**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 than1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**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 $m^2$)**

**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 subtitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppresives (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.**

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**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 **blocker**s 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 blocker**s**, 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 blocker**s**.**

**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 blocker**s** 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 Cmax 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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)] |
| | hypoaesthesia | 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

**OVERDOSE**

Symptoms

**There is no experience of overdose with TWYNSTA. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.**
**The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia, 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 amlodipine10 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. Cmax 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 (Vss) 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 (approximatively 90%) metabolised by the liver to inactive metabolites.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours.

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<br>Box contains 4 blister @ 7 tablets | Reg. No. DKI2424200910A1 |
| TWYNSTA 40/10 mg tablets<br>Box contains 4 blister @ 7 tablets | Reg. No. DKI2424200910B1 |
| TWYNSTA 80/5 mg tablets<br>Box contains 4 blister @ 7 tablets | Reg. No. DKI2424200910C1 |
| TWYNSTA 80/10 mg tablets<br>Box contains 4 blister @ 7 tablets | Reg. No. DKI2424200910D1 |

**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

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