PRODUCT MONOGRAPH

^{Pr}AA-TELMISARTAN-AMLODIPINE

Telmisartan / Amlodipine (as Amlodipine Besylate) Tablets

40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg

House Standard

Angiotensin II AT1 Receptor Blocker / Calcium Channel Blocker

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Tablet telmisartan/amlodipine 40/5mg, 40/10 mg, 80/5 mg, 80/10 mg	anhydrous dibasic calcium phosphate, black iron oxide, brilliant blue FCF Al lake, colloidal silicon dioxide, croscarmellose sodium, isomalt, magnesium stearate, mannitol, meglumine, methyl alcohol, microcrystalline cellulose, povidone, sodium hydroxide, iron oxide yellow.

INDICATIONS AND CLINICAL USE

AA-TELMISARTAN-AMLODIPINE (telmisartan/amlodipine besylate) is indicated for treatment of mild to moderate essential hypertension for whom combination therapy is appropriate.

AA-TELMISARTAN-AMLODIPINE is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**).

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 AA-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.

Geriatrics:
No dose adjustment is necessary for elderly patients. It should be recognized, however, that greater sensitivity in some older individuals cannot be ruled out.

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

CONTRAINDICATIONS

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

- Concomitant use of angiotensin receptor antagonists (ARBs) –including the telmisartan component of AA-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/1.73m^2) is contraindicated (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, Dual Blockade of the Renin-Angiotensin System (RAS) and **Renal**, and **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 **DOSAGE FORMS**, **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 **WARNINGS AND PRECAUTIONS**, **General**)
- Pregnant women (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **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, AA-TELMISARTAN-AMLODIPINE should be discontinued as soon as possible.
- Nursing women (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Nursing Women**)
- Patients with biliary obstructive disorders
- Patients with severe hepatic impairment
- Patients with cardiogenic shock
- 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: AA-TELMISARTAN-AMLODIPINE tablets contain 85.00 mg of mannitol per maximum recommended daily dose.
  - Isomalt: AA-TELMISARTAN-AMLODIPINE tablets contain 270.03 mg of isomalt per maximum recommended daily dose.
  - Meglumine: AA-TELMISARTAN-AMLODIPINE tablets contain 24.00 mg of meglumine per maximum recommended daily dose.

WARNINGS AND PRECAUTIONS

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, AA-TELMISARTAN-AMLODIPINE should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

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 and amlodipine. 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.

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, AA-TELMISARTAN-AMLODIPINE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. 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 **ADVERSE REACTIONS** - **Post Marketing Adverse Drug Reactions**; **Telmisartan**).

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be treated with AA-TELMISARTAN-AMLODIPINE (see **ADVERSE REACTIONS**, Clinical Trial Adverse Drug Reactions -Unknown Frequencies, **Immune System Disorders,** Angioedema and **ADVERSE REACTIONS** - **Post Marketing Adverse Drug Reactions**; *Telmisartan*).

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

Cardiovascular

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 and amlodipine 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.

Heart Failure

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Intravascular Hypovolaemia
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 AA-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 antagonists (ARBs), such as the telmisartan component of telmisartan and amlodipine, 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/1.73m^2). Therefore, the use of AA-TELMISARTAN-AMLODIPINE in combination with aliskiren-containing drugs is contraindicated in these patients.

Further, co-administration of ARBs, including the telmisartan component of AA-TELMISARTAN-AMLODIPINE, 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.

Concomitant Use with Strong Inhibitors of CYP 3A4
Use of telmisartan and amlodipine 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 **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)].

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 C_{max} 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 to 60% higher in patients with impaired liver function. Amlodipine should therefore be initiated at the lower end of the dosing range and titration should be slow, with careful monitoring throughout. AA-TELMISARTAN-AMLODIPINE should be used with caution in these patients.

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

Neurologic

Effects on ability to drive and use machines
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 or drowsiness may occasionally occur when taking antihypertensive therapy.

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 AA-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 and amlodipine in patients with a recent kidney transplant.

Telmisartan and amlodipine are 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 antagonist 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, AA-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 AA-TELMISARTAN-AMLODIPINE is not recommended.

Hyperkalaemia

Drugs such as AA-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.

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

Special Populations

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 AA-TELMISARTAN-AMLODIPINE.

Fertility
No data from controlled clinical studies with the fixed dose combination or with the individual components are available. Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted (See **Part II**, **Toxicology**, **Telmisartan, Amlodipine**).

Pregnant Women

AA-TELMISARTAN-AMLODIPINE
The effects of telmisartan and amlodipine during pregnancy are not known.

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

The use of angiotensin receptor (AT$_1$) 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. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

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.

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

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

Nursing Women
AA-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 **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 **CONTRAINDICATIONS**).

Geriatrics (> 65 years of age)

In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC (see ACTION AND CLINICAL PHARMACOLOGY, 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. AA-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 DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview
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.

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 1**).

Table 1. Summary of adverse events by overall treatment groups in the factorial study.

	T40/A5 n (%)	T40/A10 n (%)	T80/A5 n (%)	T80/A10 n (%)	T40 n (%)	T80 n (%)	A5 n (%)	A10 n (%)	Placebo 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)
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.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

MedDRA system organ class Preferred term	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) (%)
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
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

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

MedDRA system organ class Preferred term	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) (%)
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 (> 1%)

General Disorders: edema peripheral

Nervous System Disorders: dizziness

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

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

Clinical Trial Adverse Drug Reactions for Amlodipine

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

Blood and the Lymphatic System Disorders: leukopenia

Cardiac Disorders: myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation, cardiac failure

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: diplopia

Gastrointestinal Disorders: change of bowel habit, pancreatitis, gastritis, constipation, dysphagia

General Disorders: pain, weight increased, weight decreased, rigors

Hepato-Biliary Disorders: hepatitis, jaundice, hepatic enzyme increased (mostly consistent with cholestatis)

Immune System Disorders: hypersensitivity

Musculoskeletal and Connective Tissue Disorders: joint swelling

Nervous System Disorders: extrapyramidal disorder, hypertonia

Psychiatric Disorders: mood altered, confusional state, nervousness

Renal and Urinary Disorders: micturition disorder, pollakiuria

Reproductive System and Breast Disorders: gynecomastia

Respiratory, Thoracic and Mediastinal Disorders: rhinitis, epistaxis

Skin and Subcutaneous Tissue Disorders: alopecia, purpura, skin discolouration, erythema multiforme, dermatitis exfoliative, photosensitivity reaction, Stevens- Johnson syndrome, toxic epidermal necrolysis, angioedema with breathing difficulties
Vascular Disorders: vasculitis, peripheral ischemia

Post-Market Adverse Drug 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 and weakness have been reported. The frequency of these effects is unknown. As with other angiotensin II antagonists, rare cases of angioedema (with 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 postmarketing 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.

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 and amlodipine 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.

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).

Table 3 -Established or Potential Drug-Drug Interactions

Telmisartan Amlodipine	Source of evidence	Effect	Clinical comment
Other antihypertensive agents	T	The blood pressure lowering effect of telmisartan and amlodipine 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 and amlodipine, 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 4 - Established or Potential Drug-Drug Interactions

Telmisartan	Source of evidence	Effect	Clinical comment
Agents increasing serum potassium	T		Since the telmisartan 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.
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 AA-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		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, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia. See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, Dual Blockade of the Renin- Angiotensin System (RAS).

Telmisartan	Source of evidence	Effect	Clinical comment
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 antagonists including telmisartan.	Serum lithium level monitoring is advisable during concomitant use.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	Combinations of angiotensin- II antagonists (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 antagonists 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. |
| 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; | |

Telmisartan	Source of evidence	Effect	Clinical comment
		this decrease did not result in a change in International Normalized Ratio (INR).	
Other	Amlodipine (CT), acetaminophen (CT), glyburide (CT) and hydrochloro - thiazide (CT)		Coadministration of telmisartan also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, or hydrochlorothiazide.

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

Table 5 Established or Potential Drug-Drug Interactions

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.

Amlodipine	Source of evidence	Effect	Clinical comment
Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) Clarithromycin	T CT	May significantly increase the plasma concentrations of amlodipine to a greater extent than diltiazem. In elderly patients (>65 years of age), concomitant use of amlodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury.	AA-TELMISARTAN-AMLODIPINE should be used with caution together with CYP3A4 inhibitors and monitoring of therapy is required. Appropriate dosage adjustment of AA-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 AA-TELMISARTAN-AMLODIPINE with strong CYP3A4 inhibitors. (see WARNINGS AND PRECAUTIONS)
CYP3A4 inducers (e.g. phenobarbital, phenytoin, rifampicin,)	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 AA-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.

Amlodipine	Source of evidence	Effect	Clinical comment
Cimetidine, warfarin, digoxin	CT	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	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 AA-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 C_{max} 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.	

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 C_{max} or T_{max} 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.	Concomitant use to be taken into account Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
Immunosuppressants		Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered.	Frequent monitoring of trough blood levels of cyclosporine and tacrolimus and dose adjustment when appropriate is recommended.
Cyclosporine	CT	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.	
Tacrolimus	C	There is a risk of increased tacrolimus blood levels when co-administered with amlodipine.	
Mechanistic Target of Rapamycin (mTOR)	CT T	mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a	Caution is advised

Amlodipine	Source of evidence	Effect	Clinical comment
Inhibitors		weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.	

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).

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 **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics, Distribution**).

Administration of AA-TELMISARTAN-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.

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.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

DOSAGE

Recommended Dose and Dosage Adjustment
AA-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 AA-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. Amlodipine and telmisartan are not dialyzable.

Amlodipine dosage requirement for patients with impaired renal function is 5 mg once daily. If required, increasing the dose should be done gradually and with caution.

Hepatic impairment
In patients with mild to moderate hepatic impairment AA-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, increasing in the dose should be done gradually and with caution (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

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

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

METHOD OF ADMINISTRATION

Tablet for oral administration
AA-TELMISARTAN-AMLODIPINE should be taken consistently with or without food.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms
Telmisartan and amlodipine tablets: There is no experience of overdose with telmisartan and 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.

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.

Therapy
If symptomatic hypotension should occur, supportive treatment should be instituted.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

Telmisartan and amlodipine are not removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mode of Action

Telmisartan
Telmisartan is an orally active angiotensin II AT_1 receptor antagonist. 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 homeostatis.

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 nondihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action of amlodipine, acute hypotension was not observed.

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

Telmisartan and amlodipine combines two antihypertensive compounds with different mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, 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 and amlodipine 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 to 80 mg) was similar to that of once-daily amlodipine (5 to 10 mg), atenolol (50 to 100 mg), enalapril (5 to 20 mg) and lisinopril (10 to 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. Blood pressure in hypertensive black patients (usually a low renin population) is significantly reduced by telmisartan (compared to placebo), but less so than in non-black patients.

Amlodipine
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.

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.

Pharmacokinetics

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 to125%, and the confidence interval for the $C_{max,ss}$ ratio was within the prespecified bioequivalence limits of 80 to125%. 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 N=36	T/R ratio [%]	90% CI	
		lower limit [%]	upper limit [%]
$AUC_{\tau,ss}$	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 to 125%, and the confidence interval for the $C_{max,ss}$ ratio was within the prespecified bioequivalence limits of 75 to 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 and amlodipine 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 to 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 C_{max} 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 **DRUG INTERACTIONS**, **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.

Excretion: *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 C^{14} 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.

Women have a lower telmisartan clearance and have a greater systolic blood pressure response at trough than men.

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

Pediatric population (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 elderly and those younger than 65 years.

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.

Race

The effectiveness of telmisartan and amlodipine 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.

Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. 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.

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.

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.

Genetic Polymorphism

Telmisartan: No studies were conducted to evaluate the influence of genetic polymorphisms on the pharmacokinetics or pharmacodynamics of telmisartan.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

AA-TELMISARTAN-AMLODIPINE 40/5 mg is available as modified capsule shaped, biconvex, uncoated, two-layered tablets with one layer white and the other layer blue and "APO" engraved on one side and "40/5"on the other side for strength 40/5 mg. White layer may contain blue specks and blue layer may contain white specks.

AA-TELMISARTAN-AMLODIPINE 40/10 mg is available as modified capsule shaped, biconvex, uncoated, two-layered tablets with one layer white and the other layer blue and "APO" engraved on one side and "40/10" on the other side for strengths 40/10 mg. White layer may contain blue specks and blue layer may contain white specks.

AA-TELMISARTAN-AMLODIPINE 80/5 mg is available as modified capsule shaped, biconvex, uncoated, two-layered tablets with one layer white and the other layer blue and "APO" engraved on one side and "80/5" on the other side for strengths 80/5 mg. White layer may contain blue specks and blue layer may contain white specks.

AA-TELMISARTAN-AMLODIPINE 80/10 mg is available as modified capsule shaped, biconvex, uncoated, two-layered tablets with one layer white and the other layer blue and "APO" engraved on one side and "80/10" on the other side for strengths 80/10 mg. White layer may contain blue specks and blue layer may contain white specks.

Non-medicinal ingredients (in alphabetical order): anhydrous dibasic calcium phosphate, black iron oxide, brilliant blue FCF Al lake, colloidal silicon dioxide, croscarmellose sodium, isomalt, magnesium stearate, mannitol, meglumine, methyl alcohol, microcrystalline cellulose, povidone, sodium hydroxide, yellow iron oxide.

AA-TELMISARTAN-AMLODIPINE tablets 40/5 mg are packed in HDPE Bottle of 30's, 100's, 500's along with 30's (3x10) and 100's (10 X 10) unit dose and perforated blister pack.

AA-TELMISARTAN-AMLODIPINE tablets 40/10 mg are packed in HDPE Bottle of 30's, 100's, 500's along with 30's (3x10) and 100's (10 X 10) unit dose and perforated blister pack.

AA-TELMISARTAN-AMLODIPINE tablets 80/5 mg are packed in HDPE Bottle of 30's, 100's, 500's along with 30's (3x10) and 100's (10 X 10) unit dose and perforated blister pack.

AA-TELMISARTAN-AMLODIPINE tablets 80/10 mg are packed in HDPE Bottle of 30's, 100's, 500's along with 30's (3x10) and 100's (10 X 10) unit dose and perforated blister pack.

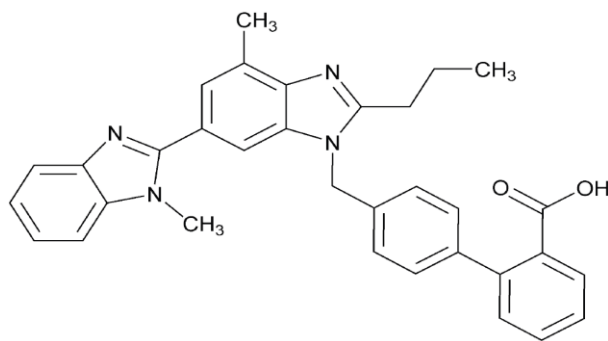**PART II: SCIENTIFIC INFORMATION**

PHARMACEUTICAL INFORMATION

Drug Substance – Telmisartan

Proper name: Telmisartan

Chemical name: [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1*H*-benzimidazol]-1'-yl)methyl-],
4'-[[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl]-2-biphenylcarboxylic acid
4'-[[4-Methyl-6-(1-methyl-1*H*-benzimidazole-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Molecular formula and molecular mass: $C_{33}H_{30}N_4O_2$, 514.62 g/mol
Structural formula:

Physicochemical Properties:

Description:
White to slightly yellowish powder

Polymorphism:
Telmisartan exhibits polymorphism. Form A with melting point of 269°C (thermodynamically more stable) & Form B with melting point of 183°C.

Melting point:
269 ±1°C (polymorphic Form A)
183 ±1°C (polymorphic Form B)

Drug Substance – Amlodipine Besylate
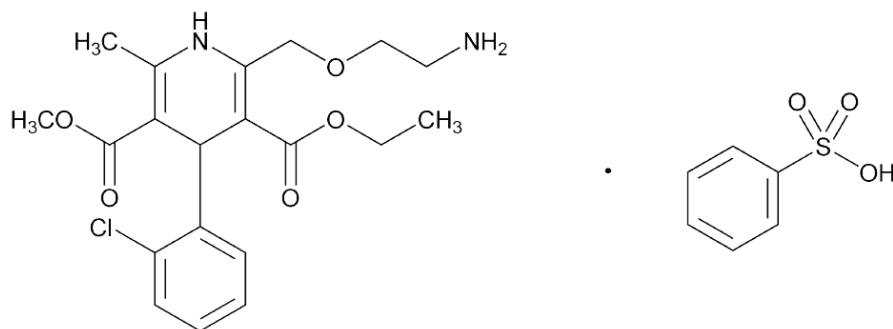
Proper name: Amlodipine Besylate

Chemical name: 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate

3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate.

3-ethyl, 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate

Molecular formula and molecular mass: $C_{20}H_{25}C_lN_2O_5 \cdot C_6H_6O_3S$, 567.05 g/mol

Structural formula:

Physicochemical Properties:

White or almost white powder

Solubility   :   It is soluble in water.

Melting point :   203°C with decomposition

pKa   :   9.0 and 0.4

CLINICAL TRIALS

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:

Telmisartan (1 x 80 mg as either telmisartan/ amlodipine besylate or MICARDIS) Arithmetic Mean (CV%) Geometric Mean				
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.h/mL)	281 (110%) 205	278 (121%) 188	109	98-120
Amlodipine (1 x 10 mg as either telmisartan/ amlodipine besylate or NORVASC) Arithmetic Mean (CV%) Geometric Mean				
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.h/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
[†] MICARDIS (telmisartan) 80 mg tablet, by Boehringer Ingelheim (Canada) Ltd/Ltee.
[€] NORVASC (amlodipine besylate) 10 mg tablet, by Pfizer Canada Inc.

A randomized, single dose, blinded, 2-way crossover comparative bioavailability study, was conducted under fasting conditions, on healthy male volunteers from 20 to 35 years of age (N=28). The rate and extent of absorption of telmisartan and amlodipine were measured and compared following a single oral dose (1 x 80/10 mg tablet) of AA-TELMISARTAN-AMLODIPINE (telmisartan and amlodipine) 80/10 mg tablet (AA Pharma Inc.) and TWYNSTA[TM] (telmisartan and amlodipine) 80/10 mg tablet (Boehringer Ingelheim (Canada) Ltd.). The results from measured data in 26 subjects are summarized in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA: TELMISARTAN DATA

Telmisartan (1 x 80 mg telmisartan/10 mg amlodipine besylate) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{0-72} (ng•h/mL)	1907.46 2229.47 (58)	1776.78 2194.35 (67)	107.4	96.4 − 119.5
AUC_I (ng•h/mL)	1988.11 2368.56 (63)	1829.46 2360.68 (70)	108.7	97.5 − 121.1
C_{max} (ng/mL)	270.32 312.29 (70)	245.98 290.62 (58)	109.9	87.9 − 137.3
T_{max}[§] (h)	1.54 (75)	1.28 (62)		
$T_{1/2}$[§] (h)	15.17 (46)	15.71 (38)		
* AA-TELMISARTAN-AMLODIPINE (telmisartan and amlodipine) 80/10 mg tablets (AA Pharma Inc.) † TWYNSTA™ (telmisartan and amlodipine) 80/10 mg tablets (Boehringer Ingelheim (Canada) Ltd.) was purchased in Canada. [§] Expressed as arithmetic means (CV%) only.				

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA: AMLODIPINE DATA

	Amlodipine (1 x 80 mg telmisartan/10 mg amlodipine besylate) From Measured Data Geometric Mean Arithmetic Mean (CV%)			
Parameter	Test*	Reference[†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{0-72} (ng•h/mL)	329.08 339.09 (23)	332.41 339.10 (19)	99.0	93.7 − 104.6
AUC_I (ng•h/mL)	526.77 554.76 (30)	549.47 570.24 (26)	95.9	88.8 − 103.5
C_{max} (ng/mL)	7.93 8.18 (23)	7.85 7.96 (17)	101.1	95.1 − 107.4
T_{max}[§] (h)	6.69 (35)	7.23 (25)		
$T_{1/2}$[§] (h)	50.46 (24)	53.27 (24)		

* AA-TELMISARTAN-AMLODIPINE (telmisartan and amlodipine) 80/10 mg tablets (AA Pharma Inc.)

[†] TWYNSTA[TM] (telmisartan and amlodipine) 80/10 mg tablets (Boehringer Ingelheim (Canada) Ltd.) was purchased in Canada.

[§] Expressed as arithmetic means (CV%) only.

Other Clinical Studies

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 and amlodipine tablets (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 to 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/m^2 with 238 (16.3%) of patients being diabetic and 12 (0.8%) with renal impairment.

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.

Results

Treatment with each combination dose of telmisartan and amlodipine 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:

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 and amlodipine was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Telmisartan and amlodipine has not been studied in any patient population other than essential hypertension.

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 (telmisartan/amlodipine tablets), 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

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. LD_{50} in rats was 150 to 200 mg/kg in males and 200 to 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.

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 to 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.

Mutagenicity
Telmisartan was not mutagenic at a concentration range of 10 to 2500 mcg/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 mcmcg/ml, with or without metabolic activation. No chromosomal aberrations were induced in human peripheral lymphocytes *in vitro* at concentrations ≤ 100 mcg/ml without metabolic activation and concentrations ≤ 200 mcg/ml with metabolic activation.

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.

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.

Amlodipine

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/m 2 basis, for a 50 kg human).

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/m^2 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

REFERENCES

1. Gandhi, Sonja, et al. Calcium-Channel Blocker-Clarithromycin Drug Interactions and Acute Kidney Injury. *JAMA* 310.23 (2013): 2544-2553.

2. Lacourcière Y, Lenis J, Orchard R, Lewanczuk R, Houde M, Pesant Y, Wright J, Wilson T, Martin K. A comparison of the efficacies and duration of action of the angiotensin II receptor blockers telmisartan and amlodipine. Blood Press Monit 1998;3(5):295-302.

3. Weber-Schoendorfer C, Hannemann D, Meister R, Elefant E, Cuppers-Maarschalkerweerd B, Arnon J, Vial T, Rodriguez-Pinilla E, Clementi M, Robert-Gnansia E, Santis M de, Malm H, Dolivo A, Schaefer C. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol 2008;26(1):24-30.

4. Product monograph - Pr Twynsta[TM] (Telmisartan / Amlodipine (as Amlodipine Besylate) Tablets), 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg, Boehringer Ingelheim (Canada) Ltd., Date of Revision: August 7, 2019 (Submission Control No: 225785).

PART III: CONSUMER INFORMATION

PrAA-TELMISARTAN-AMLODIPINE
Telmisartan/Amlodipine (as Amlodipine Besylate)
Tablets
40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg

House Standard

Read this carefully before you start taking AA-TELMISARTAN-AMLODIPINE and each time you get a refill. This leaflet is a summary and will not tell you everything about AA-TELMISARTAN-AMLODIPINE. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about AA-TELMISARTAN-AMLODIPINE.

ABOUT THIS MEDICATION

What the medication is used for:
AA-TELMISARTAN-AMLODIPINE is used to treat high blood pressure in patients who already receive telmisartan and amlodipine from separate tablets and who wish to take instead the same doses in one tablet for convenience.

What it does:
AA-TELMISARTAN-AMLODIPINE contains a combination of 2 drugs, telmisartan and amlodipine:

- 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.

These medicinal ingredients work together to lower blood pressure.

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking AA-TELMISARTAN-AMLODIPINE regularly even if you feel fine.

When it should not be used:
Do not take AA-TELMISARTAN-AMLODIPINE if you:
- Are allergic (hypersensitive) to telmisartan or amlodipine or to any non-medicinal ingredient in the formulation.
- Have experienced 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.

Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Are allergic to other medicines of the dihydropyridine type (one type of calcium channel blocker).
- Are pregnant or intend to become pregnant. Taking AA-TELMISARTAN-AMLODIPINE during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. AA-TELMISARTAN-AMLODIPINE passes into breast milk.
- Have been diagnosed with hereditary fructose intolerance, a rare genetic disorder in which a person cannot break down fructose. AA-TELMISARTAN-AMLODIPINE contains a similar type of sugar called mannitol, isomalt and meglumine.
- Have severe liver problems or biliary obstruction (problems with drainage of the bile from the liver and gallbladder).
- Suffer from low heart output because of a serious heart problem.
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.

What the medicinal ingredients are:
Telmisartan and amlodipine (as amlodipine besylate)

What the non-medicinal ingredients are:
anhydrous dibasic calcium phosphate, black iron oxide, brilliant blue FCF Al lake, colloidal silicon dioxide, croscarmellose sodium, isomalt, magnesium stearate, mannitol, meglumine, methyl alcohol, microcrystalline cellulose, povidone, sodium hydroxide, iron oxide yellow.

What dosage forms it comes in:
Tablets: 40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg and 80 mg/10 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions –Pregnancy AA-TELMISARTAN-AMLODIPINE should not be used during pregnancy. If you discover that you are pregnant while taking AA-TELMISARTAN-AMLODIPINE, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use AA-TELMISARTAN-AMLODIPINE talk to your doctor or pharmacist if you:

- Have experienced an allergic reaction to any drug used to lower blood pressure.
- Have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Have swelling of your legs.
- Have raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with AA-TELMISARTAN-AMLODIPINE is not recommended.
- Are taking an angiotensin-converting-enzyme inhibitor (ACEI).
- Have angina, narrowing of a heart valve or blood vessel, heart or blood vessel disease.
- Have diabetes mellitus, liver or kidney disease.
- Are on dialysis or have a kidney transplant.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are on a low-salt diet.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium).
- Are less than 18 years old.

In case of surgery or anaesthesia, you should tell your doctor that you are taking AA-TELMISARTAN-AMLODIPINE.

If you take AA-TELMISARTAN-AMLODIPINE together with a drug known as betablockers (e.g. acebutolol, atenolol, metoprolol, nadolol), do not suddenly stop using the beta-blocker. If your doctor advises you to discontinue use of the beta-blocker, your dose should be decreased slowly, as recommended by your doctor, before stopping it completely

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

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with AA-TELMISARTAN-AMLODIPINE:
- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill");
- Blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), or angiotensin-converting-enzyme inhibitors (ACEI);
- Clarithromycin and Erythromycin, an antibiotic used to treat infections;
- Lithium used to treat bipolar disease;
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ASA (Aspirin), ibuprofen, naproxen, and celecoxib;
- Corticosteroids taken by mouth or injection;
- Digoxin to treat heart conditions;
- Warfarin used to prevent blood clots (blood thinner);
- Anticonvulsant agents. Examples include carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone;
- Rifampicin, an antibiotic used to treat infections;
- Medicines used to treat HIV/AIDS. An example is ritonavir;
- Medicines used to treat fungal infections. Examples include ketoconazole, itraconazole;
- Atorvastatin and simvastatin used to lower cholesterol;
- Sildenafil (Viagra);
- St. John's Wort;
- Beta-blockers;
- Diltiazem
- Mechanistic Target of Rapamycin (mTOR) inhibitors, such as sirolimus, temsirolimus and reverolimus;
- Immunosuppressants, such as cyclosporine and tacrolimus.

Lower than normal blood pressure may occur when AA-TELMISARTAN-AMLODIPINE is given with the following:
- alcohol;
- antidepressants;
- barbiturates (sleeping pills);
- narcotics (strong pain medications);
- nitroglycerin or other nitrates.

PROPER USE OF THIS MEDICATION

Take AA-TELMISARTAN-AMLODIPINE exactly as prescribed. It is recommended to swallow your dose whole with water at about the same time everyday, preferably in the morning.

Take AA-TELMISARTAN-AMLODIPINE with or without food, but it should be taken the same way each day.

Remove your AA-TELMISARTAN-AMLODIPINE tablet from the blister just prior to intake.

Usual Adult Dose:
The usual dose of AA-TELMISARTAN-AMLODIPINE is one tablet once a day.

If your liver is not working properly, the usual dose should not exceed 40/5 mg or 40/10 mg once daily.

Overdose:

If you think you have taken too much AA-TELMISARTAN-AMLODIPINE contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- dizziness, vertigo (feeling of spinning);
- drowsiness, insomnia, fatigue;
- urge to urinate during the night;
- rash, eczema, redness of skin, skin eruptions, itching, hives (urticaria), scaling of the skin (dermatitis exfoliative), increased sweating, drug rash, hair loss, skin discolouration, photosensitivity reaction;
- toxic epidermal necrolysis;
- diarrhea, vomiting, constipation, nausea, upset stomach, abdominal pain, flatulence, change of bowel habit;
- taste abnormalities, enlarged gums;
- dry mouth;
- headache, migraine, anxiety, mood altered, ringing in the ears;
- sleepiness, sleeplessness, tiredness;
- back or leg pain, muscle cramps, joint pain, muscle spasms, joint swelling, hypertonia;
- visual impairment, double vision (diplopia);

- upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), flu-like illness, cough, sneezing, runny nose, shortness of breath;
- inability to obtain an erection;
- enlarging of male breasts;
- weight increased, weight decreased.

If any of these affects you severely, tell your doctor, nurse or pharmacist.

AA-TELMISARTAN-AMLODIPINE can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	Ankle swelling (edema)	√		
Uncommon	Shortness of breath	√		
	Low blood pressure: dizziness, fainting, light-headedness, trembling, flushing. May occur when you go from lying or sitting to standing up		√	
	Slow heart beat		√	
	Palpitations (awareness of your heartbeat)		√	
	Chest pain		√	
	Tingling or numbness of hands or feet	√		
	Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, muscle cramps, muscle wasting disease, pain,		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
back pain, pain in extremity, inflammation of the tendons, dark brown urine			
Increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		√	
Kidney Disorder including Acute Kidney Failure: change in frequency of urination (little or no urine), nausea, vomiting, swelling of extremities, fatigue		√	
Urinary Tract Infections (Cystitis): frequent or painful urination, feeling unwell	√		
Rare	**Decreased Platelets:** bruising, bleeding, fatigue and weakness		√	
Depression: low mood, feeling sad, loss of interest in activities, change in appetite and sleep patterns		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
Low blood sugar: shaky, irregular heartbeat, sweating, hunger, dizziness (**in diabetic patients**)		√	
Allergic reaction: rash, hives, rapid swelling of the face, lips, tongue or throat, difficulty swallowing or breathing with a potential fatal outcome			√
Sepsis (blood poisoning): Chills, confusion, fever or low body temperature, shakiness, irregular heartbeat (including fatal outcome)			√
Unknown frequency	**Confusional State**		√	
Stevens-Johnson syndrome: fever, sore throat, and fatigue followed by ulcers and other lesions to appear in the mouth and on lips but also in the genital and anal regions			√
Difficulty passing urine		√	
Liver Disorder: yellowing of the		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
	Only if severe	**In all cases**	
skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, aches, tiredness, and a general ill feeling or flu-like symptoms			
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
Inflamed pancreas: abdominal pain radiating to the back, nausea and vomiting		√	
Gastritis: nausea, vomiting, burping, bloating and feeling full after only a few bites of food		√	
Increased blood sugar: frequent urination, thirst and hunger (**in diabetic patients**)		√	
Inflammation of the blood vessels: fever, red raised spots caused by bleeding under			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
	Only if severe	**In all cases**	
the skin, aching muscles and joints, headache			
Irregular heart beat		√	
Fast heart beat		√	
Heart attack			√
Extrapyramidal symptoms: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			√

This is not a complete list of side effects. For any unexpected effects while taking AA-TELMISARTAN-AMLODIPINE, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach and sight of children.

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

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

Store at 15°C to 30°C.

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.

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.

MORE INFORMATION

If you want more information about AA-TELMISARTAN-AMLODIPINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website https://www.aapharma.ca/en/, or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., Vaughan, Ontario, L4K 4N7

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