PRODUCT MONOGRAPH

[Pr]Dom-TERAZOSIN

Terazosin Tablets as Terazosin Hydrochloride

1 mg, 2 mg, 5 mg and 10 mg

Antihypertensive Agent

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

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[Pr]Dom-TERAZOSIN

Terazosin Tablets as Terazosin Hydrochloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
oral	tablet 1 mg, 2 mg, 5 mg & 10 mg	corn starch, crospovidone, lactose, magnesium stearate, povidone and talc. 2 mg tablets also contain FD&C yellow No. 6 Lake. 5 mg tablets also contain black iron oxide, iron oxide red and yellow iron oxide. 10 mg tablets also contain FD&C Blue No. 1 Lake and FD&C Blue No. 2 Aluminum Lake.

INDICATIONS AND CLINICAL USE

Dom-TERAZOSIN (terazosin hydrochloride) is indicated for:

- the treatment of mild to moderate hypertension.
- the treatment of symptoms of benign prostatic hyperplasia (BPH).

Hypertension

Dom-TERAZOSIN is employed in a general treatment program in conjunction with a thiazide diuretic and/or other antihypertensive drugs as needed for proper patient response. Dom-TERAZOSIN may be tried as a sole therapy in those patients in whom other agents caused adverse effects or are inappropriate.

Benign Prostatic Hyperplasia

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). Terazosin hydrochloride does not retard or stop the progression of benign prostatic hyperplasia (BPH). The long-term effects of terazosin hydrochloride 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 hydrochloride therapy is initiated.

Pediatrics (< 18 years of age):
Terazosin hydrochloride has not been studied in children and therefore use in this age group is not recommended.

Geriatrics (> 65 years of age):
Patients over 75 years of age may have limited benefit from terazosin hydrochloride therapy.

CONTRAINDICATIONS

Patients who are hypersensitive to Dom-TERAZOSIN (terazosin hydrochloride) or its analogs or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Patients with a history of micturition syncope should not receive Dom-TERAZOSIN (terazosin hydrochloride). See (**WARNINGS AND PRECAUTIONS**, **Cardiovascular**, **Syncope and "First Dose" Effect)**

General
Dom-TERAZOSIN (terazosin hydrochloride) therapy does not modify the natural history of 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 has 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 Dom-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 Dom-TERAZOSIN therapy to rule out the presence of carcinoma of the prostate.

Carcinogenesis and Mutagenesis
Terazosin hydrochloride was devoid of mutagenic potential when evaluated in vivo and *in vitro*.

Terazosin hydrochloride administered in the feed to rats at doses of 8, 40, and 250 mg/kg/day for 2 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

hydrochloride was not oncogenic in mice when administered in feed for 2 years at a maximum tolerated dose of 32 mg/kg/day.

Cardiovascular

Syncope and "First dose" Effect

Terazosin hydrochloride can cause marked hypotension, especially postural hypotension, and syncope in association with the first dose or first few doses of therapy. 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 terazosin hydrochloride.

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 to 160 beats per minute.

In studies of terazosin hydrochloride 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 Dom-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 advised of the possibility of syncopal and orthostatic symptoms, and to avoid driving or hazardous tasks for 12 hours after the initial dose of Dom-TERAZOSIN after the dose is increased and after 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 patients in the recumbent position and institute supportive measures as necessary.

Patients with a history of micturition syncope should not receive Dom-TERAZOSIN.

Concomitant administration of Dom-TERAZOSIN with verapamil to hypertensive patients may result in symptomatic hypotension and in some cases tachycardia. See (**DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Table 2**).

Use with Phosphodiesterase type 5 (PDE5) Inhibitors

Caution is advised when PDE5 inhibitors such as sildenafil, tadalafil and vardenafil are co-administered with alpha-blockers. Both PDE5 inhibitors and alpha-adrenergic blocking agents are vasodilators with blood pressure lowering effects. When vasodilators are used in combination, additive effects on blood pressure may be anticipated. In some patients, concomitant use of these two classes of drugs can lower blood pressure significantly, which may lead to symptomatic hypotension. Hypotension has been reported when terazosin hydrochloride has been used with PDE5 inhibitors. (See **DRUG INTERACTIONS**). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.

- In patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose.

- Safety of combined use of PDE5 inhibitors and alpha-blockers may be adversely affected by other factors, such as intravascular volume depletion and other anti-hypertensive therapy.

Orthostatic Hypotension
While syncope is the most severe orthostatic effect of terazosin hydrochloride see (**WARNINGS AND PRECAUTIONS**, **Cardiovascular**, **Syncope and "First Dose" Effect**), 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 occupation in which such events represent potential problems should be treated with particular caution.

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

Peripheral Edema
Fluid retention resulting in weight gain may occur during terazosin hydrochloride therapy. In placebo- controlled monotherapy trials, male and female patients receiving terazosin hydrochloride 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 differences are significant.

Genitourinary

Concomitant Conditions
Dom-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/sec 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.), hydro-nephrosis, presence of carcinoma of the prostate, patients with clinically significant renal or hepatic impairment (i.e. serum creatinine > 2 mg/dL or serum glutamic oxaloacetic transaminase (SGOT) > 1.5 times the upper limit of normal (or equivalent level on the international scale).

Hepatic/Biliary/Pancreatic

Use in Patients with Liver Impairment
No information is available on the use of terazosin hydrochloride in patients with impaired liver function.

Peri-Operative Considerations

Cataract Surgery
Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients on/or previously treated with alpha-1 blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker therapy prior to cataract surgery.

Renal
The use of terazosin hydrochloride 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 hydrochloride as compared to patients with normal renal function. Approximately 40% of oral terazosin hydrochloride dose is excreted by the kidney as parent drug or metabolites.

Sensitivity/Resistance

Anaphylactoid-like Reactions
Anaphylactoid-like reactions manifested by angioedema of the lips, tongue, pharynx, and/or laryngeal spasm have been rarely reported in patients treated with terazosin hydrochloride. See (**ADVERSE REACTIONS**). In such cases, terazosin hydrochloride should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred.

Sexual Function/Reproduction
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 30 mg/kg and five 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 good correlation was reported between sperm count and subsequent pregnancy.

Oral administration of terazosin hydrochloride for 1 or 2 years elicited a statistically significant increase in the incidence of testicular atrophy in rats exposed to 40 and 250 mg/kg/day, but not in rats exposed to 8 mg/kg/day. Testicular atrophy was also observed in dogs dosed with 300 mg/kg/day for 3 months but not after 1 year when dosed with 20 mg/kg/day.

Special Populations

Pregnant Women
The safety of terazosin hydrochloride in pregnancy has not been established. Dom-TERAZOSIN is not recommended during pregnancy unless potential benefits justifies potential risks to mother and fetus.

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

Nursing Women
It is not known whether terazosin hydrochloride is excreted 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.

Pediatrics (< 18 years of age)
The use of terazosin hydrochloride in children is not recommended since safety and efficacy have not been established.

Geriatrics (> 65 years of age)
Terazosin hydrochloride should be used cautiously in elderly patients 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 Dom-TERAZOSIN therapy.

Monitoring and 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, blood urea nitrogen (BUN), liver function tests, and electrolytes.

Small but statistically significant decreases in hematocrit, hemoglobin, white blood cells, total protein and albumin were observed in controlled clinical trials. 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

Adverse Drug Reaction Overview

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

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

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

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

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

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.

Most Common Adverse Drug Reactions (>1%)

Hypertension
Adverse drug reactions occurring more commonly in 1% or more of hypertensive patients on terazosin hydrochloride monotherapy or combination therapy are shown in **Table 1**.

Table 1: Adverse Drug Reactions in Clinical Trials Involving Hypertensive Patients on Terazosin Hydrochloride Monotherapy or Combination Therapy

	Terazosin hydrochloride n= 1986 (%)
Body as a Whole	
Headache	14.1
Asthenia	11.0
Peripheral Edema	3.6
Chest Pain	2.2
AbDominal Pain	1.5
Edema	1.3
Facial Edema	1.0
Cardiovascular System	
Palpitation	4.6
Tachycardia	2.9
Syncope	1.0
Digestive System	
Nausea	3.9
Dry Mouth	1.7
Diarrhea	1.3
Nervous System	
Dizziness	18.9
Somnolence	4.8
Nervousness	2.2
Paresthesia	1.5
Insomnia	1.2
Respiratory System	
Nasal Congestion	4.6
Dyspnea	2.8
Rhinitis	1.2
Skin and Appendages	
Sweating	1.1
Special Senses	
Blurred Vision	1.4
Eye Disorder	1.2
Urogenital System	
Impotence	1.1
Miscellaneous	
Pain in Extremities	1.8

Benign Prostatic Hyperplasia

In controlled and uncontrolled clinical trials involving 1171 patients with BPH, 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 (1.0%).

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

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

Body as a Whole:	Back pain, weight gain, allergic reactions, malaise.
Cardiovascular System:	Postural hypotension, angina pectoris, arrhythmias, cerebrovascular accident, heart failure, hypotension (at times severe), migraine.
Digestive System:	Dyspepsia, vomiting, anorexia, gastritis, liver function abnormality, jaundice.
Nervous System:	Incoordination, abnormal dreams, confusion, speech disorder, tremor, vertigo, seizure, depression.
Respiratory System:	Sinusitis, cold symptoms, pharyngitis, asthma, increased cough, laryngeal spasm.
Skin and Appendages:	Pruritus, rash, photosensitivity.
Special Senses:	Tinnitus, taste perversion.
Urogenital System:	Urinary frequency, dysuria.
Miscellaneous:	Hypokalemia, hypophosphatemia, decreased libido.

Benign Prostatic Hyperplasia

Cardiovascular System:	Syncope, tachycardia.
Metabolic and Nutritional Disorders:	Peripheral edema, weight gain.
Nervous System:	Libido decrease.

Post-Market Adverse Drug Reactions

Body as a Whole:	Fever, neck pain, and shoulder pain, anaphylaxis has been reported, angioedema has been reported. Hypersensitivity has been reported**.**
Cardiovascular System:	Vasodilation, atrial fibrillation has been reported.
Digestive System:	Constipation and flatulence.
Nervous System:	Anxiety.
Respiratory System:	Bronchitis, epistaxis and flu symptoms.
Special Senses:	Conjunctivitis.
Urogentital System:	Priapism, urinary tract infection, and urinary incontinence primarily reported in post-menopausal women.
Musculoskeletal System:	Arthralgia, arthritis, joint disorder and myalgia.
Hematopoietic System:	Thrombocytopenia has been reported.
Metabolic/Nutritional Disorders:	Gout.

During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha-1 blocker therapy.

DRUG INTERACTIONS

Drug-Drug Interactions

The following table provides a list of potential drug interactions due to pharmacokinetic reasons:

Table 2: Potential Drug Interactions Associated with Terazosin Hydrochloride

Concomitant Drug Class: Drug Name	Ref	Effect	Clinical Comment
Verapamil	P/CT	Significant increases in AUC, C_{max} and C_{min} of terazosin hydrochloride in hypertensive patients. The pharmacokinetics of verapamil were not altered.	Symptomatic hypotension, and in some cases tachycardia, were observed when terazosin hydrochloride was administered concomitantly with verapamil. Caution should therefore be exercised when these drugs are administered concomitantly. See (**WARNINGS AND PRECAUTIONS**).

Concomitant Drug Class: Drug Name	Ref	Effect	Clinical Comment
PDE5 Inhibitors e.g., sildenafil, vardenafil, and tadalafil	P/C	Hypotension has been reported during the concomitant use of PDE5 inhibitors and terazosin hydrochloride See (**WARNINGS AND PRECAUTIONS**)	Symptomatic hypotension.
Definitions: C = Case Study; CT = Clinical Trials; P = Potential			

In controlled trials, terazosin hydrochloride has been added to diuretics and several beta-adrenergic blockers; except for the additive hypotensive effect, no unexpected interactions were observed. Terazosin hydrochloride has also been used in patients on a variety of concomitant therapies. While these were not formal interaction studies, no interactions were observed. terazosin hydrochloride has been used concomitantly in at least 50 patients on the following drugs or drug classes: 1) analgesic/anti-inflammatory (e.g., acetaminophen, acetylsalicylic acid, codeine, ibuprofen, inDomethacin); 2) antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole); 3) anticholinergic/ sympathomimetics (e.g., phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride); 4) antigout (e.g., allopurinol); 5) antihistamines (e.g., chlorpheniramine); 6) cardiovascular agents (e.g., atenolol, hydrochlorothiazide, methyclothiazide, propranolol); 7) corticosteroids; 8) gastrointestinal agents (e.g., antacid); 9) hypoglycemics; 10) sedatives and tranquilizers (e.g. diazepam).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Hypertension

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

When Dom-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 Dom-TERAZOSIN regimen, dosage reduction of Dom-TERAZOSIN and re-titration with careful monitoring may be necessary.

Benign Prostatic Hyperplasia

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

Recommended Dose and Dosage Adjustment

Hypertension

Initial dose
1 mg of Dom-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 to 5 mg once-a-day. Some patients may benefit from doses up to 20 mg per day which is the maximum recommended daily dose.

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

If response to Dom-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 effects such as dizziness, palpitations or orthostatic complaints are seen 2 to 3 hours after dosing.

Benign Prostatic Hyperplasia

Initial dose
1 mg of Dom-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 a stepwise fashion at weekly intervals to 2, 5, or 10 mg 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 Dom-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 patient's condition should be made.

Following the administration of the maximum recommended dosage, Dom-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. Dom-TERAZOSIN therapy should also be discontinued if side effects are more bothersome than BPH symptoms or if the patient develops a urinary complication while on Dom-TERAZOSIN therapy.

Missed Dose
If Dom-TERAZOSIN administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.

OVERDOSAGE

Should administration of Dom-TERAZOSIN (terazosin hydrochloride) 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 hydrochloride is highly protein bound; therefore, dialysis may not be of benefit.

For management of a suspect drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Hypertension
The antihypertensive effect of 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 the vessels appears to be produced mainly by selective blockade of alpha-1-adrenoceptors.

Benign Prostatic Hyperplasia
The reduction in the symptoms associated with BPH following administration of terazosin hydrochloride 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 the 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 to 10 mmHg systolic and 3.5 to 8 mmHg diastolic. The response in the standing position tended to be larger by 1 to 3 mmHg.

Limited measurements of peak response (2 to 3 hours after dosing) during chronic terazosin hydrochloride 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 hydrochloride 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 hydrochloride at 24 hours; in the standing position there is also a 6 to 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 systolic pressure fall of 30 mmHg or more from supine to standing, or standing systolic pressure below 90 mm Hg with a fall of at least 20 mmHg.

During controlled clinical studies, patients receiving terazosin hydrochloride monotherapy had a small but statistically significant decrease (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
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 hydrochloride 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.

Pharmacokinetics

Table 3: Summary of the Pharmacokinetic Parameters of Terazosin Hydrochloride

	C_{max}	$t_{½}$ (h)	AUC_{0-48}	Clearance	Volume of distribution
Single dose mean (intravenous)	--	12 h	--	Plasma: 80 mL/min Renal: 10 mL/min	25-30 L
Single dose mean (1 mg tablet)	21 ng/mL	--	202.8 ng•h/mL	--	--

Absorption
Orally administered terazosin hydrochloride is essentially completely absorbed in man. Nearly all of the circulating dose is in the form of parent drug. Food has little or no effect on the bioavailability. The plasma levels of the free base peak in about 1 hour and then decline with a $t_{½}$ of approximately 12 hours.

Metabolism
Approximately 90 to 94% of the drug is bound to plasma proteins and binding is constant over the clinically observed concentration range. Hepatic metabolism is extensive with major biliary elimination.

Excretion
Approximately 10% of an orally administered dose is excreted as parent drug in the urine and approximately 20% is excreted in the feces. The remainder is eliminated as metabolites. Overall approximately 40% of the administered dose is excreted in the urine and approximately 60% in the feces.

Special Populations and Conditions

Geriatrics
In a study that evaluated the effect of age on terazosin hydrochloride pharmacokinetics, the mean plasma half-lives were 14.0 and 11.4 hours for the age group ≥ 70 years and the age group 20 to 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 to 39 years of age.

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

STORAGE AND STABILITY

Dom-TERAZOSIN (terazosin hydrochloride) tablets should be stored at controlled room temperature between 15ºC and 30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets
1 mg: White, flat face, beveled edge, round tablet debossed "TRZ" on one side and "1" on the other. Available in HDPE bottles of 100 tablets.

2 mg: Orange, flat face, beveled edge, round tablet debossed "TRZ" on one side and "2" on the other. Available in HDPE bottles of 100 tablets.

5 mg: Brown-beige, flat face, beveled edge, round tablet debossed "TRZ" on one side and "5" on the other. Available in HDPE bottles of 100 tablets.

10 mg: Blue, flat face, beveled edge, round tablet debossed "TRZ" on one side and "10" on the other. Available in HDPE bottles of 100 tablets.

Composition
Dom-TERAZOSIN tablets contain 1 mg, 2 mg, 5 mg or 10 mg of terazosin, as terazosin hydrochloride, and the follow non-medicinal ingredients: corn starch, crospovidone, lactose, magnesium stearate, povidone and talc.

In addition, the tablets contain:
2 mg: FD&C yellow No. 6 Lake.
5 mg: Black iron oxide, iron oxide red and yellow iron oxide.
10 mg: FD&C Blue No. 1 Lake and FD&C Blue No.2 Aluminum Lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

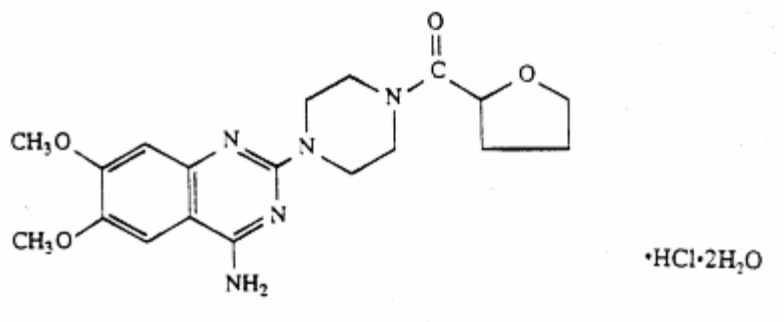
Proper name: terazosin hydrochloride dihydrate

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

Molecular formula: $C_{19}H_{25}N_5O_4HCl•2H_2O$

Molecular mass: 459.93 g/mol

Structural formula:



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

CLINICAL TRIALS

A comparative bioavailability study was performed using Dom-TERAZOSIN 5 mg tablets (Dominion Pharmacal) *versus* HYTRIN 5 mg tablets (Abbott Laboratories Ltd.) in 36 healthy male volunteers. A single 5 mg oral dose was administered in the fasting state. The results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Terazosin (1 x 5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T‡ (ng.h/mL)	1110.87 1110.87	1112.97 1132.10 (18.69)	100	97 - 102
AUC_I (ng.h/mL)	1161.71 1190.20 (22.20)	1161.53 1181.86 (18.89)	100	97 - 103
C_{max} (ng/mL)	95.60 97.92 (21.48)	95.64 98.07 (21.93)	100	94 - 106
T_{max}§ (h)	0.98(72.32)	1.21		
$T_{½}$§ (h)	14.93 (22.57)	15.18 (13.98)		

* Dom-TERAZOSIN 5 mg Tablet (Dominion Pharmacal)
†HYTRIN 5 mg tablet (Abbott Laboratories Ltd, Canada)
§Expressed as the arithmetic mean (CV%).

Study Demographics and Trial Design

Table 4: Summary of Patient Demographics for Clinical Studies in Benign Prostatic Hyperplasia (BPH)

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age in Years (Range)	Gender (%M/F)
I	Double-blind, ranDomized, parallel, placebo-controlled, titration to fixed dose, Phase III study	Placebo vs. Terazosin hydrochloride 2 mg Terazosin hydrochloride 5 mg Terazosin hydrochloride 10 mg Oral 12 weeks (3 months)	252	Placebo 62.1 (47-73) 2 mg 61.6 (44-77) 5 mg 61.7 (45-75) 10 mg 61.6 (51-75)	All males
II	Double-blind, ranDomized, parallel, placebo-controlled, titration to response, Phase III study	Placebo vs. Terazosin hydrochloride (2, 5, 10 or 20 mg) Oral 24 weeks (6 months)	177	Placebo 61.3 (39-77) Terazosin hydrochloride 62.7 (46-82)	All males
III	Double-blind, ranDomized, parallel, placebo-controlled, titration to response, Phase III study	Placebo vs. Terazosin hydrochloride (1, 2, 5 or 10 mg) Oral 24 weeks (6 months)	147	Placebo 63.8 (48-80) Terazosin hydrochloride 64.5 (44-77)	All males
IV	Open label, titration to response, long-term, Phase II study	Terazosin hydrochloride (1, 2, 5, 10 or 20 mg) Oral 2 years	475	63.1 (40-86)	All males
Definitions: n = number; F = females; M = males; vs. = versus.					

Study Results

In three placebo controlled studies, both symptom scores and peak urine flow rates showed statistically significant improvement from baseline in patients treated with terazosin hydrochloride from week 2 (or the first clinic visit) and throughout the study duration. Results from these three studies are tabulated in **Table 5**.

Table 5: Symptom Evaluation and Uroflowmetric Measurements from Three Placebo-controlled Clinical Studies

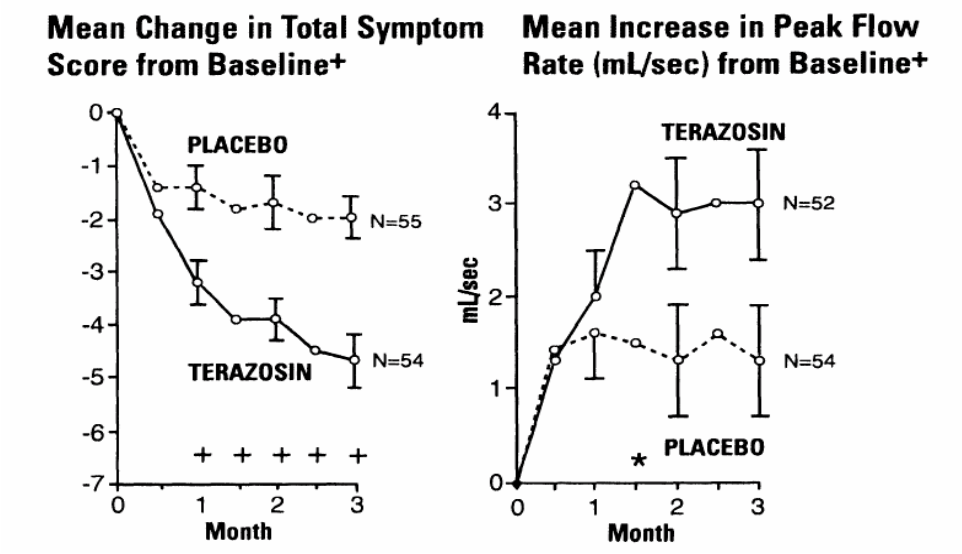
	Symptom Score (Range 0-27)			Peak Flow Rate (mL/sec)		
	N	**Mean Baseline**	**Mean Change (%)**	**N**	**Mean Baseline**	**Mean Change (%)**
Study I (10 mg)[a] Titration to fixed dose (12 wks)						
Placebo	55	9.7	-2.3 (24)	54	10.1	+1.0 (10)
Terazosin hydrochloride	54	10.1	-4.5 (45)*	52	8.8	+ 3.0 (34)*
Study II (2, 5, 10, 20 mg)[b] Titration to response (24 wks)						
Placebo	89	12.5	-3.8 (30)	88	8.8	+1.4 (16)
Terazosin hydrochloride	85	12.2	-5.3 (43)*	84	8.4	+2.9 (35)*
Study III (1, 2, 5, 10 mg)[c] Titration to response (24 wks)						
Placebo	74	10.4	-1.1 (11)	74	8.8	+1.2 (14)
Terazosin hydrochloride	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 20 mg.
[c] 67% of patients on 10 mg.
* Significantly ($p \leq 0.05$ more improvement than placebo).

Analysis of the effect of terazosin hydrochloride on individual urinary symptoms demonstrated that compared to placebo, terazosin hydrochloride 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 hydrochloride had a significantly ($p \leq 0.001$) greater overall improvement compared to placebo treated patients.

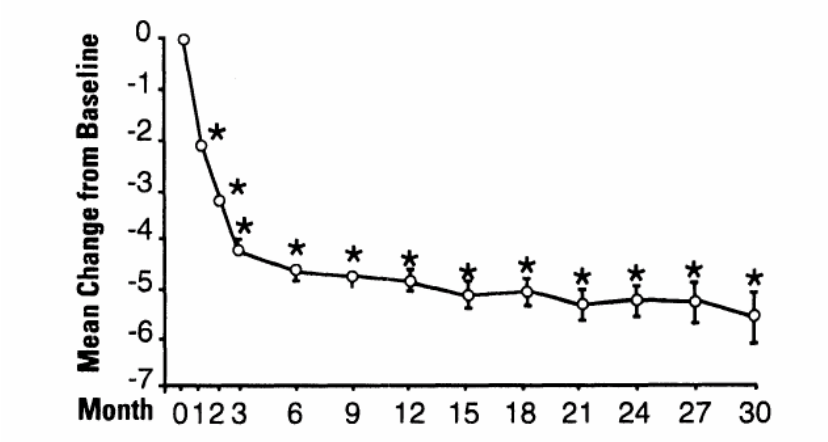
In a short-term study (Study I), patients were ranDomized to either 2, 5 or 10 mg of terazosin hydrochloride or placebo. Patients ranDomized to the 10 mg group achieved a statistically significant response in both symptoms and peak flow rate compared to placebo (**Figure 1**).



+ for baseline values see **Table 5**
* $p \leq 0.05$, compared to placebo group

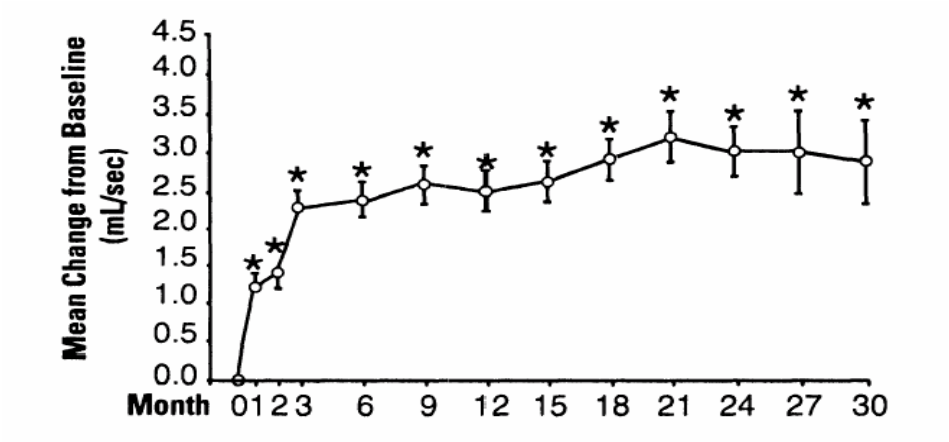
Figure 1. Short Term Study Where Patients Were RanDomized to Either 2, 5 or 10 mg of Terazosin Hydrochloride or Placebo (Study I)

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 hydrochloride on urinary symptom scores and peak flow rates was maintained throughout the study duration (**Figure 2** and **Figure 3**).



* $p \leq 0.05$ versus baseline
Mean baseline = 10.7

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



* $p \leq 0.05$ versus baseline
Mean baseline = 9.9

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

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 hypertensive patients with increased peripheral vascular resistance, terazosin hydrochloride treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (**Table 6**).

Table 6: Mean Changes in Blood Pressure from Baseline to Final Visit in all Double-blind, Placebo-controlled Studies

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

* $p \leq 0.05$ versus placebo
Definitions: DBP = diastolic blood pressure; SBP = systolic blood pressure.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Terazosin hydrochloride 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 found in deoxycorticosterone (DOC)-salt hypertensive rats.

Terazosin hydrochloride 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 hydrochloride was administered intravenously to anesthetized male dogs (4 to 5/group) at doses of 0.1 mg/kg followed 60 minutes later by 0.3 mg/kg. Terazosin hydrochloride 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 first derivative of left ventricular (LV) pressure over time (dP/dt_{max}) (20 and 17%, respectively) were observed immediately following the administration of the drug. These increases lasted only several minutes and later subsided towards the baselines. 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 hydrochloride to dogs following treatment with phenoxybenzamine greatly reduced the hypotensive effect of terazosin hydrochloride. Pre-treatment with either propranolol or atropine had no effect on the hypotensive action of terazosin hydrochloride.

Effect on Central Nervous System

In rats (6 animals), terazosin hydrochloride 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 hydrochloride at oral doses of 5 mg/kg. Oral administration of 3 mg/kg of terazosin hydrochloride to mice (4 to 11 animals/group) produced no significant reductions in locomotor activities. At 10 mg/kg of terazosin hydrochloride, significant decreases in activities of mice were observed.

In immobilized rabbits, intravenous injections of 3 mg/kg of terazosin hydrochloride caused no significant effects on the spontaneous electroencephalogram (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.

Ancillary Studies

Terazosin hydrochloride had no effect on either non-vascular 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 to 10 mg/kg) has shown that terazosin hydrochloride was rapidly absorbed, reaching peak plasma levels of 1 to 2 mcg/mL within 1 to 2 hours. The half-life was reasonably similar in both species and 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 to 38% of the dose was excreted in the urine and 16 to 17% was eliminated as the unchanged parent drug. The remainder of the dose was excreted in the feces and largely resulted from the biliary secretion of terazosin hydrochloride and its metabolites.

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

The *in vitro* plasma protein binding of terazosin hydrochloride was low, averaging 44 to 63% in rats and 40 to 45% in dogs at concentrations ranging from 1 to1000 ng/mL.

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

TOXICOLOGY

Acute Toxicity

Table 7 summarizes the acute toxicity results. Intravenous and oral median lethal dosages (LD_{50}) of terazosin hydrochloride in rats and mice ranges from 211 to 271 mg/kg and 2.7 to 10.0 g/kg, respectively. No sex difference was found in median lethal dosages. The preDominant toxic effect was central nervous system depression followed by death.

Table 7: Results of Terazosin Hydrochloride Acute Toxicity Studies

Species	Sex	Route	LD_{50} Range mg/kg	Findings
Mice	F	intravenous	264	Decreased activity, ataxia, dyspnea, twitches and convulsions.
	M	intravenous	240	
	F	oral	4 200	
	M	oral	3 700	
Rat	F	intravenous	271	Decreased activity, dyspnea and mucoid discharges from eyes and nose.
	M	intravenous	255	
	F	oral	6 000	
	M	oral	5 500	
Definitions: F = female; M = male; LD_{50} = median lethal dose.				

Subacute and Chronic Toxicity

Table 8: Results of Terazosin Hydrochloride Subacute and Chronic Toxicity Studies

Species	Route	Dose mg/kg/day	Animals per Dose Level	Duration	Findings
Rat	Oral	0 10 30 300	10 Male	2 Weeks	Dose dependent ptosis and lacrimation. Decreased growth at 300 mg/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	10 Female 10 Male	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, serum glutamic pyruvic transaminase (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	10 Female 10 Male	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.

Species	Route	Dose mg/kg/day	Animals per Dose Level	Duration	Findings
Rat	Oral	0 8 40 250	110 Female (controls) 110 Male (controls) 60 Female (treated) 60 Male (treated)	104 Weeks§	Lower survival rates for male rats dosed with 8 and 40 mg/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 serum glutamic oxaloacetic transaminase (SGOT) at 8 mg/kg and 250 mg*, sodium at 40 mg/kg**, globulin at 250 mg/kg**, and mean corpuscular volume at 250 mg/kg*. Drug-related testicular atrophy observed in mid- and high dose 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	Intravenous	0 10 40 150	10 Female 10 Male	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	110 Female (controls) 110 Male (controls) 50 Female (treated) 50 Male (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.
Dog	Oral	0 5 40 300	3 Female 3 Male	13 Weeks	Four deaths at 300 mg/kg after 2 to 3 days of treatment; gastrointestinal ulceration and myocardial degeneration found. Gastrointestinal lesions, fatty degeneration of the liver, endo- and sub-endocardial 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, lacrimation, 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/sub-endocardial hemorrhage with myocardial degeneration, thymic atrophy, lack of spermiogenesis and hydropic swelling of ciliary process in some dogs treated with 300 mg/kg.
Dog	Oral	0 2.4 7 20	6 Female 6 Male	52 Weeks	No mortalities occurred. Ptosis of eyelids observed in females at 20 mg/kg. No gross or microscopic changes of toxicologic significance observed.

Species	Route	Dose mg/kg/day	Animals per Dose Level	Duration	Findings
Dog	Intravenous	0 4 15 60	3 Female 3 Male	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.
§ Females were sacrificed approximately 6 weeks earlier.					

Mutagenicity

Table 9: Results of Terazosin Hydrochloride Mutagenicity Studies

Study	Test Organism	Dose	Route	Major Finding(s)
Ames Test	Salmonella-strains TA-1535, TA-1537 and TA-1538, activated and non-activated with hepatic microsomes	50, 100 and 500 mcg/plate	*In vitro*	No evidence of mutagenic potential.
In vivo Cytogenetics	Rat - bone marrow	60, 240 and 480 mg/kg/day for 5 days	*In vivo* Oral	No evidence of mutagenicity observed.
Dominant Lethal	Mouse	50, 165 and 500 mg/kg/day	*In vivo* Oral	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 oncogenic in mice when administered in feed for 2 years at a maximum tolerated dose of 32 mg/kg/day.

Teratogenicity

Teratology - Segment II

Table 10: Results of Teratology – Segment II Studies

Species	Route	Dose mg/kg/day	Animals per Dose Level	Duration	Findings
Rat	Oral	0 8 60 480	20 Female	Day 6 to 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 60 mg/kg.
Rabbit	Oral	0 8 22 60	15 Female	Day 6 to 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 60 mg/kg. No teratogenicity or embryotoxicity seen at 8 or 22 mg/kg.

Fertility and General Reproductive Performance - Segment I

Table 11: Results of Segment I – Fertility and General Reproductive Performance Study

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 pre-mating through mating, gestation, parturition and 3 weeks postpartum while nursing.		Ptosis of eyelids observed in all treated animals; sedation observed at 120 mg/kg (male 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.

Peri- and Post-natal Study - Segment III

Table 12: Results of Peri and Post Natal Study- Segment III

Species	Route	Dose mg/kg/day	Animals per Dose Level	Duration	Findings
Rat	Oral	0 8 30 120	20 Female	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 3 dose groups. Litter size comparable in the dose groups.

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PART III: CONSUMER INFORMATION

[Pr]Dom-TERAZOSIN
terazosin tablets as terazosin hydrochloride

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

ABOUT THIS MEDICATION

What the medication is used for:
Dom-TERAZOSIN is used to treat:
- Hypertension (high blood pressure)
- Benign prostatic hyperplasia (enlargement of the prostate gland)

Dom-TERAZOSIN is for symptomatic benign prostatic hyperplasia (BPH) and not for prostate cancer. It is possible for men to have both BPH and prostate cancer at the same time. Dom-TERAZOSIN is not a treatment for prostate cancer.

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, including Prostate Specific Antigen (PSA), should continue while you are taking Dom-TERAZOSIN.

What it does:
Dom-TERAZOSIN works by relaxing blood vessels so that blood passes through them more easily. This helps to lower blood pressure.

Dom-TERAZOSIN also 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.

When it should not be used:
Dom-TERAZOSIN should not be used if you are allergic to any component of Dom-TERAZOSIN including active ingredient and non-active ingredients.

What the medicinal ingredient is:
terazosin hydrochloride

What the non-medicinal ingredients are:
corn starch, crospovidone, lactose, magnesium stearate, povidone and talc.

In addition, the tablets contain:
2 mg: FD&C yellow No. 6 Lake.
5 mg: Black iron oxide, iron oxide red and yellow iron oxide.
10 mg: FD&C Blue No. 1 Lake and FD&C Blue No.2.

What dosage forms it comes in:
Tablets: 1 mg, 2 mg, 5 mg and 10 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Dom-TERAZOSIN should not be used if you have been diagnosed with micturition syncope (fainting shortly after or during urination).**

BEFORE you use Dom-TERAZOSIN talk to your doctor or pharmacist if:

- you have low blood pressure;
- you are using sildenafil, tadalafil or vardenafil ;
- you have liver problems;
- you have kidney problems;
- you have had or will have prostate surgery;
- you have pancreatic cancer;
- you are pregnant or nursing.

During initiation of Dom-TERAZOSIN therapy, after your Dom-TERAZOSIN dose has been increased, or after interruption of therapy when treatment with Dom-TERAZOSIN is resumed you should not drive, operate heavy machinery, or do any hazardous task, until you are used to the effects of Dom-TERAZOSIN. In these cases, for 12 hours after taking Dom-TERAZOSIN you should avoid situations where injury could result should fainting occur. If you begin to feel dizzy, sit or lie down until you feel better.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines including natural health products, prescription and non-prescription medicines.

In general, you should avoid the use of phosphodiesterase (PDE5) inhibitors such as sildenafil, tadalafil or vardenafil when taking Dom-TERAZOSIN due to the risks of developing serious hypotension (low blood pressure).

Administration of Dom-TERAZOSIN with verapamil to hypertensive patients may result in low blood pressure and/or a rapid heartbeat.

Do not take these drugs with Dom-TERAZOSIN without your doctor's advice.

PROPER USE OF THIS MEDICATION

Usual dose:
Follow your doctor's instructions very carefully about how to take Dom-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, 5 mg, or 10 mg depending on how well you respond. The maximum recommended daily dose is 20 mg per day.

You should see an effect on your symptoms in 2 to 4 weeks. While taking Dom-TERAZOSIN you should have regular check-ups to evaluate your progress regarding your BPH and to monitor your blood pressure.

Overdose:

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

If you or someone you know accidentally takes more than the stated dose, tell your doctor or hospital how much was taken and show them the tablets. Treat even small overdoses seriously.

Missed Dose:
If you forget to take a dose, take another as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed dose at all.

Never double-up on a missed dose.

Talk to your doctor if you have not taken Dom-TERAZOSIN for a few days. You may have to restart at the 1 mg dose. Be cautious about possible dizziness.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its needed effects, a medicine may cause some unwanted effects. These are referred to as "side effects". Although not all of these side effects may occur, if they do occur they may need medical attention.

Dom-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 dose, 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 Dom-TERAZOSIN at bedtime. If you take Dom-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 Dom-TERAZOSIN.

Other side effects with Dom-TERAZOSIN include back pain, constipation, diarrhea, drowsiness or sleepiness, dry mouth, flatulence, headache, impotence, indigestion, libido decreased, nasal congestion, nausea, urinary frequency, urinary incontinence primarily reported in postmenopausal women, weakness or weight gain.

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Abnormal, irregular or rapid heartbeat (palpitation)			√
Allergic reaction Swollen mouth, lips, tongue, eyes, extremities, throat or difficulty swallowing or breathing (signs of angioedema). Intestinal angioedema may also occur and is characterized by abDominal pain (with or without nausea or vomiting). **If you notice swelling or feel pain in these areas, inform your doctor immediately. You should also inform your doctor if you have unexplained fever, rash or itching.**			√
Anxiety			✓
Blurred or hazy vision			✓
Chest pain			✓
Decreased blood pressure or low blood pressure			✓
Depression	✓		
Difficulty breathing or shortness of breath			✓
Drowsiness or sleepiness			✓
Fainting			✓
Joint inflammation or joint pain	✓		
Permanent erection			✓
"Puffiness" of the feet or hands, swelling	✓		
Rash			✓
Sweating			✓
Unknown bruising or increased bleeding after a cut			✓
Urinary tract infection	✓		
Vomiting			✓
Weakness			✓

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

HOW TO STORE IT

Keep Dom-TERAZOSIN and all other medicines out of reach of children.

Dom-TERAZOSIN tablets should be stored at 15°C to 30°C.

Do not take your tablets after the expiry date shown on the label.

It is important to keep the Dom-TERAZOSIN in the original package.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:

- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
  Health Canada, Postal Locator 0701E
  Ottawa, ON
  K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Dominion Pharmacal. at, 1-888-550-6060.

This leaflet was prepared by

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