Summary of Product Characteristics

1. Name of the medicinal product

Trade name : ZYTEL AM PLUS

Generic name : (Telmisartan 80mg & Amlodipine 10mg Tablets)

2. Qualitative and Quantitative composition

Each uncoated bilayered tablet contains: Telmisartan BP 80mg Amlodipine Besilate BP Equivalent to Amlodipine 10mg

Excipients q.s.

Colour: Tartrazine Lake

3. Pharmaceutical form

Uncoated Tablets

One side white & other side yellow coloured elongated, biconvex, bilayered, uncoated tablets having both side plain

4. Clinical Particulars

4.1.Therapeutic indications

ZYTEL AM PLUS is indicated for: Treatment of essential hypertension in adults: Add on therapy

ZYTEL AM PLUS is indicated in adults whose blood pressure is not adequately controlled on amlodipine 10 mg alone.

Replacement therapy

Adult patients receiving Telmisartan and amlodipine from separate tablets can instead receive tablets of **ZYTEL AM PLUS** containing the same component doses.

4.2. Posology and method of administration

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

The maximum recommended dose is one tablet of Telmisartan 40mg/Amlodipine 5mg or Telmisartan 80mg/Amlodipine 10mg per day.

This medicinal product is indicated for long term treatment Administration of Amlodipine with grapefruit or grapefruit juice is not recommended as bioavilability may be increased in some patients resulting in increased blood pressure lowering effects.

Add on therapy: ZYTEL AM PLUS may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg alone.

Replacement therapy: Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of ZYTEL AM PLUS 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 dosage regimens are recommended in the elderly, but increase of dosage should take place with care.

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 and telmisartan are not dialysable. No posology adjustment is required for patients
with mild to moderate renal impairment.

Hepatic impairment
ZYTEL AM PLUS is contraindicated in patients with severe hepatic impairment 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.

Paediatric population
The safety and efficacy of telmisartan/amlodipine in children aged below 18 years have not been established.

Method of administration
Oral use

4.3. Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.
- Second and third trimesters of pregnancy.
- 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 products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/ 1.73 m^2)

4.4. Special warnings and precautions for use Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy.

Hepatic impairment

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance.

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.

- This product contains lactose. Patients with rare hereditary problems of galactose intolerance

, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

This product contains Tartrazine lake which may cause allergic reactions

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.

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

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and nonselective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

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.

4.6. Pregnancy, Lactation and Fertility

Pregnancy

Telmisartan

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

Studies with telmisartan in animals have shown reproductive toxicity.

Infants whose mothers have taken angiotensin II receptor antagonists 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.

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,

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

This medicinal product has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or using machines. 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 previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with ZYTEL AM PLUS as well, even if not observed in clinical trials or during the post-marketing period.

Tabulated list of adverse reactions

The safety and tolerability of ZYTEL AM PLUS has been evaluated in five controlled clinical studies with over 3,500 patients, over 2,500 of whom received telmisartan in combination

with amlodipine.

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

System Organ Class	ZYTEL AM PLUS	Telmisartan	Amlodipine
Infections and infestations			
Uncommon		upper respiratory tract infection including pharyngitis and sinusitis, urinary tract	
Rare	cystitis	sepsis including	
Blood and lymphatic system disorders:			
Uncommon		anaemia	
Rare		thrombocytopenia, eosinophilia	
Very rare			leukocytopenia, thrombocytope
Immune system disorders:			
Rare		hypersensitivity, anaphylactic reaction	
Very rare			hypersensitivity
Metabolism and nutrition disorders			
Uncommon		hyperkalaemi	
Rare		hypoglycaemia (in diabetic	
Very rare		hyperglycaemia	
Psychiatric disorders			
Uncommon			confusion
Rare	depression, anxiety,		confusion
Nervous system disorders			
Common	dizziness		
Uncommon	somnolence, migraine, headache		

Rare	syncope, peripheral		

	hypoaesthesia, dysgeusia,		
Very rare			extrapyramidal syndrome, hypertonia
Eye disorders			
Common			visual disturbance (including diplopia)
Uncommon			visual impairment
Rare		visual	
Ear and labyrinth disorders			
Uncommon	vertigo		tinnitus
Cardiac disorders			
Uncommon	bradycardia,		
Rare		tachycardia	
Very rare			myocardial infarction, arrhythmia,
Vascular disorders			
Uncommon	hypotension, orthostatic hypotensi		
Very rare			vasculitis
Respiratory, thoracic and mediastinal disorders			
Uncommon	cough	dyspno	dyspnoea,
Very rare	interstitial lung		
Gastrointestinal disorder			
Common			altered bowel habits (including diarrhoea and constipation)
Uncommon	abdominal pain, diarrhoea,	flatulence	

Rare	vomiting, gingival hypertrophy, dyspepsia, dry mouth	stomach discomfort	
Very rare			pancreatitis, gastritis
Hepato-biliary disorders			
Rare		hepatic function abnormal, liver disorder	
Very rare			hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with
Skin and subcutaneous tissue disorders			
Uncommon	pruritus	hyperhidrosis	alopecia, purpura, skin discolouration,
Rare	eczema, erythema, rash	angioedema (with fatal outcome), drug eruption, toxic skin	
Very rare			angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens
Not known			toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			
Common			ankle swelling
Uncommon	arthralgia, muscle spasms (cramps in		
Rare	back pain, pain in extremity	tendon pain (tendinitis	
Reproductive system and breast disorders			
Uncommon	erectile dysfuncti		gynaecomastia
General disorders and administration site condition			
Common	peripheral		
Uncommon	asthenia, chest pain, fatigue,		pain

Rare	malaise	influenza-like illness	
Investigation			
Uncommon	hepatic enzyme s increas	blood creatinine increased	

Rare	blood uric acid increased	blood creatine phosphokinase increased, haemoglobin	

4.9. Overdose

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.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists and calcium channel blockers;

ATC Code: C09DB04.

Telmisartan: Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. 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.

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.

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

5.2. Pharmacokinetic properties

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 (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose).

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 (Vdss) is approximately 500 l.

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 (approximatively 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 (Cmax) 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.

5.3. Preclinical safety data

Telmisartan

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation. In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These

changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offspring such as lower body weight and delayed eye opening was observed.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 8 times* the maximum recommended human dose of 10 mg/day on an mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle- stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

6. Pharmaceutical Particulars

List of Excipients

Microcrystalline Cellulose (101) Mannitol, Crospovidone (XL-10)(Polyplasdone XL-10) Sodium Hydroxide (Pellets), Polysorbate-80 Isopropyl Alcohol Purified Water Sodium Starch Glycolate (Primojel), Croscarmellose Sodium (Ac-DiSol) Microcrystalline Cellulose (PH-102) (Avicel 102) Colloidal Silicon Dioxide, Magnesium Stearate, Anhydrous Lactose (DCL 21)

Colour: Tartrazine Lake Sodium Steryl Fumarate

6.1. Incompatibilities

Not applicable.

6.2. Shelf Life

24 months from date of manufacturing

6.3. Special Precautions for Storage

Store at a temperature below 30ºC. Protect from light & moisture.

6.4. Nature and Contents of container

10 tablets packed in Alu/Alu blister and such 03 blisters packed in a printed carton along with insert.

6.5. Special precautions for disposal and other handling

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture. Remove the tablets from the blister only directly prior to intake. Any unused medicinal product or waste material should be disposed of in accordance with local requirement

6.6. Mode of selling

Prescription Only Medicine

7. Marketing Authorization Holder

Company name: Cadila Healthcare Limited

Name	**:**	Mr. Gaurav
Address	**:**	Zydus Corporate Park, Scheme No. 63, Survey No. 536 Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Ahmedabad, Gujarat, India-382481

8. Marketing Authorization Number

TAN 22 HM 0349

9. Date of First Authorization/Renewal of Authorization

21/09/2022

10. Date of Revision of the Text

29/12/2022