APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

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

2. QUALITATIVE AND QUANTITATIVE 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).

Sugar free.

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology

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 section 4.4).
Telmisartan is not removed from blood by haemofiltration and is not dialysable.
Amlodipine is 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 mg once daily (i.e. TWYNSTA 40/5 or 40/10 mg) (see section 4.3).

Elderly patients
No dose adjustment is necessary for elderly patients. Normal amlodipine dosage regimens are recommended in the elderly, but increase of dosage should take place with care (see section 4.4 and section 5.2).

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

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

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

4.3 Contraindications

- Hypersensitivity to any of the ingredients of TWYNSTA
- Hypersensitivity to dihydropyridine derivatives
- A history of angioedema related to previous therapy with 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
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.4)
- Porphyria
- Lithium therapy: Concomitant administration with TWYNSTA may lead to toxic blood concentrations of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.4 and section 4.6)
- The concomitant use of TWYNSTA with aliskiren-containing products is contraindicated (see section 4.4 and section 4.5)
- 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
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 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 contraindicated. TWYNSTA contains sorbitol (see section 4.4).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving TWYNSTA, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and section 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) 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 contraindicated (see section 4.3). TWYNSTA should not be used concomitantly with aliskiren (see section 4.3).

Pregnancy

TWYNSTA should not be initiated during pregnancy (see section 4.3).
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 section 4.6).

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. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range (i.e. TWYNSTA 40/5 mg or TWYNSTA 80/5 mg) and caution should be used, both on initial treatment and when increasing the dose.

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 section 4.3).

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 section 4.3).

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 haemofiltration and is not dialysable.
Amlodipine is not dialysable.

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.

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 ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3).
Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/Angiotensin receptor blockers 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 contraindicated 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.

Patients with cardiac failure
In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution.
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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.

Elderly patients

The increase of the amlodipine dosage should take place with care in the elderly patients (see section 4.2 and section 5.2).

Ischaemic heart disease
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.

4.5 Interaction with other medicines and other forms of interaction
No interactions between the two components of the fixed dose combinations have been observed in clinical studies.

Interactions linked to the combination
No 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.

Medicines 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 medicines. 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.

Ramipril and Ramiprilat
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 (see section 4.4).

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Increased serum levels have also been reported with telmisartan.
Concomitant administration of TWYNSTA with lithium is contraindicated (see section 4.3)

Non-steroidal anti-inflammatory medicinal products
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 their renal function should be monitored 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 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 section 4.3 and section 4.4).

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers 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 section 4.3).

Interactions linked to the amlodipine component of TWYNSTA
Grapefruit and grapefruit juice
Administration of amlodipine (as in 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
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors

(protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers
Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as TWYNSTA be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of TWYNSTA in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Ciclosporin
No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0 % - 40 %) of ciclosporin were observed. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on TWYNSTA, and ciclosporin dose reductions should be made as necessary.

Mechanistic target of rapamycin (mTOR) inhibitors
mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, TWYNSTA may increase exposure of mTOR inhibitors.

Simvastatin
Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80

mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

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

4.6 Fertility, pregnancy and lactation

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 section 4.3). When pregnancy is planned or confirmed, TWYNSTA should be discontinued (see section 4.3 and section 4.4).

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.

Amlodipine

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

Breastfeeding

TWYNSTA is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breastmilk. Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7 %, with a maximum of 15 %.
The effect of amlodipine on infants is unknown. Because of the potential adverse

reactions in breastfed infants, TWYNSTA should not be used by breastfeeding mothers (see section 4.3).

4.7 Effects on the ability to drive and use machines

Twynsta has moderate influence 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, when driving vehicles or operating machinery it should be taken into account that syncope, somnolence, dizziness, or vertigo may occasionally occur during antihypertensive therapy. If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

The following side effects derived from the use of the TWYNSTA (telmisartan and 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.

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; not known: cannot be estimated from the available data.

MedDRA preferred term:	***Frequency for TWYNSTA (telmisartan and amlodipine fixed dose combination)***	***Frequency for telmisartan as monotherapy***	***Frequency for amlodipine as monotherapy***
Infections and infestations			
Sepsis (including fatal outcome)	-	Rare	-
Upper respiratory tract infection	-	Uncommon	-
Urinary tract infection	-	Uncommon	-
Cystitis	Rare	Uncommon	-

MedDRA preferred term:	***Frequency for TWYNSTA (telmisartan and amlodipine fixed dose combination)***	***Frequency for telmisartan as monotherapy***	***Frequency for amlodipine as monotherapy***
Blood and lymphatic system disorders			
Leukopenia	-	-	Very rare
Thrombocytopenia	-	Rare	Very rare
Anaemia	-	Uncommon	-
Eosinophilia	-	Rare	-
Immune system disorders			
Anaphylactic reaction	-	Rare	-
Hypersensitivity	-	Rare	Very rare
Metabolism and nutrition disorders			
Hyperkalaemia	-	Uncommon	-
Hypoglycaemia (in diabetic patients)	-	Rare	-
Hyponatraemia	-	Rare	-
Hyperglycaemia	-	-	Very rare
Psychiatric disorders			
Depression	Rare	Uncommon	Uncommon
Anxiety	Rare	Rare	Uncommon
Confusional state	-	-	Rare
Insomnia	Rare	Uncommon	Uncommon
Mood altered	-	-	Uncommon
Nervous system disorders			
Syncope (fainting)	Rare	Uncommon	Uncommon
Somnolence	Uncommon	-	Common
Dizziness	Common	-	Common
Extrapyramidal disorder	-	-	Not known
Hypertonia	-	-	Very rare
Migraine	Uncommon	-	-
Headache	Uncommon	-	Common
Neuropathy peripheral	Rare	-	Very rare
Paraesthesia	Uncommon	-	Uncommon
Hypoaesthesia	Rare	-	Uncommon
Dysgeusia	Rare	-	Uncommon

MedDRA preferred term:	***Frequency for TWYNSTA (telmisartan and amlodipine fixed dose combination)***	***Frequency for telmisartan as monotherapy***	***Frequency for amlodipine as monotherapy***
Tremor	Rare	-	Uncommon
Eye disorders			
Visual impairment	-	Rare	Common
Diplopia	-	-	Common
Ear and labyrinth disorders			
Vertigo	Uncommon	Uncommon	-
Tinnitus	-	-	Uncommon
Cardiac disorders			
Myocardial infarction	-	-	Very rare
Ventricular tachycardia	-	-	Uncommon
Dysrhythmia	-	-	Uncommon
Atrial fibrillation	-	-	Uncommon
Bradycardia	Uncommon	Uncommon	Uncommon
Tachycardia	-	Rare	-
Palpitations	Uncommon	-	Common
Vascular disorders			
Hypotension	Uncommon	Uncommon	Uncommon
Orthostatic hypotension	Uncommon	Uncommon	-
Flushing	Uncommon	-	Common
Vasculitis	-	-	Very rare
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	-	Uncommon	Common
Cough	Uncommon	-	Uncommon
Rhinitis	-	-	Uncommon
Gastrointestinal disorders			
Pancreatitis	-	-	Very rare
Gastritis	-	-	Very rare
Abdominal pain	Uncommon	Uncommon	Common
Diarrhoea	Uncommon	Uncommon	Common
Vomiting	Rare	Uncommon	Uncommon
Gingival hypertrophy	Rare	-	Very rare
Dyspepsia	Rare	Uncommon	Common

MedDRA preferred term:	***Frequency for TWYNSTA (telmisartan and amlodipine fixed dose combination)***	***Frequency for telmisartan as monotherapy***	***Frequency for amlodipine as monotherapy***
Constipation	-	-	Common
Nausea	Uncommon	-	Common
Dry mouth	Rare	Rare	Uncommon
Flatulence	-	Uncommon	-
Abdominal discomfort	-	Rare	-
Change of bowel habit	-	-	Common
Hepatobiliary disorders			
Hepatitis	-	-	Very rare
Jaundice	-	-	Very rare
Hepatic function abnormal/liver disorder	-	Rare	-
Hepatic enzyme increased (mostly consistent with cholestasis)	-	-	Very rare
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis	-	-	Not known
Stevens-Johnson syndrome	-	-	Very rare
Angioedema (including fatal outcome)	-	Rare	Very rare
Erythema multiforme	-	-	Very rare
Dermatitis exfoliative	-	-	Very rare
Drug eruption	-	Rare	-
Toxic skin eruption	-	Rare	-
Photosensitivity reaction	-	-	Very rare
Urticaria	-	Rare	Uncommon

MedDRA preferred term:	***Frequency for TWYNSTA (telmisartan and amlodipine fixed dose combination)***	***Frequency for telmisartan as monotherapy***	***Frequency for amlodipine as monotherapy***
Eczema	Rare	Rare	-
Erythema	Rare	Rare	-
Rash	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon
Alopecia	-	-	Uncommon
Purpura	-	-	Uncommon
Skin discolouration	-	-	Uncommon
Hyperhidrosis	-	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders			
Arthralgia	Uncommon	Rare	Uncommon
Back pain	Uncommon	Uncommon	Uncommon
Pain in extremity (leg pain)	Rare	Rare	-
Tendon pain (tendonitis like symptoms)	-	Rare	-
Joint swelling	-	-	Common
Muscle spasms (cramps in legs)	Uncommon	Uncommon	Common
Myalgia	Uncommon	Uncommon	Uncommon
Renal and urinary disorders			
Renal impairment (including acute renal injury)	-	Uncommon	-
Nocturia	Rare	-	Uncommon
Micturition disorder	-	-	Uncommon
Pollakiuria	-	-	Uncommon
Reproductive system and breast disorders			
Erectile dysfunction	Uncommon	-	Uncommon
Gynaecomastia	-	-	Uncommon
General disorders and administration site conditions			
Chest pain	Uncommon	Uncommon	Uncommon
Pain	-	-	Uncommon

MedDRA preferred term:	***Frequency for TWYNSTA (telmisartan and amlodipine fixed dose combination)***	***Frequency for telmisartan as monotherapy***	***Frequency for amlodipine as monotherapy***
Oedema	Uncommon	-	Very common
Oedema peripheral	Common	-	-
Asthenia (weakness)	Uncommon	Uncommon	Common
Fatigue	Uncommon	-	Common
Malaise	Rare	-	Uncommon
Influenza like illness	-	Rare	-
Investigations			
Hepatic enzyme increased	Uncommon	Rare	-
Blood creatinine increased	-	Uncommon	-
Blood creatine phosphokinase increased	-	Rare	-
Haemoglobin decreased	-	Rare	-
Blood uric acid increased	Rare	Rare	-
Weight increased	-	-	Uncommon
Weight decreased	-	-	Uncommon

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 Overdose

Symptoms

There is no experience of overdose with TWYNSTA. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia also occurred.
Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
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, supportive treatment should be instituted.
Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
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 haemofiltration and is not dialysable.
Amlodipine is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Vascular medicines – other hypotensives

TWYNSTA combines two antihypertensive compounds with different mechanisms of action: an angiotensin II receptor blocker, telmisartan, and a dihydropyridine 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) blocker. 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 human, 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 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 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 sex and was similar in patients with and without diabetes mellitus.

TWYNSTA has not been studied in any patient population other than hypertension.

5.2 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.

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 bi-exponential decay pharmacokinetics with a terminal elimination half-life of > 20 hours.

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.

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.

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

Sex differences
Sex 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The manufacturing and expiry dates can be found on the packaging.

6.4 Special precautions for storage

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.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ingelheim Pharmaceuticals (Pty) Ltd
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8. 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 07 June 2012

10. DATE OF REVISION OF THE TEXT

04 September 2025

BOTSWANA Reg. No.		
TWYNSTA 40/5 mg	BOT1202099	S2
TWYNSTA 40/10 mg	BOT1202100	
TWYNSTA 80/5 mg	BOT1202101	
TWYNSTA 80/10 mg	BOT1202102	

NAMIBIA Reg. No.		
TWYNSTA 40/5 mg	11/7.1.3/0028	NS2
TWYNSTA 40/10 mg	11/7.1.3/0029	
TWYNSTA 80/5 mg	11/7.1.3/0030	
TWYNSTA 80/10 mg	11/7.1.3/0031	