after a heart attack.
- you are already taking a blood pressure-lowering medicine that contains aliskiren and you have diabetes or kidney disease.
- you have very low blood pressure (less than 90 mmHg systolic).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIVA-TELMISARTAN/AMLODIPINE. Talk about any health conditions or problems you may have, including if you:

- are allergic to any medicine used to lower blood pressure including angiotensin converting enzyme (ACE) inhibitors.
- have a history of allergic reactions (angioedema).
- have a condition in which your body releases too much of the hormone aldosterone in your blood (primary aldosteronism).
- are taking any of the following:
    - other blood pressure lowering medicines, such as:
        - aliskiren.
        - an angiotensin-converting-enzyme inhibitor (ACEI).
        - beta blockers (i.e. acebutolol, atenolol, metoprolol, nadolol). Do NOT stop taking your beta-blocker without talking to your healthcare professional as this can cause serious side effects.

    - medicines used to treat bacterial or fungal infections, such as:
        - macrolides, e.g., clarithromycin.
        - azole antifungals, e.g., ketoconazole.
    - ritonavir, used to treat HIV infection
- have heart problems, such as:
    - chest pain (angina).
    - narrowing of an artery or heart valve.
    - heart or blood vessel disease.
    - heart failure.
    - recent heart attack.
- have kidney problems, such as:
    - a narrowing of the blood vessels to one or both kidneys (renal artery stenosis).
    - a kidney transplant.
    - you are on dialysis.
- have diabetes.
- have liver problems.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are on a low-salt diet.
- are at risk for developing high levels of potassium in your blood (hyperkalemia). This can be serious and can happen if you are taking:
    - a salt substitute that contains potassium.
    - potassium supplements.
    - a kind of "water pill" (potassium sparing) that makes your body hold on to potassium.
    - other medicines that may increase potassium in your blood, such as the blood thinner heparin.
- are 65 years of age or older. You may be more at risk of experiencing side effects.

Other warnings you should know about:

RIVA-TELMISARTAN/AMLODIPINE can cause serious side effects, including:

- **Allergic reactions / Angioedema:** Allergic reactions (angioedema) causing swelling of tissues under the skin, sometimes affecting the face and throat, have happened in people taking RIVA-TELMISARTAN/AMLODIPINE. These allergic reactions may happen at any time during treatment with RIVA-TELMISARTAN/AMLODIPINE and can be life threatening. Very rarely, cases have been fatal. If you experience an allergic reaction, stop taking RIVA-TELMISARTAN/AMLODIPINE and get immediate medical help.
- **Hypotension (low blood pressure):** You may feel dizzy or light-headed:
    - in the first few days after you start taking RIVA-TELMISARTAN/AMLODIPINE.
    - when your dose is increased.
    - when you exercise.
    - when the weather is hot.

  You should lie down if this happens. If you faint, stop taking RIVA-TELMISARTAN/AMLODIPINE and talk to your healthcare professional.
- **Blood disorders:** RIVA-TELMISARTAN/AMLODIPINE, may cause:
    - neutropenia / agranulocytosis (decrease in white blood cells).
    - thrombocytopenia (low blood platelets).
    - anaemia (low red blood cells).

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Surgery: Before surgery or general anaesthesic (even at the dentist's office), tell your healthcare professional that you are taking RIVA-TELMISARTAN/AMLODIPINE. You may experience a sudden fall in blood pressure when you are under general anesthesia.

Increased sensitivity of the skin to sun: Your skin may become sensitive to the sun while you are taking TYWNSTA. Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside. Talk to your healthcare professional if your skin gets itchy and red after being exposed to sunlight.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to RIVA-TELMISARTAN/AMLODIPINE. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

Blood tests: Your healthcare professional may do blood tests before you take RIVA-TELMISARTAN/AMLODIPINE and/or during treatment. These tests may check:

- the level of red and white blood cells and platelets in your body.
- that your liver or kidneys are working properly.
- the potassium levels in your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do **not** take RIVA-TELMISARTAN/AMLODIPINE with other blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products, or angiotensin-converting-enzyme inhibitors (ACEI) if you have diabetes (type 1 or type 2) or serious kidney problems. When taken together with RIVA-TELMISARTAN/AMLODIPINE, they may cause very low blood pressure.

The following may interact with RIVA-TELMISARTAN/AMLODIPINE:

- medicines that increase the levels of potassium in your blood. These include:
    - salt substitutes that contain potassium.
    - potassium supplements.
    - potassium-sparing medicines.
    - heparin, used to thin the blood and prevent blood clots.
- medicines that lower your blood pressure. These include:
    - diuretics ("water pills").
    - aliskiren-containing medicines.
    - angiotensin-converting-enzyme inhibitors (ACEI).
    - beta blockers.
    - diltiazem, a calcium channel blocker.
- antibiotics, medicines used to treat bacterial infections, such as clarithromycin, erythromycin, rifampicin, and rifampin.
- lithium, a medicine used to treat bipolar disease.
- nonsteroidal anti-inflammatory drugs (NSAIDs), medicines used to reduce pain and swelling, such as acetylsalicylic acid, ibuprofen, naproxen, and celecoxib

- vasodilators (including nitrates), medicines used to treat chest pain, such as nitroglycerin.
- corticosteroids, medicines used to treat inflammation, taken by mouth or injection.
- digoxin, a medicine used to treat heart problems.
- warfarin, a medicine used to thin the blood to prevent blood clots.
- medicines used to treat epilepsy, such as carbamazepine, phenobarbital, phenytoin, fosphenytoin and primidone.
- medicines used to treat HIV/AIDS, such as ritonavir.
- medicines used to treat fungal infections, such as ketoconazole, itraconazole.
- medicines used to lower cholesterol, such as atorvastatin and simvastatin.
- sildenafil, a medicine used to treat erectile dysfunction.
- St. John's Wort, an herbal medicine used to treat depression.
- mTOR inhibitors, medicines used to prevent organ rejection, such as sirolimus, temsirolimus, and everolimus.
- medicines that suppress the immune system, such as cyclosporine and tacrolimus.
- dantrolene, a medicine used to treat muscle spasms and back pain.
- antidepressants, medicines used to treat depression, such as imipramine.
- barbiturates, medicines used to help you sleep.
- narcotics, medicines used to relieve pain.
- alcohol.
- quinidine, flecainide, and propafenone, medicines used to treat heart rhythm problems.
- terfenadine, a medicine used to treat allergies.
- benzodiazepines, medicines used to help you sleep or that help reduce anxiety.
- theophylline, a medicine used to treat breathing problems.
- grapefruit. Do not eat grapefruit or drink grapefruit juice while on RIVA-TELMISARTAN/AMLODIPINE.

How to take RIVA-TELMISARTAN/AMLODIPINE:

- Take RIVA-TELMISARTAN/AMLODIPINE:
    - exactly as prescribed
    - at about the same time everyday, preferably in the morning
    - swallowed whole, with water
    - with or without food, but it should be taken the same way each day
- Remove your RIVA-TELMISARTAN/AMLODIPINE tablet from the blister just before you take it.

Usual dose:

Your healthcare professional will decide the best dose for you based on your needs.

Overdose:

If you think you, or a person you are caring for, have taken too much RIVA-TELMISARTAN/AMLODIPINE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

What are possible side effects from using RIVA-TELMISARTAN/AMLODIPINE?

These are not all the possible side effects you may have when taking **RIVA-TELMISARTAN/AMLODIPINE**. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dizziness, vertigo (feeling of spinning)
- drowsiness, insomnia, fatigue
- urge to urinate during the night
- rash, itching, skin discolouration, photosensitivity reaction
- increased sweating
- hair loss
- diarrhea, vomiting, constipation, nausea, upset stomach, abdominal pain, flatulence, change in bowel habits
- taste abnormalities
- swelling of the gums
- dry mouth
- headache, migraine
- anxiety, mood changes
- ringing in the ears
- back or leg pain, muscle cramps, spasms or stiffness, joint pain or swelling
- vision changes (double vision, blurred vision, etc.)
- upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), flu-like symptoms, cough, sneezing, runny nose, shortness of breath
- enlargement of breasts in men
- changes in weight (increased or decreased)
- tingling or numbness of hands and feet

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Edema: unusual swelling of the arms, hands, legs, feet and ankles, face or airway passages.	✓		
UNCOMMON			
Chest pain		✓	
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat, palpitations, fluttering or pounding heart, skipping beats.		✓	

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
Cystitis (bladder infection): frequent or urgent urination, pain or burning when urinating, foul-smelling urine, cloudy or bloody urine, feeling unwell.	✓		
Erectile dysfunction (problems getting or keeping an erection)		✓	
Hyperkalemia (increased levels of potassium in the blood): irregular heartbeat, muscle weakness, or generally feeling unwell.		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, trembling, or flushing (may occur when you go from lying or sitting to standing up).		✓	
Kidney disorder (including acute kidney failure): change in frequency of urination (little or no urine), dark urine, blood in urine, nausea, vomiting, loss of appetite, swelling of extremities, fatigue, thirst, dry skin, rash, irritability, mental status changes (drowsiness, confusion, coma).		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle pain that you cannot explain, muscle tenderness or weakness, muscle cramps, or dark red-brown urine.		✓	
RARE			
Allergic reaction / Angioedema: wheezing, rash, hives, rapid swelling of the face, lips, tongue, throat, hands or feet, swelling of the digestive tract causing stomach pain, diarrhea, nausea or vomiting, difficulty swallowing, or difficulty breathing.			✓
Depression: low mood, feeling sad, loss of interest in activities, change in appetite, or change in sleep patterns.		✓	

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypoglycemia (low blood sugar): shaky, irregular or fast heartbeat, sweating, hunger, thirst, nausea, dizziness, frequent urination, nervousness, sweating, or low energy.		✓	
Hyponatremia (low sodium levels in the blood): lethargy, nausea, vomiting, abdominal cramps, agitation, confusion, muscle twitching, achy, stiff or uncoordinated muscles, seizure, or coma.		✓	
Sepsis (infection of the blood): chills, confusion, fever or dizziness, high or very low body temperature, shakiness, irregular or rapid heartbeat, palpitations, rapid breathing, little or no urine, or low blood pressure.			✓
Thrombocytopenia (decreased platelets): bruising, bleeding for longer than usual if you hurt yourself, fatigue, or weakness.		✓	
UNKNOWN FREQUENCY			
Anemia (low red blood cells levels): fatigue, loss of energy, weakness, looking pale, or shortness of breath.		✓	
Decreased white blood cells: frequent infections, fatigue, fever, chills, sore throat, aches, pains, flu-like symptoms.		✓	
Extrapyramidal symptoms (movement-related problems): muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want, tremors, or involuntary facial movements.			✓

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
Gastritis (inflammation of the stomach): nausea, vomiting, burping, bloating, or feeling full after only a few bites of food.		✓	
Hyperglycemia (increased blood sugar): frequent urination, increased thirst and hunger, dry skin, headache, blurred vision, or fatigue.		✓	
Liver disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, aches, tiredness, and a general ill feeling, or flu-like symptoms.		✓	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, or possible irregular heartbeat.			✓
Pancreatitis (inflammation of the pancreas): upper abdominal pain, nausea, vomiting, fever, rapid heartbeat, or tenderness when touching the abdomen.		✓	
Severe skin reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, or having less urine.			✓

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
Vasculitis (inflammation of the blood vessels): fever, red raised spots caused by bleeding under the skin, aching muscles and joints, or headache.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C to 30°C. Store in the original package in order to protect from moisture and light.

Do not use RIVA-TELMISARTAN/AMLODIPINE after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of reach and sight of children.

If you want more information about RIVA-TELMISARTAN/AMLODIPINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.labriva.com), or by calling the manufacturer, Laboratoire RIVA Inc., at: 1-800-363-7988.

This leaflet was prepared by Laboratoire RIVA Inc.

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www.labriva.com

The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

Last Revised: JUL 31, 2025