PRODUCT MONOGRAPH

Pr TEVA-TELMISARTAN

Telmisartan

Tablets 40 mg and 80 mg

Professed standard

Angiotensin II AT1 Receptor Blocker

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Table of Contents

Pr

TEVA-TELMISARTAN Tablets
40 mg and 80 mg

(telmisartan)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 40 mg , 80 mg	Hydroxypropyl methylcellulose, Magnesium stearate, Mannitol, Meglumine, Povidone, Sodium Hydroxide, Sorbitol

INDICATIONS AND CLINICAL USE

Treatment of Essential Hypertension
TEVA-TELMISARTAN tablets are indicated for the treatment of mild to moderate essential hypertension.

TEVA-TELMISARTAN may be used alone or in combination with thiazide diuretics.

The concurrent use with angiotensin converting enzyme inhibitors is not recommended.

Geriatrics (> 65 years of age):
No dosing adjustment is necessary. It should be recognized, however, that greater sensitivity in some older individuals can not be ruled out.

Pediatrics (< 18 years of age):
TEVA-TELMISARTAN is not recommended for use in children below 18 years due to limited data on safety and efficacy.

CONTRAINDICATIONS

TEVA-TELMISARTAN is contraindicated in:

• Patients who are hypersensitive to any components of this product
• Second and third trimesters of pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women)
• Lactation (see WARNINGS AND PRECAUTIONS, Special Populations – Nursing Women)

Sorbitol:

In case of rare hereditary condition of fructose intolerance, the use of TEVA-TELMISARTAN is contraindicated. TEVA-TELMISARTAN contains 38.4 mg of sorbitol per maximum recommended daily dose.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, TEVA-TELMISARTAN should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

Cardiovascular

Valvular Stenosis:
There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.

Hypotension:
In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy with telmisartan. Such conditions, especially volume and/or sodium depletion, should be corrected prior to administration of telmisartan. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

The use of a dual renin-angiotensin-aldosterone system (RAAS) blockade may lead to increased occurrence of hypotension when given as add-on therapy in patients with controlled blood pressure.

Endocrine and Metabolism

Hyperkalemia:
Drugs such as telmisartan that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of drugs 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 a greater risk of an increase in serum potassium.

The use of a dual renin-angiotensin-aldosterone system (RAAS) blockade may lead to increased occurrence of hyperkalemia when given as add-on therapy in patients with controlled blood pressure.

Hepatic/Biliary/Pancreatic:
Hepatic Impairment: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan. Three to four fold increases in C_{max} and AUC were observed in patients with liver impairment as compared to healthy subjects. Telmisartan tablets should be used with caution in these patients (see DOSAGE AND ADMINISTRATION).

Renal:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals (such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure).
Dual blockade of the renin-angiotensin-aldosterone system (e.g. concomitant use of an angiotensin II receptor antagonist with an ACE-inhibitor) has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. Upon treatment with such combination, renal function should be closely monitored..

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. There is no experience with long term use of telmisartan tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated. In susceptible patients, concomitant diuretic use may further increase the risk. Use of telmisartan should include appropriate assessment of renal function in these types of patients.

There is no experience regarding the administration of telmisartan tablets in patients with a recent kidney transplant.

Special Populations

Pregnant Women:
Drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, TEVA-TELMISARTAN should be discontinued as soon as possible.

The use of angiotensin receptor (AT_1) blockers (ARBs) is not recommended during pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to angotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

Infants with a history of in utero exposure to ARBs 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 may be required as a means of reversing hypotension and/or substituting for disordered renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

It is not known if telmisartan can be removed from the body by hemodialysis.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity. 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 with saline supplementation. In rabbits, fetotoxicity (total resorptions) associated with maternal toxicity (reduced body weight gain, mortality) was observed at the highest dose level (45 mg/kg/day). In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 50 mg/kg/day in late gestation and during lactation were observed to produce adverse effects in rat fetuses and neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Significant levels of telmisartan were present in rat milk and rat fetuses' blood during late gestation.

Nursing Women:
It is not known whether telmisartan is excreted in human milk but significant levels have been found in the milk of lactating rats. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age):

TEVA-TELMISARTAN is not recommended for use in children below 18 years due to limited data on safety and efficacy.

Geriatrics (> 65 years of age):
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 or older. No overall age related differences were seen in the adverse effect profile, but greater sensitivity in some older patients cannot be ruled out.

Monitoring and Laboratory Tests
For specific monitoring and laboratory tests, see WARNINGS AND PRECAUTIONS (Cardiovascular, Endocrine and Metabolism, Hepatic and Renal) and DRUG INTERACTIONS sections.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Side effects were reported in clinical trials with telmisartan in the indication hypertension or in patients 50 years or older at high risk of cardiovascular events.

Telmisartan has been evaluated for safety in 27 clinical trials involving 7968 patients treated for hypertension. Of these 7968 patients, 5788 patients were treated with telmisartan monotherapy including 1058 patients treated for ≥1 year and 1395 patients treated in placebo-controlled trials.

In 3400 patients, discontinuation of therapy due to adverse events was required in 2.8% of telmisartan patients and 6.1% of placebo patients.The following potentially serious adverse events have been reported rarely with telmisartan in controlled clinical trials: syncope and hypotension. In placebo-controlled trials, no serious adverse event was reported with a frequency of greater than 0.1% in telmisartan-treated patients.

The adverse drug reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports.

All Clinical Trials
The adverse drug events listed below have been accumulated from 27 clinical trials including 5788 hypertensive patients treated with telmisartan. Adverse events have been ranked under headings of

frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (< 1/10000)

Body as a Whole, General:

Common: Chest pain, influenza-like symptoms, symptoms of infection (e.g. urinary tract infection including cystitis), fatigue, conjunctivitis.

Uncommon: Hyperhidrosis, asthenia (weakness).

Blood and Lymphatic System:

Uncommon: Anaemia.

Rare: Thrombocytopenia.

Not known: Eosinophilia.

Cardiovascular System:

Common: Edema, palpitation.

Uncommon: Bradycardia, orthostatic hypotension, hypotension.

Rare: Tachycardia.

Central and Peripheral Nervous System:

Very Common: Headache.

Common: Dizziness, insomnia.

Uncommon: Vertigo.

Eye Disorders:

Rare: Visual disturbance.

Gastro-Intestinal System:

Common: Abdominal pain, diarrhoea, dyspepsia, nausea, constipation, gastritis.

Uncommon: Dry mouth, flatulence, vomiting.

Rare: Stomach discomfort.

Hepato-biliary Disorders:

Rare: Hepatic function abnormal/liver disorder.

Immune System:

Rare: Hypersensitivity.

Not known: Anaphylactic reaction.

Infections and Infestations:

Uncommon: Upper respiratory tract infections, urinary tract infections.

Not known: Sepsis including fatal outcome.

Investigations:

Uncommon: Blood creatinine increased.
Rare: Blood uric acid increased, hepatic enzymes increased, blood creatinine phosphokinase increased, haemoglobin decreased.

Metabolism and Nutrition Disorders:

Uncommon: Hyperkalemia.

Musculo-Skeletal System:

Common: Arthralgia, muscle spasms (cramps in legs) or pain in extremity (leg pain), myalgia, arthritis, arthrosis.
Uncommon: Tendon pain (tendonitis like symptoms), back pain.

Nervous System:

Uncommon: Syncope (faint).

Psychiatric System:

Common: Anxiety, nervousness.
Uncommon: Depression.

Renal and Urinary System:

Uncommon: Renal impairment including acute renal failure.

Respiratory System:

Common: Upper respiratory tract infections including pharyngitis and sinusitis, bronchitis, coughing, dyspnea, rhinitis.

Skin and Appendages System:

Common: Skin disorders like rash.
Uncommon: Pruritus.
Rare: Erythema, drug eruption, angioedema, eczema, toxic skin eruption.
Not known: Urticaria.

Hemoglobin:

Infrequently, a decrease in hemoglobin has been observed which occurs more often during treatment with telmisartan than with placebo.

<u>Placebo-Controlled Trials</u>

The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in controlled clinical trials. Adverse events occurring in 1% or more of 1395 hypertensive patients treated with telmisartan monotherapy in placebo-controlled clinical trials, regardless of drug relationship, include the following:

Table 1: Adverse Events Occurring in > 1% of Hypertensive Patients Treated with Telmisartan Monotherapy

Adverse Event, by System	**Telmisartan Total N = 1395 %**	**Placebo N = 583 %**
Body as a Whole		
Back Pain	2.7	0.9
Chest Pain	1.3	1.2
Fatigue	3.2	3.3
Influenza-Like Symptoms	1.7	1.5
Pain	3.5	4.3
Central & Peripheral Nervous System		
Dizziness	3.6	4.6
Headache	8.0	15.6
Somnolence	0.4	1.0
Gastrointestinal System		
Diarrhea	2.6	1.0
Dyspepsia	1.6	1.2
Nausea	1.1	1.4
Vomiting	0.4	1.0
Musculoskeletal System		
Myalgia	1.1	0.7
Respiratory System		
Coughing	1.6	1.7
Pharyngitis	1.1	0.3
Sinusitis	2.2	1.9
Upper Respiratory Tract Infection	6.5	4.6
Heart Rate and Rhythm Disorders		
ECG abnormal specific	0.2	1.0
Palpitation	0.6	1.0
Cardiovascular Disorders, General		
Hypertension	1.0	1.7
Oedema peripheral	1.0	1.2

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

Less Common Clinical Trial Adverse Drug Events (<1%)

In addition, the following adverse events, with no established causality, were reported at an incidence <1% in placebo-controlled clinical trials.

Autonomic Nervous System Disorders: sweating increased.

Body as a Whole: abdomen enlarged, allergy, cyst nos, fall, fever, leg pain, rigors, syncope.

Cardiovascular Disorders, General: hypotension, hypotension-postural, leg edema.

Central & Peripheral Nervous System Disorder: hypertonia, migraine-aggravated, muscle contraction-involuntary.

Gastrointestinal System Disorders: anorexia, appetite increased, flatulence, gastrointestinal disorder nos, gastroenteritis, gastroesophageal reflux, melena, mouth dry, abdominal pain.

Heart Rate & Rhythm Disorders: arrhythmia, tachycardia.

Metabolic & Nutritional Disorders: diabetes mellitus, hypokalaemia.

Musculoskeletal System Disorders: arthritis, arthritis aggravated, arthrosis, bursitis, fascitis plantar, tendinitis.

Myo Endo Pericardial & Valve Disorders: myocardial infarction.

Psychiatric Disorders: nervousness.

Red Blood Cell Disorders: anemia.

Reproductive Disorders, Female: vaginitis.

Resistance Mechanism Disorders: abscess, infection, bacterial, moniliasis genital, otitis media.
Respiratory System Disorders: bronchospasm, epistaxis, pneumonia, bronchitis.

Skin & Appendage Disorders: rash, skin dry.

Urinary System Disorders: Dysuria, hematuria, micturition disorder, urinary tract infection.

Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.

Vision Disorders: vision abnormal.

Abnormal Hematologic and Clinical Chemistry Findings
In placebo-controlled clinical trials involving 1041 patients treated with telmisartan monotherapy, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan.

Creatinine, Blood Urea Nitrogen:
Increases in BUN (≥11.2 mg/dl) and creatinine (≥0.5 mg/dl) were observed in 1.5% and 0.6% of telmisartan-treated patients; the corresponding incidence was 0.3% each for placebo-treated patients. These increases occurred primarily with telmisartan in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Hemoglobin, Hematocrit:
Clinically significant changes in hemoglobin and hematocrit (<10g/dl and <30%, respectively) were rarely observed with telmisartan treatment and did not differ from rates in placebo-treated patients. No patients discontinued therapy due to anemia.

Serum Uric Acid:
An increase in serum uric acid (≥2.7 mg/dl) was reported in 1.7% of patients treated with Telmisartan and in 0.0% of patients treated with placebo. Clinically significant hyperuricemia (>10mEq/L) was observed in 2.3% of patients with telmisartan, with 0.4% reported in patients at baseline. Increases in serum uric acid were primarily observed in patients who received telmisartan in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia.

Liver Function Tests:
Clinically significant elevations in AST and ALT (>3 times the upper limit of normal) occurred in 0.1% and 0.5% respectively of patients treated with telmisartan compared to 0.8% and 1.7% of patients receiving placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Serum Potassium:
Marked laboratory changes in serum potassium (≥+/- 1.4 mEq/L) occurred rarely and with a lower frequency in telmisartan -treated patients (0.3%, 0.1%, respectively) than in placebo patients (0.6%, 0.3%, respectively). Clinically significant changes in potassium (that exceeded 3 mEq/L)

were found in 0.6% of telmisartan-treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.

Cholesterol:
In placebo-controlled trials, marked increases in serum cholesterol were reported in a total of 6 telmisartan-treated patients (0.4%) and no placebo patients. Two of these patients were followed over time, in both cases cholesterol values reverted to baseline levels.

Serum elevations in cholesterol were reported as adverse events in 11 of 3445 patients (0.3%) in all clinical trials. There were no reported cases of hypercholesterolemia in telmisartan-treated patients in placebo-controlled trials.

Post-Market Adverse Drug Reactions
Since the introduction of telmisartan in the market, cases of anxiety, dizziness, vision troubled, vertigo, abdominal distension, abdominal pain, retching, hyperhidrosis, arthralgia, myalgia, muscle spasm, back pain, asthenia, pain in extremity, fatigue, chest pain, blood creatinine increased, erythema, pruritus, syncope/faint, insomnia, depression, stomach discomfort, vomiting, hypotension (including orthostatic hypotension), bradycardia, tachycardia, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, hyperkalemia, dyspnoea, anaemia, eosinophilia, thrombocytopenia, and weakness have been reported. The frequency of these effects is unknown. As with other angiotensin II antagonists, rare cases of angioedema, pruritus, rash and urticaria have been reported.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

In addition, since the introduction of telmisartan in the market, cases with increased blood creatinine phosphokinase (CPK) have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2: Established or Potential Drug-Drug Interactions

Telmisartan	Effects	Clinical comment
Agents increasing serum potassium		Since the telmisartan reduces the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that

Telmisartan	Effects	Clinical comment
		telmisartan may have on serum potassium.
Digoxin	When telmisartan was co-administered with digoxin, mean increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed.	It is recommended that digoxin levels be monitored with appropriate dose adjustments when initiating, adjusting or discontinuing telmisartan, to maintain appropriate plasma digoxin concentrations.
Diuretics	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with telmisartan.	The possibility of symptomatic hypotension with the use of telmisartan can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of telmisartan (see WARNINGS AND PRECAUTIONS – Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.
Lithium salts		Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor antagonists including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)		Combinations of angiotensin-II antagonists (telmisartan) and NSAIDs (including ASA and COX-2 inhibitors) might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and kidney function should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure. NSAIDs (including ASA and COX-2 inhibitors) and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment, this may lead to acute renal failure. Monitoring of renal function at the beginning and during the course of the treatment should be recommended. Co-administration of telmisartan did not result in a clinically significant interaction with ibuprofen.
Ramipril	In one study, the coadministration of telmisartan and ramipril led to an increase of up to 2.5 fold in the	The clinical relevance of this observation is not known.

Telmisartan	Effects	Clinical comment
	AUC_{0-24} and C_{max} of ramipril and ramiprilat.	
Warfarin	Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).	
Other		Coadministration of telmisartan also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide or hydrochlorothiazide.

Drug-Food Interactions

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from approximately 6% (40 mg) to approximately 19% (160 mg), and the reduction in C_{max} varies from approximately 26% (40 mg) to 56% (160 mg). However, three hours after administration, plasma concentrations are similar whether telmisartan is taken with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies on the effect 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 dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The antihypertensive effect is present within 2 weeks and maximal reduction is generally attained after four weeks. If additional blood pressure reduction is required, a thiazide diuretic may be added.

TEVA-TELMISARTAN tablets should be taken consistently with or without food.

Recommended Dose and Dosage Adjustment

Treatment of Essential Hypertension:
The recommended dose of TEVA-TELMISARTAN tablets is 80 mg once daily.

No initial dosing adjustment is necessary for elderly patients or for patients with renal impairment, but greater sensitivity in some older individuals cannot be ruled out. Markedly reduced telmisartan plasma levels were observed in patients on hemodialysis.

For patients with hepatic impairment a starting dose of 40 mg is recommended (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

When initiating telmisartan therapy at 80 mg dose, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Missed Dose
TEVA-TELMISARTAN tablets should be taken at the same time each day, preferably in the morning. However, if a dose is missed during the day, the next dose should be continued at the usual time. Do not double dose.

OVERDOSAGE
Limited data are available with regard to overdosage in humans. The most prominent manifestations of overdosage were hypotension and/or tachycardia; bradycardia also occurred. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

For management of a suspected drug overdose contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Telmisartan is an orally active angiotensin II AT_1 receptor antagonist. By selectively blocking the binding of angiotensin II to the AT_1 receptors telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptors, and has essentially no affinity for the AT_2 receptors. AT_2 receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. In vitro binding studies indicate that telmisartan has no relevant affinity for other receptors nor does it inhibit human plasma renin.

Telmisartan does not inhibit angiotensin converting enzyme, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostatis.

In hypertensive patients blockade of angiotensin II AT_1 receptors results in two to three fold increase in plasma renin and angiotensin II plasma concentrations. Long term effects of increased AT_2 receptor stimulation by angiotensin II are unknown.

Pharmacodynamics

Treatment of Essential Hypertension
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 with approximately 40% inhibition persisting for 24 hours.

In hypertensive patients with normal renal function, no clinically significant effects on renal plasma flow, filtration fraction, or glomerular filtration rate were observed. In multiple dose studies in hypertensive patients, telmisartan had no adverse effect on renal function as measured by serum creatinine or blood urea nitrogen.

The antihypertensive effects of telmisartan were demonstrated in six placebo-controlled clinical trials, in a total of 1773 patients, 1031 of whom were treated with telmisartan tablets. Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose and there was a gradual increase in the antihypertensive effect during continued treatment for up to 12 weeks, with most of the increase occurring during the first month. Onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. The antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. The magnitude of blood pressure reduction from baseline, after placebo subtraction, was on average (SBP/DBP) -11.3/-7.3 mmHg for Telmisartan 40 mg once daily, and -13.7/-8.1 mmHg for telmisartan 80 mg once daily. Upon abrupt cessation of treatment with Telmisartan, blood pressure gradually returned to baseline values over a period of several days. During long term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year.

For those patients treated with telmisartan 80 mg once daily who required additional blood pressure reduction, addition of a low dose of hydrochlorothiazide (12.5 mg) resulted in incremental blood pressure reductions of -9.4/-7.0 mmHg.

The antihypertensive effect of once-daily telmisartan (40-80 mg) was similar to that of once-daily amlodipine (5-10 mg), atenolol (50-100 mg), enalapril (5-20 mg) and lisinopril (10-40 mg).

There was essentially no change in heart rate in telmisartan-treated patients in controlled trials.

In clinical trials with post-dose in-clinic monitoring no excessive blood pressure lowering peak effect was observed even after the first dose, and the incidence of symptomatic orthostasis was very low (0.04%). With automated ambulatory blood pressure monitoring, the 24-hour trough-to-peak ratio for telmisartan was determined to be at least 80% for both systolic and diastolic blood pressure.

The antihypertensive effect of telmisartan is not influenced by patient age, weight or body mass index. Blood pressure in hypertensive black patients (usually a low renin population) is significantly reduced by telmisartan (compared to placebo), but less so than in non-black patients.

Pharmacokinetics

Absorption: Following oral administration, telmisartan is well absorbed, with a mean absolute bioavailability of about 50%. Mean peak concentrations of telmisartan are reached in 0.5-1 hour after dosing.
The pharmacokinetic profile is characterized by greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses greater than 40 mg. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours, and does not accumulate in plasma upon repeated once-daily dosing.

Metabolism: Telmisartan is metabolized by conjugation with glucuronic acid to form an acylglucuronide of telmisartan. This glucuronide is the only metabolite which has been identified in human plasma and urine. Following both oral dosing and intravenous administration of radiolabeled telmisartan, the parent compound represented approximately 85% and the glucuronide approximately 11% of total radioactivity in plasma. No pharmacological activity has been shown for the glucuronide conjugate.
The CYP 450 isoenzymes are not responsible for telmisartan metabolism.

Excretion: Total plasma clearance of telmisartan is > 800 mL/min. Half-life and total clearance appear to be independent of dose. Biliary excretion is the main route of elimination of telmisartan and its metabolite. Following intravenous and oral administration of C^{14} labelled telmisartan 0.91% and 0.49% of administered dose were found in the urine as glucuronide, respectively. Most of the oral and intravenous dose, >97%, was excreted in feces as the parent compound.

Women have a lower telmisartan clearance and have a greater systolic blood pressure response at trough than men.

Distribution: Telmisartan is >99.5% bound to plasma protein, mainly albumin and a1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with

therapeutic doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding sites.

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from approximately 6% (40 mg) to approximately 19% (160 mg), and the reduction in C_{max} varies from approximately 26% (40 mg) to 56% (160 mg). However, three hours after administration, plasma concentrations are similar whether telmisartan is taken with or without food.

Special Populations and Conditions

Pediatrics:
Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatrics:
The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years. (see DOSAGE AND ADMINISTRATION)

Gender:
Plasma concentrations of telmisartan are generally 2-3 fold higher in females than in males. No dosage adjustment is necessary.

Hepatic Insufficiency:
In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. A lower starting dose should be considered. (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency:
Renal excretion of telmisartan is negligible. No dosage adjustment is necessary in patients with renal insufficiency. In patients on hemodialysis both Cmax and AUC of telmisartan were markedly reduced as compared to healthy volunteers. Telmisartan is not removed by hemodialysis. (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION)

Genetic Polymorphism:
No studies were conducted to evaluate the influence of genetic polymorphisms on the pharmacokinetics or pharmacodynamics of telmisartan.

STORAGE AND STABILITY

For Bottles: Store between 15º and 30ºC. Keep container tightly closed. Protect from moisture.
For Blisters: Store between 15º and 30ºC. Protect from moisture.Tablets should not be removed from blisters until immediately prior to administration.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-TELMISARTAN is supplied as 40 mg and 80 mg tablets for oral administration.

In addition to the active ingredient telmisartan, each tablet contains the following inactive ingredients: Hydroxypropyl methylcellulose, Magnesium stearate, Mannitol, Meglumine, Povidone, Sodium Hydroxide, Sorbitol

TEVA-TELMISARTAN Tablets 40 mg are white, oblong-shaped, uncoated tablets marked with the “rph” on one side, and “T72” on the other side. Available in bottles of 30 and 500 tablets, and in blisters of 28 tablets.

TEVA-TELMISARTAN Tablets 80 mg are white, oblong-shaped, uncoated tablets marked with the “rph” on one side, and “T71” on the other side. Available in bottles of 30 and 500 tablets, and in blisters of 28 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

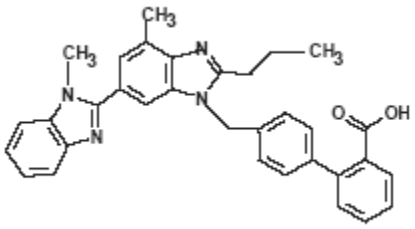
Drug Substance

Proper name: Telmisartan

Chemical name: [1,1'-Biphenyl]-2-carboxylic acid,4'-[(1,4'- dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-(CAS)[1]

Molecular formula and molecular mass: $C_{33}H_{30}N_4O_2$, 514.63

Structural formula:



Physicochemical properties:

Description:
Telmisartan is a white to off-white, odorless crystalline powder. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except HCL), and soluble in strong base.

Polymorphism:
Exhibits two different polymorphic modifications, Form A (thermodynamically more stable) and Form B, and a third pseudo polymorphic form.

Melting Point: 269 ± 1°C (polymorphic Form A)
183 ± 1°C (polymorphic Form B)

Apparent partition coefficient: $\log_{papp} = 3.2$

CLINICAL TRIALS

A single dose crossover comparative bioavailability study of TEVA-TELMISARTAN 80 mg tablets and Micardis® 80 mg tablets (CRP) following an 80 mg dose in 28 healthy male volunteers under fasting conditions was conducted. The results indicate that TEVA-TELMISARTAN tablets 80 mg are bioequivalent to Micardis® 80 mg tablets. The summary of results is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Telmisartan (1 x 80 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	TEVA-TELMISARTAN*	Micardis® †	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	901.85 1125.05 (64.5)	947.18 1161.10 (61.2)	95.21	89.16 – 101.68
AUC_{∞} (ng·h/mL)	1112.82 1359.80 (63.4)	1224.23 1493.59 (64.0)	90.90	84.30 – 98.02
C_{max} (ng/mL)	162.78 186.39 (56.1)	171.51 206.13 (72.0)	94.91	82.83 – 108.75
T_{max} [§] (h)	1.00 (0.50 – 2.00)	0.67 (0.33 – 3.00)		
$T_{½}$ [€] (h)	21.41 (27.0)	24.36 (49.7)		

* TEVA-TELMISARTAN 80 mg tablets (Teva Canada Limited).
† Micardis® 80 mg tablets (Boehringer Ingelheim (Canada) Ltd./ Ltée.) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

CLINICAL TRIALS (Continue)

Study demographics and trial design

Table 3: Summary of patient demographics for clinical trials in specific indication

Study	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, Double blind, Placebo-controlled in mild to moderate essential hypertensive patients	Treatment doses: 40 mg, 80 mg, 120 mg (40 mg + 80 mg) once daily Route of Administration: Oral Duration of treatment: 4 weeks	207	51.8 (30-68)	62% male/ 38% female
Randomized, Double blind, Placebo-controlled in mild to moderate essential hypertensive patients	Treatment doses: 20 mg, 40 mg, 80 mg, 120 mg (40 mg + 80 mg), 160 mg (80 mg + 80 mg) once daily Route of Administration: Oral Duration of treatment: 4 weeks	274	52.3 (28-72)	69% male/ 31% female
Randomized, Double blind, Placebo-controlled in mild to moderate essential hypertensive patients	Treatment doses: 40 mg, 80 mg, 120 mg, 160 mg (80 mg + 80 mg) once daily Route of Administration: Oral Duration of treatment: 12 weeks	440	54.1 (21-83)	64% male/ 36% female

*median age
T=telmisartan

CLINICAL TRIALS (Continue)

Table 4: Results of studies

Endpoint(s)	Efficacy Results
Change from baseline in supine DBP at trough (24 hours post dosing) at last double-blind visit.	**Intent-to-Treat Supine Blood Pressure Results** Adjusted Mean Changes from Baseline (mmHg) Treatment / N / Systolic / Diastolic Placebo 43 +3.5 -1.5 Telmisartan 40 mg 40 -10.0**** -7.9*** Telmisartan 80 mg 41 -15.5**** -8.7*** Telmisartan 120 mg 41 -12.5**** -9.8**** ***: p < 0.001 vs. Placebo ****: p < 0.0001 vs. Placebo
Change from baseline in supine DBP at trough (24-hours post-dosing) at the last observation during the double-blind phase	**Intent-to-Treat Analysis of the Change from Baseline in Supine Blood Pressure** Adjusted[1] Mean Change (S.E.) (mmHg) Treatment / N / Diastolic (baseline = 102.4) / Systolic (baseline = 151.2) Placebo 46 -0.4 (1.2) 3.2 (1.9) Telmisartan 20 mg 47 -6.9 (1.1)**** -3.3 (1.8)* Telmisartan 40 mg 47 -8.6 (1.2)**** -7.8 (1.9)**** Telmisartan 80 mg 44 -10.5 (1.2)**** -9.8 (1.9)**** Telmisartan 120 mg 45 -8.9 (1.2)**** -9.1 (1.9)**** Telmisartan 160 mg 44 -9.4 (1.2)**** -11.7 (2.0)**** [1] Based on a model with the effects of baseline blood pressure, center, treatment and treatment by-center interaction. Legend for treatment comparison with placebo: *: p < 0.05 (two-sided test) ****: p < 0.0001
Change from baseline in supine DBP and SBP at trough (24 hours postdosing) at the last observation during the double-blind phase.	**Intent-to-Treat Analysis of the Change from Baseline in Supine Blood Pressure at Trough** Adjusted[1] Mean Changes (S.E.) (mmHg) Treatment / N / Diastolic (baseline = 100.4) / Systolic (baseline = 153.9) Placebo 74 -1.8 (0.9) +0.8 (1.6) Telmisartan 40 mg 72 -9.3 (0.9)**** -11.6 (1.6)**** Telmisartan 80 mg 71 -9.7 (0.9)**** -11.8 (1.6)**** Telmisartan 120 mg 72 -8.8 (0.9)**** -10.0 (1.5)**** Telmisartan 160 mg 73 -8.6 (0.9)**** -11.9 (1.5)**** [1] Based on a model with the effects of baseline blood pressure, center, treatment and treatment-by-center interaction ****: p < 0.0001 Note: Significance of the treatment-by-center interaction was 0.5789 and 0.1557 for diastolic and systolic, respectively.

BP = blood pressure
DBP = diastolic blood pressure
SBP = systolic blood pressure

DETAILED PHARMACOLOGY

In *in vitro* studies, telmisartan displaced ^{125}I-angiotensin II from its binding site at the AT_1 receptor with an inhibitor constant (Ki) of 3.7 nM.

In isolated strips of rabbit aorta, telmisartan exerted potent angiotensin II antagonism: the calculated dissociation constant was K_B $3.3 \bullet 10^{-10}$ M.

In vivo results showed that telmisartan was a potent and long acting antagonist of the functional response to exogenously administered angiotensin II in rats, rabbits and dogs after both intravenous and oral administration. Telmisartan showed dose dependent and long lasting (>24h) antihypertensive effects after single or repeated oral administration in various rodent models of experimental hypertension.

TOXICOLOGY

Acute Toxicity:

In acute oral toxicity studies no deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest oral dose tested. The i.v. LD_{50} in rats was 150-200 mg/kg in males and 200-250 mg/kg in females.

Chronic Toxicity

Chronic oral toxicity of telmisartan was evaluated in studies following administration of doses up to 500 mg/kg for up to 26 weeks in rats, and up to one year in dogs. Chronic intravenous toxicity was evaluated in studies of up to four weeks at doses up to 20 mg/kg in rats and up to 50 mg/kg in dogs.

Repeated dose administration of telmisartan resulted in marked and long lasting hypotension, hyperplasia of juxtaglomerular apparatus and lesions of the gastrointestinal tract. Further effectwere reduced body weight gain, heart weight and red blood cell indices, increased potassium and AST and ALT, the latter in the absence of morphological evidence of toxicity. No effect doses were not identified for decreased erythroid indices, increased BUN and juxtaglomerular hypertrophy/hyperplasia in rats and dogs.

Reproduction

In studies on fertility and reproductive performance in male and female rats no effect on mating performance, reproductive organs, or fertility in either sex, or on litter parameters was observed with telmisartan doses of 5-100 mg/kg. No teratogenic or embryotoxic potential in rats was observed at doses up to 50 mg/kg administered from day 7 through day 16 of pregnancy. Telmisartan was detectable in the placenta, fetus and amniotic fluid of rats after single oral doses of 1 mg/kg.

Mutagenicity

Telmisartan was not mutagenic at a concentration range of 10 to 2500 ug/plate in the bacterial reverse mutation assay, with or without metabolic activation. No potential for chromosomal damage was found in the mouse micronucleus test at a dose range of 250 to 1000 mg/kg. No forward mutations at the HPRT locus in V79 cells were induced at a concentration range of 10

to 100 ug/ml, with or without metabolic activation. No chromosomal aberrations were induced in human peripheral lymphocytes *in vitro* at concentrations up to 100 ug/ml without metabolic activation and concentrations up to 200 ug/ml with metabolic activation.

Carcinogenicity

The carcinogenic potential of telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg and in rats at 3, 15 and 100 mg/kg. Drug administration did not affect survival time in either study and also tumor mortality was not increased. Incidence and time to appearance of palpable masses showed no treatment influence in mice and rats. No increases were observed in overall tumor incidence, incidence of benign and malignant tumors or tumor multiplicity.

Gastrointestinal Tract

Gastric and/or duodenal mucosal erosions and ulcers were seen in rats given ≥4 mg/kg orally or ≥2 mg/kg i.v. and in dogs given ≥40 mg/kg orally. Most lesions were small, focal or multifocal in distribution and limited to the mucosa and submucosa. Ulcers and erosions healed rapidly after drug withdrawal.

Urinary Tract and Electrolytes

Hypertrophy of the juxtaglomerular apparatus and increased granularity of renin-producing cells of the juxtaglomerular apparatus, afferent arterioles and interlobular arteries of the kidney were observed in rats at doses of 1 mg/kg and higher and in dogs at 5 mg/kg and higher. In rats and dogs subjected to long term treatment with telmisartan, plasma renin activity returned to normal levels after 26 to 52 weeks of treatment. Reversible slight to mild increases in serum potassium levels occurred in rats at oral doses of 4 mg/kg and higher. In dogs, non-progressive increases in serum potassium levels were noted at 50 and 500 mg/kg in the 52 week oral study.Minimal to mild, reversible increases in blood urea nitrogen and creatinine were evident at oral doses of 4 mg/kg and higher in rats and 5 mg/kg and higher in dogs.

Hematology

Slight to mild reversible reductions of red blood cell count, hematocrit, and/or hemoglobin were observed after repeated oral dosing with telmisartan ≥50 mg/kg in the rat and ≥5 mg/kg in the dog.

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PART III: CONSUMER INFORMATION

Pr TEVA-TELMISARTAN tablets
(Telmisartan)

This leaflet is part III of a three-part "Product Monograph" published when TEVA-TELMISARTAN tablets was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-TELMISARTAN tablets. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed TEVA-TELMISARTAN tablets to treat your mild to moderate high blood pressure.

What it does:
Angiotensin II is a naturally occurring hormone in the human body that causes the blood vessels to constrict, thus making the blood pressure higher. TEVA-TELMISARTAN tablets lowers blood pressure by specifically blocking the action of angiotensin II, and thus relaxing the blood vessels. As a result blood pressure is lowered.

When it should not be used:
- Patients who are hypersensitive to this drug or to any non-medicinal ingredient in the formulation (see the section "What the important nonmedicinal ingredients are"**)** should not take TEVA-TELMISARTAN tablets.
- Patients who are in their second/third trimester of pregnancy should not take TEVA-TELMISARTAN tablets.
- Patients who are breastfeeding should not take TEVA-TELMISARTAN tablets.
- Patients who are fructose intolerant.

What the medicinal ingredient is:
Telmisartan

What the important nonmedicinal ingredients are:
Hydroxypropyl methylcellulose, Magnesium stearate, Mannitol, Meglumine, Povidone, Sodium Hydroxide, Sorbitol.

If you are on a special diet, or if you are allergic to any substance, ask your doctor or pharmacist whether any of these ingredients may cause a problem for you.

What dosage forms it comes in:
Tablets in 40 mg and 80 mg strengths

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
TEVA-TELMISARTAN should not be used during pregnancy. If you discover that you are pregnant while taking TEVA-TELMISARTAN, stop the medication and please contact your physician.

Before you use TEVA-TELMISARTAN tablets talk to your doctor or pharmacist:
- If you have any allergies to this drug or to any ingredient in the formulation or component of the container
- If you have narrowing of a heart valve
- If you recently suffered from excess diarrhea or vomiting
- If you have any other health problems, including kidney or liver disease
- If you are taking any other medication, including diuretics, herbal preparations or any other medications you can buy without a prescription.
- If you are taking any other medication that may affect potassium levels.
- If you have hereditary fructose intolerance
- If you have been told by your doctor that you have an intolerance to some sugars

Please remember:
- To tell any other doctor, dentist or pharmacist with whom you consult that you are using TEVA-TELMISARTAN tablets.
- Dizziness or drowsiness may occasionally occur when taking any medicine to lower blood pressure. Therefore, before you perform tasks which may require special attention (driving a car or operating dangerous machinery), wait until you know how you respond to your medicine.
- If you have any other questions about TEVA-TELMISARTAN tablets, contact your doctor or pharmacist.

Effects on Pregnancy and Breastfeeding:
- Taking TEVA-TELMISARTAN during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while taking TEVA-TELMISARTAN, contact immediately your doctor. It is possible that TEVA-TELMISARTAN passes into breast milk. TEVA-TELMISARTAN should not be used in patients who are breastfeeding.

TEVA-TELMISARTAN tablets has been prescribed to treat your condition. Do not give it to other people

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interaction with other drugs is possible. Therefore, do not take any other medication without your doctor's or pharmacist's advice.

Drugs that may interact with TEVA-TELMISARTAN tablets include: Warfarin, Digoxin, Lithium, Ramipril and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as acetylsalicylic acid (ASA).

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose of TEVA-TELMISARTAN tablets is 80 mg once daily. It may be taken with or without food, but it should be taken the same way each day. You should follow any other direction that your doctor has given you for the treatment and/or monitoring of your condition.

Overdose:
If you experience dizziness and/or fainting or racing heart rate, contact your doctor immediately or go to the nearest emergency room so that medical attention may be given promptly**.**

In case of accidental drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Try to take your dose at the same time each day, preferably in the morning. However, if you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any drug product, TEVA-TELMISARTAN tablets may cause some unwanted effects along with good effects. Tell your doctor or pharmacist promptly about these or any other unusual symptoms.

If you develop an allergic reaction involving swelling of the face, lips and/or tongue, stop taking TEVA-TELMISARTAN tablets and contact your physician immediately.

Side effects such as muscle pain, muscle weakness, muscle inflammation and a muscle-wasting disease, in rare cases leading to kidney failure, have been reported with the use of angiotensin II receptor blockers, the class of drugs to which TEVA-TELMISARTAN tablets belongs. You should contact your physician promptly if you experience muscle pain that you cannot explain, muscle tenderness or weakness, generalised weakness, or when you notice dark/brown urine.

The following side effects are very common (frequency > 1/10) or common (frequency > 1/100, < 1/10): chest pain, influenza-like symptoms, symptoms of infection (e.g. urinary tract infection including cystitis), insomnia, abdominal pain, diarrhoea, dyspepsia, arthralgia, muscle spasms (cramps in legs) or pain in extremity (leg pain), myalgia, back pain, anxiety, depression, upper respiratory tract infections, dyspnea, eczema and rash. Sepsis, which is often called "blood poisoning", has occurred in some patients. It is a severe infection with whole-body inflammatory response which can lead to death.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Headache	√		
Common	Constipation	√		
	Diarrhoea	√		
	Dizziness	√		
	Eczema	√		
	Fatigue	√		
	Nausea	√		
	Pain		√	
	Rash	√		
	Upper respiratory tract infections		√	
Rare	Increased levels of potassium in the blood		√	
	Kidney disease/failure		√	
	Liver disorder		√	
	Syncope/faintness		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Not known	Allergic Reaction: Swelling of the face, lips and/or tongue accompanied by difficulty breathing		√	√
	Dark brown urine			√
	Muscle pain		√	
	Muscle wasting disease			√
	Muscle weakness		√	
	Weakness	√		

This is not a complete list of side effects. For any unexpected effects while taking TEVA-TELMISARTAN tablets, contact your doctor or pharmacist.

HOW TO STORE IT

For Bottles: Store between 15º and 30ºC.Keep container tightly closed. Protect from moisture.
For Blisters: Store between 15º and 30ºC. Protect from moisture.Tablets should not be removed from blisters until immediately prior to administration.

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at: 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  -Fax toll-free to 1-866-678-6789, or
  -Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at:
www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Teva Canada Limited, at:

1-800-268-4127 ext. 5005 (**English**)
1-877-777-9117 (**French**)
or druginfo@tevacanada.com

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