HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TWYNSTA safely and effectively. See full prescribing information for TWYNSTA.

TWYNSTA® (telmisartan/amlodipine) Tablets
Initial U.S. Approval: 2009

WARNING: AVOID USE IN PREGNANCY
See full prescribing information for complete boxed warning.
When pregnancy is detected, discontinue TWYNSTA as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus (5.1)

----------RECENT MAJOR CHANGES----------
Contraindications (4) 2/2011

----------INDICATIONS AND USAGE----------
- TWYNSTA is an angiotensin II receptor blocker (ARB) and a dihydropyridine calcium channel blocker (DHP-CCB) combination product indicated for the treatment of hypertension alone or with other antihypertensive agents (1)
- TWYNSTA tablets are indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals (1)

----------DOSAGE AND ADMINISTRATION----------
- Substitute TWYNSTA for its individually titrated components for patients on amlodipine and telmisartan. TWYNSTA may also be given with increased amounts of amlodipine, telmisartan, or both, as needed. (2.2, 2.3)
- Use TWYNSTA tablets to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan (or another angiotensin receptor blocker) alone (2.3)
- Dosage may be increased after at least 2 weeks to a maximum dose of 80/10 mg once daily, usually by increasing one component at a time but both components can be raised to achieve more rapid control (2.1, 2.2)
- Majority of antihypertensive effect is attained within 2 weeks (2.1)
- Initiate with 40/5 mg or 80/5 mg once daily (2.4)
- Switch patients who experience dose-limiting adverse reactions on amlodipine to TWYNSTA tablets containing a lower dose of that component (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine or any other component of this product (4)

----------WARNINGS AND PRECAUTIONS----------
- Avoid fetal or neonatal exposure (5.1)
- Hypotension: Correct any volume or salt depletion before initiating therapy. Observe for signs and symptoms of hypotension. (5.2)
- Titrate slowly in patients with hepatic (5.4) or severe renal impairment (5.5)
- Heart failure: Monitor for worsening (5.8)
- Avoid concomitant use of an ACE inhibitor and angiotensin receptor blocker (5.6)
- Myocardial infarction: Uncommonly, initiating a CCB in patients with severe obstructive coronary artery disease may precipitate myocardial infarction or increased angina (5.7)

----------ADVERSE REACTIONS----------
In the placebo-controlled factorial design study, the most common reasons for discontinuation of therapy with TWYNSTA tablets were peripheral edema, dizziness, and hypotension, each leading to discontinuation of ≤0.5% of TWYNSTA-treated patients. Adverse reactions that occurred at a ≥2% higher incidence on TWYNSTA tablets than placebo were peripheral edema (4.8% vs 0%), dizziness (3.0% vs 2.2%), and back pain (2.2% vs 0%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- NSAIDS: Increased risk of renal impairment and loss of anti-hypertensive effect (7)

----------USE IN SPECIFIC POPULATIONS----------
- Patients ≥75 years of age or hepatically impaired patients: Start with amlodipine or add amlodipine 2.5 mg to telmisartan (2.5, 8.5, 8.6)
- Nursing Mothers: Choose to discontinue nursing or drug (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved patient labeling.

Revised: 4/2011

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FULL PRESCRIBING INFORMATION

WARNING: AVOID USE IN PREGNANCY

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, TWYNSTA tablets should be discontinued as soon as possible. *See Warnings and Precautions (5.1).*

1 INDICATIONS AND USAGE

TWYNSTA (telmisartan/amlodipine) tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents.

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

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

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

Data from an 8-week, placebo-controlled, multidose, factorial trial provide estimates of the probability of reaching a blood pressure goal with TWYNSTA compared to telmisartan or amlodipine monotherapy and placebo *[see Clinical Studies (14.1)]*.

The figures below provide estimates of the likelihood of achieving systolic and diastolic blood pressure control with TWYNSTA 80/10 mg tablets, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

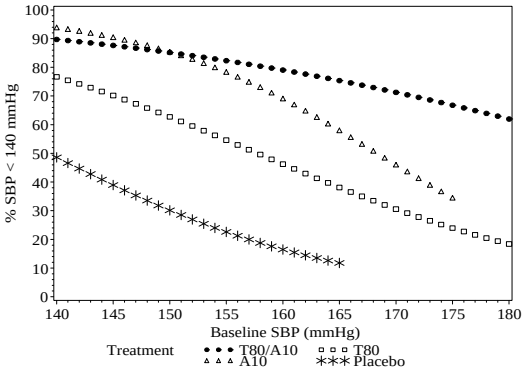

Figure 1a: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

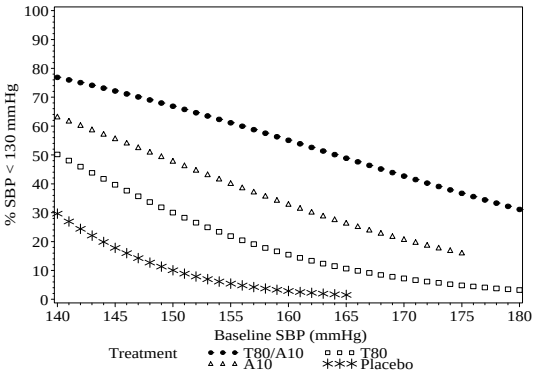

Figure 1b: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

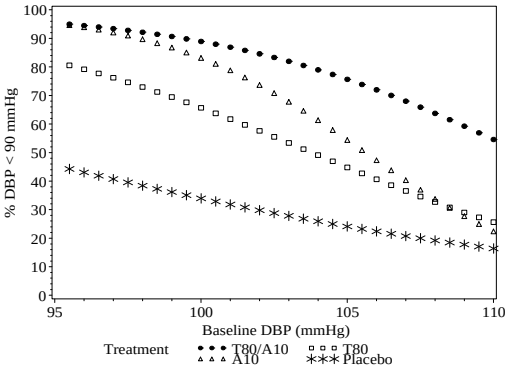

Figure 2a: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

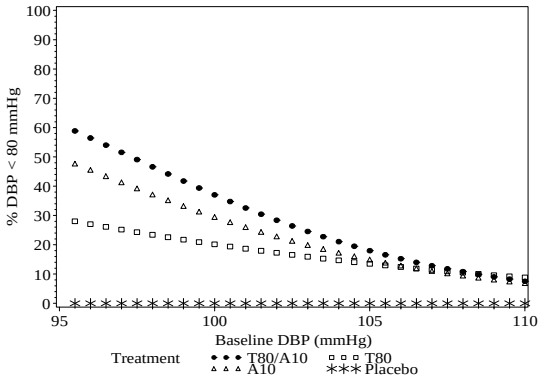

Figure 2b: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

The figures above provide an approximation of the likelihood of reaching a targeted blood pressure goal at 8 weeks. For example, a patient with a baseline blood pressure of 160/110 mmHg has about a 16% likelihood of achieving a goal of <140 mmHg (systolic) and 16% likelihood of achieving <90 mmHg (diastolic) on placebo. The likelihood of achieving these same goals on telmisartan is about 46% (systolic) and 26% (diastolic). The likelihood of achieving these same goals on amlodipine is about 69% (systolic) and 22% (diastolic). These likelihoods rise to 79% for systolic and 55% for diastolic with TWYNSTA.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Telmisartan is an effective treatment of hypertension in once daily doses of 20-80 mg while amlodipine is effective in doses of 2.5-10 mg.

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Dosage must be individualized and may be increased after at least 2 weeks. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of TWYNSTA tablets is 80/10 mg once daily.

The adverse reactions of telmisartan are uncommon and independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter *[see Adverse Reactions (6.1)]*.

TWYNSTA may be taken with or without food.

2.2 Replacement Therapy
Patients receiving amlodipine and telmisartan from separate tablets may instead receive TWYNSTA tablets containing the same component doses once daily. When substituting for individual components, increase the dose of TWYNSTA if blood pressure control has not been satisfactory.

2.3 Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Antihypertensive Monotherapy
TWYNSTA tablets may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan (or another angiotensin receptor blocker) alone.

Patients treated with 10 mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to TWYNSTA 40/5 mg tablets once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response *[see Adverse Reactions (6.1)]*.

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

Initial therapy with TWYNSTA is not recommended in patients ≥75 years old or with hepatic impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.4), and Use in Specific Populations (8.5, 8.6)]*.

Correct imbalances of intravascular volume- or salt-depletion, before initiating therapy with TWYNSTA tablets *[see Warnings and Precautions (5.2)]*.

2.5 Dosing in Specific Populations
Renal Impairment
No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.

Hepatic Impairment
In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients with hepatic impairment.

Patients 75 Years of Age and Older
In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients 75 years of age and older.

3 DOSAGE FORMS AND STRENGTHS
TWYNSTA tablets are formulated for oral administration in the following strength combinations:

	40/5 mg	**40/10 mg**	**80/5 mg**	**80/10 mg**
telmisartan	40	40	80	80
amlodipine equivalent	5	10	5	10

The telmisartan/amlodipine non-scored, multilayer tablets are of oval, biconvex shape. Tablets are white to off-white on one side and blue on the other side. The white side is debossed with the BOEHRINGER INGELHEIM symbol and with either A1, A2, A3, or A4 for the 40/5 mg, 40/10 mg, 80/5 mg, and 80/10 mg strengths, respectively.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Fetal/Neonatal Morbidity and Mortality
Telmisartan
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue TWYNSTA tablets as soon as possible *[see Boxed Warning]*.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Inform mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester that most reports of fetal toxicity have been associated with second or third trimester exposure. Nonetheless, when patients become pregnant or are considering pregnancy, physicians should have the patient discontinue the use of TWYNSTA tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, TWYNSTA tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

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Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5.2 Hypotension

Telmisartan

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with TWYNSTA tablets. Either correct this condition prior to administration of TWYNSTA tablets, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Amlodipine

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, observe patients with severe aortic stenosis closely when administering amlodipine, as one should with any vasodilator.

5.3 Hyperkalemia

Telmisartan

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

5.4 Patients with Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients *[see Dosage and Administration (2.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients *[see Use in Specific Populations (8.6)]*.

5.5 Renal Function Impairment

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan *[see Clinical Pharmacology (12.3)]*.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

5.6 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended.

5.7 Risk of Myocardial Infarction or Increased Angina

Amlodipine

Uncommonly, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

5.8 Heart Failure

Amlodipine

Closely monitor patients with heart failure.

Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In the PRAISE-2 study, 1654 patients with NYHA class III (80%) or IV (20%) heart failure without evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%), and diuretics (99%) were randomized 1:1 to receive placebo or amlodipine and followed for a mean of 33 months. While there was no statistically significant difference between amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine), there were more reports of pulmonary edema in the patients on amlodipine.

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

TWYNSTA Tablets

The concomitant use of telmisartan and amlodipine has been evaluated for safety in more than 3700 patients with hypertension; approximately 1900 of these patients were exposed for at least 6 months and over 160 of these patients were exposed for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In the placebo-controlled factorial design study, the population treated with a telmisartan and amlodipine combination had a mean age of 53 years and included approximately 50% males, 79% were Caucasian, 17% Blacks, and 4% Asians. Patients received doses ranging from 20/2.5 mg to 80/10 mg orally, once daily.

The frequency of adverse reactions was not related to gender, age, or race.

The adverse reactions that occurred in the placebo-controlled factorial design trial in ≥2% of patients treated with TWYNSTA and at a higher incidence in TWYNSTA-treated patients (n=789) than placebo-treated patients (n=46) were peripheral edema (4.8% vs 0%), dizziness (3.0% vs 2.2%), and back pain (2.2% vs 0%). Edema (other than peripheral edema), hypotension, and syncope were reported in <2% of patients treated with TWYNSTA tablets.

In the placebo-controlled factorial design trial, discontinuation due to adverse events occurred in 2.2% of all treatment cells of patients in the telmisartan/amlodipine-treated patients and in 4.3% in the placebo-treated group. The most common reasons for discontinuation of therapy with TWYNSTA tablets were peripheral edema, dizziness, and hypotension (each ≤0.5%).

Peripheral edema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan. In the factorial design study, the incidence of peripheral edema during the 8 week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was notably lower when telmisartan was used in combination with amlodipine 10 mg.

Table 1: Incidence of Peripheral Edema During the 8 Week Treatment Period

		Telmisartan		
		Placebo	40 mg	80 mg
Amlodipine	Placebo	0%	0.8%	0.7%
	5 mg	0.7%	1.4%	2.1%
	10 mg	17.8%	6.2%	11.3%

Telmisartan

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) monotherapy for up to 12 weeks, an overall incidence of adverse events was similar to the patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 2.

Table 2: Adverse Events Occurring at an Incidence of ≥1% in Patients Treated with Telmisartan and at a Greater Rate than Patients Treated with Placebo

	Telmisartan n=1455 %	**Placebo n=380 %**
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in >0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets:
Autonomic Nervous System: impotence, increased sweating, flushing; *Body as a Whole:* allergy, fever, leg pain, malaise; *Cardiovascular:* palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; *CNS:* insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; *Gastrointestinal:* flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; *Metabolic:* gout, hypercholesterolemia, diabetes mellitus; *Musculoskeletal:* arthritis, arthralgia, leg cramps; *Psychiatric:* anxiety,

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depression, nervousness; *Resistance Mechanism:* infection, fungal infection, abscess, otitis media; *Respiratory:* asthma, bronchitis, rhinitis, dyspnea, epistaxis; *Skin:* dermatitis, rash, eczema, pruritus; *Urinary:* micturition frequency, cystitis; *Vascular:* cerebrovascular disorder; and *Special Senses:* abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings
In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.
Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.
Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.
Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Amlodipine
Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1730) in doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine-treated patients and was not significantly different from that seen in placebo-treated patients (about 1%). The most common side effects were headache and edema. The incidence (%) of side effects which occurred in a dose-related manner are presented in Table 3.

Table 3: Incidence (%) of Dose-Related Adverse Effects with Amlodipine at Doses of 2.5 mg, 5.0 mg, and 10.0 mg or Placebo

Adverse Event	**Amlodipine 2.5 mg n=275 %**	**Amlodipine 5.0 mg n=296 %**	**Amlodipine 10.0 mg n=268 %**	**Placebo n=520 %**
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1% in placebo-controlled clinical trials are presented in Table 4.

Table 4: Incidence (%) of Adverse Effects Not Clearly Dose Related but Reported at an Incidence of >1% in Placebo-Controlled Clinical Trials

Adverse Event	**Amlodipine n=1730 %**	**Placebo n=1250 %**
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis; *Central and Peripheral Nervous System:* hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo; *Gastrointestinal:* anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change of bowel habit; *General:* allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease; *Musculoskeletal System:* arthralgia, arthrosis, muscle cramps,** myalgia; *Psychiatric:* sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change; *Respiratory System:* dyspnea,** epistaxis; *Skin and Appendages:* angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular; *Special Senses:* abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; *Urinary System:* micturition frequency, micturition disorder, nocturia; *Autonomic Nervous System:* dry mouth, sweating increased; *Metabolic and Nutritional:* hyperglycemia, thirst; *Hemopoietic:* leukopenia, purpura, thrombocytopenia.
**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc®.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these

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reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine.

Telmisartan
The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis),
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Amlodipine
Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

7 DRUG INTERACTIONS

7.1 Drug Interactions with TWYNSTA Tablets
The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with TWYNSTA tablets and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of TWYNSTA tablets, as described below:

7.2 Drug Interactions with Telmisartan
Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Co-administration of telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

7.3 Drug Interactions with Amlodipine
In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, Maalox®, sildenafil.

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects, *Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions (5.1).*

8.3 Nursing Mothers
Telmisartan
It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Amlodipine
It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered.

8.4 Pediatric Use
Safety and effectiveness of TWYNSTA in pediatric patients have not been established.

8.5 Geriatric Use
TWYNSTA Tablets

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Of the total number of 3282 hypertensive patients receiving a telmisartan/amlodipine combination in clinical studies, 605 (18%) patients were 65 years of age or older and of these, 88 (3%) patients were 75 years and older. No overall differences in efficacy or safety of TWYNSTA tablets were observed in this patient population.

Telmisartan
Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine
Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in patients 75 years of age and older *[see Dosage and Administration (2.5)]*.

8.6 Hepatic Insufficiency
Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency *[see Dosage and Administration (2) and Warnings and Precautions (5.4)]*. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients *[see Dosage and Administration (2.4)]*.

8.7 Race
The magnitude of blood pressure lowering in black patients approached that observed in non-black patients but the number of black patients was limited (237 of 1461 patients).

10 OVERDOSAGE
Telmisartan
Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

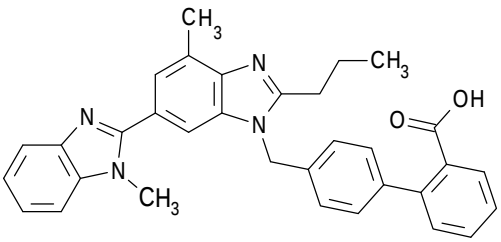
Amlodipine
Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

11 DESCRIPTION
TWYNSTA is a fixed dose combination of telmisartan and amlodipine.

TWYNSTA tablets contain telmisartan, a non-peptide angiotensin II receptor (type AT_1) antagonist. Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base. Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$ and its structural formula is:



TWYNSTA tablets contain the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$ and its structural formula is:

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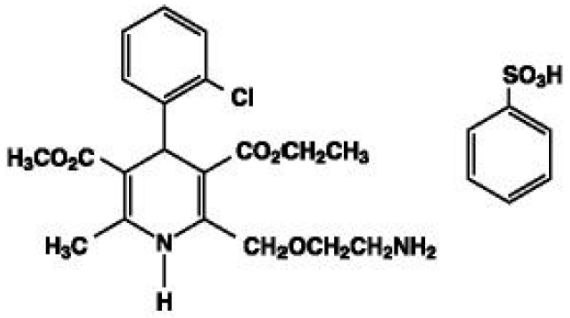

TWYNSTA tablets are formulated in four strengths for oral administration with a combination of amlodipine besylate, equivalent to 5 mg or 10 mg of amlodipine free-base, with 40 mg, or 80 mg of telmisartan provided in the following four combinations: 40/5 mg, 40/10 mg, 80/5 mg, and 80/10 mg.

TWYNSTA tablets also contain the following inactive ingredients: sodium hydroxide, povidone, meglumine, sorbitol, magnesium stearate, microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silicon dioxide, ferric oxide black, ferric oxide yellow and FD&C blue #1.

TWYNSTA tablets are hygroscopic and require protection from moisture.

TWYNSTA tablets require protection from light.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Telmisartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

12.2 Pharmacodynamics

TWYNSTA Tablets

TWYNSTA tablets have been shown to be effective in lowering blood pressure. TWYNSTA is a combination of two drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, telmisartan.

Both telmisartan and amlodipine, lower blood pressure by reducing peripheral resistance but through complementary mechanisms.

Telmisartan

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

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In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Amlodipine
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

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.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Amlodipine has indications other than hypertension which can be found in the Norvasc® package insert.

12.3 Pharmacokinetics
TWYNSTA Tablets
The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately.

After administering TWYNSTA 80/10 mg tablet with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and C_{max} for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and C_{max} were not altered *[see Dosage and Administration (2.1)]*.

Telmisartan
Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10 to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Amlodipine
Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Distribution
Telmisartan
Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1 - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Amlodipine
The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Metabolism and Elimination
Telmisartan
Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Amlodipine

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Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Special Populations

Renal Insufficiency

Telmisartan: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration *[see Warnings and Precautions (5.5)]*.

Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Hepatic Insufficiency

Telmisartan: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of amlodipine.

Gender

Plasma concentrations of telmisartan are generally 2–3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Geriatric Patients

Telmisartan: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years *[see Dosage and Administration (2.1)]*.

Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of amlodipine *[see Dosage and Administration (2.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Telmisartan

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m^2 basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

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/m^2 basis).

13.3 Developmental Toxicity

Telmisartan

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a mg/m^2 basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

14 CLINICAL STUDIES

14.1 TWYNSTA Tablets

The efficacy of TWYNSTA tablets for treatment of hypertension was studied in 1 placebo-controlled and 2 active-controlled trials.

Reference ID: 2961870

An 8-week multicenter, randomized, double-blind, placebo-controlled, parallel group factorial study in patients with mild to severe hypertension was conducted to determine if treatment with TWYNSTA was more effective in reducing blood pressure compared to the respective monotherapies. The study randomized 1461 patients with baseline systolic blood pressure between 117 and 179 mmHg (mean 153 mmHg) and a baseline diastolic blood pressure between 90 and 119 (mean 102 mmHg) to one of the 16 treatment arms. Patients assigned to receive amlodipine 10 mg started on amlodipine 5 mg or combinations thereof for the first two weeks. The four key treatment combinations (including combinations of telmisartan 40 or 80 mg and amlodipine 5 or 10 mg) had statistically significant reduction in in-clinic seated trough cuff systolic and diastolic blood pressure compared to the respective individual monotherapies (Table 6).

Table 6: Placebo-Subtracted Mean Change from Baseline in Seated Systolic/Diastolic Blood Pressure (mmHg): Combination Therapy vs Monotherapy Components

Amlodipine, mg	Telmisartan, mg		
	0	40	80
0	—	-12.1/-7.2	-11.8/-7.8
5	-12.9/-7.2	-19.3/-10.3	-19.6/-12.0
10	-18.2/-10.9	-22.2/-14.0	-23.9/-13.9

The majority of the antihypertensive effect of the telmisartan/amlodipine combination was attained within 2 weeks after initiation of therapy. In patients receiving a telmisartan/amlodipine combination significantly larger reductions in seated diastolic and systolic blood pressure compared to patients treated with the respective monotherapies were observed at every assessment (Week 2, 4, 6, and 8).

The antihypertensive effect of TWYNSTA tablets was similar in patients ≥65 years than below 65 years of age, in male and female patients, and in patients with and without diabetes.

The magnitude of blood pressure lowering in black patients approached that observed in non-black patients but the number of black patients was limited (237 of 1461 patients).

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 over the entire 24-hours dosing period.

In a double-blind, active-controlled study, a total of 1097 patients with mild to severe hypertension (mean baseline systolic/diastolic BP 149.5/96.6 mmHg) 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 administration, each of the combination treatments was statistically significantly superior to both amlodipine monotherapy doses in reducing diastolic and systolic blood pressures. Edema related events (peripheral edema, generalized edema, and edema) in patients who received TWYNSTA (40/5 mg or 80/5 mg) were significantly lower as compared to patients who received amlodipine 10 mg (4.3% vs 27.2%, respectively).

Table 7: Effect on Seated Systolic/Diastolic Blood Pressure: Combination Therapy vs Monotherapy

Treatment Group	Mean Change[1]	Difference from amlodipine 5 mg	Difference from amlodipine 10 mg
Twynsta 40/5 mg; n=270	-13.6 / -9.4	-7.4* / -3.6*	-2.4* / -1.4*
Twynsta 80/5 mg; n=271	-15.0 / -10.6	-8.8* / -4.9*	-3.9* / -2.7*
Amlodipine 5 mg; n=255	-6.2 / -5.7	----	----
Amlodipine 10 mg; n=261	-11.1 / -8.0	----	----

*$p<0.05$
[1]Mean change from baseline at Week 8 in seated systolic/diastolic blood pressure

In a second double-blind, active-controlled study, a total of 947 patients with mild to severe hypertension (mean baseline systolic/diastolic BP 147.5/95.6 mmHg) 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.

Table 8: Effect on Seated Systolic/Diastolic Blood Pressure: Combination Therapy vs Monotherapy

Treatment Group	Mean Change[1]	Difference from amlodipine 10 mg
Twynsta 40/10 mg; n=306	-11.1 / -9.2	-3.7* / -2.8*
Twynsta 80/10 mg; n=310	-11.3 / -9.3	-3.9* / -2.8*
Amlodipine 10 mg; n=305	-7.4 / -6.5	----

*$p<0.05$
[1]Mean change from baseline at Week 8 in seated systolic/diastolic blood pressure

14.2 Telmisartan

The antihypertensive effects of telmisartan have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20-160 mg; one of these examined the antihypertensive effects of telmisartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95 to 114 mmHg), 1031 of whom were treated with telmisartan. Following once daily administration of telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with telmisartan tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year. The antihypertensive effect of telmisartan is not influenced by patient age, gender, weight, or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors.

In a controlled study, the addition of telmisartan to hydrochlorothiazide produced an additional dose-related reduction in blood pressure that was similar in magnitude to the reduction achieved with telmisartan monotherapy. Hydrochlorothiazide also had an added blood pressure effect when added to telmisartan.

Reference ID: 2961870

The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 20, 40, and 80 mg, the antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24-hour trough-to-peak ratio for 40 to 80 mg doses of telmisartan was 70 to 100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).

There were no changes in the heart rate of patients treated with telmisartan in controlled trials.

14.3 Amlodipine

The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours post-dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect.

16 HOW SUPPLIED/STORAGE AND HANDLING

TWYNSTA tablets are available as non-scored, white–off-white/blue, multilayer tablets of oval, biconvex shape containing telmisartan and amlodipine in the strengths described below. TWYNSTA tablets are debossed with a BOEHRINGER INGELHEIM symbol and an individual product tablet code on one side. TWYNSTA tablets are supplied for oral administration in the following strengths and package configurations:

Tablet strength (telmisartan/ amlodipine equivalent) mg	**Package Configuration**	**NDC#**	**Product Code**
40/5 mg	Blister of 30	0597-0124-37	Al
40/10 mg	Blister of 30	0597-0125-37	A2
80/5 mg	Blister of 30	0597-0126-37	A3
80/10 mg	Blister of 30	0597-0127-37	A4

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature]. Do not remove from blisters until immediately before administration. Protect from moisture and light.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.(17.2)

17.1 Pregnancy

Inform female patients of childbearing age about the consequences of exposure to drugs that act on the renin-angiotensin system. Advise these patients to report pregnancies to their physicians as soon as possible *[see Warnings and Precautions (5.1)]*.

17.2 FDA-Approved Patient Labeling

Patient labeling is provided as a tear-off leaflet at the end of this prescribing information.

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Maalox is a registered trademark of Novartis.

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Reference ID: 2961870

Patient Information

TWYNSTA® (TWIN-stah)
(telmisartan/amlodipine)
Tablets

Read this Patient Information before you start taking TWYNSTA tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about TWYNSTA tablets?

TWYNSTA is not for pregnant women. Taking TWYNSTA tablets during your pregnancy can cause injury and even death to your unborn baby. If you become pregnant, stop taking TWYNSTA tablets and call your doctor right away. If you plan to become pregnant, talk to your doctor about other ways to lower your blood pressure.

What is TWYNSTA?

TWYNSTA is a prescription medicine that contains telmisartan and amlodipine.

TWYNSTA tablets may be used to treat high blood pressure (hypertension):

- when one of these medicines (or a similar one) is not enough to lower your high blood pressure
- as the first medicine to lower your high blood pressure if your doctor decides you are likely to need more than one medicine

It is not known if TWYNSTA is safe and effective in children.

What should I tell my doctor before taking TWYNSTA tablets?

Before you take TWYNSTA tablets, tell your doctor if you:

- have liver problems
- have kidney problems
- have heart problems
- have any other medical conditions
- are pregnant or are planning to become pregnant. See "**What is the most important information I should know about TWYNSTA tablets**?"
- are breast-feeding or plan to breast-feed. It is not known if TWYNSTA passes into your breast milk. You and your doctor should decide if you will take TWYNSTA tablets or breast-feed. You should not do both. Talk with your doctor about the best way to feed your baby if you take TWYNSTA tablets.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

TWYNSTA may affect the way other medicines work, and other medicines may affect how TWYNSTA works. Especially tell your doctor if you take:

- digoxin (Lanoxin®, Lanoxicaps®)

- lithium (Eskalith®, Lithobid®)
- medicines used to treat pain and arthritis, called non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors
- ramipril (Altace®) or other medicines that may be used to treat high blood pressure or a heart problem
- water pills (diuretics)

Know the medicines you take. Keep a list of them and show it to your doctor or pharmacist when you get a new medicine.

How should I take TWYNSTA tablets?

- Take TWYNSTA tablets exactly as your doctor tells you to take it.
- Your doctor will tell you how much TWYNSTA to take and when to take it. Your doctor may change your dose if needed.
- Take TWYNSTA one time each day at the same time.
- Take TWYNSTA tablets with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much TWYNSTA, call your doctor or go to the nearest hospital emergency room right away.
- Read the "**How to Open the Blister**" at the end of this leaflet before you use TWYNSTA. Talk with your doctor if you do not understand the instructions.

What are possible side effects of TWYNSTA tablets?

TWYNSTA tablets may cause serious side effects, including:

- **Injury or death to your unborn baby.** See "**What is the most important information I should know about TWYNSTA tablets?**"
- **Low blood pressure (hypotension)** is most likely to happen if you also:
  - take water pills (diuretics)
  - are on a low-salt diet
  - get dialysis treatments
  - have heart problems
  - get sick with vomiting or diarrhea

  If you feel faint or dizzy, lie down and call your doctor right away.
- **Kidney problems.** Kidney problems may get worse if you already have kidney disease. You may have changes in your kidney test results, and you may need a lower dose of TWYNSTA tablets. Call your doctor if you get:
  - swelling in your feet, ankles, or hands
  - unexplained weight gain

  Call your doctor right away if you get any of the symptoms listed above.
- **Heart problems or heart attack.** Heart problems may get worse in people that already have heart disease. This may happen when you start TWYNSTA tablets or when there is an

increase in your dose of TWYNSTA. Get emergency help if you get worse chest pain or chest pain that does not go away.

- **High potassium in the blood (hyperkalemia).** Your doctor may check your potassium levels as needed.

Rare, serious allergic reactions may happen. Tell your doctor right away if you get any of these symptoms:

- swelling of face, tongue, throat
- difficulty breathing

The most common side effects of TWYNSTA tablets include:

- swelling in your hands, ankles, or feet
- feeling like your heart is pounding or racing
- flushing or sudden redness of the face and neck
- dizziness
- back pain
- feeling tired or sleepy
- abdominal pain, nausea, or diarrhea
- low blood pressure or a sudden drop in blood pressure with fainting

These are not all the possible side effects of TWYNSTA tablets. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TWYNSTA tablets?

- Store TWYNSTA tablets between 59° to 86°F (15° to 30°C).
- Do not remove TWYNSTA tablets from blisters until right before you take them.
- Keep TWYNSTA tablets out of the light and away from moisture.

Keep TWYNSTA tablets and all medicines out of the reach of children.

General information about TWYNSTA tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TWYNSTA tablets for a condition for which it was not prescribed. Do not give TWYNSTA tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about TWYNSTA tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TWYNSTA tablets that is written for health professionals. For more information, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906.

What are the ingredients in TWYNSTA tablets?

Active ingredients: telmisartan and amlodipine besylate

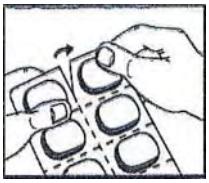
Inactive ingredients: sodium hydroxide, povidone, meglumine, sorbitol, magnesium stearate, microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silicon dioxide, ferric oxide black, ferric oxide yellow and FD&C blue #1.

What is high blood pressure (hypertension)?

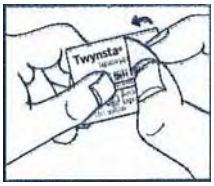
Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. TWYNSTA tablets can help your blood vessels relax so your blood pressure is lower. High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

How to open the blister:

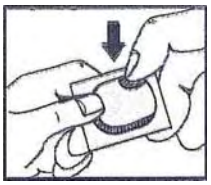
1. Tear (You may also use scissors to tear the blister apart)



2. Peel (Peel off the paper layer from the aluminum foil)



3. Push (Push the tablet through the foil)



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/s/

MARY R SOUTHWORTH
06/06/2011