AUSTRALIAN PRODUCT INFORMATION – PRITOR®/AMLODIPINE (telmisartan/amlodipine) tablet

1 NAME OF THE MEDICINE

telmisartan and amlodipine (as besilate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PRITOR/AMLODIPINE is available in four tablet strengths for oral administration, containing 40 mg or 80 mg telmisartan and 5 mg or 10 mg amlodipine (as besilate), in the following combinations:

- PRITOR/AMLODIPINE 40 mg/5 mg containing telmisartan 40 mg/amlodipine 5 mg
- PRITOR/AMLODIPINE 40 mg/10 mg containing telmisartan 40 mg/amlodipine 10 mg
- PRITOR/AMLODIPINE 80 mg/5 mg containing telmisartan 80 mg/amlodipine 5 mg
- PRITOR/AMLODIPINE 80 mg/10 mg containing telmisartan 80 mg/amlodipine 10 mg

Excipients with known effect:

- Each PRITOR/AMLODIPINE 40/5 mg and 40/10 mg tablet contains 168.64 mg of sorbitol
- Each PRITOR/AMLODIPINE 80/5 mg and 80/10 mg tablet contains 337.28 mg of sorbitol

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

PRITOR/AMLODIPINE 40 mg/5 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A1’. The blue side is plain. Each tablet contains 40 mg telmisartan and 5 mg amlodipine.

PRITOR/AMLODIPINE 40 mg/10 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A2’. The blue side is plain. Each tablet contains 40 mg telmisartan and 10 mg amlodipine.

PRITOR/AMLODIPINE 80 mg/5 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A3’. The blue side is plain. Each tablet contains 80 mg telmisartan and 5 mg amlodipine.

PRITOR/AMLODIPINE 80 mg/10 mg tablets are oval, biconvex shaped two layer tablets, white to off white on one side and blue on the other side. The white side is debossed with Boehringer Ingelheim company logo and ‘A4’. The blue side is plain. Each tablet contains 80 mg telmisartan and 10 mg amlodipine.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension. Treatment should not be initiated with this fixed-dose combination. (see Section 4.2 Dose and Method of Administration)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

PRITOR/AMLODIPINE should be taken once daily.

PRITOR/AMLODIPINE can be administered with other antihypertensive drugs.

Replacement therapy

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

Add on therapy

PRITOR/AMLODIPINE may be administered in patients whose blood pressure is not adequately controlled with amlodipine or telmisartan alone.

Individual dose titration with the components (i.e. telmisartan and amlodipine) is recommended before changing to the fixed-dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to PRITOR/AMLODIPINE 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Renal impairment

No dosage adjustment is required for patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by haemofiltration and is not dialysable. Amlodipine is not dialysable (see Section 4.4 Special Warnings and Precautions for Use).

Hepatic impairment

In patients with mild to moderate hepatic impairment, PRITOR/AMLODIPINE should be administered with caution. For telmisartan, the dosage should not exceed 40 mg once daily (see Section 4.4 Special Warnings and Precautions for Use).

PRITOR/AMLODIPINE is contraindicated in patients with severe hepatic impairment (see Section 4.3 Contraindications).

Elderly patients

No dose adjustment is necessary for elderly patients.

Normal amlodipine dosage regimens are recommended in the elderly, but increase of dosage should take place with care (see Section 4.4 Special Warnings and Precautions for Use).

Paediatric Use

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

Method of Administration

Tablet for oral administration.

PRITOR/AMLODIPINE may be taken with or without food.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active ingredients or to any of the excipients
- Hypersensitivity to dihydropyridine derivatives
- Pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction
- The concomitant use of PRITOR/AMLODIPINE with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2)

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated (see Section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Renovascular hypertension

Telmisartan: 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.

Increases in serum creatinine have been observed in studies with ACE-inhibitors in patients with single or bilateral renal artery stenosis. An effect similar to that observed with ACE inhibitors should be anticipated with PRITOR/AMLODIPINE.

Sodium- and/or volume-depleted patients

Telmisartan: Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of PRITOR/AMLODIPINE.

Dual blockade of the renin-angiotensin-aldosterone system

Telmisartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. PRITOR/AMLODIPINE can be administered with other antihypertensive drugs, however dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor blocker) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function (see Section 4.3 Contraindications).

In the ONTARGET trial, patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of hyperkalaemia, renal failure, hypotension and syncope compared with groups receiving telmisartan alone or ramipril alone (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). Concomitant use of PRITOR/AMLODIPINE and ramipril is therefore not recommended in patients with already controlled blood pressure.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

Telmisartan: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products (e.g. angiotensin converting enzyme inhibitors and angiotensin II receptor blockers has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure and/or death.

Combination use of ACE inhibitors or angiotensin receptor blockers, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor blocker, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Primary aldosteronism

Telmisartan: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Diabetes Mellitus

Exploratory post-hoc analyses of two placebo-controlled telmisartan trials suggested an increased risk of fatal myocardial infarction and unexpected cardiovascular death (death occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular cause, and without clinical or post mortem evidence of other etiology) in patients with diabetes mellitus who have no documented medical history of either coronary heart disease or myocardial infarction. In patients with diabetes mellitus, coronary heart disease may be asymptomatic and can therefore remain undiagnosed. Treatment with the blood pressure lowering agent PRITOR/AMLODIPINE may further reduce coronary perfusion in these patients. For this reason, patients with diabetes mellitus should undergo specific diagnostics and be treated accordingly before initiating therapy with PRITOR/AMLODIPINE.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Both telmisartan and amlodipine: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction

There are no data to support the use of PRITOR/AMLODIPINE in unstable angina pectoris and during or within one month of a myocardial infarction.

Amlodipine: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration 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.

Beta-blocker withdrawal

Amlodipine: Amlodipine is not a beta-blocker and therefore provides no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with cardiac failure

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

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

Hyperkalaemia

Telmisartan: During treatment with medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (e.g. heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with telmisartan.

Sorbitol

PRITOR/AMLODIPINE 40/5 mg and 40/10 mg tablets contain 168.64 mg sorbitol in each tablet.

PRITOR/AMLODIPINE 80/5 mg and 80/10 mg tablets contain 337.28 mg sorbitol in each tablet. Sorbitol is a source of fructose. PRITOR/AMLODIPINE 80/5 mg and 80/10 mg tablets are not recommended for use in patients with hereditary fructose intolerance. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use affect the bioavailability of other medicinal products for oral use administered concomitantly.

Ethnic differences

PRITOR/AMLODIPINE was effective when treating black patients (usually a low-renin population). The magnitude of blood pressure lowering in black patients approached that observed in non-black patients.

Telmisartan: As observed for angiotensin converting enzyme inhibitors, angiotensin receptor blockers are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Ischaemic heart disease

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

Use in hepatic impairment

Telmisartan: Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. PRITOR/AMLODIPINE is therefore, contraindicated for use in these patients.

PRITOR/AMLODIPINE should only be used with caution in patients with mild to moderate hepatic impairment (see Section 4.2 Dose and Method of Administration).

Amlodipine: The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Worsening of liver function test values may occur. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose (see Section 4.2 Dose and Method of Administration). Amlodipine should therefore be administered with caution in these patients and careful monitoring should be performed.

PRITOR/AMLODIPINE should therefore be used with caution in these patients.

Use in renal impairment and kidney transplantation

When PRITOR/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 PRITOR/AMLODIPINE in patients with a recent kidney transplant.

Telmisartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Amlodipine: Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses. Amlodipine is not dialysable.

Use in the elderly

The increase of the amlodipine dosage should take place with care in the elderly patients (see Sections 4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties, Pharmacokinetics in special patient groups, Elderly patients).

Paediatric Use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Interactions linked to the combination

No drug interaction studies have been conducted with PRITOR/AMLODIPINE and other medicinal products.

<u>To be taken into account with concomitant use</u>

Other antihypertensive agents: The blood pressure lowering effect of PRITOR/AMLODIPINE can be increased by concomitant use of other antihypertensive medicinal products and vice versa.

Medicinal products with blood pressure lowering potential: Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including PRITOR/AMLODIPINE, e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route): Reduction of the antihypertensive effect.

Interactions linked to telmisartan

To be taken into account with concomitant use

Other antihypertensive agents: Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Others: Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered particularly when initiating, adjusting or discontinuing concomitant PRITOR/AMLODIPINE.

Concomitant use requiring caution

Non-steroidal anti-inflammatory drugs (NSAIDs): Treatment with NSAIDs (i.e. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin-system like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Ramipril: In one study, the co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1 fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16% respectively. The clinical relevance of this observation is not fully known. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combining telmisartan with ramipril in the ONTARGET trial resulted in a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope compared to telmisartan alone or ramipril alone (see Section 5.1 Pharmacodynamic Properties, telmisartan). Concomitant use of telmisartan and ramipril is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor blockers including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.

Interactions linked to amlodipine

Concomitant use requiring caution

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

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required. Amlodipine should be used with caution together with CYP3A4 inhibitors.

CYP3A4 inducers: Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum). Amlodipine should be used with caution together with CYP3A4 inducers.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

To be taken into account with concomitant use

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Ciclosporin: No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases of ciclosporin were observed. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin dose reductions should be made as necessary.

Mechanistic Target of Rapamycin (mTOR) Inhibitors: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77% compared to simvastatin alone. Therefore, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Others: In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Additional information

Co-administration of amlodipine with cimetidine had no significant effect on the pharmacokinetics of amlodipine.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Nonclinical studies investigating the reproductive toxicity of PRITOR/AMLODIPINE have not been conducted. Nonclinical data available for the components of this fixed dose combination are reported below.

Telmisartan: Fertility of male and female rats was unaffected at oral telmisartan doses up to 100 mg/kg/day.

Amlodipine: There was no effect on the fertility of rats treated orally at doses of up to 18 mg/kg/day (about 16 times the MRHD of 10 mg/day on a mg/m^2 basis).

Use in pregnancy (Category D)

The effects of PRITOR/AMLODIPINE during pregnancy are not known. Nonclinical studies investigating the reproductive toxicity of PRITOR/AMLODIPINE have not been conducted. Effects related to the individual components are described below.

Telmisartan: Angiotensin II receptor blockers should not be initiated during pregnancy. The use of angiotensin II receptor blockers is not recommended during the first trimester of pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.
Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

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

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

Although there is no clinical experience with telmisartan in pregnant women, *in utero* exposure to drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and even death. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. Therefore, when pregnancy is detected, telmisartan should be discontinued as soon as possible.

Angiotensin II receptor blocker exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Oligohydramnios reported in this setting, presumably resulting from decreased fetal renal function, has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to occur when drug exposure has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor blocker only during the first trimester should be so informed. Women of child-bearing age should be warned of the potential hazards to their fetus should they become pregnant.

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

Telmisartan has been shown to cross the placenta in rats. There were no teratogenic effects when telmisartan was administered orally to rats and rabbits during the period of organogenesis at doses up to 50 and 45 mg/kg/day, respectively. However, fetal resorptions were observed at the highest dose level in rabbits. Administration of 50 mg/kg/day telmisartan to rats during pregnancy and lactation caused a decrease in birth weight and suppression of postnatal growth and development of the offspring. The no-effect dose level in rabbits was 15 mg/kg/day, and corresponded to a plasma AUC value that was about 9 times higher than that anticipated in women at the highest recommended dose. Plasma drug levels were not measured at the high dose level in rats, but data

from other studies suggest that they would have been similar to those in women at the maximum recommended dose.

Amlodipine: Calcium channel blockers carry the potential to produce fetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the fetus.

The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine (10 mg/kg as besilate salt, 7 mg/kg base), administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

Use in lactation

PRITOR/AMLODIPINE is contraindicated during lactation, since it is not known whether telmisartan is excreted in human milk. Nonclinical studies investigating the effects of PRITOR/AMLODIPINE during lactation have not been conducted.

Animal studies have shown excretion of telmisartan in breast milk. When administered orally to lactating rats at 50 mg/kg/day, telmisartan suppressed postnatal growth and development of the offspring.

Experience in humans indicates that amlodipine is transferred into human breast milk. The median amlodipine concentration ratio of milk/plasma in 31 lactating women with pregnancy-induced hypertension was 0.85 following amlodipine administration at an initial dose of 5 mg once daily which was adjusted as needed (mean daily dose and body weight adjusted daily dose: 6 mg and 98.7 microgram/kg, respectively). The estimated daily dose of amlodipine in the infant via breast milk was 4.17 microgram/kg.

Lactating women should either not be prescribed PRITOR/AMLODIPINE or should discontinue breastfeeding if PRITOR/AMLODIPINE is administered (see Section 4.3 Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems

Fixed dose combination

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

Adverse reactions reported in clinical trials with telmisartan plus amlodipine are shown below according to system organ class.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare
Infections and infestations			cystitis
Psychiatric disorders			depression, anxiety, insomnia
Nervous system disorders	dizziness	somnolence, migraine, headache, paraesthesia	syncope (faint), neuropathy peripheral, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders		vertigo	
Cardiac disorders		bradycardia, palpitations	
Vascular disorders		hypotension, orthostatic hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		cough	
Gastro-intestinal disorders		abdominal pain, diarrhoea, nausea	vomiting, gingival hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders		pruritus	eczema, erythema, rash
Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms (cramps in legs), myalgia, back pain	pain in extremity (leg pain)
Renal and urinary disorders			nocturia
Reproductive system and breast disorders		erectile dysfunction	
General disorders and administration site conditions	oedema peripheral	asthenia (weakness), chest pain, fatigue, oedema	malaise
Investigations		hepatic enzyme increased	blood uric acid increased

Additional information on the combination

Peripheral oedema, a recognised dose dependent adverse reaction of amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received PRITOR/AMLODIPINE as compared to patients who

received amlodipine 10 mg. In the factorial design trial, the oedema rates were 1.3% with PRITOR/AMLODIPINE 40 mg/5 mg and PRITOR/AMLODIPINE 80 mg/5 mg, 8.8 % with PRITOR/AMLODIPINE 40 mg/10 mg and PRITOR/AMLODIPINE 80 mg/10 mg and 18.4% with amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4% for PRITOR/AMLODIPINE 40 mg/5 mg and PRITOR/AMLODIPINE 80 mg/5 mg and 24.9% for amlodipine 10 mg.

Additional information on individual components

Adverse reactions previously reported with one of the individual components (amlodipine or telmisartan) may be potential adverse reactions with PRITOR/AMLODIPINE as well, even if not observed in clinical trials or during the post-marketing period.

Telmisartan

Other additional adverse reactions reported with telmisartan monotherapy in the hypertension indication, irrespective of causal association, were as follows:

Infections and infestations: sepsis including fatal outcome, urinary tract infections, cystitis, upper respiratory tract infections, bronchitis, infection, abcess, otitis media

Blood and lymphatic system disorders: anaemia, eosinophilia, thrombocytopenia

Immune system disorders: anaphylactic reaction, hypersensitivity, allergy

Metabolism and nutrition disorders: hyperkalaemia, hypoglycaemia (in diabetic patients), gout, hypercholesterolaemia, diabetes mellitus, hyponatraemia

Psychiatric disorders: nervousness, depression, anxiety, insomnia

Nervous system disorders: syncope (faint)

Eye disorders: visual impairment, conjunctivitis

Ear and labyrinth disorders: tinnitus, earache, vertigo

Cardiac disorders: tachycardia, angina pectoris, bradycardia

Vascular disorders: cerebrovascular disorder, hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders: dyspnoea, asthma, epistaxis

Gastrointestinal disorders: flatulence, abdominal discomfort, constipation, gastritis, haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, abdominal pain, diarrhoea, vomiting, dyspepsia, dry mouth

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

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

Musculoskeletal and connective tissue disorders: tendon pain (tendonitis like symptoms), arthritis, arthralgia, back pain, pain in extremity (leg pain), muscle spasms (cramps in legs), myalgia

Renal and urinary disorders: renal impairment (including acute kidney injury) (see also Section 4.4 Special Warnings and Precautions for Use), micturition frequency

General disorders: influenza like illness, pain, fever, chest pain, asthenia (weakness)

Investigations: haemoglobin decreased, blood creatinine increased, blood creatine phosphokinase (CPK) increased, abnormal ECG, hepatic enzyme increased, blood uric acid increased

Amlodipine

Other additional adverse reactions reported with amlodipine monotherapy, irrespective of causal association, were as follows:

Blood and lymphatic system disorders: leukopenia, thrombocytopenia

Immune system disorders: hypersensitivity

Metabolism and nutrition disorders: hyperglycaemia, anorexia, increased appetite

Psychiatric disorders: mood altered, confusional state, abnormal dreams, depersonalisation, nervousness, apathy, agitation, depression, anxiety, insomnia

Nervous system disorders: extrapyramidal disorder, postural dizziness, ataxia, amnesia, parosmia, hypertonia, syncope (faint), somnolence, headache, neuropathy peripheral, paraesthesia, hypoaesthesia, dysgeusia, tremor

Eye disorders: visual impairment, conjunctivitis, diplopia, eye pain, accommodation disorder, xerophthalmia

Ear and labyrinth disorders: tinnitus, vertigo

Cardiac disorders: myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation, tachycardia, cardiac failure, extrasystoles, bradycardia, palpitations

Vascular disorders: vasculitis, hot flush, peripheral ischaemia, hypotension

Respiratory, thoracic and mediastinal disorders: dyspnoea, rhinitis, epistaxis, cough

Gastrointestinal disorders: change of bowel habit, pancreatitis, gastritis, constipation, dysphagia, flatulence, abdominal pain, diarrhoea, vomiting, gingival hypertrophy, dyspepsia, nausea, dry mouth

Hepatobiliary disorders: hepatitis, jaundice, hepatic enzyme increased (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders: alopecia, purpura, skin discolouration, hyperhidrosis, angioedema (including fatal outcome), erythema multiforme, urticaria, dermatitis exfoliative, Stevens-Johnson syndrome, photosensitivity reaction, toxic epidermal necrolysis, dry skin, cold sweat, rash erythematous, rash maculopapular, pruritus

Musculoskeletal and connective tissue disorders: arthrosis, muscular weakness, muscle twitching, joint swelling, arthralgia, back pain, musle spasms (cramps in legs), myalgia

Renal and urinary disorders: micturition disorder, pollakiuria, micturition frequency, dysuria, polyuria, nocturia

Reproductive system and breast disorders: gynaecomastia, sexual dysfunction (male and female)

General disorders and administration site conditions: pain, chills, thirst, chest pain, oedema, asthenia (weakness), fatigue, malaise

Investigations: heart rate irregular, weight increased, weight decreased

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on telephone 13 11 26 (Australia).

Symptoms

There is no experience of overdose with PRITOR/AMLODIPINE. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.

The most prominent manifestations of telmisartan overdosage were hypotension, or tachycardia; bradycardia also occurred.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonist. Hypotension and bradycardia are usually seen within 1 to 5 hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome may occur.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid resuscitation) to maintain perfusion and cardiac output may be precipitating factors due to volume overload.

Treatment

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support, including elevation of the extremities, and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium may help to reverse the effects of calcium entry blockade. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-emesis is not recommended since haemodynamic instability and CNS depression may rapidly develop. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Telmisartan is not removed from blood by haemofiltration and is not dialysable. Amlodipine is not dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: angiotensin II receptor blocker, plain (telmisartan) combinations with dihydropyridine derivatives (amlodipine).

ATC code: C09DB04

Mechanism of action

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

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

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

Telmisartan

Telmisartan is an orally effective and specific angiotensin II receptor (type AT_1) blocker. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor and does not reveal relevant affinity for other receptors nor does it inhibit human plasma renin or block ion channels. The clinically relevant effect of AT_1 receptor blockade is to lower blood pressure by inhibition of angiotensin II mediated vasoconstriction leading to reduction of systemic vascular resistance. During administration with telmisartan, removal of angiotensin II negative feedback on renin secretion results in increased plasma renin activity, which in turn leads to increases in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppressed aldosterone levels indicate effective angiotensin II receptor blockade. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects or cause oedema.

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

After administration of the first dose of telmisartan, onset of antihypertensive activity occurs gradually within 3 hours. The maximal reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. With ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24 hour trough to peak ratio was consistently above 80% for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) after doses of 40 mg and 80 mg of telmisartan in placebo controlled clinical studies.

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is independent of gender or age, and is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, ramipril, hydrochlorothiazide, lisinopril and valsartan).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril

on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, transient ischaemic attack, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of patients at high risk of cardiovascular events.

The co-primary objectives of the ONTARGET trial were to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg is superior to ramipril 10 mg alone and if (b) telmisartan 80 mg is not inferior to ramipril 10 mg alone in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. Hypothesis tests were performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The principal patient exclusion criteria included: symptomatic heart failure or other specific cardiac diseases, syncopal episodes of unknown aetiology or planned cardiac surgery within 3 months of the start of study, uncontrolled hypertension or haemorrhagic stroke.

Patients were randomised to one of the three following treatment groups: telmisartan 80 mg (n=8542), ramipril 10 mg (n=8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n=8502), and followed for a mean observation time of 4.5 years. The population studied was 73% male, 74% Caucasian, 14% Asian and 43% were 65 years of age or older. Hypertension was present in nearly 83% of randomised patients: 69% of patients had a history of hypertension at randomisation and an additional 14% had actual blood pressure readings ≥ 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76%), statins (62%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%).

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. During the study, significantly less telmisartan patients (22.0%) discontinued treatment, compared to ramipril patients (24.4%) and telmisartan/ramipril patients (25.3%). The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Comparison of telmisartan versus ramipril: The choice of the non-inferiority margin of 1.13 was solely based on the results of the HOPE (Heart Outcomes Prevention Evaluation) study. Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7%) and ramipril (16.5%) groups. In the intention-to-treat (ITT) analysis, the hazard ratio for telmisartan versus ramipril was 1.01 (97.5% CI 0.93-1.10, p(non-inferiority)=0.0019). The non-inferiority result was confirmed in the per-protocol (PP) analysis, where the hazard ratio was 1.02 (97.5% CI 0.93-1.12, p (non-inferiority) =0.0078). Since the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 and the p-value for non-inferiority was below 0.0125 in both the ITT and PP analyses, the trial succeeded in demonstrating the non-inferiority of telmisartan versus ramipril in the prevention of the composite primary endpoint. The non-inferiority conclusion was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint in subgroups based on age, gender, race, baseline concomitant therapies or underlying diseases.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE, which had investigated the effect of ramipril versus placebo. The ITT hazard ratio of telmisartan versus ramipril for this endpoint in

ONTARGET was 0.99 (97.5% CI 0.90-1.08, p(non-inferiority)=0.0004), and confirmed by the PP hazard ratio of 1.00 (97.5% CI 0.91-1.11, p(non-inferiority)=0.0041.

Comparison of telmisartan plus ramipril combination versus ramipril monotherapy alone: Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone, thus superiority of the combination could not be demonstrated. The incidence of the primary endpoint was 16.3% in the telmisartan plus ramipril combination group, compared to the telmisartan (16.7%) and ramipril (16.5%) groups. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination group. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

Amlodipine

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

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, acute hypotension is not a feature of amlodipine administration.

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.

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Clinical Trials

Fixed dose combination (PRITOR/AMLODIPINE)

There have been no long-term clinical outcome studies conducted using the fixed-dose combination tablets.

The efficacy of PRITOR/AMLODIPINE for treatment of hypertension was studied in over 3400 patients in three pivotal randomised double-blind studies (one placebo-controlled and two active-controlled trials) and over 1400 patients in two supportive open-label follow-up trials. Adults with mild to severe uncomplicated essential hypertension (mean seated diastolic blood pressure ≥95 mmHg and <119 mmHg) were enrolled in the placebo-controlled trial. In the two active-controlled trials, adult patients with mean seated diastolic blood pressure ≥95 mmHg (if on antihypertensive treatment) or ≥100 mmHg (if not treated with an antihypertensive) and also did not respond adequately (mean seated diastolic blood pressure ≥90 mmHg) after 6 weeks of open-label amlodipine monotherapy were enrolled. Exclusion criteria for the trials were consistent with the Contraindications in the Product Information, and the conditions listed in the Special warnings and precautions for use. Patients with secondary hypertension, uncontrolled hypertension, and symptomatic congestive heart failure were excluded. No study was conducted specifically in telmisartan non-responders. The efficacy and safety of PRITOR/AMLODIPINE compared to telmisartan monotherapy was demonstrated in the pivotal placebo-controlled, parallel group factorial study.

In the 8-week multicentre, randomised, double-blind, placebo-controlled, parallel group factorial study, 1461 patients with mild to severe hypertension (mean baseline seated systolic/diastolic blood pressure 153.2/101.8 mmHg) underwent a 3-4 week placebo run-in period in order to wash out all antihypertensive medications before they were randomised to a double-blind active treatment. Treatment with each combination dose of PRITOR/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 across the therapeutic dose range:

PRITOR/AMLODIPINE dose	**mmHg reduction**
40/5 mg	-21.8/-16.5
80/5 mg	-22.1/-18.2
40/10 mg	-24.7/-20.2
80/10 mg	-26.4/-20.1

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

PRITOR/AMLODIPINE dose	**%**
40/5 mg	71.6
80/5 mg	74.8
40/10 mg	82.1
80/10 mg	85.3

A subset of 1050 patients in the study had moderate to severe hypertension (DBP ≥100 mmHg). In these patients who are likely to need more than one antihypertensive agent to achieve blood pressure goal, the mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40 mg/5 mg; -22.5/-19.1 mmHg with 80 mg/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg).

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 systolic and diastolic blood pressure reductions consistently over the entire 24-hour dosing period.

In a further multicentre, double-blind, active-controlled study, a total of 1097 patients with mild to severe hypertension (mean seated baseline systolic/diastolic blood pressure 149.5/96.6 mmHg) who were not adequately controlled on amlodipine 5 mg received PRITOR/AMLODIPINE (40 mg/5 mg or 80 mg/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the

combination was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures:

Dose	mmHg reduction
PRITOR/AMLODIPINE 40/5 mg	-13.6/-9.4
PRITOR/AMLODIPINE 80/5 mg	-15.0/-10.6
amlodipine 5 mg	-6.2/-5.7
amlodipine 10 mg	-11.1/-8.0

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were: 56.7% with PRITOR/AMLODIPINE 40 mg/5 mg and 63.8% with PRITOR/AMLODIPINE 80 mg/5 mg compared to 42.0% with amlodipine 5 mg and 56.7% with amlodipine 10 mg.

Oedema related events (peripheral oedema, generalised oedema, and oedema) were significantly lower in patients who received PRITOR/AMLODIPINE (40 mg/5 mg or 80 mg/5 mg) as compared to patients who received amlodipine 10 mg (4.4% vs. 24.9%, respectively).

In another multicentre, double-blind, active-controlled study, a total of 947 patients with mild to severe hypertension (mean seated baseline systolic/diastolic blood pressure 147.5/95.6 mmHg) who were not adequately controlled on amlodipine 10 mg received PRITOR/AMLODIPINE (40 mg/10 mg or 80 mg/10 mg) or amlodipine alone (10 mg). After 8 weeks, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressures:

Dose	mmHg reduction
PRITOR/AMLODIPINE 40/10 mg	-11.1/-9.2
PRITOR/AMLODIPINE 80/10 mg	-11.3/-9.3
amlodipine 10 mg	-7.4/-6.5

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were 63.7% with PRITOR/AMLODIPINE 40 mg/10 mg and 66.5% with PRITOR/AMLODIPINE 80 mg/10 mg compared to 51.1% with amlodipine 10 mg.

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of PRITOR/AMLODIPINE was maintained over the trial period.

In patients not adequately controlled on amlodipine 5 mg, PRITOR/AMLODIPINE achieved similar (40 mg/5 mg) or better (80 mg/5mg) blood pressure control compared to amlodipine 10 mg with significantly less oedema.

In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, PRITOR/AMLODIPINE 40 mg/5 mg or PRITOR/AMLODIPINE 80 mg/5 mg may achieve similar blood pressure control with less oedema.

The antihypertensive effect of PRITOR/AMLODIPINE was similar irrespective of age and gender, and was similar in patients with and without diabetes.

PRITOR/AMLODIPINE has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease (see also Section 5.1 Pharmacodynamic Properties, amlodipine).

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of the fixed dose combination

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

The bioavailability study (1235.12) conducted with the fixed dose combination showed that administration of a high-fat meal with the PRITOR/AMLODIPINE 80 mg/10 mg tablet decreased the total area under the plasma concentration-time curve (AUC) and C_{max} for telmisartan by about 24% and 60%, respectively. For amlodipine, AUC and C_{max} were not altered (see Section 4.2 Dose and Method of Administration). However, considering the flat dose response curve and the wide therapeutic range of telmisartan, the food effect on telmisartan pharmacokinetics observed in the study 1235.12 would translate into only minor differences with regard to the blood pressure lowering effect, which are not considered to be clinically relevant, neither for efficacy, nor for safety.

Pharmacokinetics of the single components

Absorption

Telmisartan: Following oral administration of telmisartan, absorption is rapid (t_{max} ranges from 0.5 to 2 hours) although the amount absorbed varies. Absolute bioavailability of telmisartan was shown to be dose dependent. The mean absolute bioavailability of 40 mg telmisartan was 40%, whereas the mean absolute bioavailability of the 160 mg dose amounted to about 60%.

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). The small reduction in AUC should not cause a reduction in the therapeutic efficacy. Therefore, telmisartan may be taken with or without food.

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 highly bound to plasma protein (>99.5%), mainly albumin and alpha-1-acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 6.6 L/kg.

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 drugs is bound to plasma proteins in hypertensive patients.

Metabolism

Telmisartan: Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for the conjugate. Telmisartan is not metabolised by the cytochrome P450 system.

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

Excretion

Telmisartan: Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of 18.3-23.0 hours.

The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose interval.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose.

Amlodipine: Amlodipine elimination from the plasma is biphasic, with a termination elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous

administration for 7-8 days. 10% of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Pharmacokinetics in special patient groups

Paediatric population (age below 18 years)

No pharmacokinetic data for PRITOR/AMLODIPINE are available in the paediatric population.

Elderly patients

Telmisartan: The pharmacokinetics of telmisartan does not differ between younger and elderly patients (i.e. patients older than 65 years of age).

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) and elimination half-life.

Gender

Telmisartan: Plasma concentrations are generally 2-3 times higher in females than in males. In clinical trials, however, no clinically significant increases in blood pressure response or incidences of orthostatic hypotension were found in females. No dosage adjustment is necessary.

Renal impairment

Telmisartan: Lower plasma concentrations were observed in patients with renal insufficiency (creatinine clearance 30-80 mL/min) undergoing dialysis, however, this has proved not to be of clinical significance. Telmisartan is highly bound to plasma proteins in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Amlodipine: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment.

Hepatic impairment

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with the telmisartan/amlodipine combination. Nonclinical data available for the individual components are reported below.

Telmisartan: Telmisartan was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Amlodipine: Amlodipine was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Carcinogenicity

No carcinogenicity studies have been conducted with the telmisartan/amlodipine combination. Nonclinical data available for the individual components are reported below.

Telmisartan: There was no evidence of carcinogenicity in rats and mice. Two-year studies in mice and rats did not show any increases in tumour incidences when telmisartan was administered in the diet at doses up to 1000 and 100 mg/kg/day, respectively. Plasma AUC values at the highest dose levels were approximately 60 and 15 times greater, respectively, than those anticipated in humans at the maximum recommended dose.

Amlodipine: Preclinical data reveal no special hazard for humans based on conventional studies of carcinogenic potential. Amlodipine did not induce tumours in rats at oral doses up to 2.5 mg/kg (plasma levels similar to those achieved clinically).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each PRITOR/AMLODIPINE tablet also contains sodium hydroxide, povidone, meglumine, sorbitol, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, maize starch, colloidal anhydrous silica and Pigment Blend PB-57699 GREY (ARTG PI 106387) as colouring agent.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

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

Due to the hygroscopic property of PRITOR/AMLODIPINE tablets, they should not be removed from their foil pack until required for administration.

6.5 NATURE AND CONTENTS OF CONTAINER

PRITOR/AMLODIPINE tablets are available in PA/Al/PVC/Al blister packs containing 7*, 14*, 28, 30*, 56* and 98* tablets.

** Not currently distributed in Australia.*

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

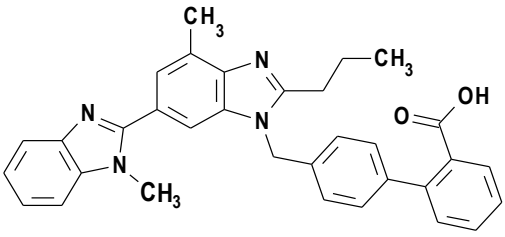
6.7 PHYSICOCHEMICAL PROPERTIES

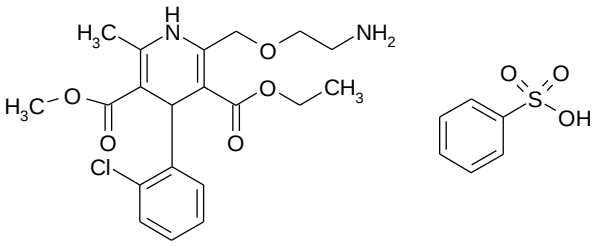
Chemical structure

Telmisartan is an off-white to yellowish crystalline powder. It is practically insoluble in water, very slightly soluble in ethanol, slightly soluble in methanol and soluble in a mixture of chloroform and methanol (1:1).

Amlodipine besilate is a white or almost white powder that is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol.

Structural formula:





and enantiomer

Telmisartan	Amlodipine (as besilate)
Chemical name:	*Chemical name:*
4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)-methyl]-[1,1'-biphenyl]-2-carboxylic acid	3-ethyl-5-methyl (4RS)-2-[-(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3,5-dicarboxylate benzenesulphonate
Molecular formula: $C_{33}H_{30}N_4O_2$	*Molecular formula*: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$
Molecular weight: 514.6	*Molecular weight*: 567.1

CAS number

Telmisartan: 144701-48-4

Amlodipine (as besilate): 111470-99-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

5 June 2013

10 DATE OF REVISION

13 July 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.9	Updated section to add the risk of potential non-cardiogenic pulmonary oedema due to amlodipine overdose