PRODUCT MONOGRAPH

NTP-TERAZOSIN

(Terazosin Hydrochloride)

Tablets

Anti-Hypertensive Agent

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

Date of Preparation:
June 21, 2013

Control Number: 165703

PRODUCT MONOGRAPH

NTP-TERAZOSIN

(Terazosin Hydrochloride)

Tablets

THERAPEUTIC CLASSIFICATION

Anti-Hypertensive Agent

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

ACTION AND CLINICAL PHARMACOLOGY

Hypertension

The antihypertensive effect of NTP-TERAZOSIN (terazosin hydrochloride) is believed to be a direct result of peripheral vasodilation. Although the exact mechanism by which the lowering of blood pressure is achieved is not known, the relaxation of vessels appears to be produced mainly by selective blockade of alpha-1-adrenoceptors.

Benign Prostatic Hyperplasia (BPH

The reduction in the symptoms associated with BPH following administration of terazosin may be related to the changes in muscle tone produced by a blockade of alpha-1-adrenoceptors in the smooth muscle of the bladder neck and prostate.

Pharmacodynamics

Hypertension

Systolic and diastolic blood pressure is lowered in both supine and standing positions. In clinical trials, blood pressure responses were measured at the end of the dosing interval (24 hours) with the usual supine response 5 – 10 mmHg systolic and 3.5-8 mmHg diastolic. The response in the standing position tended to be larger by 1-3 mmHg.

Limited measurements of peak response (2-3 hours after dosing) during chronic terazosin administration indicate that this response is somewhat greater than the trough (24-hour) response, suggesting some attenuation of response at 24 hours, presumably due to a fall in blood terazosin concentrations at the end of the dose interval.

The greater blood pressure effect associated with peak plasma concentrations appears to be more position dependent (greater in the standing position) than the effect of terazosin at 24 hours; in the standing position there is also a 6-10 beat per minute increase in heart rate in the first few hours after dosing. During the first 3 hours after dosing 12.5% of patients had a decrease in systolic pressure of 30 mmHg or more from supine to standing, or standing systolic pressure below 90 mmHg with a decrease of at least 20 mmHg.

During controlled clinical trials, patients receiving terazosin monotherapy had a small but statistically significant fall (a 3% fall) compared to placebo in total cholesterol and the combined low-density and very-low density lipoprotein fractions. No significant changes were observed in high-density lipoprotein fraction and triglycerides compared to placebo.

Benign Prostatic Hyperplasia (BPH)

The symptoms associated with BPH are related to bladder outlet obstruction. The bladder outlet obstruction is comprised of a static obstruction due to the enlarged prostate and a dynamic obstruction which is dependent upon the sympathetically controlled tone of the smooth muscle in the prostate and the bladder neck. Stimulation of alpha-1-adrenoceptors in the smooth muscle of the bladder neck and the prostate causes smooth muscle contraction and an increase in muscle tone.

In three placebo-controlled studies in men with symptomatic BPH, symptom evaluation and uroflowmetric measurements were performed approximately 24 hours following dosing. Results from these studies indicated that terazosin significantly improved symptoms and peak urine flow rates over placebo.

In 30 to 70% of patients with symptomatic BPH placebo has also shown a remarkable and sometimes dramatic effect in controlled short-term studies. The symptoms may subside or fade away without treatment in approximately 20% of patients.

Additional pharmacodynamic data are provided under Human Pharmacology.

Pharmacokinetics

Orally administered terazosin hydrochloride is essentially completely absorbed in man. Nearly all of the circulating dose is in the form of the parent drug. Food has little or no effect on bioavailability. The plasma levels of the free base peak in about 1 hour and then decline with a half-life of approximately 12 hours. About 90-94% of terazosin is bound to plasma proteins and binding is constant over the clinically observed concentration range.

Hepatic metabolism is extensive with major biliary elimination. Approximately 10% of an orally administered dose is excreted as parent drug in the urine and approximately 20% is eliminated in

the feces. The remainder is excreted as metabolites. Overall approximately 40% of the administered dose is excreted in the urine and approximately 80% in the feces. Additional pharmacokinetic data are provided under Human Pharmacology.

A two-way, double-blind, single dose, comparative, randomized, bioavailability study was conducted in twelve healthy male volunteers between two 5 mg terazosin tablet products. The pharmacokinetic plasma data calculated for both NTP-Terazosin and Hytrin® tablet formulations are tabulated below:

Pharmacokinetic Indices for Terazosin:

	Geometric Mean Arithmetic Mean (C.V.)		
	NTP-TERAZOSIN (1 x 5 mg)	**HYTRIN®** (1 x 5 mg)**	**Percentage of Hytrin®**
AUC_T (ng·h/ml)	1097 1130 (29)	1075 1099 (22)	102
AUC_I (ng/ml)	1141 1181 (30)	1119 1140 (22)	102
C_{max} (ng/ml)	104 108 (30)	106 108 (22)	98
T_{max}* (h)	1.37 (0.87)	1.12 (0.97)	-
$T_{½}$* (h)	11.1 (1.2)	10.6 (1.0)	-

*For T_{max} and $T_{½}$ parameters these are the arithmetic means (standard deviation),

**Hytrin® manufactured by Abbott Laboratories Ltd., Montreal, Canada.

Hypertension

NTP-TERAZOSIN (terazosin hydrochloride) is indicated in the treatment of mild to moderate hypertension. It is employed in a general treatment program in conjunction with a thiazide diuretic and/or other antihypertensive drugs as needed for sufficient patient response. NTP-TERAZOSIN can be tried as a sole therapy in those patients in whom other agents caused adverse effects or are inappropriate.

Benign Prostatic Hyperplasia (BPH)

NTP-TERAZOSIN (terazosin hydrochloride) is also indicated for the treatment of symptoms of benign prostatic hyperplasia (BPH). The onset of effect is rapid, with improvement in peak flow rate and symptoms observed at 2 weeks. The effect on these variables was well maintained throughout the study duration (18 months). NTP-TERAZOSIN does not retard or stop the progression of BPH. The long-term effects of NTP-TERAZOSIN on the incidence of surgery, acute urinary obstruction or other complications of BPH, are yet to be determined.

A number of clinical conditions can mimic symptomatic BPH (i.e., stricture of urethra, stricture of bladder neck, urinary bladder stones, neurogenic bladder dysfunction secondary to diabetes, Parkinsonism, etc.). These conditions should therefore be ruled out before terazosin therapy is initiated.

CONTRAINDICATIONS

In individuals who have shown hypersensitivity to NTP-TERAZOSIN or its analogs.

WARNINGS

Syncope and Fist-Dose Effect

Terazosin can cause marked hypotension, particularly postural hypotension, and syncope in association with the first dose or first few doses of treatment. A similar effect can occur if therapy is re-instated following interruption for more than a few doses. Syncope has also occurred in association with rapid dosage increases or the introduction of another antihypertensive agent into the regimen of a patient taking high doses of NTP-TERAZOSIN.

Syncope is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120 beats per minute.

In studies with terazosin the incidence of syncopal episodes was approximately 1% in hypertensive patients and 0.7% in patients with BPH.

The likelihood of syncopal episodes or excessive hypotension can be minimized by limiting the initial dose of the drug to 1 mg of terazosin given at bedtime, by increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (See DOSAGE AND ADMINISTRATION).

Patients should be warned about the possibility of syncopal and orthostatic symptoms, and to avoid driving or hazardous tasks for 12 hours following the initial dose of terazosin, after the dose is increased and after an interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur.

If syncope occurs, place the patient in the recumbent position and institute supportive measures as necessary.

Patients with a history of micturition syncope should not be given terazosin hydrochloride.

Concomitant administration of NTP-TERAZOSIN (terazosin hydrochloride) with verapamil in hypertensive patients may result in symptomatic hypotension and in some cases tachycardia (see PRECAUTIONS).

Anaphylactoid Reactions

Anaphylactoid-like reactions manifested as angioedema of the lips, tongue pharynx, and/or laryngeal spasm have occurred rarely in patients taking terazosin (see ADVERSE REACTIONS). In such cases, NTP-TERAZOSIN should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained disappearance of signs and symptoms has occurred.

PRECAUTIONS

General

NTP-TERAZOSIN therapy does not modify the natural history of benign prostatic hyperplasia (BPH). It does not retard or stop the progression of BPH, nor does it improve urine flow sufficiently to significantly reduce the residual urine volume. However, significant reduction of the mean residual volume have been shown in patients with baseline residual volumes of >50 ml. The patient may continue to be at risk of developing urinary retention and other BPH complications during terazosin therapy.

Prostatic Cancer

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting NTP-TERAZOSIN therapy to rule out the presence of carcinoma of the prostate.

Orthostatic Hypotension

While syncope is the most severe orthostatic effect of terazosin (see WARNINGS), other symptoms of lowered blood pressure, such as dizziness, lightheadedness, and palpitations are more common with one or more of these occurring in 28% of patients in clinical trials of hypertension. In BPH clinical trials, 21% of the patients experienced one or more of the following: dizziness, hypotension, postural hypotension, syncope and vertigo. Patients should be advised to lie down when these symptoms occur and then wait for a few minutes before standing to prevent their recurrence.

Patients with occupations where such events could result in potential problems should be treated with particular caution.

There is evidence that the orthostatic effect of terazosin is greater, even in chronic use, shortly after dosing.

Concomitant Conditions:

NTP-TERAZOSIN should not be prescribed to patients with symptomatic BPH who have the following concomitant conditions: chronic urinary retention, high residual urine (over 200 ml), peak urine flow of 5 ml/second or less, history of prior prostatic surgery, chronic fibrous or granulomatous prostatitis, urethral stricture, history of pelvic irradiation, presence of prostatic calculi, presence of large median lobe of prostate, presence of calculi in urinary bladder, recent history of epididymitis, gross hematuria, presence of neurogenic bladder dysfunction (diabetes mellitus, Parkinsonism, uninhibited neurogenic bladder, etc.), hydronephrosis, presence of carcinoma of the prostate, patients with clinically significant renal or hepatic impairment (i.e., serum creatinine >2 mg/dl or SGOT >1.5 times the upper limit of normal (or equivalent level on the international scale).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Terazosin was devoid of mutagenic potential when evaluated *in viva* and *in vitro*.

Terazosin administered in the feed to rats at doses of 8, 40, and 250 mg/kg/day for two years, was associated with a statistically significant increase in benign adrenal medullary tumors of male rats exposed to the 250 mg/kg dose. Female rats were unaffected. Terazosin was not oncogenic in mice when administered in feed for 2 years at a maximum tolerated dose of 32 mg/kg/day.

Effect on fertility was assessed in a standard fertility/reproductive performance study in which male and female rats were administered oral doses of 8, 30 and 120 mg/kg/day. Four of 20 male rats given 30mg/kg and 5 of 19 male rats given 120 mg/kg failed to sire a litter. Testicular weights and morphology were unaffected by treatment. Vaginal smears at 30 and 120 mg/kg, however, appeared to contain less sperm than smears from control matings and a good correlation was reported between sperm count and subsequent pregnancy.

Oral administration of terazosin for one or two years resulted in a statistically significant rise in the frequency of testicular atrophy in rats given 40 and 250 mg/kg/day, but not in rats given 8 mg/kg/day. Testicular atrophy also occurred in dogs given 300 mg/kg/day for 3 months but not in those given 20 mg/kg/day for 1 year.

Use in the Elderly

Terazosin should be used cautiously in the elderly because of the possibility of orthostatic hypotension. There was an age-related trend towards an increased incidence of dizziness, blurred

vision, and syncope in elderly patients treated with this drug. Patients over 75 years of age may have limited benefit from terazosin therapy.

Use in Children

The use of terazosin in children is not recommended since the safety and efficacy have not been established.

Use in Patients With Renal Impairment

The use of terazosin in patients with impaired renal function requires careful monitoring. Limited pharmacokinetic studies using low doses (1 mg) showed no difference in the pharmacokinetics of terazosin as compared to patients with normal renal function. Approximately 40% of an oral terazosin dose is excreted by the kidney as parent drug or metabolites.

Use in Patients With Liver Impairment

No Information is available on the use of terazosin in patients with impaired liver function.

Peripheral Edema

Fluid retention resulting in weight gain may occur during terazosin therapy. In a placebo-controlled monotherapy trials, male and female patients receiving terazosin gained a mean 0.8 and 1 kg respectively, compared to losses of 0.1 and 0.5 kg respectively, in the placebo group. Both of these differences are significant.

Use in Pregnancy

The safety of terazosin in pregnancy has not been established. NTP-TERAZOSIN is not recommended during pregnancy unless the potential benefits outweigh the risks to the mother and fetus.

In animal studies there was no teratogenic effect. In peri- and postnatal development studies in rats, significantly more pups died in the group dosed with 120 mg/kg/day than in the control group during the 3 week postpartum period.

Use in Nursing Mothers

It is not known whether terazosin is eliminated in human milk. Because of possible adverse reactions in nursing infants an alternate method of infant feeding should be considered when the use of drug is essential.

Drug Interactions

In controlled studies, terazosin has been added to diuretics and several beta adrenergic blockers; except for the additive hypotensive effect, no unexpected interactions were observed. Terazosin has also been used in patients in various concurrent therapies. While these were not formal interaction studies, no interactions were observed. Terazosin has been given concomitantly in at least 50 patients on the following drugs or classes of drugs: a) analgesic/anti-inflammatory (e.g. acetaminophen, aspirin, codeine, ibuprofen, indomethacin) b) antibiotics (e.g. erythromycin, trimethoprim and sulfamethoxazole) c) anticholinergic/sympathomimetics (e.g. phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride), d) antigout (e.g. allopurinol) e) antihistamines (e.g. chlorpheniramine) f) cardiovascular drugs (e.g. atenolol, hydrochiorothiazide, methyclothiazide, propranolol) g) corticosteroids h) gastrointestinal drugs (e.g. antacid) i) hypoglycemics j) sedatives and tranquilizers (e.g. diazepam).

Concomitant treatment of terazosin with verapamil in hypertensive patients resulted in significant increases in AUC, C_{max} and C_{min} of terazosin. The pharmacokinetics of verapamil were not altered. Symptomatic hypotension and in some cases tachycardia, were observed. Caution should therefore be exercised when these drugs are administered concomitantly (see WARNINGS).

Laboratory Tests

Long-term (6 months or longer) administration of terazosin hydrochloride has produced no pattern of clinically significant changes attributable to the drug in the following clinical laboratory measurements: glucose, uric acid, creatinine, BUN, liver function tests, and electrolytes.

Small but statistically significant reductions in hematocrit, hemoglobin, white blood cells, total protein and albumin were observed in controlled clinical studies. These laboratory findings suggested the possibility of hemodilution. Treatment with terazosin hydrochloride for up to 24 months had no significant effect on prostate specific antigen (PSA) levels.

ADVERSE REACTIONS

Hypertension

The incidence of adverse effects is derived from clinical trials involving 1986 hypertensive patients on terazosin monotherapy or combination therapy.

The most serious adverse reaction encountered with terazosin is syncope occurring in about 1% of patients.

The most common reactions were dizziness (18.9%), headache (14.1%), asthenia (11%), somnolence (4.8%), nasal congestion (4.5%) and palpitation (4.6%).

The most frequently reported adverse effects which resulted in termination of terazosin were dizziness (3.5%), asthenia (2.1%) and headache (1.8%).

The following events were reported in less than 1% of cases except as indicated in brackets. The order of presentation corresponds within each heading to the relative frequency of occurrence.

Body as a Whole: Headache (14.1%), asthenia (11%), peripheral edema (3.6%), chest pain (2.2%), abdominal pain (1.5%), edema (1.3%), facial edema (1.0%), back pain, weight gain, allergic reactions, malaise.

Cardiovascular System: Palpitation (4.6%), tachycardia (2.9%), syncope (1%), postural hypotension, angina pectoris, arrhythmias, cerebrovascular accident, heart failure, hypotension (at times severe), migraine.

Digestive System: Nausea (3.9%), dry mouth (1.7%), diarrhea (1.3%), dyspepsia, vomiting, anorexia, gastritis, liver function abnormality, jaundice.

Nervous System: Dizziness (18.9%), somnolence (4.5%), nervousness (2.2%), paresthesia (1.5%), insomnia (1.2%), incoordination, abnormal dreams, confusion, speech disorder, tremor, vertigo, seizure, depression.

Respiratory System: Nasal congestion (4.6%), dyspnea (2.8%), rhinitis (1.2%), sinusitis, cold symptoms, pharyngitis, asthma, increased cough, laryngeal spasm.

Skin and Appendages: Sweating (1.1%), pruritus, rash, photosensitivity.

Special Senses: Blurred vision (1.4%), eye disorder (1.2%), tinnitus, taste perversion.

Urogenital System: Impotence (1.1%), urinary frequency, dysuria.

Miscellanous: Pain In extremities (1.8%), hypokalemia, hypophosphatemia, decreased libido.

At least two cases of severe anaphylactoid reactions were reported to be associated with administration of terazosin hydrochloride (see WARNINGS).

Post-marketing experience: Body as a Whole: Fever, neck pain, and shoulder pain. Cardiovascular System: Vasodilation, atrial fibrillation has been reported; however, a cause and effect relationship has not been established. Digestive System: Constipation, and flatulence. Nervous System: Anxiety. Respiratory System: Bronchitis, epitaxis, and flu symptoms. Special Senses: Conjunctivitis. Urogenital System: Priapism, urinary tract infection, and urinary incontinence primarily reported in post-menopausal women. Musculoskeletal System: Arthralgia, arthritis, joint disorder, and myalgia. Hematopoletic System: thrombocytopenia has been reported. Metabolic/Nutritional Disorders: Gout.

Benign Prostatic Hyperplasia (BPH)

In clinical trials involving 1171 patients with BPH, syncope was reported in 0.7% of patients following treatment with terazosin.

The most common reactions (≥ 1%) were dizziness (14.0%), asthenia (9.0%), headache (6.4%), somnolence (4.5%), postural hypotension (3.8%), impotence (3.5%), urinary tract infection (3.1%), pharyngitis (2.7%), dyspnea (2.5%), rhinitis (2.2%), dysuria (2%), back pain (1.8%), nausea (1.8%), flu syndrome (1.7%), rash (1.7%), sinusitis (1.7%), hypotension (1.5%), chest pain (1.5%), vertigo (1.3%), dyspepsia (1.1%), diarrhea (1%), palpitation (1%), abdominal pain (1%) and amblyopia (1%).

Post-marketing experience: Thrombocytopenia has been reported. Atrial fibrillation has been reported; however, a cause and effect relationship has not been established. Priapism has also been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Should administration NTP-TERAZOSIN lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used and the renal function should be monitored and supported as needed. Laboratory data indicate that terazosin is highly protein bound; therefore, dialysis may not be of benefit.

DOSAGE AND ADMINISTRATION

Hypertension:

The dose and dosing intervals (12 - 24 hours) of NTP-TERAZOSIN (terazosin hydrochloride) should be adjusted to the patient's individual blood pressure response.

When NTP-TERAZOSIN is being added to the existing antihypertensive therapy, the patient should be carefully monitored for the occurrence of hypotension. If a diuretic or other antihypertensive agent is being added to NTP-TERAZOSIN regimen, dosage reduction of NTP-TERAZOSIN and retitration with careful monitoring may be necessary. The following is a guide to its administration:

Initial Dose

1 mg of terazosin at bedtime is the starting dose for all patients and this dose should not be exceeded; compliance with this initial dosage recommendation should be strictly observed to minimize the potential for acute hypotensive episodes.

Subsequent Doses

The dose may be slowly increased to achieve the desired blood pressure response. The usual dose range is 1-5 mg once a day. Some patients may benefit from doses up to 20 mg/day which is the maximum recommended daily dose.

The blood pressure should be monitored at the end of the dosing interval to ensure that control is maintained. It is also helpful to measure the blood pressure 2-3 hours after dosing to see if maximum and minimum responses are similar and to evaluate symptoms.

If response to terazosin is substantially diminished at 24 hours, patients may be tried on a larger dose or twice daily dosage regimen. The latter should also be considered if adverse reactions such as dizziness, palpitations or orthostatic complaints are seen 2-3 hours after dosing.

If NTP-TERAZOSIN administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosage regimen.

Benign Prostatic Hyperplasia (BPH)

The dose of NTP-TERAZOSIN should be adjusted to the patient's individual response.

Initial Dose

1 mg of terazosin at bedtime is the starting dose for all patients, and this dose should not be exceeded for the first week. Compliance with this initial dosage should be strictly observed to minimize the potential for acute hypotensive episodes.

Subsequent Doses

The dose should be increased in stepwise fashion at weekly intervals to 2, 5 or 10mg once daily to achieve the desired improvement of symptoms and/or flow rates. Maintenance doses of 5 to 10 mg once daily are generally required for the clinical response. The duration and dosage of treatment should be carefully titrated. Four weeks of terazosin therapy may be required before statistically significant improvement in the objective parameters of flowmetry (peak urine flow) are obtained. Improvement in the symptoms may appear as early as 2 weeks, but may be delayed as late as 6 weeks or more. Some patients may not achieve a clinical response despite appropriate titration. Following 18 months of treatment a complete re evaluation of the patients condition should be made.

Following the administration of the maximum recommended dosage, terazosin should be discontinued if improvement in uroflowmetry is not clinically significant from baseline level or improvement in the American Urology Association (AUA) scores are not translated into improvements in quality of life. NTP-TERAZOSIN therapy should also be discontinued if terazosin side effects are more bothersome than BPH symptoms or if the patient develops a urinary complication while on terazosin therapy.

If terazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.

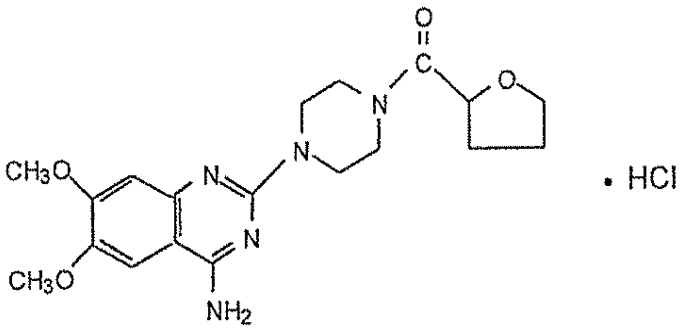
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Terazosin Hydrochloride

Chemical Name: 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl])carbonyl]-piperazine, monohydrochloride.

Structural Formula:



Molecular Formula: $C_{19}H_{25}N_5O_4HDI$ Molecular Weight: 423.93

Description: Terazosin hydrochloride is a white, crystalline substance, freely soluble in water and isotonic saline.

Composition:

NTP-TERAZOSIN (terazosin hydrochloride) Tablets:

1 mg - corn starch, lactose, magnesium stearate, povidone, talc.

2 mg - corn starch, FD&C yellow #6 aluminum lake, lactose, magnesium stearate, povidone, talc.

5 mg - corn starch, D&C red #30 aluminum lake, FD&C blue #1 aluminum lake, FD&C yellow #6 aluminum lake, lactose, magnesium stearate, povidone, talc.

10 mg - corn starch, D&C yellow #10 aluminum lake, FD&C blue #2 aluminum, lake, lactose, magnesium stearate, povidone, talc.

STABILITY AND STORAGE RECOMMENDATION

Store between 15 - 30°C and protect from light and high humidity. Store unit dose boxes between 15 - 25°C and protect from light and high humidity.

AVAILABILITY OF DOSAGE FORMS

NTP-TERAZOSIN (terazosin hydrochloride) is available as:

1 mg - white, round, flat faced, bevelled edged, compressed tablets engraved with **novo** on one side and **1** on the other side.

2 mg - orange, round, flat faced, bevelled edged, compressed tablets engraved with **novo** on one side and **2** on the other side.

5 mg - tan, round, flat faced, bevelled edged, compressed tablets engraved with **novo** on one side and **5** on the other side.

10 mg - green, round, flat faced, bevelled edged, compressed tablet engraved with **novo** on one side and **10** on the other side.

All strengths are available in bottles of 100.

INFORMATION FOR THE PATIENT

Benign Prostatic Hyperplasia

Please read this leaflet before you start taking NTP-TERAZOSIN. Also read it each time you renew your prescription, in the event that something has changed. Remember that this leaflet does not replace careful discussions with your doctor.

Why your doctor has prescribed NTP-TERAZOSIN?

Your doctor has prescribed NTP-TERAZOSIN because you have a medical condition called benign prostatic hyperplasia or BPH. This condition occurs only in men. NTP-TERAZOSIN is also used to treat high blood pressure (hypertension), but this leaflet describes NTP-TERAZOSIN only as a treatment for BPH.

What is BPH?

BPH is an enlargement of the prostate gland. After age 50, most men develop enlarged prostates. The prostate is located below the bladder and surrounds the urethra which is a tube that drains urine from the bladder. The symptoms of BPH, however, can be caused by an increase in the tightness of muscles in the prostate. If the muscles inside the prostate tighten, they can squeeze the urethra and slow the flow of urine. This can lead to symptoms such as:

- weak or interrupted urinary stream
- sensation that you cannot completely empty your bladder
- sensation of delay or hesitation when you start to urinate

- need to urinate often, especially at night, or
- sensation that you must urinate immediately

Treatment Options for BPH

There are three main treatment options for BPH:

(1) Monitoring Program or "Watchful Waiting"

If you have an enlarged prostate gland but suffer no symptoms or suffer from symptoms that are not bothersome, you and your doctor may decide to follow a monitoring program which includes regular check-ups instead of medication or surgery.

(2) Medication

There are different kinds of medication used to treat BPH. Your doctor has prescribed NTP-TERAZOSIN for you. See "How does NTP- TERAZOSIN work?", below.

(3) Surgery

Some patients may require surgery. Your doctor can prescribe several different surgical procedures for BPH. The procedure which is best for you, depends on your symptoms and medical condition.

How does NTP-TERAZOSIN work?

NTP-TERAZOSIN blocks smooth muscle receptors of the bladder neck and the prostate called alpha-1- adrenoceptors. This blockade causes the smooth muscles of the bladder neck and prostate to relax and decreases muscle tone, This can lead to a rapid improvement in urine flow and symptoms within a 2 week period. However, not all patients respond in the same way, and since each case of BPH is different, you should keep in mind the following:

- Prior to treatment with NTP-TERAZOSIN, you should have a thorough urological evaluation to determine the severity of your condition, and to exclude the need for immediate surgery or the possibility of carcinoma of the prostate.
- Even though taking NTP-TERAZOSIN has helped your condition, it is not known whether NTP-TERAZOSIN reduces the need for surgery.
- Terazosin will not cure your benign prostatic hyperplasia (BPH). Terazosin will make your urine flow better and improve the symptoms of BPH. In some patients, bothersome adverse effects will occur as a result of the terazosin therapy.

What you need to know while taking NTP-TERAZOSIN

- You should see an effect on your symptoms in 2 to 4 weeks.While taking NTP-TERAZOSIN, you must have regular check-ups to evaluate your progress

regarding your BPH and to monitor your blood pressure. Follow your doctor's advice about when to have these check-ups.

- NTP-TERAZOSIN can cause a sudden drop in blood pressure after the very first dose. You may feel dizzy, faint, or "light-headed", particularly after you get up from bed or from a chair. This is more likely to occur after you have taken the first few doses, but can occur at any time while you are taking the drug. It can also occur if you stop taking the drug and then restart treatment. Because of this effect, your doctor may have told you to take NTP-TERAZOSIN at bedtime. If you take NTP-TERAZOSIN at bedtime but need to get up from bed to go to the bathroom, get up slowly and cautiously until you are sure how the medicine affects you. It is also important to get up slowly from a chair or bed at anytime until you learn how you react to NTP-TERAZOSIN. You should not drive or do any hazardous tasks until you are used to the effects of the medication. If you begin to feel dizzy, sit or lie down until you feel better.
- Other side effects you could have while taking NTP-TERAZOSIN include drowsiness or somnolence, blurred or hazy vision, nausea, or "puffiness" of the feet or hands. Discuss any unexpected effects you notice with your doctor.
- Your doctor has prescribed NTP-TERAZOSIN for symptomatic BPH and not for prostatic cancer. It is possible for men to have both BPH and prostate cancer at the same time. Doctors usually recommend that men be checked for prostate cancer once a year when they turn 50 (or 40 if a family member has had prostate cancer). These checks should continue while you are taking NTP-TERAZOSIN. NTP-TERAZOSIN is not a treatment for prostate cancer.
- *About Prostate Specific Antigen (PSA)*. Your doctor may have done a blood test called PSA. Your doctor is aware that NTP-TERAZOSIN does not affect PSA levels. You may want to ask your doctor more about this if you have a PSA test done.

How to take NTP-TERAZOSIN HYDROCHLORIDE

Follow your doctor's instructions very carefully about how to take NTP-TERAZOSIN. The starting dose is 1 mg at bedtime. The 1 mg dose should be maintained during the first week of treatment, and should be taken every day as prescribed by your doctor. Your doctor will then gradually increase the strength of your prescription to 2 mg, 5mg, and 10mg depending on how well you respond. Talk to your doctor if you do not take NTP-TERAZOSIN for a few days. You may have to restart at the 1 mg dose. Be cautious about possible dizziness.

If your doctor prescribed the Starter Pack, it is important to complete the Starter Pack as indicated before starting your NTP-TERAZOSIN prescription.

Do not share NTP-TERAZOSIN with anyone else. It was prescribed for you only.

Notify your doctor about any illness which may develop during your treatment with NTP-TERAZOSIN and about any new prescription or non-prescription medication you may take. If you require medical help for other reasons, inform the attending physician that you are taking NTP-TERAZOSIN.

THIS MEDICINE IS PRESCRIBED FOR YOUR SPECIFIC MEDICAL PROBLEM AND FOR YOUR OWN USE. USE ONLY AS DIRECTED AND DO NOT GIVE TO OTHER PEOPLE.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN. FOR MORE INFORMATION ABOUT NTP-TERAZOSIN AND BPH, TALK WITH YOUR DOCTOR OR PHARMACIST.

Teva Canada Limited

Toronto, Canada

PHARMACOLOGY

Human Pharmacology

In three placebo controlled studies, both symptoms scores and peak urine flow rates showed statistically significant improvement from baseline in patients treated with in NTP-TERAZOSIN from week 2 (or the first clinic visit) and throughout the study duration. Results from these three studies are tabulated in Table 1.

Table 1: Symptom evaluation and uroflowmetric measurements from three placebo-controlled clinical studies.

	Symptom Score (Score 0-27)			Peak Flow Rate (mL/sec)		
	N	**Mean Base-line**	**Mean Change (%)**	**N**	**Mean Base-line**	**Mean Change (%)**
Study 1 (10 mg)[a]						
Titation to fixed dose (12 wks)						
Placebo	55	9.7	-2.3(24)	54	10.1	+ 1.0(10)
Terazosin	54	10.1	-4.5(45)*	52	8.8	+3.0(34)*
Study 2 (2, 5, 10, 20 mg)[b]						
Titation to response (24 wks)						
Placebo	89	12.5	-3.8(30)	88	8.8	+ 1.4(16)
Terazosin	85	12.2	-5.3(43)*	84	8.4	+2.9(35)*
Study 3 (1, 2, 5, 10 mg)[c]						
Titation to response (24 wks)						
Placebo	74	10.4	-1.1(11)	74	8.8	+ 1.2(14)
Terazosin	73	10.9	-4.6(42)*	73	8.6	+2.6(30)*

[a] Highest dose 10 mg shown

[b] 23% of patients on 10 mg, 41% of patients on 20mg.

[c] 67% of patients on 10mg.

* Significantly ($p \leq 0.05$) more improvement than placebo.

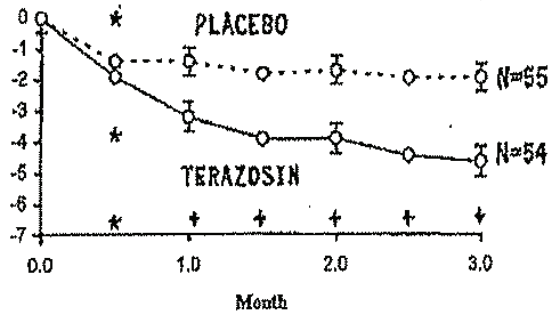
Analysis of the effect of terazosin on individual urinary symptoms demonstrated that compared to placebo, terazosin significantly improved the symptoms of hesitancy, intermittency, impairment in size and force of urinary stream, sensation of incomplete emptying, terminal dribbling, daytime frequency and nocturia.

Global assessments of overall urinary function and symptoms were also performed by investigators who were blinded to patient treatment assignment. In studies 1 and 3, patients treated with terazosin had significantly ($P \leq 0.001$) greater overall improvement compared to placebo treated patients.

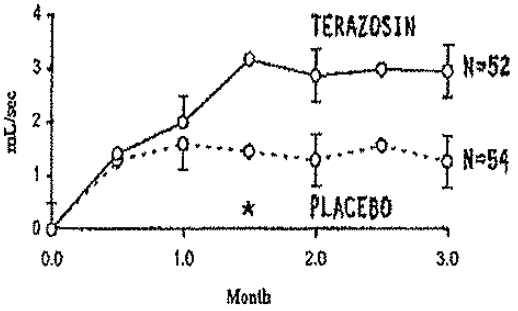
In a short-term study (Study 1), patients were randomized to either 2, 5, or 10 mg of terazosin or placebo. Patients randomized to the 10 mg group achieved a statistically significant response in both symptoms and peak flow rate compared to placebo. (See Figure 1).

Figure 1 (Study 1): Short-term study where patients were randomized to either 2, 5, or 10 mg of terazosin or placebo.

Mean Change in Total Symptom Score from Baseline +



Mean Increase In Peak Flow Rate (mL/sec) from Baseline +

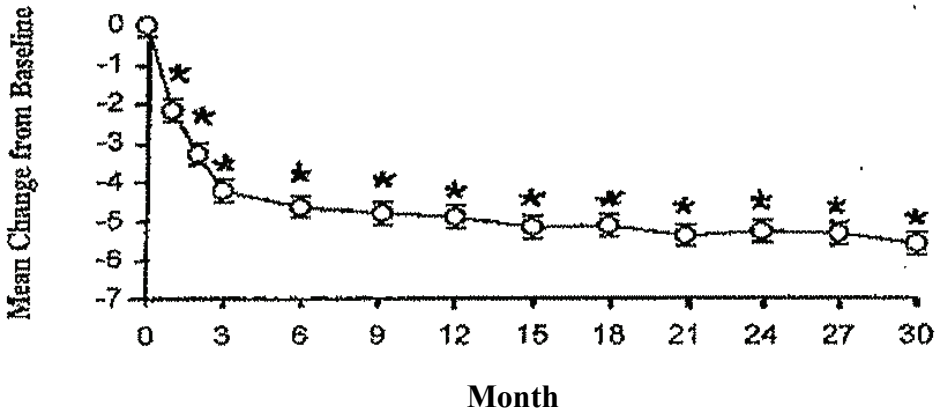


+ For baseline values see Table 1.

* $p \leq 0.05$, compared to placebo group.

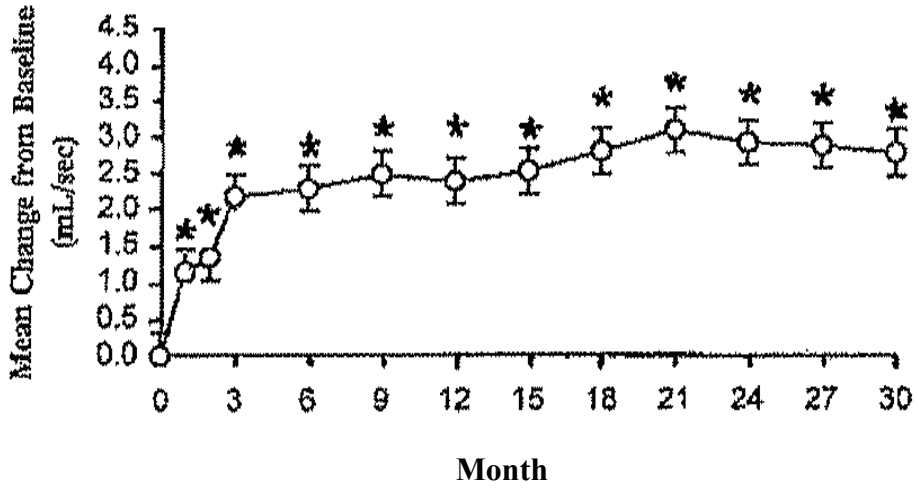
In a long-term, open-label, non-placebo controlled clinical trial, 181 men were followed for 2 years and 58 of these men were followed for 30 months. The effect of terazosin on urinary symptom scores and peak flow rates was maintained throughout the study duration (see Figures 2 and 3).

Figure 2: Mean Change in Total Symptom Score from Baseline - Long-Term, Open-Label, Non-Placebo Controlled Study (N = 494)



*p ≤ 0.05 versus baseline
mean baseline = 10.7

Figure 3: Mean Change in Peak Flow Rate From Baseline- Long-Term, Open- Label, Non-Placebo Controlled Study (N =494)



*p ≤ 0.05 versus baseline
mean baseline = 9.9

In this long-term trial, both symptom scores and peak urinary flow rates showed statistically significant improvement suggesting a relaxation of smooth muscle cells.

Although blockade of alpha-1-adrenoceptors also lowers blood pressure in hypersensitive patients with increased peripheral vascular resistance, terazosin treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect. (See Table 2).

Table 2: Mean Changes in Blood Pressure from Baseline to Final Visit in all Double-Blind, Placebo-Controlled Studies.

	Normotensive Patients DBP < 90 mmHg			Hypertensive Patients DBP > 90 mmHg	
	Group	**N**	**Mean Change**	**N**	**Mean Change**
SBP (mmHg)	Placebo	293	-0.1	45	-5.8
	Terazosin	519	-3.3*	65	-14.4*
DBP (mmHg)	Placebo	293	+0.4	45	-7.1
	Terazosin	519	-2.2*	65	-15.1*

*$p \leq 0.05$ versus placebo

Human Pharmacokinetics

In a study that evaluated the effect of age on terazosin pharmacokinetics, the mean plasma half-lives were 14.0 and 11.4 hours for the age group ≥ 70 years and the age group 20 - 39 years, respectively. After oral administration, the plasma clearance was decreased by 31.7% in patients 70 years of age or older compared to that in patients 20 - 39 years of age.

Impaired renal function had no significant effect on the elimination of terazosin, and dosage adjustment of terazosin to compensate for the drug removal during haemodialysis (approximately 10%) does not appear to be necessary.

The disposition of the compound in animals is qualitatively similar to that in man.

Animal Pharmacology

Pharmacodynamics

Terazosin was found to decrease blood pressure by up to 44% when administered orally to spontaneously hypertensive rats at doses of 0.1 mg/kg to 30 mg/kg. Similar findings were reported in DOC-salt hypertensive rats.

Terazosin produced small decreases in blood pressure (4%) in some normal rats. No significant changes in heart rate were observed.

Effects on the Cardiovascular System

Terazosin was administered intravenously to anesthetized male dogs (4-5 per group) at doses of 0.1 mg/kg followed 60 minutes later by 0.3 mg/kg. Terazosin decreased arterial blood pressure (6 and 13%, respectively, slightly more pronounced for systolic than diastolic), left ventricular systolic pressure (11 and 21%, respectively), and total peripheral resistance (14 and 19%, respectively). Transient increases in heart rate (7 and 18%, respectively), cardiac output (13 and 21%, respectively) and left ventricular dP/dt max (20 and 17%, respectively) were observed immediately following the administration of the drug, These increases lasted only several minutes and later returned towards normal. In the case of LVdP/dt max, the effects reversed into a mild reduction of 18% for the 0.3 mg/kg dose.

Intravenous administration of terazosin to dogs following treatment with phenoxybenzamine greatly reduced the hypotensive effect of terazosin. Pre-treatment with either propranolol or atropine had no effect on the hypotensive action of terazosin.

Effect on Central Nervous System

In rats (6 animals), terazosin produced a significant decrease in spontaneous motor activity at an oral dose of 80 mg/kg.

In dogs (4 animals), changes in gross behaviour (decreased activity, ataxia, tremors) were produced by terazosin at oral doses of 5 mg/kg. Oral administration of 3 mg/kg of terazosin to mice (4 to 11 animals/group) produced no significant reductions in locomotor activities. At 10 mg/kg of terazosin, significant decreases in activities of mice were observed.

In immobilized rabbits, intravenous injections of 3 mg/kg terazosin caused no significant effects on the spontaneous EEG patterns. Drowsiness patterns were recorded after the administration of 10 mg/kg. However, a normal EEG pattern was again observed 2 to 3 hours after drug administration.

Terazosin had no effect on either nonvascular smooth muscle (intestinal motility in mice at doses of 100 and 300 mg/kg, isolated guinea pig trachea in concentrations of 10^{-8} to 10^{-4} M, and motility of pregnant and non-pregnant rat uteri in concentrations of 10^{-6} to 10^{-4} M) or skeletal muscle (isolated nerve muscle of rat diaphragm in concentrations of 10^{-5} to 10^{-4} M).

Pharmacokinetics

Oral administration of terazosin hydrochloride to the rat (9.5 mg/kg) and the dog (0.2- 10 mg/kg) has shown that terazosin was rapidly absorbed, reaching peak plasma levels of 1-2 µg/ml within 1-2 hours. The half-life was reasonably similar in both species averaged 6.5 hours in rats and 5.7 hours in dogs.

After oral administration of ^{14}C terazosin hydrochloride (0.33 mg/kg) to rats and dogs, 28-38% of the dose was excreted in the urine and 16-17% was eliminated unchanged as the unchanged parent drug. The remainder of the dose was excreted in the feces and largely resulted from the biliary secretion of terazosin and its metabolites,

Pregnancy did not appear to affect the pharmacokinetics of terazosin in rats or rabbits.

The *in vitro* plasma protein binding of terazosin was low, with means of 44-63% in rats and 40 - 45% in dogs at concentrations ranging from 1-1000 ng/ml.

TOXICOLOGY

Acute Toxicity:

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)	FINDINGS
Mice	F M F M	I.V. I.V. P.O. P.O.	264 240 4 200 3 700	Decreased activity, ataxia, dyspnea, twitches and convulsions.
Rats	F M F M	I.V. I.V. P.O. P.O.	271 255 6 000 5 500	Decreased activity, dyspnea and mucoid discharges from eyes and nose.

Intravenous and oral median lethal doses (LD50) of terazosin hydrochloride in rats and mice ranges from 211-271 mg/kg and 2.7-10 g/kg, respectively. No sex difference was found in median lethal dosages. The predominant toxic effect was central nervous system depression followed by death.

TOXICOLOGY

Subacute and Chronic Toxicity

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 10 30 300	10M	2 Weeks	Dose dependent ptosis and lacrimation. Decreased growth at 300mg/kg. Increased absolute and relative adrenal weights at 30 and 300 mg/kg. Increased relative spleen and kidney weights at 30 and 300 and 10 and 300 mg/kg, respectively. Splenic congestion judged to be drug-related. Dose-related increase in urinary protein. Histopathological examination of the liver, kidney and spleen revealed no changes.
Rat	Oral	0 8 60 480	10F 10M	13 Weeks	Ptosis, cutaneous erythema, ocular and nasal discharges, soft Feces, increased food consumption, urine output and growth* at 480 mg/kg. Transient decreases in serum protein, sodium and globulin.** Increased bilirubin, SGPT** and potassium*, and relative and absolute liver, kidney, adrenal and heart weights*, primarily at 480 mg/kg. Gastric erosion and/or hemorrhage in some high dose rats. Splenic congestion in the majority of rats in the high dose group, decreased activity, decreased rectal temperature and increased water consumption. *females only **males only-
Rat	Oral	0 8 40 250	10F 10M	52 Weeks	Ptosis in rats dosed with 250 mg/kg, and for a short time, with 40 mg/kg. Food consumption, body weight and body weight gains decreased in male rats receiving 250 mg/kg. Decreases in the mean erythrocyte number, hemoglobin and hematocrit values in male rats dosed with 250 mg/kg. Increased liver weights in rats dosed with 250 mg/kg at necropsy. Degeneration of hepatocytes of rats fed 40 and 250 mg/kg. Testicular atrophy in 10% of the male rats dosed with 40 mg/kg and in 50% of male rats dosed with 250 mg/kg for one year.

TOXICOLOGY

Subacute and Chronic Toxicity

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 8 40 250	110F (controls) 110M (controls) 60F (treated) 60M (treated)	104 Weeks†	Lower survival rates for mate rats dosed with 8 and 40mg/kg. Decreased survival rates in female rats that received 40 and 250 mg/kg. Food consumption decreased in male rats treated with 250 mg/kg. Average body weight gains depressed by 32% (in males) and 14% (in females) dosed with 250 mg/kg. Absolute body weight of males (-24%) and of females (-10%) affected in rats treated with 250 mg/kg. Increased SGOT at 8 mg/kg and 250 mg*, sodium at40 mg/kg**, globulin at 250 mg/kg**, and mean corpuscular volume at 250 mg/kg*. Drug-related testicular atrophy observed in mid and high male rats. A number of neoplasms observed in control and test rats. Increased incidence of adrenal medullary secretory cell tumor at 250 mg/kg. *males only **females only
Rat	I.V.	0 10 40 150	10F 10M	4 Weeks	Deaths (3 males and 6 females) occurred within minutes after administration of 150 mg/kg. Decreased activity and ptosis observed in all groups. Rats treated with 150 mg/kg generally exhibited increased proteinuria and ketonuria. No evidence of renal histopathology. Splenic congestion observed at 40 and 150 mg/kg.
Mouse	Oral	0 2 8 32	110F (controls) 110M (controls) 50F (treated) 50M (treated)	104 Weeks	Body weight gains reduced by 17, 9 and 14%, respectively, in the 2, 8 and 32 mg/kg; reductions statistically significant in the 2 and 32 mg/kg. Positive trends for eye adenoma in male mice and for malignant lymphomas in female mice.

†Females were sacrificed approximately 6 weeks earlier.

TOXICOLOGY

Subacute and Chronic Toxicity

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Dog	Oral	0 5 40 300	3F 3M	13 Weeks	Four deaths at 300 mg/kg after 2-3 days of treatment; gastrointestinal ulceration and myocardial degeneration found. Gastrointestinal lesions, fatty degeneration of the liver, endo- and subendocardial hemorrhages and myocardial degeneration, nephrosis, thymic atrophy and hydropic degeneration of the ciliary process observed in 2 dogs killed after 22 and 44 days of treatment. Scleral and conjunctival redness, ptosis, lacrirnation, salivation (prior to treatment), and erythema at 5 and 40 mg/kg. One duodenal ulcer in one male dog treated with 40 mg/kg. Gastrointestinal ulceration, tubular nephrosis and uremia, fatty degeneration of liver, endocardial/subendocardial hemorrhage with myocardial degeneration, thymic atrophy, lack of spermiogenesis and hydropic swelling of ciliaiy process in some dogs treated with 300 mg/kg.
Dog	Oral	0 2.4 7 20	6F 6M	52 Weeks	No mortalities occurred. Ptosis of eyelids observed in females at 20 mg/kg. No gross or microscopic changes of toxicologic significance observed.
Dog	I.V.	0 4 15 60	3F 3M	4 Weeks	Two deaths (females) at 60 mg/kg; perforated gastric and duodenal ulcers accompanied by focal peritonitis observed. No histopathologic changes were observed in survivors. Treatment-related signs including dehydration, decreased activity, black or bloody feces, emesis and tremors. Dose-related trends toward lower erythropoietic parameters and evident decreased bone marrow myeloid/erythroid ratios observed at 60 mg/kg.

Mutagenicity

Study	Test Organism	Dose	Route	Major Findings
Ames Test	Salmonella-strains TA-1535, TA-1537 and TA-1538, activated and non-activated with hepatic microsomes.	50, 100 and 500 µg/plate	*In vitro*	No evidence of Mutagenic potential.
In Vivo Cyctogenetica	Rat-bone marrow	60, 240 and 480 mg/kg/day for 5 days	*In Vivo* P.O.	No evidence of mutagenicity Observed.
Dominant Lethal	Mouse	50, 165 and 500 mg/kg/day	*In Vivo* P.O.	No evidence of dominant lethality/ mutagenicity found.

Carcinogenicity

Terazosin hydrochloride, administered in the feed to Sprague-Dawley rats (60/sex/dose) at dosages of 0, 8, 40 and 250 mg/kg/day for up to 104 weeks was associated with a statistically significant increase of benign adrenal medullary secretory cell tumors in male rats exposed to the 250 mg/kg dose. This dose is 695 times the maximum recommended human dose (20 mg/55 kg patients). Female rats were unaffected, Terazosin hydrochloride was not found to be oncogenic in mice when administered in the feed for two years at a maximum tolerated dose of 32 mg/kg/day.

Teratogenicity

Teratology - Segment II

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 8 60 480	20F	Day 6 – 15 of gestation	Maternal toxic effects observed at 480 mg/kg. Ptosis, ocular discharge and decreased activity seen in all dose groups. Tremors, ataxia, dehydration, hypothermia and death (12 out of 25) occurred in the 480 mg/kg dams, marked decreased maternal body weight gains and food consumption. Litter of 480 mg/kg group resorbed (83%). No teratogenicity or embryotoxicity seen at 8 or 60mg/kg.
Rabbit	Oral	0 8 22 60	15F	Day 6 – 18 of gestation	Weight loss and decreased food consumption, increased incidence of fetal resorptions observed at 60 mg/kg; fetal weights also decreased. Increased number of supernumerary ribs in off-springs at 60mg/kg. No teratogenicity or embryotoxicity seen at 8 or 22 mg/kg.

Fertility and General Reproductive Performance - Segment I

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 8 30 120	Males dosed for 2 months prior to mating. Females dosed 14 days premating through mating, gestation, parurition, and 3 weeks postpartum while nursing.		Ptosis of eyelids observed in all treated animals; sedation observed at 120 mg/kg (males and females). Diminished fertility observed at 30 and 120 mg/kg. No evidence of embryolethality, embryotoxicity or teratogenicity observed. Normal parturition in all groups. Litter size of treated dams not statistically different from control values. Postnatal survival of pups not significantly affected. Pups from dams treated at 120 mg/kg were slower in acquiring surface righting, air-drop righting, auditory startle reflexes, forward locomotion and visual placing.

Teratogenicity {cont'd)

Pen- and Postnatal Study - Segment III

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 8 30 120	20F	From day 15 of gestation through postpartum day 20.	Eyelid ptosis observed in all treated animals. Mild sedation noted in the dams at 120 mg/kg. Gestation length not significantly altered in the three dose groups. Litter size comparable in the dose groups.

REFERENCES

1. Abraham PA, Haistenson CE, Matzke GR, et at Antihypertensive therapy with once-daily administration of terazosin, a new alpha-1-adrenergic receptor blocker, Pharmacotherapy 1985; 5: 285-9.

2. Achari R, Laddu A. Terazosin: A new alpha adrenoceptor blocking drug. J Clin Pharmacol 1992; 32: 520-3.

3. Black HR, Chrysant SG, Curry CL, et al. Antihypertensive and metabolic effects of concomitant administration of terazosin and methyclothiazide for the treatment of essential hypertension. J Clin Pharmacol 1992; 32: 351.

4. Cohen A. Placebo-controlled study of once-daily administration of terazosin to patients with mild-to-moderate hypertension. Curr Ther Res 1987; 41:105-13.

5. Cohen JD, Long-term efficacy and safety of terazosin alone and in combination with other antihypertensive agents. Am Heart J 1991; 122: 919-25.

6. Fort FL, Tekeli S, Majors K, et al. Terazosin: Intravenous safety evaluation in rats. Drug Chem Toxicol 1984; 7: 435-9.

7. Frishman WH, Elsen G, Lapsker J. Terazosin: A new long-acting α-adrenergic antagonist for hypertension. Med Clin North Am 1988; 72: 441-8,

8. Hayduk K, Schneider HT. Antihypertensive effects of doxazosin in systemic hypertension and comparison with terazosin. Am J Cardiol 1987; 59: 95G-8G.

9. Hosmane BS, Maurath CJ, Jordan DC, Laddu A. Effect of age and dose on the incidence of adverse events in the treatment of hypertension in patients receiving terazosin. J Clin Pharmacol 1992; 32: 434-43.

10. Kyncl JJ, Pharmacology of terazosin. Am J Med 1986; 80 (Suppl 5B): 12-9.

11. Lytle TB, Coles SJ, Waite MA, A multicentre, hospital study of the efficacy and safety of terazosin and its effects on the plasma cholesterol levels of patients with essential hypertension. J Clin Pharm Ther 1991; 16: 263-73.

12. Mersey HG. Long-term experience with terazosin for treatment of mild to moderate hypertension. Am J Med 1986; 80 (Suppl 5B): 68-72.

13. Pool JL. Combination antihypertensive therapy with terazosin and other antihypertensive agents: Results of clincial trials. Am Heart J 1991; 122:926-31.

14. Studer JA, Piepho RW. Antihypertensive therapy in the geriatric patient: II. A review of the alpha-1 -adrenergic blocking agents. J Clin Pharmacol 1993; 33: 2-13.

15. Titmarsh S, Monk JP. Terazosin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. Drugs 1987; 33: 461-77.

16. USA-FDA summary basis of approval for Hytrin (terazosin hydrochloride) by Abbott Laboratories, NDA 19-057.

17. Hytrin. In: Krogh CME, Gillis MC, Welbanks L et al., eds, Compendium of Pharmaceuticals and Specialties 28th edition. Ottawa, Canadian Pharmaceutical Association, 1993: 556-7.

18. Product monograph for Hytrin® (terazosin hydrochloride) by Abbott Laboratories Ltd., Montreal, Canada. May 21, 1996.