

## 1. NAME OF THE MEDICINAL PRODUCT

TWYNSTA 40 mg/5 mg tablets  
TWYNSTA 40 mg/10 mg tablets  
TWYNSTA 80 mg/5 mg tablets  
TWYNSTA 80 mg/10 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg or 80 mg telmisartan and 5 mg or 10 mg amlodipine (as amlodipine besilate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

The tablets are for oral administration.

TWYNSTA 40 mg/5 mg tablets are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A1.

TWYNSTA 40 mg/10 mg tablets are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A2.

TWYNSTA 80 mg/5 mg tablets are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A3.

TWYNSTA 80 mg/10 mg tablets are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A4.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of essential hypertension in adults.

#### Replacement Therapy

Patients receiving telmisartan and amlodipine from separate tablets may instead receive TWYNSTA containing the same component doses.

#### Add on therapy

TWYNSTA is indicated in patients whose blood pressure is not adequately controlled on telmisartan or amlodipine monotherapy.

#### Initial therapy

TWYNSTA may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Base the choice of Twynsta tablets as initial therapy for hypertension on an assessment of potential benefits and risks including whether the patient is likely to tolerate the starting dose of Twynsta tablets.

Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as stroke, heart attacks and heart failure), kidney failure and vision problems, so prompt treatment is clinically relevant. Consider the patient's baseline blood pressure, the target goals and the incremental likelihood of achieving goals with a combination compared to monotherapy when deciding whether to use Twynsta tablets as initial therapy. Individual blood pressure goals may vary based upon the patient's risk.

## **4.2 Posology and method of administration**

### **DOSAGE**

#### **Adults**

TWYNSTA should be taken once daily. The maximum recommendation dose is Twynsta 80mg/10mg one tablet per day.

#### **Replacement Therapy**

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

#### **Add on therapy**

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

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

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

#### **Initial therapy**

A patient may be initiated on TWYNSTA if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of TWYNSTA is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on TWYNSTA 80/5 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.

Initial therapy with Twynsta is not recommended in patients  $\geq 75$  years old or with hepatic impairment. Correct imbalances on intravascular volume- or salt-depletion, before initiating therapy with Twynsta tablets.

TWYNSTA can be administered with other antihypertensive drugs.

### **Special populations**

#### **Geriatric patients**

No dose adjustment is necessary for geriatric 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 (see sections Special warnings and precautions, and Pharmacokinetics).

#### **Paediatric patients**

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

#### **Renal impairment**

No posology adjustment is required for patients with renal impairment, including those on haemodialysis. Limited experience is available with severe renal impairment or haemodialysis. Caution is advised when using Twynsta in such patients as amlodipine and telmisartan are not dialysable. Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable

### **Hepatic impairment**

In patients with mild to moderate hepatic impairment TWYNSTA should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section Contraindications).

### **Method of administration**

TWYNSTA tablets are for once-daily oral administration and should be swallowed whole with liquid. TWYNSTA can be taken with or without food.

### **Handling Instructions**

Due to the hygroscopic property of the tablets they should be taken out of the sealed blister shortly before administration.

### **4.3 Contraindications**

- Hypersensitivity to the active substances, or to any of the excipients
- Hypersensitivity to dihydropyridine derivatives
- Second and third trimesters of pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction
- The concomitant use of TWYNSTA with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m<sup>2</sup>)

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see section Special warnings and precautions) the use of the product is contraindicated.

### **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 anti-hypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with angiotensin II receptor blocker should be stopped immediately, and if appropriate, alternative therapy should be started.

#### **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 antagonists, 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, extend trauma).

Serum potassium should be monitored closely in these patients.

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 TWYNSTA.

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; dosage 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.

TWYNSTA 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.

Renal impairment and kidney transplant:

When TWYNSTA 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 TWYNSTA in patients with a recent kidney transplant.

Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

Dual blockade of the renin-angiotensin-aldosterone system:

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

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.

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

#### Sorbitol:

TWYNSTA tablets 40/5 mg contains 168.64 mg sorbitol in each tablet.

TWYNSTA tablets 40/10 mg contains 168.64 mg sorbitol in each tablet.

TWYNSTA tablets 80/5 mg contains 337.28 mg sorbitol in each tablet. Sorbitol is a source of fructose. TWYNSTA tablets 80/5 mg is not recommended for use in patients with hereditary fructose intolerance.

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#### 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 agents such as ARBs or ACE-inhibitors. 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 TWYNSTA.

#### Geriatric patients

The increase of the amlodipine dosage should take place with care in the geriatric patients (see sections Dosage and Administration and Pharmacokinetics).

#### Ethnic differences:

TWYNSTA was effective when treating black patients (usually a low-renin population).

#### Ischaemic heart disease:

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

### **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 drugs interaction studies have been performed with TWYNSTA and other medicinal products.

#### *Other antihypertensive agents*

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

#### *Agents 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 TWYNSTA, e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

#### *Corticosteroids (systemic route)*

Reduction of the antihypertensive effect.

#### Interactions linked to telmisartan

Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC<sub>0-24</sub> and C<sub>max</sub> of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.

Cases have also been reported with angiotensin II receptor blocker including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with NSAIDs (i.e. ASA at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and their renal function should be monitored at the beginning of combined treatment.

A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

### Interactions linked to amlodipine

#### *Grapefruit and grapefruit juice*

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

#### *CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. 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.

#### *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, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

### *Additional information*

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

## **4.6 Fertility, Pregnancy and Lactation**

The effects of TWYNSTA during pregnancy and lactation are not known. Effects related to the mono components are described below.

### Pregnancy

#### Telmisartan:

The use of angiotensin II receptor blocker is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blocker should be stopped immediately, and, if appropriate, alternative therapy should be started.

Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

The use of angiotensin II receptor blockers is contraindicated during the second and third trimester of pregnancy. Angiotensin II receptor blocker exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II receptor blocker 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 blocker 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.

### Lactation

Twynsta is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Non-clinical studies have shown excretion of telmisartan in breast milk.

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 nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of this therapy for the mother (see section Contraindications).

### Fertility

No studies on fertility in humans with the fixed dose combination or with the individual components have been performed.

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

In non-clinical 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.

#### 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, 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. If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

#### 4.8 Undesirable effects

##### Summary of the safety profile

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

No additional adverse reactions were identified in clinical trials with the combination telmisartan plus amlodipine compared to the adverse reactions of the monocomponents. Peripheral oedema, a recognised dose dependent adverse reaction of the monocomponent amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

Adverse reactions previously reported with one of the monocomponents (telmisartan or amlodipine) may be potential adverse reactions with TWYNSTA as well, even if not observed in clinical trials or during the post-marketing period. Therefore in addition to the reported adverse reactions during the TWYNSTA development programme all adverse reactions reported in patients who received telmisartan or amlodipine monotherapy, have been listed for TWYNSTA.

##### Tabulated summary of adverse reactions

The following adverse reactions derived from the use of the telmisartan/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.

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 Organ Class	TWYNSTA	Telmisartan	Amlodipine
<b><i>Infections and infestations:</i></b>			
Uncommon		upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis	
Rare	cystitis	sepsis including fatal outcome <sup>1</sup>	
<b><i>Blood and lymphatic system disorders:</i></b>			
Uncommon		anaemia	
Rare		thrombocytopenia, eosinophilia	
Very rare			leukopenia, thrombocytopenia
<b><i>Immune system disorders:</i></b>			
Rare		hypersensitivity, anaphylactic reaction	
Very rare			hypersensitivity
<b><i>Metabolism and nutrition disorders:</i></b>			
Uncommon		hyperkalaemia	
Rare		hypoglycaemia (in	

		diabetic patients), hyponatraemia	
Very rare			hyperglycaemia
<b><i>Psychiatric disorders:</i></b>			
Uncommon		depression, insomnia	depression, anxiety, insomnia, mood altered
Rare	depression, anxiety, insomnia	anxiety	confusional state
<b><i>Nervous system disorders:</i></b>			
Common	dizziness		somnolence, dizziness, headache
Uncommon	somnolence, migraine, headache, paraesthesia	syncope (faint)	syncope (faint), paraesthesia, hypoesthesia, dysgeusia, tremor
Rare	syncope (faint), neuropathy peripheral, hypoesthesia, dysgeusia, tremor		
Very rare			hypertonia, neuropathy peripheral
Not known			extrapyramidal disorder
<b><i>Eye disorders:</i></b>			
Common			visual impairment, diplopia
Rare		visual impairment	
<b><i>Ear and labyrinth disorders:</i></b>			
Uncommon	vertigo	vertigo	tinnitus
<b><i>Cardiac disorders:</i></b>			
Common			palpitations
Uncommon	bradycardia, palpitations	bradycardia	ventricular tachycardia, arrhythmia, atrial fibrillation, bradycardia
Rare		tachycardia	
Very rare			myocardial infarction
<b><i>Vascular disorders:</i></b>			
Common			flushing
Uncommon	hypotension, orthostatic hypotension, flushing	hypotension, orthostatic hypotension	hypotension
Very rare			vasculitis
<b><i>Respiratory, thoracic and mediastinal disorders:</i></b>			
Common			dyspnoea
Uncommon	cough	dyspnoea	cough, rhinitis
<b><i>Gastrointestinal disorders:</i></b>			
Common			abdominal pain, diarrhoea, dyspepsia, constipation, nausea,

			change of bowel habit
Uncommon	abdominal pain, diarrhoea, nausea	abdominal pain, diarrhoea, vomiting, dyspepsia, flatulence	vomiting, dry mouth,
Rare	vomiting, gingival hypertrophy, dyspepsia, dry mouth	dry mouth, abdominal discomfort	
Very rare			gingival hypertrophy, pancreatitis, gastritis
<b><i>Hepato-biliary disorders:</i></b>			
Rare		hepatic function abnormal, liver disorder <sup>2</sup>	
Very rare			hepatitis, jaundice, hepatic enzyme increased (mostly consistent with cholestasis)
<b><i>Skin and subcutaneous tissue disorders:</i></b>			
Uncommon	pruritus	rash, pruritus, hyperhidrosis	urticaria, rash, pruritus, alopecia, purpura, skin discolouration, hyperhidrosis
Rare	eczema, erythema, rash	angioedema (including fatal outcome), drug eruption, toxic skin eruption, urticaria, eczema, erythema	
Very rare			angioedema, erythema multiforme, dermatitis exfoliative, Stevens-Johnson syndrome, photosensitivity reaction
Not known			toxic epidermal necrolysis
<b><i>Musculoskeletal and connective tissue disorders:</i></b>			
Common			joint swelling, muscle spasms
Uncommon	arthralgia, back pain, muscle spasms (cramps in legs), myalgia	back pain, muscle spasms, myalgia	arthralgia, back pain, myalgia
Rare	pain in extremity (leg pain)	arthralgia, pain in extremity (leg pain), tendon pain (tendonitis like symptoms)	
<b><i>Renal and urinary disorders:</i></b>			
Uncommon		renal impairment including acute renal failure	nocturia, micturition disorder, pollakiuria
Rare	nocturia		
<b><i>Reproductive system and breast disorders:</i></b>			
Uncommon	erectile dysfunction		erectile dysfunction, gynaecomastia
<b><i>General disorders and administration site condition:</i></b>			

Very common			oedema
Common	oedema peripheral		asthenia, fatigue
Uncommon	asthenia, chest pain, fatigue, oedema	chest pain, asthenia	chest pain, pain, malaise
Rare	malaise	influenza-like illness	
<b>Investigations:</b>			
Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased
Rare	blood uric acid increased	hepatic enzymes increased, blood creatine phosphokinase increased, haemoglobin decreased, blood uric acid increased	

<sup>1</sup>: the event may be a chance finding or related to a mechanism currently not known

<sup>2</sup>: 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.

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

## 4.9 Overdose

### Symptoms:

There is no experience of overdose with TWYNSTA. 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 also occurred. 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. 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. If symptomatic hypotension should occur, 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.

Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

ATC Code: C09DB04.

### Mode of action

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 effective 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 effects.

In man, 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.

#### Amlodipine:

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

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

### **Pharmacodynamics**

#### Telmisartan:

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 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 SBP. In this respect data concerning DBP are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan).

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

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

Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.

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:

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.

### **Clinical Trials**

#### Telmisartan:

##### Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of cardiovascular high risk patients.

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

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure.

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

Telmisartan had similar efficacy to ramipril in reducing the primary endpoint. The incidence of the primary endpoint was similar in the telmisartan (16.7%), ramipril (16.5%) and telmisartan plus ramipril combination (16.3%) arms. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5% CI 0.93 - 1.10, p (non-inferiority) = 0.0019). The treatment effect was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint based on age, gender, race, baseline therapies or underlying disease.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo. The hazard ratio of telmisartan vs. ramipril for this endpoint in ONTARGET was 0.99 (97.5% CI 0.90 - 1.08, p (non-inferiority) = 0.0004).

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore, the use of a combination of telmisartan and ramipril is not recommended in this population.

### Amlodipine:

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

#### Use in Patients with Heart Failure:

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

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

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

#### Fixed dose combination (TWYNSTA)

In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure  $\geq 95$  and  $< 110$  mmHg) underwent a 3-4 week placebo run-in period in order to wash out all antihypertensive medications before they were randomised to a double-blind active treatment. Treatment with each combination dose of TWYNSTA resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

The telmisartan/amlodipine combinations showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range:

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

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

%	TWYNSTA dose
71.6	40/5 mg
74.8	80/5 mg
82.1	40/10 mg
85.3	80/10 mg

A subset of 1050 patients in the factorial design study had moderate to severe hypertension (DBP  $\geq 100$  mmHg). In these patients who are likely to need more than one antihypertensive agent to achieve blood pressure goal, the observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40/5 mg; -22.5/-19.1 mmHg with 80/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg). Additionally, combination therapy showed notably lower oedema rates (1.4% with 40/5 mg; 0.5% with 80/5 mg; 17.6% with amlodipine 10 mg).

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, double-blind, active-controlled study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received TWYNSTA (40/5 mg or 80/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combination was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures:

mmHg reduction	Dose
-13.6 / -9.4	TWYNSTA 40/5 mg
-15.0 / -10.6	TWYNSTA 80/5 mg
-6.2 / -5.7	Amlodipine 5 mg
-11.1 / -8.0	Amlodipine 10 mg

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

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

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

mmHg reduction	Dose
-11.1 / -9.2	TWYNSTA 40/10 mg
-11.3 / -9.3	TWYNSTA 80/10 mg
-7.4 / -6.5	Amlodipine 10 mg

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

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

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

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

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

TWYNSTA has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

## 5.2 Pharmacokinetics properties

### Pharmacokinetics 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.

### Pharmacokinetic 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 telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The small 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 biexponential decay pharmacokinetics with a terminal elimination half-life of > 20 hours.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, exclusively 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 1500 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 per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

### Linearity

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.

### **PK in Specific Populations**

#### Paediatric population (age below 18 years)

No pharmacokinetic data for TWYNSTA are available in the paediatric population.

#### Gender differences

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.

#### Geriatric patients

The pharmacokinetics of telmisartan do not differ between younger and geriatric 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.

#### 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.

### 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**

Colloidal anhydrous silica, FD&C blue No 1 aluminium lake (E133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

Please refer to the packaging for information on shelf-life.

### **6.4 Special precautions for storage**

Do not store above 30°C.

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

### **6.5 Nature and contents of container**

10 bilayer tablets per blister strip (blister strip made from aluminium foil).

Cartons containing 1 or 3 blister strips (10 x 1, 10 x 3 bilayer tablets).

Not all presentations are available locally.

## **7. MANUFACTURER**

Manufactured by:

Cipla Limited

Verna Industrial Estate

Goa-403 722

INDIA

Packed & released by:

Rottendorf Pharma GmbH

59320 Ennigerloh

GERMANY

For Boehringer Ingelheim International GmbH

Ingelheim am Rhein

Germany

## **8. PRODUCT REGISTRATION NUMBER**

40 mg/5 mg - MAL20112135ACZ

40 mg/10 mg - MAL20112136ACZ

80 mg/5 mg - MAL20112137ACZ

80 mg/10 mg - MAL20112138ACZ

## **9. DATE OF REVISION OF THE TEXT**

11 Jan 2024

**Store in a safe place out of the reach of children!**