APPROVED PROFESSIONAL INFORMATION - TWYNSTA

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

Twynsta® 40/5 mg abcd
Twynsta® 40/10 mg
Twynsta® 80/5 mg
Twynsta® 80/10 mg
tablets

COMPOSITION:
TWYNSTA 40/5 mg tablets: Each tablet contains 40 mg telmisartan and 5 mg amlodipine base (as besylate salt).

TWYNSTA 40/10 mg tablets: Each tablet contains 40 mg telmisartan and 10 mg amlodipine base (as besylate salt).

TWYNSTA 80/5 mg tablets: Each tablet contains 80 mg telmisartan and 5 mg amlodipine base (as besylate salt).

TWYNSTA 80/10 mg tablets: Each tablet contains 80 mg telmisartan and 10 mg amlodipine base (as besylate salt).

Inactive ingredients: Colloidal anhydrous silica, FD&C blue No. 1 aluminium lake, ferric oxide black, ferric oxide yellow, magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinised starch, sodium hydroxide, sorbitol.
Contains sugar (sorbitol). TWYNSTA 40/5 mg and 40/10 mg tablets contain 168,64 mg sorbitol and TWYNSTA 80/5 mg and 80/10 mg tablets contain 337,28 mg sorbitol in each tablet.

CATEGORY AND CLASS:
A 7.1.3 Vascular medicines – other hypotensives

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
TWYNSTA combines two antihypertensive compounds with different mechanisms of action: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.
The combination of these substances has an additive antihypertensive effect.

Telmisartan:
Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. The binding is long lasting.

Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan monotherapy. Telmisartan monotherapy does not inhibit human plasma renin or block ion channels.
In man, an 80 mg dose of telmisartan monotherapy almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and is still measurable up to 48 hours.
After administration of the first dose of telmisartan monotherapy, onset of antihypertensive activity occurs within 3 hours. The maximum reduction in blood pressure is generally attained 4 weeks after the start of treatment and is sustained during long-term therapy.

There is an apparent trend to a dose relationship with regard to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent. In patients with hypertension telmisartan monotherapy reduces both systolic and diastolic blood pressure without affecting pulse rate.

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

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

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without a change in filtration fraction or proteinuria.

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

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.

Pharmacokinetic properties:

Pharmacokinetics of the fixed dose combination:
The rate and extent of absorption of TWYNSTA are similar to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetics of the single components:

Absorption:
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When the fixed dose combination is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan was approximately 25 % at a dose of 80/10 mg. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 – 12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected by food ingestion.

Distribution:
Telmisartan is largely bound to plasma protein (> 99,5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{ss}) is approximately 500 L. The volume of distribution of amlodipine is approximately 21 L/kg. *In vitro* studies with amlodipine have shown that approximately 97,5 % of circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism:
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.

Excretion:
Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of > 20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is < 2 % of dose. Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min) compared with hepatic blood flow (about 1 500 mL/min).

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

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

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

Elderly patients:
The pharmacokinetics of telmisartan do not differ between younger and elderly patients. Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the plasma concentration-time curve (AUC) and elimination half-life.

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

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

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

Add on therapy:
TWYNSTA is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.

CONTRAINDICATIONS:
- Hypersensitivity to any of the ingredients of TWYNSTA
- Hypersensitivity to dihydropyridine derivatives

- A history of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30 mL/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **WARNINGS AND SPECIAL PRECAUTIONS**)
- Porphyria
- Lithium therapy: Concomitant administration with TWYNSTA may lead to toxic blood concentrations of lithium (see **INTERACTIONS**)
- Pregnancy and lactation (see **WARNINGS AND SPECIAL PRECAUTIONS** and **HUMAN REPRODUCTION**)
- The concomitant use of TWYNSTA with aliskiren-containing products is contra-indicated (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**)
- Biliary obstructive disorders
- Severe hepatic impairment
- Cardiogenic shock
- Concomitant use of fluoroquinolones with Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance $\leq$ 30 mL/min) and in elderly patients.

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of TWYNSTA is contra-indicated. TWYNSTA contains sorbitol. (Please refer to **WARNINGS AND SPECIAL PRECAUTIONS**.)

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving TWYNSTA, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine. (See CONTRAINDICATIONS and HUMAN REPRODUCTION.)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of TWYNSTA and aliskiren is therefore contra-indicated (see **CONTRAINDICATIONS**). TWYNSTA should not be used concomitantly with aliskiren (see **CONTRAINDICATIONS**).

Pregnancy:
TWYNSTA should not be initiated during pregnancy (see **CONTRAINDICATIONS**).

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 TWYNSTA should be stopped immediately, and if appropriate, alternative therapy should be started. (See **HUMAN REPRODUCTION**.)

Hepatic impairment: Telmisartan (ingredient of TWYNSTA) is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. TWYNSTA should therefore be used with caution in patients with mild to moderate impairment of liver function and should not be used in patients with severe liver impairment (see **CONTRAINDICATIONS)**.

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 (see **CONTRAINDICATIONS)**.

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 and amlodipine are not dialysable.

Intravascular hypovolaemia:
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of TWYNSTA.

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 TWYNSTA, that affects this system, has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Concomitant use of fluoroquinolones:
Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (See **CONTRAINDICATIONS**.) Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or Angiotensin-converting enzymes (ACE) inhibitors/Angiotensin receptor blockers (ARBs) whether used separately and/or concomitantly.

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 TWYNSTA is not recommended.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy:
TWYNSTA is contra-indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction:
There are no data to support the use of 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 non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema.

Hyperkalaemia:
During treatment with TWYNSTA hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin-system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with TWYNSTA.

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.

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

Sorbitol:
TWYNSTA tablets contain sorbitol. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Effects on the ability to drive and use machines:
No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as syncope (fainting), somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a vehicle or operating machinery. If patients experience these adverse effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

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

Interactions common to the combination:
No interaction studies have been performed with TWYNSTA and other medicinal products.

Concomitant use to be taken into account:

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 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 the telmisartan component of TWYNSTA:
Telmisartan may increase the hypotensive effect of other antihypertensive agents. Other interactions of clinical significance have not been identified.

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_{0-24} and C_{max} 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 (ACE) inhibitors. Increased serum levels have also been reported with telmisartan.

Treatment with NSAIDs (i.e. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin-system like telmisartan may have synergistic effects. Patients receiving NSAIDs and TWYNSTA should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.
A reduced effect of antihypertensive medicines like TWYNSTA by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

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

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see **CONTRAINDICATIONS**).

Interactions linked to the amlodipine component of TWYNSTA:

Concomitant use requiring caution:

Grapefruit and grapefruit juice:
Administration of TWYNSTA 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:
A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50 % and the effect of amlodipine is increased).
The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum):
Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

Concomitant use to be taken into account:

Simvastatin:
Co-administration of multiple doses 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.

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:
In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines. 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.
Co-administration of amlodipine with cimetidine had no significant effect on the pharmacokinetics of amlodipine.
Co-administration of amlodipine with atorvastatin, digoxin or warfarin had no significant effect on the pharmacokinetics or pharmacodynamics of these agents.

HUMAN REPRODUCTION:
TWYNSTA should not be used during pregnancy and lactation. Effects related to the mono components are described below.

Pregnancy:

Telmisartan:
Safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS**). When pregnancy is planned or confirmed, TWYNSTA should be discontinued. Refer to **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**.

Medicines affecting the renin-angiotensin system, such as TWYNSTA, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. Women of childbearing age should ensure effective contraception.

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 TWYNSTA should be stopped immediately, and, if appropriate, alternative therapy should be started.
Should exposure to TWYNSTA have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken TWYNSTA should be closely observed for hypotension.

Lactation:
It is not known whether telmisartan (as in TWYNSTA) is excreted in human milk. Animal studies have shown excretion of telmisartan in breastmilk. 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 breastfed infants, TWYNSTA should not be used by breastfeeding mothers (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE:

DOSAGE:
Adults:
TWYNSTA should be taken once daily.

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

Add on therapy:
TWYNSTA may be administered in patients whose blood pressure is not adequately controlled with amlodipine alone.

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

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

Special populations:

Renal impairment:
No dosage adjustment is required for patients with mild to moderate renal impairment (see **WARNINGS AND SPECIAL PRECAUTIONS**). Amlodipine and telmisartan are not dialysable.

Hepatic impairment:
In patients with mild to moderate hepatic impairment TWYNSTA should be administered with caution. For telmisartan the dose should not exceed 40/5 mg or 40/10 mg once daily.

Elderly:
No dose adjustment is necessary for elderly patients.

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

DIRECTIONS FOR USE:
Tablet for oral administration.

TWYNSTA may be taken with or without food.

SIDE EFFECTS

Side effects:

Fixed Dose Combination:
The safety and tolerability of TWYNSTA has been evaluated in five controlled clinical studies with over 3 500 patients, over 2 500 of whom received telmisartan in combination with amlodipine.

The following frequency classification is used:
very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1 000 and < 1/100; rare ≥ 1/10 000 and < 1/1 000; very rare < 1/10 000.

Infections and infestations:
Rare: cystitis

Psychiatric disorders:
Rare: depression, anxiety, insomnia

Nervous system disorders:
Common: dizziness
Uncommon: somnolence, migraine, headache, paraesthesia
Rare: syncope (fainting), peripheral neuropathy, hypoaesthesia, dysgeusia, tremor

Ear and labyrinth disorders:
Uncommon: vertigo

Cardiac disorders:
Uncommon: bradycardia, palpitations

Vascular disorders:
Uncommon: hypotension, orthostatic hypotension, flushing

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Uncommon: abdominal pain, diarrhoea, nausea
Rare: vomiting, gingival hypertrophy, dyspepsia, dry mouth

Skin and subcutaneous tissue disorders:
Uncommon: pruritus
Rare: eczema, erythema, rash

Musculoskeletal, connective tissue and bone disorders:
Uncommon: arthralgia, muscle spasms, myalgia, back pain
Rare: pain in extremity

Renal and urinary disorders:
Rare: nocturia

Reproductive system and breast disorders:
Uncommon: erectile dysfunction

General disorders:
Common: oedema peripheral
Uncommon: asthenia, chest pain, fatigue, oedema
Rare: malaise

Investigations:
Uncommon: hepatic enzymes increased
Rare: blood uric acid increased

The following side effects are expected based on experience with telmisartan monotherapy:

Infections and infestations:
Uncommon: urinary tract infections, upper respiratory tract infections
Rare: sepsis including fatal outcome

Blood and the lymphatic system disorders:
Uncommon: anaemia
Rare: eosinophilia, thrombocytopenia

Immune system disorders:
Rare: angioedema (with fatal outcome), anaphylactic reaction, hypersensitivity

Metabolism and nutritional disorders:
Uncommon: hyperkalaemia
Rare: hypoglycaemia (in diabetic patients)

Eye disorders:
Rare: visual disturbance

Cardiac disorders:
Rare: tachycardia

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea

Gastrointestinal disorders:
Uncommon: flatulence

Rare: stomach discomfort

Hepato-biliary disorders:
Rare: hepatic function abnormal, liver disorder

Skin and subcutaneous tissue disorders:
Uncommon: hyperhidrosis
Rare: urticaria, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders:
Rare: tendon pain

Renal and urinary disorders:
Uncommon: renal impairment

General disorders:
Rare: influenza-like illness

Investigations:
Uncommon: blood creatinine increased
Rare: haemoglobin decreased, blood creatine phosphokinase (CPK) increased

The following side effects are expected based on experience with amlodipine monotherapy, but the frequencies are not known (cannot be determined from the reference data set):

Blood and the lymphatic system disorders:
Leucopenia, thrombocytopenia

Immune system disorders:
Angioedema, hypersensitivity

Metabolism and nutritional disorders:
Hyperglycaemia

Psychiatric disorders:
Mood change, confusional state

Nervous system disorders:
Extrapyramidal disorder

Eye disorders:
Visual impairment

Ear and labyrinth disorders:
Tinnitus

Cardiac disorders:

Myocardial infarction, dysrhythmia, ventricular tachycardia, atrial fibrillation

Vascular disorders:
Vasculitis

Respiratory, thoracic and mediastinal disorders:
Dyspnoea, rhinitis

Gastrointestinal disorders:
Change of bowel habit, pancreatitis, gastritis

Hepato-biliary disorders:
Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders:
Hyperhidrosis, urticaria, alopecia, purpura, skin discolouration, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity reaction

Renal and urinary disorders:
Micturition disorder, pollakiuria

Reproductive system and breast disorders:
Gynaecomastia

General disorders:
Pain, weight increased, weight decreased

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
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 might also occur.
Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome may occur.

Therapy:
Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and amlodipine are not removed by haemodialysis.

IDENTIFICATION:
TWYNSTA 40/5 mg: Oval shaped, biconvex, bilayered uncoated tablets with one layer white to off-white and other layer blue, debossed with "Boehringer Ingelheim company symbol" and "A1" on white layer and plain on other side.

TWYNSTA 40/10 mg: Oval shaped, biconvex, bilayered uncoated tablets with one layer white to off-white and other layer blue, debossed with "Boehringer Ingelheim company symbol" and "A2" on white layer and plain on other side.

TWYNSTA 80/5 mg: Oval shaped, biconvex, bilayered uncoated tablets with one layer white to off-white and other layer blue, debossed with "Boehringer Ingelheim company symbol" and "A3" on white layer and plain on other side.

TWYNSTA 80/10 mg: Oval shaped, biconvex, bilayered uncoated tablets with one layer white to off-white and other layer blue, debossed with "Boehringer Ingelheim company symbol" and "A4" on white layer and plain on other side.

PRESENTATION:
Printed cartons containing 28 tablets, packed in silver aluminium foil blister strips. Each blister strip contains 7 tablets.

STORAGE INSTRUCTIONS:
Store at or below 30 °C.

The tablets should not be removed from their foil pack until required for administration in order to protect the product from light and moisture.

Keep out of reach of children.

REGISTRATION NUMBERS:
TWYNSTA 40/5 mg: 44/7.1.3/0857
TWYNSTA 40/10 mg: 44/7.1.3/0858
TWYNSTA 80/5 mg: 44/7.1.3/0859
TWYNSTA 80/10 mg: 44/7.1.3/0860

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:
Ingelheim Pharmaceuticals (Pty) Ltd
407 Pine Avenue
Randburg
South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:
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