

TWYNSTA®

Telmisartan and Amlodipine besilate

COMPOSITION

1 tablet contains:

[1,1'-biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6-bi-1H-benzimidazole]-1'-yl)methyl] (= telmisartan) 40 or 80 mg

3-ethyl-5-methyl (4RS)-2-[-(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (= amlodipine) 5 or 10 mg, as besilate

Excipients: colloidal anhydrous silica, FD&C blue No 1 aluminium lake (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol

TWYNSTA tablets 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

PHARMACEUTICAL FORM

TWYNSTA tablets 40/5 mg

Telmisartan / amlodipine layered tablets 40/5 mg 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 tablets 40/10 mg

Telmisartan / amlodipine layered tablets 40/10 mg 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 tablets 80/5 mg

Telmisartan / amlodipine layered tablets 80/5 mg 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 tablets 80/10 mg

Telmisartan / amlodipine layered tablets 80/10 mg 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.

INDICATIONS

Treatment of essential hypertension.

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.

DOSAGE AND ADMINISTRATION

Dosage

Adults

TWYNSTA should be taken once daily.

The maximum recommended dose is TWYNSTA 80mg/10mg, one tablet per day. TWYNSTA is indicated for long term treatment.

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. 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 TWYNSTA 40/5mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

TWYNSTA can be administered with other antihypertensive drugs.

Special Populations

Geriatric patients

No dose adjustment is necessary for geriatric patients.

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. Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using TWYNSTA in such patients as 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.

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 m²)

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see SPECIAL WARNINGS AND PRECAUTIONS) the use of the product is contraindicated.

SPECIAL WARNINGS AND PRECAUTIONS

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.

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 melitus, 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 ischaemia, 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. If hypotension occurs with TWYNSTA, 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.

Hepatic impairment

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium blockers, amlodipine half-life in patients with impaired liver function and dosage recommendations have not been established. 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, hypotension and 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 blocker) is not recommended in patients with already controlled blood pressure 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.

Heart failure:

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Sorbitol:

TWYNSTA tablets 40/5 mg contain 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.

TWYNSTA tablets 80/10 mg contains 337.28 mg sorbitol in each tablet. Sorbitol is a source of fructose. TWYNSTA tablets 80/10 mg is not recommended for use in patients with hereditary fructose intolerance.

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.

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.**

INTERACTIONS

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

Interactions linked to the combination

No drug interaction studies have been 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

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements Angiotensin II **blockers** such as telmisartan, attenuate diuretic induced potassium loss.

Potassium sparing diuretics e.g. spirinolactone, 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.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage 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 the caution, especially in the elderly. Patients should be adequately hydrated and their renal function should be monitored 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.

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

With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased 22% and 50% respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, Hypericum perforatum) may lead to a lower plasma concentration of amlodipine.

Simvastatin

Co-administration of multiple doses of amlodipine with simvastatin 80mg 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.

Immunosuppressants

Amlodipine may increase the systemic exposure of ciclosporin or tacrolimus when co-administered. Frequent monitoring of trough blood levels of ciclosporin and tacrolimus and dose adjustment when appropriate is recommended.

Others

Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, ciclosporin, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Additional information

Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine.

USE IN SPECIFIC POPULATIONS

Pregnancy, Lactation and Fertility

Pregnancy

Telmisartan:

The use of angiotensin II receptor blockers 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative 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.

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

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.

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

Amlodipine:

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor blockers have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

Pregnancy:

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

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 has been identified in breastfed infants of treated women. 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 preclinical studies, no effects of telmisartan on male and female fertility were observed. Similarly, no effects on male and female fertility were reported for amlodipine (see TOXICOLOGY).

Driving and Using 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.

ADVERSE REACTIONS

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.

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1000 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).

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

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.

MedDRA System Organ Class terminology	Adverse Reaction	Frequencies according to EU SmPC guideline
Infections and infestations	sepsis (including fatal outcome)	rare ²⁾
	upper respiratory tract infection	uncommon ²⁾
	urinary tract infection	uncommon ²⁾
	cystitis	rare ¹⁾ , uncommon ²⁾
Blood and lymphatic system disorders	leukopenia	very rare ³⁾
	thrombocytopenia	rare ²⁾ , very rare ³⁾
	anaemia	uncommon ²⁾
	eosinophilia	rare ²⁾
Immune system disorders	anaphylactic reaction	rare ²⁾
	hypersensitivity	rare ²⁾ , very rare ³⁾
Metabolism and nutrition disorders	hyperkalaemia	uncommon ²⁾
	hypoglycaemia (in diabetic patients)	rare ²⁾
	hyperglycaemia	very rare ³⁾
	Hyponatraemia ²⁾	rare ²⁾
Psychiatric disorders	depression	rare ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	anxiety	rare ¹⁾ , rare ²⁾ , uncommon ³⁾
	insomnia	rare ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	mood altered	uncommon ³⁾
Nervous system disorders	syncope (faint)	rare ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	somnolence	uncommon ¹⁾ , common ³⁾
	dizziness	common ¹⁾ , common ³⁾
	extrapyramidal disorder	not known ³⁾
	migraine	uncommon ¹⁾
	headache	uncommon ¹⁾ , common ³⁾
	neuropathy peripheral	rare ¹⁾ , very rare ³⁾

	paraesthesia	uncommon ¹⁾ , uncommon ³⁾
	hypoesthesia	rare ¹⁾ , uncommon ³⁾
	dysgeusia	rare ¹⁾ , uncommon ³⁾
	tremor	rare ¹⁾ , uncommon ³⁾
Eye disorders	visual impairment	rare ²⁾ , common ³⁾
Ear and labyrinth disorders	vertigo	uncommon ¹⁾ , uncommon ²⁾
	tinnitus	uncommon ³⁾
Cardiac disorders	myocardial infarction	very rare ³⁾
	ventricular tachycardia	uncommon ³⁾
	arrhythmia	uncommon ³⁾
	atrial fibrillation	uncommon ³⁾
	bradycardia	uncommon ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	tachycardia	rare ²⁾
	palpitations	uncommon ¹⁾ , common ³⁾
Vascular disorders	hypotension	uncommon ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	orthostatic hypotension	uncommon ¹⁾ , uncommon ²⁾
	flushing	uncommon ¹⁾ , common ³⁾
	vasculitis	very rare ³⁾
Respiratory, thoracic and mediastinal disorders	dyspnoea	uncommon ²⁾ , common ³⁾
	cough	uncommon ¹⁾ , uncommon ³⁾
	rhinitis	uncommon ³⁾
Gastrointestinal disorders	pancreatitis	very rare ³⁾
	gastritis	very rare ³⁾
	abdominal pain	uncommon ¹⁾ , uncommon ²⁾ , common ³⁾
	diarrhoea	uncommon ¹⁾ , uncommon ²⁾ , common ³⁾
	vomiting	rare ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	gingival hypertrophy	rare ¹⁾ , very rare ³⁾
	dyspepsia	rare ¹⁾ , uncommon ²⁾ , common ³⁾
	nausea	uncommon ¹⁾ , common ³⁾
	dry mouth	rare ¹⁾ , rare ²⁾ , uncommon ³⁾
	flatulence	uncommon ²⁾
	abdominal discomfort	rare ²⁾
	change of bowel habit	common ³⁾

Hepatobiliary disorders	hepatitis	very rare ³⁾
	jaundice	very rare ³⁾
	hepatic function abnormal/ liver disorder	rare ²⁾
	hepatic enzyme increased (mostly consistent with cholestasis)	very rare ³⁾
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome	very rare ³⁾
	angioedema (including fatal outcome)	rare ²⁾ , very rare ³⁾
	erythema multiforme	very rare ³⁾
	dermatitis exfoliative	very rare ³⁾
	drug eruption	rare ²⁾
	toxic skin eruption	rare ²⁾
	photosensitivity reaction	very rare ³⁾
	urticaria	rare ²⁾ , uncommon ³⁾
	eczema	rare ¹⁾ , rare ²⁾
	erythema	rare ¹⁾ , rare ²⁾
	rash	rare ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	pruritus	uncommon ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	alopecia	uncommon ³⁾
	purpura	uncommon ³⁾
	skin discolouration	uncommon ³⁾
	hyperhidrosis	uncommon ²⁾ , uncommon ³⁾
Musculoskeletal and connective tissue disorders	arthralgia	uncommon ¹⁾ , rare ²⁾ , uncommon ³⁾
	back pain	uncommon ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	pain in extremity (leg pain)	rare ¹⁾ , rare ²⁾
	tendon pain (tendinitis like symptoms)	rare ²⁾
	muscle spasms (cramps in legs)	uncommon ¹⁾ , uncommon ²⁾ , common ³⁾
	myalgia	uncommon ¹⁾ , uncommon ²⁾ , uncommon ³⁾
Renal and urinary disorders	renal impairment (including acute renal failure)	uncommon ²⁾

	nocturia	rare ¹⁾ , uncommon ³⁾
	micturition disorder	uncommon ³⁾
	pollakiuria	uncommon ³⁾
Reproductive system and breast disorders	erectile dysfunction	uncommon ¹⁾ , uncommon ³⁾
	gynaecomastia	uncommon ³⁾
General disorders and administration site conditions	chest pain	uncommon ¹⁾ , uncommon ²⁾ , uncommon ³⁾
	pain	uncommon ³⁾
	oedema	uncommon ¹⁾ , very common ³⁾
	oedema peripheral	common ¹⁾
	asthenia (weakness)	uncommon ¹⁾ , uncommon ²⁾ , common ³⁾
	fatigue	uncommon ¹⁾ , common ³⁾
	malaise	rare ¹⁾ , uncommon ³⁾
	influenza like illness	rare ²⁾
Investigations	hepatic enzyme increased	uncommon ¹⁾ , rare ²⁾
	blood creatinine increased	uncommon ²⁾
	blood creatine phosphokinase increased	rare ²⁾
	haemoglobin decreased	rare ²⁾
	blood uric acid increased	rare ¹⁾ , rare ²⁾
	weight increased	uncommon ³⁾
	weight decreased	uncommon ³⁾

1 Adverse reactions of FDC telmisartan+amlodipine

2 Adverse reactions of telmisartan as monotherapy

3 Adverse reactions of amlodipine as monotherapy

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via following contact: Telephone: +62 21 21684084 Or Email: IDafety@zuelligpharma.com

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 overdose were hypotension, 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 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.

Therapy

If symptomatic hypotension should occur.

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

The patients 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 patients should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly

PHARMACOLOGICAL 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.

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 contribution of the medicinal products diuretic and natriuretic effect to its hypotensive activity has still to be defined.

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.

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 blocker) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

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

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

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

Use in Patients with Heart Failure:

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

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

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

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 ≥ 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:

- 21.8/-16.5 mmHg with 40/5 mg,
- 22.1/-18.2 mmHg with 80/5 mg,
- 24.7/-20.2 mmHg with 40/10 mg, and
- 26.4/-20.1 mmHg with 80/10 mg.

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

- 71.6% with 40/5 mg,
- 74.8% with 80/5 mg,
- 82.1% with 40/10 mg, and
- 85.3% with 80/10 mg.

A subset of 1050 patients in the factorial design study had moderate to severe hypertension (DBP ≥ 100 mmHg). In these patients who are likely to need more than one antihypertensive agent to achieve blood pressure goal, the 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:

- 13.6/-9.4 mmHg with TWYNSTA 40/5 mg,
- 15.0/-10.6 mmHg with TWYNSTA 80/5 mg,
- 6.2/-5.7 mmHg with amlodipine 5 mg, and
- 11.1/-8.0 mmHg with 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:

- 11.1/-9.2 mmHg with TWYNSTA 40/10 mg
- 11.3/-9.3 mmHg with TWYNSTA 80/10 mg
- 7.4/-6.5 mmHg with 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. Furthermore it was shown

that some patients not adequately controlled with TWYNSTA 40 mg/ 10 mg had additional blood pressure reduction by up-titration to TWYNSTA 80 mg/ 10 mg.

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 overall incidence of adverse reactions with TWYNSTA in the clinical trial programme was low with only 12.7% of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received TWYNSTA as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3% with TWYNSTA 40 mg/5 mg and 80 mg/ 5 mg, 8.8% with controlled on amlodipine 5 mg the oedema rates were 4.4% for 40 mg/ 5 mg and 80 mg/ 5 mg and 24.9% for amlodipine 10 mg.

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 25,620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Pharmacokinetics

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.

The small reduction in AUC 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. 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 taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

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.

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

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

TOXICOLOGY

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

This has been shown in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested. In this study no additive or greater than additive adverse effects of amlodipine and telmisartan in combination as well as no change of the toxicity profile with regard to target organs were observed.

With respect to telmisartan/amlodipine (TWYNSTA), separate reproductive toxicity studies assessing the potential effects of telmisartan and amlodipine on male or female fertility when both compounds are given in combination.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan

In preclinical safety studies doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit) and 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 side effects, known from non-clinical studies with both angiotensin converting enzyme inhibitors and angiotensin II blockers, 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 ACE-inhibitors and other angiotensin II blockers, do not appear to have clinical significance .

No clear evidence of a teratogenic effect was observed; at toxic doses levels, however, non-clinical studies indicated some hazardous potential of telmisartan to foetal development (increased number of late resorptions in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality.

No effects of telmisartan on male or female fertility were observed.

There was no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice.

Amlodipine

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen at high doses. 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 10 times the MRHD of 10 mg/day on a mg/m² basis).

No effects of amlodipine on male or female fertility were observed.

Availability

TWYNSTA 40/5 mg tablets

Reg. No. DK12424200910A1

Box contains 4 blister @ 7 tablets

TWYNSTA 40/10 mg tablets

Reg. No. DK12424200910B1

Box contains 4 blister @ 7 tablets

TWYNSTA 80/5 mg tablets

Reg. No. DK12424200910C1

Box contains 4 blister @ 7 tablets

TWYNSTA 80/10 mg tablets

Reg. No. DK12424200910D1

Box contains 4 blister @ 7 tablets

Store below 30°C, in original packages to protect from light and moisture.

Keep out of reach and sight of children

Only on doctor's prescription.

Harus dengan resep dokter.

Manufactured by:

CIPLA Limited

Goa / India

Packaged and Released by:

Rottendorf Pharma GmbH

Ennigerloh / Germany

For:

Boehringer Ingelheim International GmbH

Ingelheim am Rhein, Germany

Registered by:
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Version: 09-0326

Informasi Produk untuk Pasien
TWYNSTA® 40 mg/5 mg tablet
TWYNSTA® 40 mg/10 mg tablet
TWYNSTA® 80 mg/5 mg tablet
TWYNSTA® 80 mg/10 mg tablet
Telmisartan/amlodipine besilate

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisikan informasi penting untuk Anda.

- Simpanlah leaflet ini. Suatu saat Anda mungkin perlu membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka meskipun gejala penyakit mereka mirip dengan Anda.
- Bila Anda mengalami efek samping obat, bicarakan kepada dokter atau apoteker Anda, termasuk efek samping obat yang tidak terdaftar dalam leaflet ini. Lihat bagian 4.

Apa saja yang terdapat dalam leaflet ini

1. Apakah Twynsta® dan digunakan untuk apa
2. Apakah yang perlu Anda ketahui sebelum Anda menggunakan Twynsta®
3. Bagaimana cara menggunakan Twynsta®
4. Kemungkinan efek samping
5. Bagaimana cara menyimpan Twynsta®
6. Isi paket dan informasi lainnya

1. Apakah Twynsta® dan digunakan untuk apa

Tablet Twynsta mengandung dua zat aktif yang disebut telmisartan dan amlodipine. Kedua zat ini membantu mengendalikan tekanan darah tinggi Anda:

- Telmisartan termasuk dalam kelompok zat yang disebut "penghambat reseptor angiotensin-II". Angiotensin II adalah zat yang diproduksi dalam tubuh yang menyebabkan pembuluh darah menyempit, sehingga meningkatkan tekanan darah. Telmisartan bekerja dengan menghalangi efek angiotensin II.
- Amlodipine termasuk dalam kelompok zat yang disebut "penghambat saluran kalsium". Amlodipine menghentikan kalsium bergerak ke dinding pembuluh darah yang menghentikan pembuluh darah dari penyempitan.

Ini berarti bahwa kedua zat aktif ini bekerja sama untuk membantu menghentikan penyempitan pembuluh darah Anda. Akibatnya, pembuluh darah rileks dan tekanan darah menurun

Twynsta® digunakan untuk mengobati tekanan darah tinggi

- pada pasien dewasa yang tekanan darahnya tidak cukup terkontrol dengan amlodipine saja atau telmisartan saja.
- pada pasien dewasa yang sudah menerima telmisartan dan amlodipine pada tablet terpisah dan ingin mengonsumsi dosis yang sama dalam satu tablet demi kenyamanan.

Tekanan darah tinggi, jika tidak diobati, dapat merusak pembuluh darah di beberapa organ, yang membuat pasien berisiko mengalami kejadian serius seperti serangan jantung, gagal jantung atau ginjal, stroke, atau kebutaan.

Biasanya tidak ada gejala tekanan darah tinggi sebelum kerusakan terjadi. Jadi, penting untuk mengukur tekanan darah secara teratur untuk memverifikasi apakah tekanan darah berada dalam kisaran normal.

2. Apakah yang perlu Anda ketahui sebelum Anda menggunakan Twynsta®

Jangan menggunakan Twynsta®

- jika Anda alergi terhadap telmisartan atau amlodipine atau bahan lain dari obat ini (tercantum di bagian 6).
- jika Anda alergi terhadap obat lain dari jenis dihidropiridin (salah satu jenis penghambat saluran kalsium).
- jika Anda hamil lebih dari 3 bulan. (Lebih baik juga untuk menghindari Twynsta pada awal kehamilan – lihat bagian Kehamilan.)

- jika Anda memiliki masalah hati yang parah atau obstruksi bilier (masalah dengan drainase empedu dari hati dan kantong empedu).
- jika Anda memiliki riwayat tekanan darah rendah (hipotensi) yang berat
- jika Anda memiliki penyempitan katup jantung aorta (stenosis aorta) atau syok kardiogenik (kondisi di mana jantung Anda tidak dapat memasok cukup darah ke tubuh).
- jika Anda menderita gagal jantung setelah serangan jantung.
- jika Anda memiliki diabetes atau gangguan fungsi ginjal dan Anda diobati dengan obat penurun tekanan darah yang mengandung aliskiren.

Jika salah satu hal di atas berlaku bagi Anda, beri tahu dokter atau apoteker Anda sebelum mengonsumsi Twynsta.

Peringatan dan Perhatian

Bicaralah dengan dokter Anda sebelum mengonsumsi Twynsta jika Anda menderita atau pernah menderita salah satu dari kondisi atau penyakit berikut:

- Penyakit ginjal atau transplantasi ginjal.
- Penyempitan pembuluh darah ke satu atau kedua ginjal (stenosis arteri renalis).
- Penyakit hati.
- Masalah jantung.
- Peningkatan kadar aldosteron (yang menyebabkan retensi air dan garam dalam tubuh bersamaan dengan ketidakseimbangan berbagai mineral darah).
- Tekanan darah rendah (hipotensi), kemungkinan terjadi jika Anda mengalami dehidrasi (kehilangan air tubuh yang berlebihan) atau kekurangan garam akibat terapi diuretik ('tablet air'), diet rendah garam, diare, atau muntah.
- Peningkatan kadar kalium dalam darah Anda.
- Diabetes.
- Penyempitan aorta (stenosis aorta).
- Nyeri dada yang berhubungan dengan jantung, baik saat istirahat atau dengan sedikit usaha (angina pectoris tidak stabil).
- Serangan jantung dalam empat minggu terakhir.

Tanyakan kepada dokter Anda sebelum menggunakan Twynsta:

- jika Anda mengonsumsi salah satu obat berikut yang digunakan untuk mengobati tekanan darah tinggi:
 - ACE-inhibitor (misalnya enalapril, lisinopril, ramipril), khususnya jika Anda memiliki masalah ginjal terkait diabetes.
 - aliskiren.

Dokter Anda mungkin akan memeriksa fungsi ginjal, tekanan darah, dan jumlah elektrolit (misalnya kalium) dalam darah Anda secara berkala. Lihat juga "Jangan mengonsumsi Twynsta".

- jika Anda sudah lanjut usia dan dosis Anda perlu ditingkatkan

Bicaralah dengan dokter jika Anda mengalami sakit perut, mual, muntah, atau diare setelah mengonsumsi Twynsta. Dokter akan memutuskan perawatan lebih lanjut. Jangan berhenti mengonsumsi Twynsta sendiri.

Jika Anda akan menjalani operasi atau anestesi, Anda harus memberi tahu dokter bahwa Anda mengonsumsi Twynsta

Anak-anak dan remaja

Twynsta tidak direkomendasikan untuk anak-anak dan remaja hingga usia 18 tahun.

Obat-obatan lain dan Twynsta

Beri tahu dokter atau apoteker jika Anda sedang mengonsumsi, baru saja mengonsumsi, atau mungkin mengonsumsi obat-obatan lain. Dokter Anda mungkin perlu mengubah dosis obat-obatan lain ini atau mengambil tindakan pencegahan lainnya. Dalam beberapa kasus, Anda mungkin harus berhenti mengonsumsi salah satu obat. Hal ini berlaku khususnya untuk obat-obatan yang tercantum di bawah ini:

- Obat-obatan yang mengandung litium untuk mengobati beberapa jenis depresi.
- Obat-obatan yang dapat meningkatkan kadar kalium dalam darah seperti pengganti garam yang mengandung kalium, diuretik hemat kalium ('tablet air' tertentu).
- Penghambat reseptor angiotensin II.

- ACE-inhibitor atau aliskiren (lihat juga informasi di bawah judul “Jangan konsumsi Twynsta” dan “Peringatan dan tindakan pencegahan”).
- NSAID (obat antiinflamasi nonsteroid, misalnya asam asetilsalisilat atau ibuprofen), heparin, immunosupresif (misalnya siklosporin atau takrolimus), dan antibiotik trimetoprim.
- Rifampisin, eritromisin, klaritromisin (antibiotik).
- St. John's wort.
- Dantrolene (infus untuk kelainan suhu tubuh yang parah).
- Obat yang digunakan untuk mengubah cara kerja sistem kekebalan tubuh (misalnya sirolimus, temsirolimus, dan everolimus).
- Obat yang digunakan untuk HIV/AIDS (misalnya ritonavir) atau untuk pengobatan infeksi jamur (misalnya ketokonazol).
- Diltiazem (obat jantung).
- Simvastatin untuk mengobati kadar kolesterol tinggi.
- Digoksin.

Seperti halnya obat penurun tekanan darah lainnya, efek Twynsta dapat berkurang saat Anda mengonsumsi NSAID (obat antiinflamasi nonsteroid, misalnya asam asetilsalisilat atau ibuprofen) atau kortikosteroid.

Twynsta dapat meningkatkan efek penurunan tekanan darah dari obat lain yang digunakan untuk mengobati tekanan darah tinggi atau obat dengan potensi penurunan tekanan darah (misalnya baklofen, amifostine, neuroleptik, atau antidepresan).

Twynsta dengan makanan dan minuman

Tekanan darah rendah dapat diperburuk oleh alkohol. Anda mungkin merasakannya sebagai pusing saat berdiri.

Jus jeruk bali dan jeruk bali tidak boleh dikonsumsi saat Anda mengonsumsi Twynsta. Hal ini karena jeruk bali dan jus jeruk bali dapat menyebabkan peningkatan kadar bahan aktif amlodipine dalam darah pada beberapa pasien dan dapat meningkatkan efek penurunan tekanan darah dari Twynsta.

Kehamilan dan menyusui

Kehamilan

Anda harus memberi tahu dokter jika Anda merasa mungkin sedang hamil atau berencana untuk memiliki bayi. Dokter biasanya akan menyarankan Anda untuk berhenti mengonsumsi Twynsta sebelum Anda hamil atau segera setelah Anda tahu Anda hamil dan akan menyarankan Anda untuk mengonsumsi obat lain sebagai pengganti Twynsta. Twynsta tidak direkomendasikan pada awal kehamilan, dan tidak boleh dikonsumsi saat kehamilan lebih dari 3 bulan, karena dapat menyebabkan bahaya serius pada bayi Anda jika digunakan setelah bulan ketiga kehamilan.

Menyusui

Amlodipine terbukti dapat masuk ke dalam ASI dalam jumlah kecil.

Beri tahu dokter jika Anda sedang menyusui atau akan mulai menyusui. Twynsta tidak direkomendasikan untuk ibu yang sedang menyusui, dan dokter Anda mungkin akan memilih pengobatan lain jika Anda ingin menyusui, terutama jika bayi Anda baru lahir atau lahir prematur.

Mintalah saran dari dokter atau apoteker sebelum mengonsumsi obat apa pun.

Mengemudi dan menggunakan mesin

Beberapa orang mungkin mengalami efek samping seperti pingsan, mengantuk, pusing, atau perasaan berputar (vertigo) saat mereka menjalani perawatan tekanan darah tinggi. Jika Anda mengalami efek samping ini, jangan mengemudi atau menggunakan mesin.

Twynsta mengandung sorbitol

Obat ini mengandung 168,64 mg sorbitol dalam setiap tablet.

Twynsta mengandung natrium

Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per tablet, yang berarti pada dasarnya 'bebas natrium'.

3. Bagaimana cara menggunakan Twynsta®

Selalu minum obat ini sesuai petunjuk dokter. Konsultasikan dengan dokter atau apoteker jika Anda tidak yakin.

Dosis yang dianjurkan adalah satu tablet sehari. Dosis maksimum yang disarankan adalah TWYNSTA 80mg/10mg, satu tablet per hari. Usahakan untuk minum tablet pada waktu yang sama setiap hari. Keluarkan tablet Twynsta dari blister hanya sebelum diminum.

Anda dapat minum Twynsta dengan atau tanpa makanan. Tablet harus ditelan dengan air atau minuman nonalkohol lainnya.

Jika hati Anda tidak berfungsi dengan baik, dosis yang biasa tidak boleh melebihi satu tablet 40 mg/5 mg atau satu tablet 40 mg/10 mg per hari.

Jika Anda menggunakan Twynsta lebih banyak dari yang seharusnya

Jika Anda tidak sengaja minum terlalu banyak tablet, segera hubungi dokter, apoteker, atau unit gawat darurat rumah sakit terdekat. Anda mungkin mengalami tekanan darah rendah dan detak jantung cepat. Detak jantung lambat, pusing, penurunan fungsi ginjal termasuk gagal ginjal, tekanan darah rendah yang nyata dan berkepanjangan termasuk syok dan kematian juga telah dilaporkan.

Cairan berlebih dapat terkumpul di paru-paru (edema paru) yang menyebabkan sesak napas yang dapat terjadi hingga 24-48 jam setelah asupan.

Jika Anda lupa konsumsi Twynsta

Jika Anda lupa minum satu dosis, minumlah segera setelah Anda ingat dan lanjutkan seperti sebelumnya. Jika Anda tidak minum tablet pada suatu hari, minumlah dosis normal pada hari berikutnya. Jangan minum dosis ganda untuk mengganti dosis yang terlupa.

Jika Anda berhenti minum Twynsta

Penting bagi Anda untuk minum Twynsta setiap hari sampai dokter memberi tahu Anda sebaliknya. Jika Anda merasa efek Twynsta terlalu kuat atau terlalu lemah, konsultasikan dengan dokter atau apoteker Anda.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Kemungkinan efek samping

Seperti semua obat, Twynsta dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Beberapa efek samping bisa serius dan memerlukan perhatian medis segera

Anda harus segera menemui dokter jika mengalami salah satu gejala berikut:

Sepsis (sering disebut "keracunan darah", adalah infeksi parah pada seluruh tubuh disertai demam tinggi dan perasaan sakit parah), pembengkakan cepat pada kulit dan mukosa (angioedema); efek samping ini jarang terjadi (dapat memengaruhi hingga 1 dari 1.000 orang) tetapi sangat serius dan pasien harus berhenti minum obat dan segera menemui dokter. Jika efek ini tidak diobati, efek ini bisa berakibat fatal. Peningkatan kejadian sepsis telah diamati dengan telmisartan saja, namun tidak dapat dikesampingkan untuk Twynsta.

Efek samping umum (dapat memengaruhi hingga 1 dari 10 orang)

Pusing, pembengkakan pergelangan kaki (edema).

Efek samping tidak umum (dapat memengaruhi hingga 1 dari 100 orang)

Mengantuk, migrain, sakit kepala, kesemutan atau mati rasa pada tangan atau kaki, perasaan berputar (vertigo), denyut jantung lambat, palpitasi (kesadaran akan detak jantung), tekanan darah rendah (hipotensi), pusing saat berdiri (hipotensi ortostatik), muka memerah, batuk, sakit perut (nyeri perut), diare, merasa mual, gatal, nyeri sendi, kram otot, nyeri otot, ketidakmampuan untuk ereksi, lemas, nyeri dada, kelelahan, pembengkakan (edema), peningkatan kadar enzim hati.

Efek samping yang jarang terjadi (dapat memengaruhi hingga 1 dari 1.000 orang)

Infeksi kandung kemih, perasaan sedih (depresi), perasaan cemas, sulit tidur, pingsan, kerusakan saraf di tangan atau kaki, berkurangnya indra peraba, kelainan pengecap, gemetar, muntah, gusi membesar, rasa tidak nyaman di perut, mulut kering, eksim (kelainan kulit), kemerahan pada kulit, ruam, nyeri punggung, nyeri kaki, keinginan untuk buang air kecil di malam hari, perasaan tidak enak badan (malaise), peningkatan kadar asam urat dalam darah. Efek samping yang sangat jarang terjadi (dapat memengaruhi hingga 1 dari 10.000 orang)

Jaringan parut progresif pada jaringan paru-paru (penyakit paru interstisial [terutama pneumonia interstitium dan pneumonia dengan eosinofil berlebih])

Efek samping berikut telah diamati dengan komponen telmisartan atau amlodipine dan dapat terjadi juga dengan Twynsta:

Telmisartan

Pada pasien yang mengonsumsi telmisartan saja, efek samping tambahan berikut telah dilaporkan:

Efek samping yang tidak umum (dapat memengaruhi hingga 1 dari 100 orang)

Infeksi saluran kemih, infeksi saluran pernapasan atas (misalnya sakit tenggorokan, sinusitis, flu biasa), kekurangan sel darah merah (anemia), kadar kalium tinggi dalam darah, sesak napas, kembung, peningkatan keringat, kerusakan ginjal termasuk ketidakmampuan ginjal untuk bekerja secara tiba-tiba, peningkatan kadar kreatinin.

Efek samping yang jarang terjadi (dapat memengaruhi hingga 1 dari 1.000 orang)

Peningkatan sel darah putih tertentu (eosinofilia), jumlah trombosit rendah (trombositopenia), reaksi alergi (misalnya ruam, gatal, kesulitan bernapas, mengi, pembengkakan wajah atau tekanan darah rendah), kadar gula darah rendah (pada pasien diabetes), gangguan penglihatan, detak jantung cepat, sakit perut, fungsi hati abnormal, gatal-gatal (urtikaria), ruam obat, radang tendon, penyakit mirip flu (misalnya nyeri otot, merasa tidak enak badan secara umum), penurunan hemoglobin (protein darah), peningkatan kadar kreatinin fosfokinase dalam darah, kadar natrium rendah.

Sebagian besar kasus fungsi hati abnormal dan gangguan hati akibat pengalaman pasca pemasaran dengan telmisartan terjadi pada pasien Jepang. Pasien Jepang lebih mungkin mengalami efek samping ini.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)

Angioedema intestinal: pembengkakan pada usus yang disertai gejala seperti nyeri perut, mual, muntah, dan diare telah dilaporkan setelah penggunaan produk serupa.

Amlodipine

Pada pasien yang mengonsumsi amlodipine saja, efek samping tambahan berikut telah dilaporkan:

Efek samping umum (dapat memengaruhi hingga 1 dari 10 orang)

Kebiasaan buang air besar yang berubah, diare, konstipasi, gangguan penglihatan, penglihatan ganda, pembengkakan pergelangan kaki.

Efek samping yang tidak umum (dapat memengaruhi hingga 1 dari 100 orang)

Perubahan suasana hati, gangguan penglihatan, telinga berdenging, napas pendek, bersin/hidung berair, rambut rontok, memar dan pendarahan yang tidak biasa (kerusakan sel darah merah), perubahan warna kulit, peningkatan keringat, kesulitan buang air kecil, peningkatan kebutuhan buang air kecil terutama di malam hari, pembesaran payudara pria, nyeri, berat badan meningkat, berat badan menurun.

Efek samping yang jarang terjadi (dapat memengaruhi hingga 1 dari 1.000 orang)

Kebingungan.

Efek samping yang sangat jarang terjadi (dapat memengaruhi hingga 1 dari 10.000 orang)

Jumlah sel darah putih yang berkurang (leukopenia), jumlah trombosit yang rendah (trombositopenia), reaksi alergi (misalnya ruam, gatal, kesulitan bernapas, mengi, pembengkakan wajah atau tekanan darah rendah), kelebihan gula dalam darah, gerakan berkedut atau menyentak yang tidak terkendali, serangan jantung, detak jantung tidak teratur, radang pembuluh darah, radang pankreas, radang lapisan lambung (gastritis), radang hati, menguningnya kulit (penyakit kuning), peningkatan kadar enzim hati dengan penyakit kuning, pembengkakan cepat pada kulit dan mukosa (angioedema), reaksi kulit yang parah, gatal-gatal (urtikaria), reaksi alergi parah dengan erupsi melepuh pada kulit dan selaput lendir (dermatitis eksfoliatif, Sindrom Stevens-Johnson), peningkatan sensitivitas kulit terhadap sinar matahari, peningkatan ketegangan otot.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)

Reaksi alergi parah dengan ruam kulit dan selaput lendir yang melepuh (nekrosis epidermal toksik).

Pelaporan efek samping

Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut:

Telepon: +62 21 21684084 atau Email IDSafety@zuelligpharma.com

Dengan melaporkan efek samping, Anda membantu mengumpulkan informasi mengenai keamanan dari obat ini.

5. Bagaimana cara menyimpan Twynsta®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada karton dan blister setelah "EXP". Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan suhu khusus. Simpan dalam kemasan asli untuk melindungi dari cahaya dan kelembapan. Keluarkan tablet Twynsta dari blister hanya sebelum dikonsumsi.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda cara membuang obat yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya**Kandungan Twynsta**

- Zat aktif Twynsta adalah telmisartan dan amlodipine.
- Bahan lainnya adalah silika koloid anhidrat, FCF biru cemerlang (E133), oksida besi hitam (E172), oksida besi kuning (E172), magnesium stearat, pati jagung, meglumine, selulosa mikrokristalin, povidone K25, pati pregelatinisasi yang dibuat dari pati jagung, natrium hidroksida (lihat bagian 2), sorbitol (E420) (lihat bagian 2).

Seperti apa bentuk Twynsta® dan isi kemasannya

Tablet Twynsta 40 mg/5 mg berupa tablet berlapis berbentuk oval, bikonveks. Kedua lapisan memiliki warna yang berbeda, dengan lapisan telmisartan berwarna putih hingga putih kekuningan, dan lapisan amlodipine berwarna biru. Pada lapisan putih tersebut embos dengan simbol perusahaan Boehringer Ingelheim dan kode A1.

Tablet Twynsta 40 mg/10 mg berupa tablet berlapis berbentuk oval, bikonveks. Kedua lapisan memiliki warna yang berbeda, dengan lapisan telmisartan berwarna putih hingga putih kekuningan, dan lapisan amlodipine berwarna biru. Pada lapisan putih tersebut embos dengan simbol perusahaan Boehringer Ingelheim dan kode A2.

Tablet Twynsta 80 mg/5 mg berupa tablet berlapis berbentuk oval, bikonveks. Kedua lapisan memiliki warna yang berbeda, dengan lapisan telmisartan berwarna putih hingga putih kekuningan, dan lapisan amlodipine berwarna biru. Pada lapisan putih tersebut embos dengan simbol perusahaan Boehringer Ingelheim dan kode A3.

Tablet Twynsta 80 mg/10 mg berupa tablet berlapis berbentuk oval, bikonveks. Kedua lapisan memiliki warna yang berbeda, dengan lapisan telmisartan berwarna putih hingga putih kekuningan, dan lapisan amlodipine berwarna biru. Pada lapisan putih tersebut embos dengan simbol perusahaan Boehringer Ingelheim dan kode A4.

Twynsta tersedia dalam kemasan berisi 28 tablet dalam blister aluminium

Reg.No.

TWYNSTA 40/5 mg tablets

Reg. No. DK12424200910A1

Box contains 4 blister @ 7 tablets

TWYNSTA 40/10 mg tablets

Reg. No. DK12424200910B1

Box contains 4 blister @ 7 tablets

TWYNSTA 80/5 mg tablets
Box contains 4 blister @ 7 tablets

Reg. No. DK12424200910C1

TWYNSTA 80/10 mg tablets
Box contains 4 blister @ 7 tablets

Reg. No. DK12424200910D1

Harus dengan resep dokter

Diproduksi oleh:

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Goa / India

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Ingelheim am Rhein, Jerman

Diregistrasikan oleh:

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