PRODUCT MONOGRAPH

[Pr]NTP-TELMISARTAN HCTZ

Telmisartan (as Telmisartan Sodium) and Hydrochlorothiazide Tablets
80 mg/12.5 mg and 80 mg/25 mg

NTP standard

Angiotensin II AT_1 Receptor Blocker/Diuretic

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Date of Preparation:
September 23, 2013

Submission Control No: 167610

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 80/12.5 mg Tablet 80/25 mg	hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose, lactose monohydrate, meglumine, mannitol, magnesium stearate, purified water, red iron oxide (for 80/12.5 mg only), sodium hydroxide, sorbitol, talc and yellow iron oxide (for 80/25 mg only.

INDICATIONS AND CLINICAL USE

NTP-TELMISARTAN HCTZ (80 mg telmisartan and 12.5 mg hydrochlorothiazide) is indicated for:

- treatment of mild to moderate essential hypertension in patients in whom combination therapy is considered appropriate.

NTP-TELMISARTAN HCTZ (80 mg telmisartan and 25 mg hydrochlorothiazide) is indicated for:

- treatment of patients whose blood pressure is not adequately controlled by NTP-TELMISARTAN HCTZ 80/12.5 mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

This fixed-dose combination is not indicated as initial therapy (see DOSAGE AND ADMINISTRATION).

Geriatrics *(*> 65 years of age):
No dosage 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):
Safety and efficacy of telmisartan hydrochlorothiazide have not been established in children and in adolescents up to 18 years.

CONTRAINDICATIONS

NTP-TELMISARTAN HCTZ (telmisartan and hydrochlorothiazide) is contraindicated in:

- Patients who are hypersensitive to any component 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)
- Due to the hydrochlorothiazide component, NTP-TELMISARTAN HCTZ is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-related drugs.

Sorbitol

Patients with rare hereditary problems of fructose intolerance should not take this medicine. A recommended daily dose of NTP-TELMISARTAN HCTZ 80/12.5 mg tablets contains 56.74 mg sorbitol. NTP-TELMISARTAN HCTZ is therefore unsuitable for patients with rare hereditary fructose intolerance.

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption should not take this medication. The maximum recommended daily dose of NTP-TELMISARTAN HCTZ contains 175.10 mg of lactose monohydrate in the dose strength of 80/12.5 mg and 354.20 mg of lactose monohydrate in the dose strength of 80/25 mg. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, should not take this medicine.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, NTP-TELMISARTAN HCTZ should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

Carcinogenesis and Mutagenesis

See TOXICOLOGY, Carcinogenicity and Mutagenicity.

Cardiovascular

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 with telmisartan should be initiated 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.

Valvular Stenosis
There is a 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.

Endocrine and Metabolism

Electrolyte and Metabolic Imbalances

Telmisartan & Hydrochlorothiazide
In controlled trials using telmisartan (80 mg) and hydrochlorothiazide (12.5 mg) in combination, there were no reports of hyperkalemia. Hypokalemia was reported in 1.4% of patients treated with the combination. No discontinuations due to hypokalemia occurred during treatment. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion by the kidney.

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.

Hydrochlorothiazide
During thiazide diuretic therapy, periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, particularly hyponatremia, hypokalemia and hypochloremic alkalosis. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids.

Hypokalemia may develop especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may induce cardiac arrhythmia and may also sensitize or exacerbate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require special treatment except under extraordinary circumstances (as in liver or renal disease), chloride replacement therapy may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Calcium excretion is decreased by thiazide diuretics which may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may also be evidence of hyperparathyroidism. In the event of significant hypercalcemia, NTP-TELMISARTAN HCTZ should be discontinued followed by assessment of parathyroid function.

Thiazide diuretics have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.

Hyperuricemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be altered and latent diabetes mellitus may become manifest during thiazide diuretic therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy.

Thiazide may decrease serum PBI levels without signs of thyroid disturbance.

Hepatic

Hepatic Impairment

As the predominant route of elimination of telmisartan is through biliary excretion, patients with cholestasis, biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance leading to increased systemic exposure. NTP-TELMISARTAN HCTZ should therefore be used with caution in these patients. Dosage reduction should be considered which would necessitate usage of the individual tablet formulations.

NTP-TELMISARTAN HCTZ is not recommended for patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment).

Immune

Hypersensitivity Reactions
Hypersensitivity reactions to the hydrochlorothiazide component of NTP-TELMISARTAN HCTZ may occur in patients with or without a history of allergy or bronchial asthma.

Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Renal

Renal Impairment
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 and 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. In susceptible patients, concomitant diuretic use may further increase risk. Appropriate assessment of renal function should be conducted prior to use of NTP-TELMISARTAN HCTZ.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. Although there has been no long-term experience with telmisartan in this patient population, an effect similar to that observed with ACE inhibitors should be anticipated.

Due to the hydrochlorothiazide component, NTP-TELMISARTAN HCTZ is not recommended in patients with severe renal impairment (creatinine clearance $\leq$ 30 mL/min).

Thiazide diuretics should be used with caution in patients with renal impairment.

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

Azotemia
Azotemia may be precipitated or increased by the hydrochlorothiazide component of

NTP-TELMISARTAN HCTZ. Cumulative effects of the drug may develop in patients with impaired renal function since the primary route of excretion is through the urine.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

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, NTP-TELMISARTAN HCTZ 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.

Thiazides cross the placenta and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary risks, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

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

There has been no clinical experience with telmisartan hydrochlorothiazide in pregnancy.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Nursing Women: NTP-TELMISARTAN HCTZ is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk but significant levels have been found in the milk of lactating rats. Animal studies have shown excretion of telmisartan in breast milk. 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. Thiazide diuretics are excreted in human milk at low levels.

Pediatrics (<18 years of age): Safety and effectiveness of telmisartan hydrochlorothiazide in pediatric patients have not been established.

Geriatrics (> *65* years of age): In clinical trials (n=1725) of patients treated with the combination of telmisartan and hydrochlorothiazide, 348 (20.2%) were 65 to 74 years of age and 78 (4.5%) were 75 years of age or older. No overall differences in the safety or efficacy profiles were observed in elderly patients compared with younger patients. It should be recognized however, that greater sensitivity of some older individuals 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*.

Telmisartan and Hydrochlorothiazide Used in Combination

The overall incidence and pattern of adverse events reported with NTP-TELMISARTAN HCTZ (80/25 mg) was comparable with NTP-TELMISARTAN HCTZ (80/12.5 mg). A dose-

relationship of undesirable effects was not established and they showed no correlation with gender, age or race of the patients.

The combination of telmisartan and hydrochlorothiazide has been evaluated for safety in 1725 patients including 716 treated for over six months and 420 for over one year. In clinical trials with the individual components used in combination, no unexpected adverse events have been observed. Adverse experiences have been limited to those that have been previously reported with telmisartan and hydrochlorothiazide monotherapy. In general, treatment with the combination was well tolerated; most adverse experiences were mild and transient in nature and did not require discontinuation of therapy.

Adverse events at an incidence of 1% or more in patients treated with 80/12.5 mg telmisartan/hydrochlorothiazide combination, irrespective of their causal relationship, are presented in the following table. This table includes the results of two pivotal studies. One study, a factorial design, compared the use of various doses of telmisartan tablets and hydrochlorothiazide tablets in combination to telmisartan alone, hydrochlorothiazide alone and placebo. The other study compared the fixed dose combination 80/12.5 mg of telmisartan/hydrochlorothiazide to telmisartan 80 mg alone.

Table 1: ADVERSE EVENTS OCCURRING IN ≥ 1% OF PATIENTS TREATED WITH 80/12.5 MG TELMISARTAN/HYDROCHLOROTHIAZIDE IN PIVOTAL CLINICAL TRIALS

	Telmisartan/ HCTZ 80/12.5 mg (n=320) %	**Telmisartan 80 mg (n=322) %**	**HCTZ 12.5 mg (n=75) %**	**Placebo (n=74) %**
Total with any adverse event	39.1	41.3	46.7	41.9
Autonomic nervous system				
Sweating increased	1.3	0.3	0	0
Body as a whole				
Back Pain	1.6	2.5	1.3	0
Fatigue	2.8	2.2	4.0	1.4
Influenza-Like Symptoms	1.6	1.2	2.7	1.4
Pain	2.2	2.2	4.0	6.8
Central & peripheral nervous system				
Dizziness	6.9	3.7	2.7	1.4
Headache	2.5	4.0	13.3	16.2
Gastro-intestinal system				
Abdominal Pain	1.6	0.9	0	0
Diarrhoea	4.1	1.6	0	0
Nausea	1.6	0.9	1.3	0

	Telmisartan/ HCTZ 80/12.5 mg (n=320) %	Telmisartan 80 mg (n=322) %	HCTZ 12.5 mg (n=75) %	Placebo (n=74) %
Respiratory system				
Pharyngitis Upper	1.6	0.3	0	0
Respiratory Tract infection	2.5	3.7	9.3	6.8

HCTZ = hydrochlorothiazide
Note: Telmisartan 80 mg open label treatment is not included in the Telmisartan 80 mg column

Additional adverse reactions reported in clinical trials with telmisartan plus hydrochlorothiazide are listed below according to system organ class:

Autonomic Nervous System: Impotence

Body as a Whole: Allergy, leg pain

Central and Peripheral Nervous System: Vertigo

Gastro-intestinal System: Dyspepsia, gastritis, gastro-intestinal disorder

Metabolic and Nutritional System: Hypokalaemia, loss of diabetic control, hyperuricaemia

Musculo-Skeletal System: Myalgia, arthralgia, arthrosis

Psychiatric System: Anxiety

Respiratory System: Bronchitis, sinusitis

Skin and Appendages System: Eczema, skin disorder

Urinary System: Urinary tract infection

In controlled trials with 1017 patients, 0.3% of patients treated with telmisartan (80 mg) and hydrochlorothiazide (12.5 mg) used in combination discontinued due to hypotension.

Adverse events occurred at approximately the same rates in men and women, older and younger patients and black and non-black patients.

Abnormal Hematologic and Clinical Chemistry Findings

In controlled trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan and hydrochlorothiazide in combination.

Table 2: Laboratory Parameter Results in Patients Treated with Telmisartan and Hydrochlorothiazide in Combination

Laboratory Parameter	% of Patients Treated with Telmisartan / Hydrochlothiazide	Clinical Comment
Increases in Blood Urea Nitrogen (BUN) (≥ 11.2 mg/dL)	2.8%	No patient discontinued treatment due to an increase in BUN.
Increases in Serum Creatinine (≥ 0.5 mg/dL)	1.4%	No patient discontinued treatment due to an increase in creatinine.
Decreases in Hemoglobin (≥ 2 g/dL)	1.2%	Changes in hemoglobin were not considered clinically significant and there were no discontinuations due to anemia.
Decreases in Hematocrit (≥ 9%)	0.6%	Changes in hematocrit were not considered clinically significant and there were no discontinuations due to anemia.

Liver function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. No telmisartan/hydrochlorothiazide treated patients discontinued therapy due to abnormal liver function.

Serum Electrolytes: see WARNINGS AND PRECAUTIONS.

Telmisartan

Additional 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. 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.

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.

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:	Anemia
Rare:	thrombocytopenia
Unknown:	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
Unknown:	Anaphylactic reaction

Infection and Infestation:

Uncommon:	Upper respiratory tract infections, urinary tract infections
Not known:	Sepsis including fatal outcome

Investigations:

Uncommon:	Blood creatinine increased
Unknown:	Haemoglobin decreased
Rare:	Blood uric acid increased, blood creatinine 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:

Rare: 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.

Unknown: Urticaria

Placebo-Controlled Trials

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 3: Adverse Events Occurring in 1% or more of 1395 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

Adverse Event, by System	Telmisartan Total N=1395 %	Placebo N=583 %
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 Reactions (<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, fasciitis plantar, tendon pain.

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 (including cystitis).

Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.

Vision Disorders: vision abnormal.

Angioedema has been reported rarely in patients treated with telmisartan.

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.

Table 4: Laboratory Parameter Results in Placebo-Controlled Clinical Trials Involving 1041 Patients Treated With Telmisartan Monotherapy

Laboratory Parameter	% of Placebo Patients	% of Patients Treated with Telmisartan	Clinical Comment
Increases in ALT > 3 times the upper limit of normal	1.7%	0.5%	No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.
Increases in AST > 3 times the upper limit of normal	0.8%	0.1%	No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.
Increases in Blood Urea Nitrogen (BUN) ≥ 11.2 mg/dl	0.3%	1.5%	These increases occurred primarily with telmisartan in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in blood urea nitrogen and creatinine.
Increases in Creatinine ≥ 0.5 mg/dl	0.3%	0.6%	These increases occurred primarily with telmisartan in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in blood urea nitrogen and creatinine.
Increases in Serum Potassium (≥ 1.4 mEq/L	0.6%	0.3%	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%.
Decreases in Serum Potassium (≥ 1.4 mEq/L	0.3%	0.1%	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%.
Increases in Serum Uric Acid ≥ 2.7 mg/dl	0.0%	1.7%	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.

Hemoglobin, Hemotocrit

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.

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.

Other Clinical Trials
Gastrointestinal: constipation

Respiratory: rhinitis, dyspnea

Special senses: conjunctivitis

Post-Market Adverse Drug Reactions

Telmisartan
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.

Hydrochlorothiazide
Adverse experiences that have been reported with hydrochlorothiazide alone without regard to causality are listed below:

Body as a Whole: fever

Gastro-Intestinal System: pancreatitis, sialadenitis, gastric irritation, anorexia, nausea, vomiting, diarrhea, constipation;

Hepatobiliary Disorders: Jaundice (hepatocellular cholestatic jaundice).

Blood and Lymphatic System: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia;

Hypersensitivity: purpura

Respiratory Disorders: respiratory distress including pneumonia and pulmonary edema

Musculoskeletal: muscle spasm, weakness, cramps in legs.

Central and Peripheral Nervous System: dizziness, vertigo, paraesthesia, restlessness, nervousness;

Cardiovascular: orthostatic hypotension;

Heart rate and rhythm disorder: cardiac arrhythmias;

Renal: renal failure, renal dysfunction, interstitial nephritis;

Skin and Subcutaneous Tissue Disorders: rash, urticaria, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, photosensitivity reactions, necrotizing angiitis (vasculitis, cutaneous vasculitis), anaphylactic reactions, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Eye Disorders: transient blurred vision, xanthopsia.

Laboratory Findings: Metabolic: hyperglycaemia, glucosuria, hyperuricaemia;

Other: electrolyte imbalances (including hyponatraemia and hypokalaemia), increases in triglycerides, hypercholesterolemia.

DRUG INTERACTIONS

Overview

Telmisartan

Cytochrome P450: Telmisartan is not metabolized by the cytochrome P450 (CYP) isoenzymes; as such, it is not expected that a pharmacokinetic interaction of telmisartan with drugs which inhibit or induce CYP isozymes will occur.

Hydrochlorothiazide

Cytochrome P450: Hydrochlorothiazide is not metabolized by humans; as such, no pharmacokinetic interaction with agents known to inhibit or induce CYP isozymes or other enzymes systems is expected.

Drug-Drug Interactions

Table 5- Established or Potential Drug-Drug Interactions

Telmisartan	Effect	Clinical comment
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 - Hypotension and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.
Agents increasing serum potassium		Since the telmisartan component of telmisartan hydrochlorothiazide 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 may have on serum potassium.
Digoxin	When telmisartan was coadministered 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 hydrochlorothiazide, to maintain appropriate plasma digoxin concentrations.

Telmisartan	Effect	Clinical comment
Lithium Salts	As with other drugs which enhance sodium excretion, lithium clearance may be reduced in the presence of telmisartan.	Lithium generally should not be administered with thiazide diuretics.
Ramipril	In one study, the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat.	The clinical relevance of this observation is not known.
Warfarin	Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in the International Normalized Ratio (INR).	
Acetaminophen, amlodipine, glibenclamide, hydrochlorothiazide, or ibuprofen		Co-administration of telmisartan did not result in a clinically significant pharmacokinetic interaction.

Table 6- Established or Potential Drug-Drug Interactions

Hydrochlorothiazide	Effect	Clinical comment
Alcohol, barbiturates and narcotics	Potentiation of orthostatic hypotension may occur.	
Anti-diabetic drugs (oral agents and insulin)	Potential for hyperglycemia in patients on thiazides.	Dosage adjustment of the antidiabetic drugs may be required.

Hydrochlorothiazide	Effect	Clinical comment
Cholestyramine and colestipol resins	Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.	
Corticosteroids, ACTH	Intensified electrolyte depletion, particularly hypokalemia may occur.	
Lithium Salts		Lithium should not generally be administered concurrently with diuretics; if lithium must be administered concurrently with telmisartan hydrochlorothiazide, serum lithium levels should be carefully monitored.
Non-steroidal Anti-Inflammatory drugs (NSAIDs including ASA and COX-2 inhibitors).	The co-administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. The potential for acute renal insufficiency in patients who are dehydrated may be enhanced.	Patients receiving NSAIDs and telmisartan hydrochlorothiazide should be adequately hydrated and be monitored for renal function at the beginning of the combined treatment. Monitoring of renal function at the beginning and during the course of the treatment is recommended as well as regular hydration of the patient. Therefore, when telmisartan hydrochlorothiazide and NSAIDs are used concomitantly, the patient should be observed closely to determine whether the desired effect of the diuretic is obtained.
Pressor amines (e.g. norepinephrine).	Decreased response to pressor amines may occur, but the effect is considered not sufficient to preclude their concurrent use.	
Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine).	Possible increased responsiveness to the muscle relaxant.	

Hydrochlorothiazide	Effect	Clinical comment
Other antihypertensive Drugs.	Additive effect or potentiation of antihypertensive effect.	
β-adrenergic receptor blocking agents propranolol, metoprolol, sotalol, or acebutolol.		No significant pharmacokinetic interactions were noted when these agents were administered concomitantly, separately or in fixed combination.
Spironolactone, indomethacin, allopurinol and phenytoin.		No significant interactions have been noted.

Drug-Food Interactions
Interactions with food have not been established.

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
Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
NTP-TELMISARTAN HCTZ may be substituted in patients who have been stabilized on the individual telmisartan 80 mg and hydrochlorothiazide 12.5 mg components as described below.

NTP-TELMISARTAN HCTZ may be administered with or without food, however it should be taken consistently with regard to food intake.

Recommended Dose and Dosage Adjustment
NTP-TELMISARTAN HCTZ (telmisartan/hydrochlorothiazide) is not for initial therapy.

A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg, may be switched to NTP-TELMISARTAN HCTZ, (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) once daily.

A patient whose blood pressure is not adequately controlled with NTP-TELMISARTAN HCTZ (telmisartan 80 mg/hydrochlorothiazide 12.5 mg), may be switched to NTP-TELMISARTAN HCTZ (telmisartan 80 mg/hydrochlorothiazide 25 mg) once daily.

Telmisartan Monotherapy
The recommended dose of telmisartan is 80 mg once daily. 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.

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.

Diuretic Treated Patients
In patients receiving diuretics, telmisartan therapy should be initiated with caution, since these patients may be volume depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of telmisartan to reduce the likelihood of hypotension (See WARNINGS AND PRECAUTIONS, Hypotension). If this is not possible because of the patients' condition, telmisartan should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Patients with Renal Impairment
The usual regimens of therapy with telmisartan hydrochlorothiazide may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides; in this instance, NTP-TELMISARTAN HCTZ is not recommended.

Patients with Hepatic Impairment
For patients with hepatic impairment, a starting dose of 40 mg of telmisartan is recommended. NTP-TELMISARTAN HCTZ is not recommended for patients with severe hepatic impairment.

Missed Dose
If a dose is missed, patients should not take a double dose; patients should just carry on with the next dose at the usual time.

Administration
NTP-TELMISARTAN HCTZ may be administered with or without food, however it should be taken consistently with regard to food intake.

OVERDOSAGE

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

Limited information is available for telmisartan hydrochlorothiazide with regard to overdose in humans. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly. For the individual components of telmisartan hydrochlorothiazide, the following information is available:

Telmisartan
Based on limited data, the most prominent manifestations of overdose are hypotension, dizziness and tachycardia; bradycardia also occurred in this setting as a result of parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Telmisartan is not removed by hemodialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
NTP-TELMISARTAN HCTZ (telmisartan/hydrochlorothiazide) is a combination of telmisartan, a selective angiotensin II antagonist and hydrochlorothiazide, a thiazide diuretic.

Telmisartan
Telmisartan is an orally active, AT_1 selective angiotensin II receptor antagonist. By selectively blocking the binding of angiotensin II to the AT_1 receptors, telmisartan inhibits the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Telmisartan blocks AT_1 receptors, and has essentially no affinity for the AT_2 receptors. AT_2 receptors have been found in many tissues; to date, they have not been found to be associated with cardiovascular homeostasis.

Telmisartan does not inhibit angiotensin converting enzyme (ACE, 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 homeostasis.

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

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic which affects the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in the distal tubule, thus promoting water excretion. The diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss and decreases in serum potassium. The latter effects of the renin-aldosterone link are mediated by angiotensin II; as such, co-administration of an angiotensin II AT_1 receptor antagonist may prevent the potassium loss associated with thiazide diuretics. The precise mechanism of the antihypertensive effect of thiazides however, is not fully understood.

Pharmacodynamics

Telmisartan
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. 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.

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 is significantly reduced by telmisartan (compared to placebo), but less so than in non-black patients.

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.

Hydrochlorothiazide
After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

Telmisartan and Hydrochlorothiazide Combination
In a placebo-controlled clinical study, the combination of telmisartan and hydrochlorothiazide resulted in decreases in trough systolic blood pressure (SBP) and diastolic blood pressure (DBP) which were greater than the decreases induced by either agent administered as monotherapy.

In a controlled clinical trial directly comparing telmisartan hydrochlorothiazide with telmisartan (80mg) monotherapy, trough SBP and DBP reductions observed with telmisartan hydrochlorothiazide were significantly greater than with telmisartan alone.

Similarly, in other controlled studies with patients who did not achieve or maintain adequate response with telmisartan monotherapy, the addition of 12.5 mg hydrochlorothiazide to titrated doses of telmisartan further reduced systolic and diastolic pressure.

The antihypertensive effect of telmisartan/hydrochlorothiazide (80 mg/12.5mg) was independent of age or gender. The overall response to the combination was similar for black and non-black patients.

There was essentially no change in heart rate in patients treated with the combination of telmisartan and hydrochlorothiazide in the placebo-controlled trial.

Pharmacokinetics

There are no pharmacokinetic interactions between telmisartan and hydrochlorothiazide as the pharmacokinetic parameters of the individual components are unchanged by their coadministration as telmisartan hydrochlorothiazide. The results of a randomized, crossover

study demonstrated that the bioavailabilities of telmisartan and hydrochlorothiazide were the same, whether administered as the fixed-dose combination or as the single entity formulations.

Table 7: Single Dose Pharmacokinetics in Normotensive Subjects (10 Male and 10 Female Caucasian Subjects, 18 to 45 years of age). Given are arithmetic means (%CV).

Drug	Therapy	C_{max} (ng/mL)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng.h/mL)	Clearance (CL/f) (mL/min.)	Volume of Distribution (Vz/f) (L)
Telmisartan: monotherapy	A	246 (%CV 69.4)	22.2 (%CV 30)	1439 (%CV 94)	1650 (%CV 62)	2908 (%CV 60)
Telmisartan: combination therapy	B	266 (%CV 103)	24.4 (%CV 33)	1467 (%CV 94)	1565 (%CV 63)	3091 (%CV 63)
Hydrochlorothiazide: combination therapy	A	75.3 (%CV 26)	11.4 (%CV 43)	580.4 (%CV 27)	380 (%CV 23)	363.8 (%CV 43)
Hydrochlorothiazide: monotherapy	B	75.7 (%CV 22)	11.5 (%CV 36)	563.9 (%CV 20)	384 (%CV 20)	380.4 (%CV 40)

Telmisartan

Absorption: Following oral administration, telmisartan is well absorbed with a mean absolute bioavailability of about 50%. Mean peak plasma concentrations (C_{max}) of telmisartan are reached in 0.5 -1.0 hour after dosing. The pharmacokinetic profile is characterized by greater than proportional increases in plasma concentrations (C_{max} and AUC) with increasing doses greater than 40 mg. Telmisartan shows bi-exponential decay kinetics with terminal elimination half life of approximately 24 hours, and does not accumulate in plasma upon repeated once daily administration. Food slightly reduces the bioavailability of telmisartan.

Distribution: Telmisartan is extensively bound to plasma proteins (>99.5%) at concentrations achieved at the recommended dosage. The apparent volume of distribution is approximately 500 L, suggesting extensive tissue binding sites.

Metabolism: Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; this is the only metabolite that has been detected in human plasma and urine. Following both oral dosing and intravenous administration of radiolabelled telmisartan, the parent compound represented approximately 85%, and the glucuronide approximately 11% of total radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Excretion: Total plasma clearance of telmisartan is > 800 mL/min. Biliary excretion is the predominant route of elimination of telmisartan and its metabolite.

Hydrochlorothiazide

Absorption: Following oral administration, peak concentrations of hydrochlorothiazide were reached approximately 2.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60% to 70%.

Distribution: Hydrochlorothiazide is 40% protein bound in the plasma and its apparent volume of distribution is 2 to 5 L/kg.

Excretion: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma-half life has been observed to vary between 5.6 and 14.8 hours when the plasma levels can be followed for up to 24 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placenta but not the blood-brain barrier and is excreted in breast milk.

Special Populations and Conditions

Telmisartan

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

Geriatrics:
The pharmacokinetics of telmisartan does not differ between elderly patients and those younger than 65 years of age.

Gender:
Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males administered the same oral dose. 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 on the basis of gender.

Hepatic Insufficiency:
In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). Reduction of the dose of telmisartan should be considered which would necessitate usage of the individual tablet formulations.

Renal Insufficiency:
Renal excretion of telmisartan is negligible. In patients with mild to moderate renal impairment, (creatinine clearance of 30-80 mL/min), no dosage adjustment is necessary (see WARNINGS

AND PRECAUTIONS, Renal Impairment and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment). Telmisartan is not removed by hemodialysis.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. 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. In susceptible patients, concomitant diuretic use may further increase risk. Appropriate assessment of renal function should be conducted prior to use of NTP-TELMISARTAN HCTZ.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. Although there has been no long-term experience with telmisartan in this patient population, an effect similar to that observed with ACE inhibitors should be anticipated.

Due to the hydrochlorothiazide component, NTP-TELMISARTAN HCTZ is not recommended in patients with severe renal impairment (creatinine clearance $\leq$ 30 mL/min).

Thiazide diuretics should be used with caution in patients with renal impairment.

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

No initial dosing adjustment for telmisartan 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.

The usual regimens of therapy with NTP-TELMISARTAN HCTZ may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides; in this instance NTP-TELMISARTAN HCTZ is not recommended.

Azotemia

Azotemia may be precipitated or increased by the hydrochlorothiazide component of NTP-TELMISARTAN HCTZ. Cumulative effects of the drug may develop in patients with impaired renal function since the primary route of excretion is through the urine.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

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

STORAGE AND STABILITY

Store at room temperature (15-30°C). Protect from moisture.

Blisters: Tablets should not be removed from blisters until immediately prior to administration.
Bottles: Keep container tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NTP-TELMISARTAN HCTZ 80/12.5 mg is a red and white to off white colored, capsule shaped bilayer tablet, embossed with ‘rph’ on one side and ‘T91’ on the other side.

NTP-TELMISARTAN HCTZ (telmisartan / hydrochlorothiazide, 80/12.5 mg) tablets are available in bottles of 30, 500 and blisters of 30.

NTP-TELMISARTAN HCTZ 80/25 mg is a yellow and white to off white colored, capsule shaped bilayer tablet embossed with ‘T92’ on the yellow colored side and with ‘rph’ on the other side.

NTP-TELMISARTAN HCTZ (telmisartan / hydrochlorothiazide, 80/25 mg) tablets are available in bottles of 30, 100, 500 and blisters of 30.

NTP-TELMISARTAN HCTZ tablets are formulated for oral administration with a combination of 80 mg of telmisartan and 12.5 mg hydrochlorothiazide or 25 mg hydrochlorothiazide.

Non-medicinal ingredients: hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose, lactose monohydrate, meglumine, mannitol, magnesium stearate, purified water, red iron oxide (for 80/12.5 mg strength only), sodium hydroxide, sorbitol, talc and yellow iron oxide (for 80/25 mg strength only).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

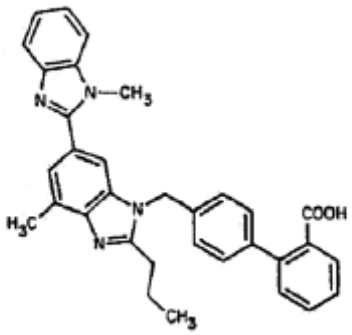
Drug Substance - Telmisartan

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].

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, odourless 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:
Form A (thermodynamically stable)

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

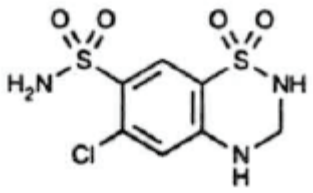
Drug Substance - Hydrochlorothiazide

Proper name: Hydrochlorothiazide

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Molecular formula and molecular mass: $C_7H_8ClN_3O_4S_2$, 297.75

Structural formula:



Physicochemical properties:

Description:
Hydrochlorothiazide is a white to practically white, crystalline powder. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.

Melting Point:
273-275°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A single dose crossover comparative bioavailability study of 1 x 80 mg/12.5 mg NTP-TELMISARTAN HCTZ tablets and 1 x 80/12.5 mg Micardis® Plus (telmisartan/HCTZ) tablets in 26 healthy male volunteers was conducted under fasting conditions. The summary of results for telmisartan and HCTZ are presented in the following tables:

Telmisartan (1 x 80 mg/12.5 mg (telmisartan/HCTZ) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-TELMISARTAN HCTZ Teva Canada Ltd.	Micardis® Plus Boehringer Ingelheim Ltd., Canada*	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	1116.64 1356.49 (65.61)	1181.52 1421.66 (64.71)	94.51 %	87.39 % to 102.21 %
AUC_{0-inf} (ng·h/mL)	1233.67 1489.02 (64.13)	1366.12 1618.77 (61.37)	90.30 %	83.03 % to 98.22 %
C_{max} (ng/mL)	155.53 180.65 (54.94)	154.81 185.99 (65.40)	100.47 %	77.52 % to 130.21 %
T_{max} € (h)	1.39 (68.26)	1.22 (65.60)		
$T_{½ el}$ (h)	23.00 (35.87)	27.13 (47.79)		

* Micardis® Plus 80 mg/12.5 mg tablets (Boehringer Ingelheim Canada Ltd./Ltee) were purchased in Canada.
 Expressed as the arithmetic mean (CV%) only

Hydrochlorothiazide (HCTZ) (1 x 80 mg/12.5 mg (telmisartan/HCTZ) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-TELMISARTAN-HCTZ Teva Canada Ltd.	Micardis® Plus Boehringer Ingelheim Ltd., Canada *	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	476.66 485.89 (23.44)	485.37 500.46 (27.81)	98.21 %	92.96 % to 103.75 %
AUC_{0-inf} (ng·h/mL)	519.78 527.61 (20.66)	529.77 544.68 (26.34)	98.11 %	92.97 % to 103.54 %
C_{max} (ng/mL)	70.21 71.74 (22.30)	80.94 84.12 (32.51)	86.75 %	78.90 % to 95.37 %

Hydrochlorothiazide (HCTZ) (1 x 80 mg/12.5 mg (telmisartan/HCTZ) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-TELMISARTAN-HCTZ Teva Canada Ltd.	Micardis® Plus Boehringer Ingelheim Ltd., Canada *	% Ratio of Geometric Means	90% Confidence Interval
T_{max}€ (h)	2.30 (43.41)	1.59 (33.63)		
$T_{½ el}$ □ (h)	8.94 (23.32)	9.01 (20.18)		

* Micardis® Plus 80/12.5 mg tablets (Boehringer Ingelheim Canada Ltd./Ltee) were purchased in Canada.
□ Expressed as the arithmetic mean (CV%) only

A single dose, crossover comparative bioavailability study of 1 x 80/25 mg NTP-TELMISARTAN HCTZ tablets and 1 x 80/25 mg Micardis® Plus (telmisartan/HCTZ) tablets in 30 healthy, adult male and female volunteers was conducted under fasting conditions. The summary of results for telmisartan and HCTZ are presented in the following tables:

Telmisartan

Telmisartan (1 x 80/25 mg telmisartan/HCTZ) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-TELMISARTAN HCTZ* Teva Canada Ltd.	Micardis®Plus† Boehringer Ingelhein Ltd, Canada Reference	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72}† (ng·h/mL)	1124.74 1429.08 (78.00)	1174.16 1519.36 (82.77)	97.79	89.96 – 102.00
AUC_I‡ (ng·h/mL)	1282.79 1677.55 (88.01)	1284.54 1731.78 (91.51)	99.86	92.62 - 107.67
C_{max} (ng/mL)	188.88 241.71 (67.97)	226.59 279.29 (69.24)	83.36	71.24 - 97.53
T_{max} € (h)	1.40 (67.24)	1.06 (55.03)		
$T_{½}$ □ ‡ (h)	26.17 (41.23)	26.29 (47.04)		

* NTP-TELMISARTAN HCTZ 80/25 mg tablets, manufactured by Teva Canada Ltd.
† Micardis® Plus 80 /25 mg tablets, Boehringer Ingelheim Ltd, were purchased in Canada

†For this parameter, N=30
‡For this parameter, N=26
[€] Expressed as the arithmetic mean (CV%) only

Hydrochlorothiazide

Hydrochlorothiazide (1 x 80/25 mg telmisartan/HCTZ) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-TELMISARTAN HCTZ* Teva Canada Ltd.	Micardis®Plus† Boehringer Ingelhein Ltd, Canada Reference	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	953.97 983.50 (24.21)	996.26 1025.76 (23.63)	95.76	92.21 - 99.43
$AUC_{0\text{-inf}}$ (ng·h/mL)	992.55 1019.39 (22.66)	1028.31 1055.67 (22.49)	96.52	93.44 - 99.71
C_{max} (ng/mL)	136.32 140.76 (24.89)	147.46 153.91 (28.81)	92.45	88.03 - 97.09
T_{max}[€] (h)	1.88 (44.93)	1.65 (43.30)		
$T_{½}$ (h)	9.44 (15.04)	9.63 (13.93)		

* NTP-TELMISARTAN HCTZ 80/25 mg tablets, manufactured by Teva Canada Ltd.
† Micardis® Plus 80 /25 mg tablets, Boehringer Ingelheim Ltd, were purchased in Canada
[€] Expressed as the arithmetic mean (CV%) only

Study demographics and trial design

Table 13- Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=numbers)	Mean age (Range)	Gender
502.261	Randomised, double blind	80 mg telmisartan and 80/12.5 mg telmisartan/hydrochlorothiazide, oral, 8 weeks	491 (245 telmisartan 80 mg; 246 telmisartan/hydrochlorothiazide (80/12.5 mg) patients)	55.3 (20 – 79)	males and females
502.204	Randomized, double blind,	Combinations of telmisartan &	818	53.0* (19 – 80)	males and females

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=numbers)	Mean age (Range)	Gender
	Placebo controlled	hydrochlorothiazide (T/H): 20/6.25, 20/12.5, 20/25, 40/6.25, 40/12.5, 40/25, 80/6.25, 80/12.5, 80/25, 160/6.25, 160/12.5/ 160/25 mg once daily, oral, 8 weeks			
502.480	Randomized, double blind, Placebo controlled trial in non-responders of the 80/12.5 mg strength	80 mg telmisartan/12.5 mg hydrochlorothiazide and 80 mg telmisartan/ 25 mg hydrochlorothiazide, oral, 8 weeks	713 (361 telmisartan/ hydrochlorothiazide (80/12.5 mg); 352 telmisartan/ hydrochlorothiazide (80/25 mg)	57.2 (28 – 93)	males and females

* median age
T = telmisartan
H = hydrochlorothiazide

Study results

In controlled clinical trials 571 patients were exposed to telmisartan 80 mg and concomitant hydrochlorothiazide 12.5 mg.

Table 14

Study #	Primary Measure of Efficacy	Patient Population	Summary of Results
502.261	Change from baseline in seated trough diastolic blood pressure (DBP) after 8 weeks of treatment.	Patients with mild to moderate hypertension who were taking no more than 3 antihypertensive agents at screening and who failed to respond adequately to telmisartan monotherapy	Treatment with telmisartan/ hydrochlorothiazide fixed dose combination (80/12.5 mg) lowered trough DBP by an additional 3.1 mmHg and systolic blood pressure (SBP) by 5.7 mmHg compared to telmisartan 80 mg monotherapy. Reductions in both DBP and SBP were clinically and statistically significant ($p<0.01$).
502.204	Change from baseline in supine trough DBP after 8 weeks of treatment. Over 800 patients completed this study with approximately 70 patients in each of the primary dose groups	Patients with mild to moderate essential hypertension	The combination of telmisartan and hydrochlorothiazide (80/12.5 mg) was significantly ($p<0.01$) better than either of its components administered as monotherapy in reducing trough supine diastolic blood pressure. Similar results were observed for supine systolic blood pressure and standing diastolic blood pressure.
502.480	Change from baseline in trough seated DBP after 8 weeks of treatment or at last trough observation during the double-blind treatment period	Patients without adequately controlled BP who failed to respond adequately to telmisartan/hydrochlorothiazide (80/12.5 mg)	Treatment with T80/H25 in patients with hypertension not adequately controlled by T80/H12.5 led to an additional, clinically relevant BP reduction. T80/H25 was superior to T80/H12.5 in reducing trough seated DBP after 8 weeks of randomised treatment. All analyses of secondary efficacy endpoints such as trough seated SBP, standing BP, and BP control and response showed better results for the T80/H25 group than for the T80/H12.5 group. Both treatments were safe and well tolerated.

BP = blood pressure
DBP = diastolic blood pressure
H = hydrochlorothiazide
SBP = systolic blood pressure
T = telmisartan
V = valsartan

Table 15: Observed Mean Reduction from Baseline in Trough Supine Diastolic Blood Pressure (mmHg)

	Placebo	Telmisartan 80 mg
Placebo	3.8	11.5 [1]
HCTZ 12.5 mg	7.3[1]	14.9[2,3]

[1] compared to placebo; p<0.01
[2] compared to HCTZ 12.5 mg alone; p<0.01
[3] compared to telmisartan 80 mg alone; p<0.01

In 30 patients with mild to moderate hypertension, an 8-week randomized double-blind, parallel group comparison of the effect of telmisartan 80 mg versus telmisartan combined with hydrochlorothiazide (80/12.5 mg) on renal function in patients with mild to moderate hypertension was conducted. All patients randomized for the study had normal renal function. Renal parameters measured included: renal blood flow, effective renal plasma flow, glomerular filtration rate, urinary albumin, urinary protein, filtration fraction and renovascular resistance. Treatment with either regimen daily for 8 weeks did not significantly compromise renal function and there was no difference in renal function between telmisartan and telmisartan administered concomitantly with hydrochlorothiazide.

Study 502.480

At baseline, trough seated DBP means were comparable for both treatment groups with a mean of 95.0 mmHg for T80/H12.5 and 95.3 mmHg for T80/H25. Both groups showed a reduction in DBP by the end of study, with a larger reduction being observed in the T80/H25 treatment group. An adjusted mean change from baseline of -5.5 mmHg was observed for the T80/H12.5 group compared with an adjusted mean change of -7.1 mmHg for the T80/H25 group. The difference (95% CI) in the adjusted means of -1.6 mmHg (-2.5 mmHg, -0.6 mmHg) indicated the additional reduction in mean trough DBP present in the T80/H25 group. This difference was statistically significant (p=0.0012), which shows the superiority of T80/H25 over T80/H12.5 in reducing mean trough seated DBP in patients not responding adequately to T80/H12.5.

The analysis of the change from baseline in trough seated SBP at the last visit during the double-blind treatment phase was performed using the same methodology as for the primary endpoint. At baseline, trough seated SBP means of the 2 groups were comparable, with a mean of 147.4 mmHg for T80/H12.5 and 147.9 mmHg for T80/H25. Mean trough seated SBP decreased in both treatment groups by the end of study; the larger reduction was observed in the T80/H25 group. The adjusted mean change from baseline in the T80/H12.5 group was -7.1 mmHg, while for T80/H25 it was -9.8 mmHg. The difference (95% CI) between the groups in the adjusted means was -2.7 mmHg (-4.2 mmHg, -1.2 mmHg) with a p-value of 0.0003. The data show that treatment with T80/H25 reduced mean trough seated SBP more than T80/H12.5.

Table 16: Analysis of Change from Baseline to the End of Study in Trough Seated DBP (FAS)

Trough Seated DBP [mmHg]		T80/H12.5 N = 347	T80/H25 N = 340
Baseline:	Mean (SD)	95.0 (4.4)	95.3 (4.7)
End of Study:	Mean (SD)	89.6 (7.3)	88.3 (7.5)
	Adjust Mean* (SE)	89.6 (0.4)	88.0 (0.5)
Change to End of Study:	Mean (SD)	- 5.3 (6.4)	- 7.0 (6.8)
	Adjusted Mean* (SE)	- 5.5 (0.4)	- 7.1 (0.5)
Difference to T80/H12.5:	Adjusted Mean* (SE)	- 1.6 (0.5)	
	95% CI	(- 2.5, - 0.6)	
	p-value	0.0012	

*Adjusted for baseline trough seated DBP and pooled country.

Table 17: Analysis of Change from Baseline to the End of Study in Trough Seated SBP (FAS)

Trough Seated SBP [mmHg]		T80/H12.5 N = 347	T80/H25 N = 340
Baseline:	Mean (SD)	147.4 (13.2)	147.9 (12.8)
End of Study:	Mean (SD)	141.8 (13.8)	139.5 (12.3)
	Adjust Mean* (SE)	140.6 (0.7)	137.9 (0.7)
Change to End of Study:	Mean (SD)	- 5.7 (11.0)	- 8.4 (10.6)
	Adjusted Mean* (SE)	- 7.1 (0.7)	- 9.8 (0.7)
Difference to T80/H12.5:	Adjusted Mean* (SE)	- 2.7 (0.7)	
	95% CI	(- 4.2, - 1.2)	
	p-value	0.0003	

*Adjusted for baseline trough seated SBP and pooled country.

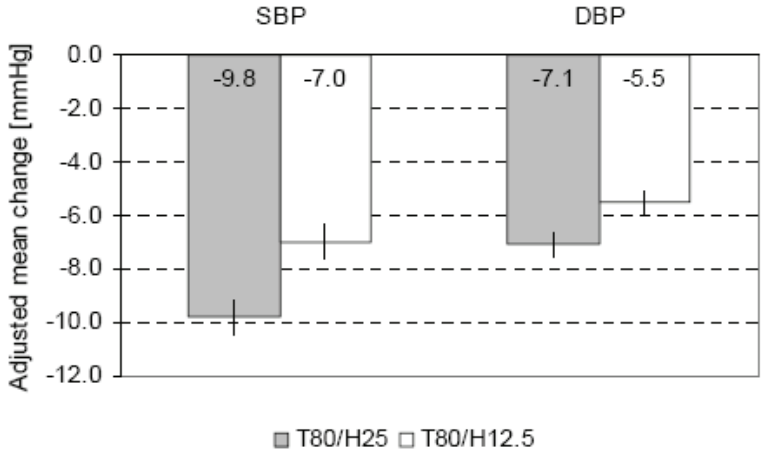


Figure 1: Adjusted (for baseline and country) mean change from baseline (with SE) of trough seated BP in the pivotal trial 502.480

In this study, both treatments were generally well tolerated as evidenced by a similar incidence of adverse event (AE) frequencies between T80/H12.5 (29.6%) and T80/H25 (31.5%) and the data obtained were consistent with the known safety profile of telmisartan hydrochlorothiazide. Frequently reported AEs in one or the other treatment arm (overall incidence ≥1% or 8 patients)

were back pain (1.9% of the T80/H12.5 patients and vs. 2.0% of the T80/H25 patients), bronchitis (2.2% vs. 1.1%), headache (2.8% vs. 0.6%), palpitations (1.4% vs. 0.9%), and nasopharyngitis (0.6% vs. 1.7%). The frequency of AEs events considered drug related was also similar (5.0% for T80/H12.5 and 5.7% for T80/H25). Two serious AEs considered drug-related by the investigators were reported in the trial (atrioventricular block third degree in the T80/H12.5 group and atrial flutter in the T80/H25 group).

Comparative Bioavailability Studies

An open-label, randomized, 4-way crossover, replicate-design study was conducted to compare the bioavailability following single oral administration of telmisartan (80 mg) and hydrochlorothiazide (12.5 mg) administered as either telmisartan hydrochlorothiazide or as the individual monotherapy formulations. Twenty (10M/10F) healthy subjects participated in this study. Comparative measures of exposure to telmisartan and hydrochlorothiazide were based on AUC and Cmax. The results of this study demonstrated that both telmisartan and hydrochlorothiazide had similar bioavailabilities administered as either telmisartan hydrochlorothiazide or as the single entity formulations.

Conventional average bioequivalence, average scaled bioequivalence, and individual bioequivalence (as a secondary analysis) using a moment-based scaled approach were evaluated with respect to Telmisartan pharmacokinetic variables. With respect to HCTZ pharmacokinetic variables, conventional average bioequivalence was evaluated. The upper bounds of the onesided 95% confidence interval for the average, scaled bioequivalence measure M_{as} are, on the ratio scale, 109.4% and 113.8% for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max}, respectively. These upper bounds of the confidence intervals are below the upper bound of the bioequivalence range, 125%. Thus average, scaled bioequivalence with respect to the variables $AUC_{0-\infty}$ and C_{max} is shown. Similarly, average, scaled bioequivalence with respect to the secondary variable AUC_{0-48h} was shown. The 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max} are 100.0% to 111.0% and 106.8% to 129.0%, respectively. The confidence interval for $AUC_{0-\infty}$ falls in the bioequivalence range of 80% to 125%, while the confidence interval for C_{max} falls in the bioequivalence range of 75% to 133%.. The confidence interval for the "test/reference" mean ratio of the secondary variable AUC_{0-48h} falls in the 80% to 125%, bioequivalence range.

Table 18: Results for Telmisartan

Telmisartan (80 mg) From measured data
Adjusted Geometric Mean Arithmetic Mean (CV %)

Parameter	Fixed dose combination (Test)*	Individual tablets (Reference)†	% Ratio of Adjusted Geometric Means	90% Confidence Interval
AUC $_{0\text{-}48h}$ (ng·h/ml)	875.9 1158(85.51)	820.7 1082 (83.46)	106.7	101.1 -112.7
AUC $_{0\text{-}\infty}$ ng·h/ml)	1034.5 1414 (92.50)	981.9 1364 (91.97)	105.4	100.0-111.0
C_{MAX} (ng/mL)	196.4 251.5 (87.88)	167.3 207.0 (71.58)	117.4	106.8 - 129.0
T_{MAX} § (h)	1.00(0.50-2.00)	1.00(0.50-2.00)		
$T_{1/2}$ [1] (h)	24.12(29.65)	24.73 (35.90)		

* Batch no. 9960326

† Micardis © 80 mg oblong tablet, batch no. 9960326;

§ Expressed as the median (range) only.

1 Expressed as the arithmetic mean (CV%) only.

For hydrochlorothiazide, the 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max} are 91.8% to 109.5% and 90.8% to 107.4%, respectively. The confidence intervals for the "test/reference" mean ratio of the pharmacokinetic variable Ae $_{0\text{-}48h}$ is 91.0% to 103.9%. All confidence intervals fall in the bioequivalence range of 80% to 125%.

Table 19: Results for Hydrochlorothiazide

Hydrochlorothiazide (12.5 mg) From measured data Adjusted Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Fixed dose combination (Test)***	**Individual tablets (Reference)†**	**% Ratio of Adjusted Geometric Means**	**90% Confidence Interval**
$AUC_{0\text{-}24h}$ (ng.h/ml)	478.1 493.9 (25.73)	467.2 475.04 (19.09))	102.3	97.3 - 107.6
$AUC_{0\text{-}\infty}$ (ng.h/ml)	575.4 580.4 (27.46)	574.0 563.9 (19.85)	100.3	91.8-109.5
C_{MAX} (ng/mL)	73.1 75.33(26.14)	74.1 75.72 (26.61)	98.7	90.8 - 107.4
T_{MAX} (h) §	2.00 (1.00 -3.00)	2.00 (1.00 -3.00)		

$T_{1/2}$[1] (h)	11.35(43.10)	11.51(36.33)		

* batch no. 9960326
† Hydrochlorothiazide 12.5 mg tablet, batch no.F4260;
§ Expressed as the median (range) only.
1 Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Animal

The effect of telmisartan in combination with hydrochlorothiazide was investigated in spontaneously hypertensive rats. Repeated oral administration of telmisartan at a dose of 3 mg/kg/day for 5 days to conscious rats reduced mean arterial blood pressure (MAP) significantly and persistently with maximal decrease in MAP of approximately 36 mmHg. Hydrochlorothiazide alone (10 mg/kg/day) had no effect on blood pressure in this model, however when administered in combination with telmisartan (3 mg/kg/day), induced a significantly greater antihypertensive effect than with telmisartan alone, with a maximal reduction of about 53 mmHg. Furthermore, the telmisartan/hydrochlorothiazide combination ameliorated the alteration in potassium balance when compared to hydrochlorothiazide alone in this model.

A slight, significant increase in heart rate (~ 20 bpm) was observed during treatment with telmisartan and hydrochlorothiazide in combination; this increase reverted to control values during the washout period.

Human

Drug Interaction - Telmisartan and Hydrochlorothiazide

A randomized, 3-way crossover study was conducted in 14 healthy subjects to investigate the potential for a pharmacokinetic interaction between telmisartan and hydrochlorothiazide when administered concomitantly. Oral doses of either hydrochlorothiazide alone (25 mg, qd x 7), telmisartan alone (160 mg, qd x 7) or both drugs at the respective doses in combination, daily for 7 days were administered. Plasma concentrations of both telmisartan and hydrochlorothiazide were assessed at steady state. Based on a comparative analysis, it was concluded that there is no pharmacokinetic interaction between telmisartan and hydrochlorothiazide when administered concomitantly.

Bioavailability

See CLINICAL TRIALS, Comparative Bioavailability Studies.

TOXICOLOGY

Chronic Toxicity

Telmisartan and Hydrochlorothiazide

Repeated-dose toxicity studies of 26 weeks duration were conducted in both rats and dogs. These studies were designed to compare the toxicological profiles of telmisartan and hydrochlorothiazide administered alone, with that of the drugs given in combination.

Table 20: Repeat Dose Toxicity Studies Conducted with Telmisartan/Hydrochlorothiazide

Species	Dose Telmisartan/HCTZ (mg/kg/day)	Duration	NOTEL (mg/kg/day)
Rat (Chbb:THOM) (20/sex/dose)	0/0 0.1/0.03 4/1.2 50/7.8 50/15.6 50/0 0/15.6	26 weeks	0.1/0.03
Dogs (Beagle) (4/sex/dose)	0/0 0.25/0.08 1/0.31 4/0.63 4/1.25 4/0 0/1.25	26 weeks	0.25/0.08

HCTZ= hydrochlorothiazide

Repeated, oral doses of telmisartan with and without hydrochlorothiazide for 26 weeks in rats induced a pronounced and persistent dose-related decrease of blood pressure without reflex tachycardia. At 50 mg/kg of telmisartan, the addition of hydrochlorothiazide had an additive effect on the blood pressure-lowering effect of telmisartan. Clinical laboratory and histopathological changes were similar to those observed in previous toxicity studies in rats with telmisartan alone. Essentially, there were no new toxicities observed with the addition of hydrochlorothiazide.

In dogs, repeated oral doses of telmisartan with hydrochlorothiazide administered for 26 weeks was associated with nephrotoxicity, which is consistent with the findings from previous studies with telmisartan alone. The addition of 0.63 mg/kg of hydrochlorothiazide to 4 mg/kg telmisartan did not increase renal toxicity whereas the co-administration of 1.25 mg/kg hydrochlorothiazide significantly increased toxicity. The exacerbation of nephrotoxicity in this species can be ameliorated by saline supplementation.

Reproductive Toxicity

Telmisartan and hydrochlorothiazide: A developmental toxicity study was conducted in rats with oral doses of telmisartan and hydrochlorothiazide used in combination (3.2/1.0, 15/4.7, 50/15.6 and 0/15.6 mg/kg/day). Although the two higher dose combinations appeared to be more

toxic to the dams than either drug alone, the results indicated the lack of teratogenic, fetotoxic or embryotoxic potential of the telmisartan/hydrochlorothiazide combination at the doses tested in this animal model.

Telmisartan: 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 oral doses of 5-100 mg/kg. No teratogenic or embryotoxic potential in rats was observed at oral doses of up to 50 mg/kg administered during gestation. Telmisartan was detectable in the placenta, fetus and amniotic fluid of rats after single oral doses of 1 mg/kg.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during gestation, at doses of up to 3000 and 1000 mg/kg/day respectively. There was no evidence of fetotoxicity or teratogenicity.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies where these species were exposed via their diet, to doses of up to 100 and 4 mg/kg respectively, prior to mating and throughout gestation.

Carcinogenicity and Mutagenicity

No carcinogenicity or mutagenicity studies have been conducted with the combination of telmisartan and hydrochlorothiazide. However, these studies have been conducted for telmisartan and hydrochlorothiazide alone. Based on the preclinical safety profile of the telmisartan and hydrochlorothiazide combination and on human pharmacokinetic studies, there is no indication of any adverse interaction between telmisartan and hydrochlorothiazide.

Telmisartan

The carcinogenic potential of telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg/day in rats at 3, 15, and 100 mg/kg/day. Drug administration did not affect overall survival time in either study nor did it affect the rate of tumour-induced mortality. There were no increases in overall tumour incidence, incidence of benign or malignant tumours or in tumour multiplicity associated with telmisartan administration.

The standard battery of genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella *typhimurium* and *E. coli*, a gene mutation test with CHO cells, a cytogenetic test with human lymphocytes and an in vivo mouse micronucleus assay.

Hydrochlorothiazide

The carcinogenic potential of hydrochlorothiazide was assessed in 2-year feeding studies in mice at doses of up to 600 mg/kg/day and rats at doses of up to 100 mg/kg/day. There was no evidence

of carcinogenic potential in female mice or male and female rats; equivocal evidence for hepatocarcinogenicity in male mice was reported.

Hydrochlorothiazide was not genotoxic in the Ames mutagenicity assay with Salmonella *typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations or *in vivo* assays using mouse germ cell chromosomes, Chinese hamster bone marrow chromosomes and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL and in the Aspergillus *nidulans* non-disjunction assay at unspecified concentrations.

REFERENCES

McGill JB, Reilly PA. Combination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension. Clin Cardiol 2001; 24(1):66-72.

Neutel JM, Smith DHG. Dose response and antihypertensive efficacy of the AT1 receptor antagonist telmisartan in patients with mild to moderate hypertension. Adv Ther 1998;15(4):206-217.

Young CL, Dias VC, Stangier J. Multiple-dose pharmacokinetics of telmisartan and of hydrochlorothiazide following concurrent administration in healthy subjects. J Clin Pharmacol 2000; 40(12 Pt 1):1323-30.

Boehringer Ingelheim (Canada) Ltd., Micardis Plus® Product Monograph , Control # 124801, revision date March, 2, 2009.

PART III: CONSUMER INFORMATION

PrNTP-TELMISARTAN HCTZ
(Telmisartan/Hydrochlorothiazide tablets)

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

ABOUT THIS MEDICATION

What the medication is used for:
NTP-TELMISARTAN HCTZ is prescribed to treat patients with high blood pressure where treatment with just one drug was not effective. The two drugs contained in this combination tablet treat high blood pressure in different ways, so it is expected that this combination may be more effective than either drug taken alone. In addition, it may be more convenient for you to take just one tablet than two tablets every day.

What it does:
NTP-TELMISARTAN HCTZ contains a combination of two drugs. The drug telmisartan, acts to inhibit the naturally occurring substances in your body that induce constriction of blood vessels, which plays a part in development of high blood pressure. The drug hydrochlorothiazide, acts by a different mechanism, that being to induce diuresis or urination which leads to decreased amount of body water which is beneficial in patients with high blood pressure.

When it should not be used:
- NTP-TELMISARTAN HCTZ should not be used in patients who are hypersensitive to any component of this product (see the section "What the nonmedicinal ingredients are").
- Patients who are in their second/third trimester of pregnancy should not take NTP-TELMISARTAN HCTZ.
- Patients who are breastfeeding should not take NTP-TELMISARTAN HCTZ.
- Patients who are fructose intolerant and lactose intolerant.
- Due to the hydrochlorothiazide component, NTP-TELMISARTAN HCTZ should not be used in patients with an absent production of urine or hypersensitivity to other sulfonamide-related drugs.

What the medicinal ingredients are:
Telmisartan (as Telmisartan Sodium) and hydrochlorothiazide

What the important nonmedicinal ingredients are:
hydroxy propyl cellulose, hydroxyl propyl methyl cellulose, lactose monohydrate, meglumine, mannitol, magnesium stearate, purified water, red iron oxide (for 80/12.5 mg only), sodium hydroxide, sorbitol, talc and yellow iron oxide (for 80/25 mg only).

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

What dosage forms it comes in:
NTP-TELMISARTAN HCTZ 80 /12.5 mg and 80/25 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

Before you use NTP-TELMISARTAN HCTZ, you should tell your doctor the following:
• If you have any allergies to this drug or to any ingredient in the formulation or component of the container.
• If you have a history of allergy or bronchial asthma.
• If you have narrowing of a heart valve.
• If you recently suffered from excess sweating, diarrhea or vomiting.
• If you have any other health problems, including liver or kidney disease, gout, diabetes, lupus erythematosus, or if you are being treated with other diuretics (known as water pills).
• If you are taking any other medication, including both prescription and over-the -counter (non-prescription).
• Before surgery and general anesthesia, (even at the dentist's office), tell the doctor or dentist that you are taking NTP-TELMISARTAN HCTZ as there may be a sudden fall in blood pressure associated with general anesthesia.
• If you have hereditary fructose intolerance.
• Lactose is a non-medicinal ingredient in NTP-TELMISARTAN HCTZ. Do not take NTP-TELMISARTAN HCTZ if a doctor has told you that you have one of the following rare hereditary disease:
  • Galactose intolerance
  • Lapp lactase deficiency
  • glucose-galactose malabsorption

Please remember:
• 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 NTP-TELMISARTAN HCTZ, contact your doctor or pharmacist.

Effects on Pregnancy and Breastfeeding:

• Taking NTP-TELMISARTAN HCTZ 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 NTP-TELMISARTAN HCTZ, contact immediately your doctor. It is possible that NTP-TELMISARTAN HCTZ passes into breast milk. NTP-TELMISARTAN HCTZ should not be used in patients who are breastfeeding.

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

INTERACTIONS WITH THIS MEDICATION

Foods - Use potassium-containing salt substitutes only after consulting with your doctor.

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 NTP-TELMISARTAN HCTZ include:

Drugs that may interact with telmisartan:
Diuretics (also known as water pills); Agents Increasing Serum Potassium; Digoxin; Lithium salts; Warfarin; Ramipril and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as acetylsalicylic acid (ASA).

Drugs that may interact with hydrochlorothiazide:
Alcohol, Barbiturates and Narcotics; Anti-Diabetic Drugs (oral agents and insulin); Cholestyramine and Colestipol Resins (cholesterol lowering drugs); Corticosteroids, ACTH; Lithium Salts; Non-Steroidal Anti-Inflammatory Drugs (NSAIDs including acetylsalicylic acid (ASA) and COX-2 Inhibitors); Pressor Amines (e.g. norepinephrine); Skeletal Muscle Relaxants, Nondepolarizing (e.g. tubocurarine); Other Antihypertensive Drugs.

PROPER USE OF THIS MEDICATION

Usual dose:
Take NTP-TELMISARTAN HCTZ exactly as instructed by your doctor. The usual dosing schedule is one tablet daily, taken at the same time each day, preferably in the morning.
NTP-TELMISARTAN HCTZ may be taken with or without food, but it should be taken the same way each day.

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

If you experience dizziness and/or fainting, racing heart rate, or have taken too many pills, contact your doctor immediately or go to the nearest emergency room so that medical attention may be given promptly.

Missed Dose:
If you have missed a dose, do not take a double dose. Just carry on with the next dose at the usual time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any drug product, NTP-TELMISARTAN HCTZ may cause some undesirable 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 NTP-TELMISARTAN HCTZ and contact your doctor 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 a component of NTP-TELMISARTAN HCTZ 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 for telmisartan are very common (frequency $\geq$ 1/10) or common (frequency $\geq$ 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.

IMPORTANT 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	Dizziness	√		
Common	Diarrhea	√		
	Headache	√		
	Fatigue	√		
	Upper respiratory tract infection		√	
	Pain		√	

IMPORTANT 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	
Rare	Increased levels of potassium in the blood		√	
	Kidney disease/failure		√	
	Liver disorder		√	
	Transient blurred Vision		√	
	If diabetic, loss of control of diabetes		√	
	Itchiness/ skin blisters/ rash/hives		√	
	Syncope/ faintness		√	
Not known	Allergic reaction involving swelling of the face, lips or tongue accompanied by difficulty breathing		√	√
	Unexplained muscle pain or weakness or dark/brown urine		√	√
	Muscle pain		√	
	Muscle wasting disease/Muscle weakness		√	√
	Weakness	√		
	Heart Rhythm/Heart Rate disturbances (e.g. heart racing or skipping a beat)		√	

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

HOW TO STORE IT

Store **NTP-TELMISARTAN HCTZ** at room temperature (15-30°C) in the package provided by your doctor or pharmacist and protect from excessive moisture. Do not remove tablets from blisters until immediately prior to administration.

Store NTP-TELMISARTAN HCTZ out of the 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 :
Teva Canada Ltd. at:
at: 1-800-268-4127 ext. 5005
or druginfo@tevacanada.com

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Last revised: September 23, 2013