

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BP-TEL 10/80 AM TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Amlodipine Besilate BP Equivalent to Amlodipine 10mg

Telmisartan USP 80mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A brown circular shape biconvex film coated tablet, plain on both the sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy

It is indicated in adults whose blood pressure is not adequately controlled on Telmisartan 40 mg/Amlodipine 10 mg or Telmisartan 80 mg/Amlodipine 5 mg.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of BP-TEL 10/80 AM containing the same component doses.

4.2 Posology and method of administration

Posology

The recommended dose of this medicinal product is one tablet per day.

The maximum recommended dose is one tablet 80 mg telmisartan/10 mg amlodipine per day. This medicinal product is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (see section 4.5).

Add on therapy

Telmisartan 80 mg/Amlodipine 10 mg may be administered in patients whose blood pressure is not adequately controlled on Telmisartan 40 mg/Amlodipine 10 mg.

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

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

Replacement therapy

Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of telmisartan 80mg/amlodipine containing the same component doses in one tablet once daily.

Elderly (> 65 years)

No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Normal amlodipine dose regimens are recommended in the elderly, but increase of dose should take place with care (see section 4.4).

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using telmisartan/amlodipine in such patients as amlodipine is not dialysable and telmisartan is not removed from blood by haemofiltration and not dialysable (see also section 4.4).

No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

It is contraindicated in patients with severe hepatic impairment (see section 4.3). In patients with mild to moderate hepatic impairment telmisartan/amlodipine should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section 4.4).

Paediatric population

The safety and efficacy of telmisartan/amlodipine in children aged below 18 years have not been established. No data are available.

Method of administration

Oral use.

It can be taken with or without food. It is recommended to take it with some liquid. It should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration (see section 6.6).

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Biliary obstructive disorders and severe hepatic impairment
- 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 telmisartan/amlodipine with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Pregnancy

Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker therapy is considered essential, 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 angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 and 4.6).

Hepatic impairment

Telmisartan 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 is prolonged and AUC values are higher in patients with impaired liver function; dose recommendations have not been established. 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.

Telmisartan/amlodipine should therefore be used with caution in these patients.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery

to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system (RAAS).

Renal impairment and kidney transplantation

When telmisartan/amlodipine is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan/amlodipine in patients with a recent kidney transplant. Amlodipine is not dialysable and telmisartan is not removed from blood by haemofiltration and not dialysable.

Volume and/or sodium depleted patients

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 telmisartan. If hypotension occurs with telmisartan/amlodipine, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure (see section 4.8).

Primary aldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Unstable angina pectoris, acute myocardial infarction

There are no data to support the use of telmisartan/amlodipine 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 (see section 5.1). 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.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. Hyperkalaemia may be fatal in the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events,.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated. The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extensive trauma).

Serum potassium should be monitored closely in these patients (see section 4.5).

Elderly patients

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

Ischaemic heart disease

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

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor blockers (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor blockers. If intestinal angioedema is diagnosed, telmisartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

4.5 Interaction with other medicinal products and other forms of interaction

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 performed.

To be taken into account with concomitant use

Other antihypertensive medicinal products

The blood pressure lowering effect of telmisartan/amlodipine can be increased by concomitant use of other antihypertensive medicinal products.

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 this medicinal product, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor blockers 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 blockers, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other antihypertensive agents acting on the renin-angiotensin-aldosterone system (RAAS)

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 (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dose regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor blockers.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor blockers and medicinal products that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Ramipril

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC₀₋₂₄ and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Concomitant use to be taken into account

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 amlodipine

Concomitant use requiring caution

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 PK 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 be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

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.

Concomitant use to be taken into account

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.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed.

Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine 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, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal reproductive toxicity studies with telmisartan/amlodipine have not been performed.

Telmisartan

The use of angiotensin II receptor blockers is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor blockers is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Studies with telmisartan in animals have shown reproductive toxicity (see section 5.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor blockers, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor blocker therapy is considered essential, 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 angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor blocker therapy 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) (see section 5.3).

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 (see sections 4.3 and 4.4).

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Breast-feeding

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 no information is available regarding the use of telmisartan during breast-feeding, telmisartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility

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

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.

In preclinical studies, no effects of telmisartan on male and female fertility were observed. In some patients treated by calcium channel blockers, reversible biochemical changes in the head of spermatozoa have been reported. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

It has moderate influence on the ability to drive and use machines. When driving vehicles or operating machinery it should be taken into account that syncope, somnolence, dizziness, or vertigo may occasionally occur

when taking antihypertensive therapy (see section 4.8). If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

Adverse reactions have been ranked under headings of frequency using the following convention:

very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Class	Organ	Twynsta	Telmisartan	Amlodipine
<i>Infections and infestations</i>				
Uncommon			upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis	
Rare	cystitis		sepsis including fatal outcome ¹	
<i>Blood and lymphatic system disorders:</i>				
Uncommon			anaemia	
Rare			thrombocytopenia, eosinophilia	
Very rare				leukocytopenia, thrombocytopenia
<i>Immune system disorders:</i>				
Rare			hypersensitivity, anaphylactic reaction	
Very rare				hypersensitivity

Metabolism and nutrition disorders			
Uncommon		hyperkalaemia	
Rare		hypoglycaemia (in diabetic patients), hyponatraemia	
Very rare			hyperglycaemia

Psychiatric disorders			
Uncommon			mood change
Rare	depression, anxiety, insomnia		confusion

Nervous system disorders			
Common	dizziness		
Uncommon	somnolence, migraine, headache, paraesthesia		
Rare	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor		
Very rare			extrapyramidal syndrome, hypertonia

Eye disorders			
Common			visual disturbance (including diplopia)
Uncommon			visual impairment
Rare		visual disturbance	

Ear and labyrinth disorders			
Uncommon	vertigo		tinnitus

Cardiac disorders			
Uncommon	bradycardia, palpitations		

Rare		tachycardia	
Very rare			myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation
Vascular disorders			
Uncommon	hypotension, orthostatic hypotension, flushing		
Very rare			vasculitis

Respiratory, thoracic and mediastinal disorders			
Uncommon	cough	dyspnoea	dyspnoea, rhinitis
Very rare	interstitial lung disease ³		
Gastrointestinal disorder			
Common			altered bowel habits (including diarrhoea and constipation)
Uncommon	abdominal pain, diarrhoea, nausea	flatulence	
Rare	vomiting, gingival hypertrophy, dyspepsia, dry mouth	stomach discomfort	
Very rare			pancreatitis, gastritis
Hepato-biliary disorders			
Rare		hepatic function abnormal, liver disorder ²	
Very rare			hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders			
Uncommon	pruritus	hyperhidrosis	alopecia, purpura, skin discolouration, hyperhidrosis

Rare	eczema, erythema, rash	angioedema (including fatal outcome), drug eruption, toxic skin eruption, urticaria	
Very rare			angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity
Not known			toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			
Common			ankle swelling
Uncommon	arthralgia, muscle spasms (cramps in legs), myalgia		
Rare	back pain, pain in extremity (leg pain)	tendon pain (tendinitis like symptoms)	
Renal and urinary disorders			
Uncommon		renal impairment including acute renal failure	micturition disorder, pollakiuria
Rare	nocturia		
Reproductive system and breast disorders			
Uncommon	erectile dysfunction		gynaecomastia
General disorders and administration site condition			
Common	peripheral oedema		
Uncommon	asthenia, chest pain, fatigue, oedema		pain
Rare	malaise	influenza-like illness	
Investigations			
Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased

Rare	blood uric acid increased	blood creatine phosphokinase increased, haemoglobin decreased	
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¹: the event may be a chance finding or related to a mechanism currently not known

²: most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

³: cases of interstitial lung disease (predominantly interstitial pneumonia and eosinophilic pneumonia) have been reported from post-marketing experience with telmisartan

Description of selected adverse reactions

Intestinal angioedema

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor blockers (see section 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

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 have been reported.

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 overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since

ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose of both telmisartan and amlodipine. 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.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Amlodipine is not dialysable and telmisartan is not removed from blood by haemofiltration and not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs) and calcium channel blockers, ATC code: C09DB04.

Twynsta 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.

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

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT₁) blocker. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT₁ receptor. Telmisartan selectively binds the AT₁ receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT₂ and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin.

Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

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

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 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. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship 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 reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of substances representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

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

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.

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 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.

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination

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

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. 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). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected 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_{dss}) is approximately 500 l.

The volume of distribution of amlodipine is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5 % of circulating amlodipine 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 biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration ($C_{\max}$) and, to a smaller extent, the 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. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

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

Linearity/non-linearity

The small reduction in AUC for telmisartan is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. $C_{\max}$ and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Amlodipine exhibits linear pharmacokinetics.

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Gender

Differences in plasma concentrations of telmisartan were observed, with $C_{\max}$ and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ in young and elderly patients.

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan was observed. However, lower plasma concentrations 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.

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 of telmisartan 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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Maize Starch
Crospovidone
Povidone K30
Purified Talc
Croscarmellose Sodium
Colloidal Anhydrous Silica
Magnesium Stearate
Hypromellose E15
Titanium Dioxide
Iron Oxide of Red
Isopropyl Alcohol
Dichloromethane

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's
3 x 10's (10 tablets are packed in one Alu-Alu blister and 3 such Alu-Alu blisters are kept in one carton along with package insert).

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6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Marketing authorisation holder:

Company name: INNOCIA LIFESCIENCES PVT. LTD.,

Address: Block A, No.12, Balaji Nagar, Ambattur, Chennai-600 053

Country: INDIA.

Manufacturing Site:

ATOZ Pharmaceuticals Pvt.Ltd.,

No.12, Balaji Nagar, Ambattur, Chennai-600053,

India.

8. MARKETING AUTHORISATION NUMBER

CTD8971

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/03/2022

10. DATE OF REVISION OF THE TEXT

21/03/2022