SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TELINOD 40/5; 40/10; 80/5; 80/10; Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TELINOD 40/5: Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).
TELINOD 40/10: Each tablet contains 40 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).
TELINOD 80/5: Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).
TELINOD 80/10: Each tablet contains 80 mg telmisartan 10 mg amlodipine (as amlodipine besilate).
TELINOD is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
TELINOD 40/5: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L389’.
TELINOD 40/10: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L390’.
TELINOD 80/5: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L391’.
TELINOD 80/10: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L388’.

4. CLINICAL PARTICULARS

a. Therapeutic indications

Replacement therapy:

Treatment of essential hypertension in patients who have been stabilised on the two component medicines used at the same dose.

Add on therapy:

TELINOD is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.

b. Posology and method of administration

Posology:

Adults

TELINOD should be taken once daily.

Replacement Therapy:

Patients taking telmisartan and amlodipine as separate tablets can instead take TELINOD containing the same component doses in one tablet once daily.

Add on therapy:

TELINOD may be administered in patients whose blood pressure is not adequately controlled with amlodipine alone.

The usual starting dose of TELINOD is 40/5 mg once daily.

If additional blood pressure lowering is needed after at least 2 weeks of therapy, the dose may be titrated up to a maximum of 80 /10 mg once daily.

Special populations

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (see section 4.4). Amlodipine and telmisartan are not dialysable.

Hepatic impairment

In patients with mild to moderate hepatic impairment TELINOD should be administered with caution. For telmisartan the dose should not exceed 40 mg once daily (i.e TELINOD 40/5 mg or 40/10 mg).

Elderly

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 and section 5.2).

Paediatric population

Children and adolescents

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

Method of administration

Tablet for oral administration.

TELINOD may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to telmisartan, amlodipine, dihydropyridine derivatives, or to any of the ingredients of TELINOD listed in section 6.1.

- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30 mL/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- Porphyria
- Lithium therapy: Concomitant administration with TELINOD may lead to toxic blood concentrations of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.6)
- The concomitant use of TELINOD with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5)
- 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
- Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin blockers such as TELINOD is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving Telinod, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of TELINOD and aliskiren is therefore contraindicated (see section 4.3).
TELINOD should not be used concomitantly with aliskiren (see section 4.3).

Pregnancy
TELINOD should not be initiated during pregnancy (see section 4.3).

Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with TELINOD should be stopped immediately, and if appropriate, alternative therapy should be started (see section 4.6).

Hepatic impairment
Telmisartan as contained in TELINOD is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. The half-life of amlodipine as contained in TELINOD is prolonged in patients with impaired liver function and dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range (i.e. TELINOD 40/5 or 80/5) and caution should be used, both on initial treatment and when increasing the dose. TELINOD should therefore be used with caution in patients with mild to moderate impairment of liver function and should not be used in patients with severe liver impairment (see section 4.3).

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 medicines that affect the renin-angiotensin-aldosterone system (see section 4.3).

Renal impairment and kidney transplant
When TELINOD 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 TELINOD in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia
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 TELINOD.

Other conditions with stimulation of the renin-angiotensin- aldosterone system
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 TELINOD, that affects this system, has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Concomitant use of fluoroquinolones
Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers such as TELINOD may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (See section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE

inhibitors/angiotensin receptor blockers (i.e., TELINOD) whether used separately and/or concomitantly.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin-system. Therefore, the use of TELINOD is not recommended.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
TELINOD is contraindicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy.

Unstable angina pectoris; acute myocardial infarction
There are no data to support the use of TELINOD in unstable angina pectoris and during or within one month of a myocardial infarction.

Patients with cardiac failure
In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution.
Calcium channel blockers, including amlodipine as contained in TELINOD, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Hyperkalaemia
During treatment with TELINOD 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 medicines that affect the renin-angiotensin-system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with TELINOD.

Diabetes mellitus
In diabetic patients with an additional cardiovascular risk, i.e., patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering medicines such as ARBs or ACE-inhibitors such as TELINOD. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g., exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with TELINOD.

Elderly patients
The increase of the amlodipine dose as contained in TELINOD should take place with care in the elderly patients (see section 4.2 and section 5.2).

Other
Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease may result in a myocardial infarction or stroke.

Sodium
Each tablet contains less than 1 mmol sodium (23 mg) per tablet, essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction
No interactions between the two components of the fixed dose combinations have been observed in clinical studies.

Interactions linked to the combination
No interaction studies have been performed with TELINOD and other medicines.

Other antihypertensive medicines
The blood pressure lowering effect of TELINOD can be increased by concomitant use of other antihypertensive medicines.

Medicines with blood pressure lowering potential
Based on their pharmacological properties it can be expected that the following medicines may potentiate the hypotensive effects of TELINOD: 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 the telmisartan component of TELINOD
Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

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

Dual blockage of the RAAS with ARBs, ACE inhibitors or aliskiren
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Non-steroidal anti-inflammatory medicines
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. Medicines 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 medicines like TELINOD by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Ramipril
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.

Fluoroquinolones
Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers such as TELINOD, may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Digoxin
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49 %) and in trough concentration (20 %) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

Interactions linked to the amlodipine component of TELINOD
Grapefruit and grapefruit juice
Administration of TELINOD 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.

The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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).

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 coadministration of calcium channel blockers such as amlodipine contained in TELINOD be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

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 TELINOD 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 (average 0 % - 40 %) of ciclosporin were observed. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on TELINOD, 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, TELINOD 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.

4.6 Fertility, pregnancy and lactation
TELINOD should not be used during pregnancy and lactation (see section 4.3).
Effects related to the mono components are described below.

Women of Childbearing Potential
Women of childbearing age should ensure effective contraception.

Pregnancy
Telmisartan
Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed TELINOD should be discontinued.
Medicines affecting the renin-angiotensin system, such as TELINOD, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.
Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
Should exposure to TELINOD have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken TELINOD should be closely observed for hypotension.

Amlodipine
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding
TELINOD is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breastmilk. Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7 %, with a maximum of 15 %.
The effect of amlodipine on infants is unknown. Because of the potential adverse reactions in breastfed infants, TELINOD should not be used by breastfeeding mothers (see section 4.3).

Fertility
No data from controlled clinical studies with the fixed dose combination or with the individual components are available.

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 (fainting), somnolence, dizziness, or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a vehicle or operating machinery. If patients experience these adverse effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects
Summary of the safety profile
The most frequent adverse reactions include dizziness and peripheral oedema. Serious syncope may occur less frequently.

Tabulated summary of adverse reactions

The following side effects derived from the use of the TELINOD (telmisartan and amlodipine combination) or the use of the monocomponents (telmisartan or amlodipine) in clinical trials or from post-marketing experience are shown in the table below classified by MedDRA System organ class and MedDRA Preferred terms.

MedDRA SOC	**Fixed Dose Combination**	**Telmisartan monotherapy**	**Amlodipine monotherapy**
Infections and infestations			
Sepsis (including fatal outcome)	-	Less frequent	-
Upper respiratory tract infection	-	Less frequent	-
Urinary tract infection	-	Less frequent	-
Cystitis	Less frequent	Less frequent	-
Blood and the lymphatic system disorders			
Leukopenia	-	-	Less frequent
Thrombocyto-penia	-	Less frequent	Less frequent
Anaemia	-	Less frequent	-
Eosinophilia	-	Less frequent	-
Immune system disorders			
Anaphylactic reaction	-	Less frequent	-
Hypersensitivity	-	Less frequent	Less frequent
Angioedema (with fatal outcome)	-	Less frequent	Less frequent
Metabolism and nutrition disorders			
Hyperkalaemia	-	Less frequent	-
Hypoglycaemia (in diabetic patients)	-	Less frequent	-
Hyperglycaemia	-	-	Less frequent
Psychiatric disorders			
Depression	Less frequent	Less frequent	Less frequent
Anxiety	Less frequent	Less frequent	Less frequent

Confusional state	-	-	Less frequent
Insomnia	Less frequent	Less frequent	Less frequent
Altered mood	-	-	Less frequent
Nervous system disorders			
Syncope (fainting)	Less frequent	Less frequent	Less frequent
Somnolence	Less frequent	-	Frequent
Dizziness	Frequent	-	Frequent
Extrapyramidal disorder	-	-	Frequency unknown
Hypertonia	-	-	Less frequent
Migraine	Less frequent	-	-
Headache	Less frequent	-	Frequent
Neuropathy peripheral	Less frequent	-	Less frequent
Paraesthesia	Less frequent	-	Less frequent
Hypoaesthesia	Less frequent	-	Less frequent
Dysgeusia	Less frequent	-	Less frequent
Tremor	Less frequent	-	Less frequent
Eye disorders			
Visual impairment	-	Less frequent	Frequent
Diplopia	-	-	Frequent
Ear and labyrinth disorders			
Vertigo	Less frequent	Less frequent	-
Tinnitus	-	-	Less frequent
Cardiac disorders			
Myocardial infarction	-	-	Less frequent
Ventricular tachycardia	-	-	Less frequent
Dysrhythmia	-	-	Less frequent

Atrial fibrillation	-	-	Less frequent
Bradycardia	Less frequent	Less frequent	Less frequent
Tachycardia	-	Less frequent	-
Palpitations	Less frequent	-	Frequent
Vascular disorders			
Hypotension	Less frequent	Less frequent	Less frequent
Orthostatic hypotension	Less frequent	Less frequent	-
Flushing	Less frequent	-	Frequent
Vasculitis	-	-	Less frequent
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	-	Less frequent	Frequent
Cough	Less frequent	-	Less frequent
Rhinitis	-	-	Less frequent
Gastrointestinal disorders			
Pancreatitis	-	-	Less frequent
Gastritis	-	-	Less frequent
Abdominal pain	Less frequent	Less frequent	Frequent
Diarrhoea	Less frequent	Less frequent	Frequent
Vomiting	Less frequent	Less frequent	Less frequent
Gingival hypertrophy	Less frequent	-	Less frequent
Dyspepsia	Less frequent	Less frequent	Frequent
Constipation	-	-	Frequent
Nausea	Less frequent	-	Frequent
Dry mouth	Less frequent	Less frequent	Less frequent
Flatulence	-	Less frequent	-
Abdominal discomfort	-	Less frequent	-
Change of bowel habit	-	-	Frequent
Hepato-biliary disorders			

Hepatitis	-	-	Less frequent
Jaundice	-	-	Less frequent
Hepatic function abnormal/liver disorder	-	Less frequent	-
Hepatic enzyme increased (mostly consistent with cholestasis)	-	-	Less frequent
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis	-	-	Frequency unknown
Stevens-Johnson syndrome	-	-	Less frequent
Erythema multiforme	-	-	Less frequent
Dermatitis exfoliative	-	-	Less frequent
Drug eruption	-	Less frequent	-
Toxic skin eruption	-	Less frequent	-
Photosensitivity reaction	-	-	Less frequent
Urticaria	-	Less frequent	Less frequent
Eczema	Less frequent	Less frequent	-
Erythema	Less frequent	Less frequent	-
Rash	Less frequent	Less frequent	Less frequent
Alopecia	-	-	Less frequent
Purpura	-	-	Less frequent
Skin discolouration	-	-	Less frequent
Hyperhidrosis	-	Less frequent	Less frequent
Musculoskeletal, connective tissue and bone disorders			
Arthralgia	Less frequent	Less frequent	Less frequent
Back pain	Less frequent	Less frequent	Less frequent

Pain in extremity (leg pain)	Less frequent	Less frequent	-
Tendon pain (tendonitis like symptoms)	-	Less frequent	-
Joint swelling	-	-	Frequent
Muscle spasms (cramps in legs)	Less frequent	Less frequent	Frequent
Myalgia	Less frequent	Less frequent	Less frequent
Renal and urinary disorders			
Renal impairment (including acute renal injury)	-	Less frequent	-
Nocturia	Less frequent	-	Less frequent
Micturition disorder	-	-	Less frequent
Pollakiuria	-	-	Less frequent
Reproductive system and breast disorders			
Erectile dysfunction	Less frequent	-	Less frequent
Gynaecomastia	-	-	Less frequent
General disorders and administration site conditions			
Chest pain	Less frequent	Less frequent	Less frequent
Pain	-	-	Less frequent
Oedema	Less frequent	-	Frequent
Oedema peripheral	Frequent	-	-
Asthenia (weakness)	Less frequent	Less frequent	Frequent
Fatigue	Less frequent	-	Frequent
Malaise	Less frequent	-	Less frequent
Influenza like illness	-	Less frequent	-

Investigations			
Increased hepatic enzyme	Less frequent	Less frequent	-
Increased blood creatinine	-	Less frequent	-
Increased blood creatine phosphokinase	-	Less frequent	-
Decreased haemoglobin	-	Less frequent	-
Increased blood uric acid	Less frequent	Less frequent	-
Increased weight	-	-	Less frequent
Decreased weight	-	-	Less frequent

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

There is no experience of overdose with TELINOD. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.
The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia might also occur.
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

Supportive treatment should be instituted.
If ingestion is recent, induction of vomiting may be considered. In healthy volunteers the use of charcoal up to 2 hours after rate administration of amlodipine 10 mg has been shown to reduce the absorption of amlodipine.
Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted.

Telmisartan and amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicines – other hypotensives
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs) and calcium channel blockers; ATC Code: C09DB04.

TELINOD combines two antihypertensive compounds with different mechanisms of action: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect.

Telmisartan:
Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II 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.
The binding is long lasting.
Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan monotherapy. Telmisartan monotherapy does not inhibit human plasma renin or block ion channels.
In man, an 80 mg dose of telmisartan monotherapy almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and is still measurable up to 48 hours.
After administration of the first dose of telmisartan monotherapy, onset of antihypertensive activity occurs within 3 hours. The maximum reduction in blood pressure is generally attained 4 weeks after the start of treatment and is sustained during long-term therapy.
There is an apparent trend to a dose relationship with regard to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent.
In patients with hypertension, telmisartan monotherapy reduces both systolic and diastolic blood pressure without affecting pulse rate.

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 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 a change in filtration fraction or proteinuria.

Combination of substances:
Treatment with each combination dose of TELINOD resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.
The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.
The antihypertensive effect of the combination of telmisartan and amlodipine was similar irrespective of age and gender and was similar in patients with and without diabetes.
The combination of telmisartan and amlodipine has not been studied in any patient population other than hypertension.

5.2 Pharmacokinetic properties
Pharmacokinetics of the Fixed Dose Combination
The rate and extent of absorption of the fixed dose combination are similar to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetics of the single components
Absorption
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When the fixed dose combination is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan was approximately 25 % at a dose of 80/10 mg. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.
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 is largely bound to plasma protein (> 99,5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{ss}) is approximately 500 L.
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.

Biotransformation
Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.
Amlodipine is extensively (approximately 90 %) metabolised by the liver to inactive metabolites.

Elimination
Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of > 20 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.
After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is < 2 % of dose. Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min) compared with hepatic blood flow (about l 500 ml/min).
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 percent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Paediatric patients (age below 18-years)
No pharmacokinetic data are available in the paediatric population.

Gender effects
Gender differences in plasma concentrations of telmisartan were observed, C_{max} and AUC being approximately 3 and 2 fold higher, respectively, in females compared to males without relevant influence on efficacy.

Elderly patients
The pharmacokinetics of telmisartan do not differ between younger and elderly patients. 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.

Patients with renal impairment
Lower plasma concentrations of telmisartan were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Patients with hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40 - 60 % in AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Telmisartan layer:
Magnesium stearate
Mannitol (Pearlitol SD 200)
Meglumine
Povidone K-25
Sodium hydroxide
Sodium Stearyl Fumarate
Amlodipine layer:
Cellulose, microcrystalline
Crospovidone (Polyplasdone XL 10)
Magnesium stearate
FD & C Blue #1/ Brilliant Blue FCF AC 11-13 %
Iron Oxide Black
Starch, maize

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30 ˚C. Store in the original package until required to use.

6.5 Nature and contents of container

TELINOD tablets are packed in (Aluminium Foil & Cold Form Blister Foil) blister strips.
The blisters are placed into cardboard boxes.
Pack size: 30 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

TELINOD 40/5: 57/7.1.3/0574
TELINOD 40/10: 57/7.1.3/0575
TELINOD 80/5: 57/7.1.3/0576
TELINOD 80/10: 57/7.1.3/0577

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 June 2025

10. DATE OF REVISION OF THE TEXT