

PRODUCT MONOGRAPH

Pr **HYTRIN**[®]

terazosin hydrochloride

1, 2, 5 and 10 mg tablets

Antihypertensive Agent

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

Abbott Laboratories, Limited
8401 Trans-Canada Highway
St. Laurent (Quebec) Canada
H4S 1Z1

Date of Preparation:
May 15, 1997

Date of Revision:
June 15, 2006

Submission Control No: 104433

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE..... 3
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS..... 10
DRUG INTERACTIONS 14
DOSAGE AND ADMINISTRATION..... 15
OVERDOSAGE 16
ACTION AND CLINICAL PHARMACOLOGY 17
STORAGE AND STABILITY..... 19
DOSAGE FORMS, COMPOSITION AND PACKAGING 19

PART II: SCIENTIFIC INFORMATION20
PHARMACEUTICAL INFORMATION..... 20
CLINICAL TRIALS..... 21
DETAILED PHARMACOLOGY 25
TOXICOLOGY 27
REFERENCES 34

PART III: CONSUMER INFORMATION.....36

HYTRIN®

Terazosin hydrochloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|---------------------------------|---|
| oral | Tablet / 1 mg, 2mg, 5 mg, 10 mg | corn starch, lactose, magnesium stearate, povidone (for 1, 2, 5 mg only), pregelatinized starch (for 10 mg only) and talc. Also contains FD&C yellow No. 6 (for 2 mg), iron oxide (for 5 mg) and FD&C blue No. 2 (for 10 mg). |

INDICATIONS AND CLINICAL USE

HYTRIN® (terazosin hydrochloride) is indicated for:

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

Hypertension

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

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). HYTRIN® does not retard or stop the progression of BPH. The long-term effects of HYTRIN® 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):

HYTRIN[®] has not been studied in children and therefore use in this age group is not recommended.

Geriatrics (> 75 years of age):

Patients over 75 years of age may have limited benefit from HYTRIN[®] therapy.

CONTRAINDICATIONS

- Patients who are hypersensitive to HYTRIN[®] (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 terazosin hydrochloride (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Syncope and "First dose" Effect**)

General

HYTRIN[®] (terazosin hydrochloride) 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 hydrochloride 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 terazosin hydrochloride 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 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 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 terazosin hydrochloride 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 terazosin hydrochloride, 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 terazosin hydrochloride.

Concomitant administration of terazosin hydrochloride with verapamil to hypertensive patients may result in symptomatic hypotension and in some cases tachycardia (see **WARNINGS AND PRECAUTIONS**).

Use with Phosphodiesterase type 5 (PDE5) Inhibitors

Caution is advised when PDE5 inhibitors such as VIAGRA[®] (sildenafil), CIALIS[®] (tadalafil) and LEVITRA[®] (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. 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 RECAUTIONS - Cardiovascular**) 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

Terazosin hydrochloride 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 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 pharmacokinetic of terazosin as compared to patients with normal renal function. Approximately 40% of oral terazosin 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 one or two 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 one year when dosed with 20 mg/kg/day.

Special Populations

Pregnant Women: The safety of terazosin hydrochloride in pregnancy has not been established. Terazosin hydrochloride 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 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 seventy-five years of age may have limited benefit from terazosin hydrochloride 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, 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 HYTRIN[®] (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 (BPH)

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= 1867 (%) |
| 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 (BPH)

In clinical trials involving 1171 patients with BPH, the most common reactions ($\geq 1\%$) 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.

Post-Market Adverse Drug Reactions

Hypertension

Body as a whole: fever, neck pain, and shoulder pain, anaphylaxis has rarely been reported;

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, epistaxis, 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;

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.

Benign Prostatic Hyperplasia (BPH)

Thrombocytopenia has been reported. Atrial fibrillation has been reported; however, a cause and effect relationship has not been established. Priapism has also been reported. Anaphylaxis has rarely been reported.

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). |
| PDE5 Inhibitors e.g., VIAGRA [®] (sildenafil), LEVITRA [®] (vardenafil), and CIALIS [®] (tadalafil) | P/C | Hypotension has been reported during the concomitant use of PDE5 inhibitors and HYTRIN [®] (see WARNINGS AND PRECAUTIONS) | Symptomatic hypotension |

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 HYTRIN® (terazosin hydrochloride) should be adjusted to the patient's individual blood pressure response.

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

Benign Prostatic Hyperplasia (BPH)

The dose of terazosin hydrochloride should be adjusted to the patient's individual response.

Recommended Dose and Dosage Adjustment

Hypertension

Initial dose:

1 mg of terazosin hydrochloride 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 two to three hours after dosing to see if the maximum and minimum responses are similar and to evaluate symptoms.

If response to terazosin hydrochloride 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 two to three hours after dosing.

Benign Prostatic Hyperplasia (BPH)

Initial dose:

1 mg of terazosin hydrochloride 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 mg, 5 mg, 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 terazosin hydrochloride 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 six 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, terazosin hydrochloride 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. Terazosin hydrochloride therapy should also be discontinued if terazosin hydrochloride side effects are more bothersome than BPH symptoms or if the patient develops a urinary complication while on terazosin hydrochloride therapy.

Missed Dose

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

OVERDOSAGE

Should administration of HYTRIN[®] (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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Hypertension

The antihypertensive effect of HYTRIN[®] (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 (BPH)

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 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 (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 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

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 $t_{1/2}$ 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

HYTRIN® (terazosin hydrochloride) tablets should be stored at controlled room temperature between 15 and 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each tablet contains terazosin hydrochloride dihydrate 1 mg, 2 mg, 5 mg, or 10 mg. Non-medicinal ingredients: corn starch, lactose, magnesium stearate, povidone (for 1, 2, 5 mg only), pregelatinized starch (for 10 mg only) and talc. Also contains FD&C yellow No. 6 (for 2 mg), iron oxide (for 5 mg) and FD&C blue No. 2 (for 10 mg).

HYTRIN® (terazosin hydrochloride) is available as round tablets in four different dosage strengths, packaged in a Starter Pack format and in plastic bottles of 100 tablets each. Terazosin hydrochloride tablets are available as white tablets of 1 mg; orange tablets of 2 mg; tan tablets of 5 mg; or blue tablets of 10 mg.

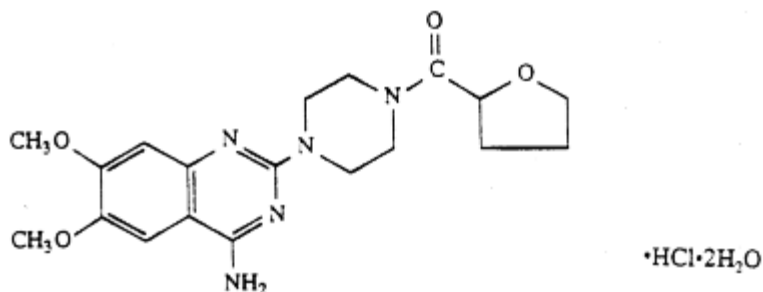
Starter Pack - one strip (seven) of each 1 mg and 2 mg tablets and, two strips (two times seven) of 5 mg tablets in blisters.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | |
|---------------------|--|
| Proper name: | Terazosin hydrochloride dihydrate |
| Chemical name: | 1-(4-amino-6,7-dimethoxy-2-quinazoliny)-4-[(tetrahydro-2-furanyl) carbonyl]-piperazine, monohydrochloride, dihydrate |
| Molecular formula: | $C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$ |
| Molecular mass: | 459.93 |
| Structural formula: | |



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

CLINICAL TRIALS

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 HYTRIN[®] (terazosin hydrochloride) from week 2 (or the first clinic visit) and throughout the study duration. Results from these three studies are tabulated in Table 3.

| Table 3 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 1 (10 mg)^a Titration 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 Titration 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 Titration 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 20 mg. c 67% of patients on 10 mg. * Significantly ($p \leq 0.05$ more improvement than placebo. | | | | | | |

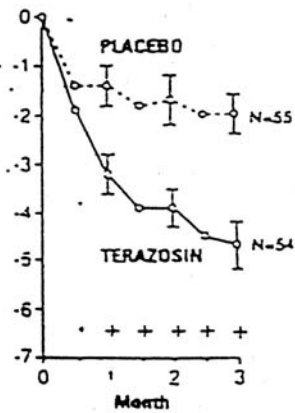
Analysis of the effect of terazosin hydrochloride on individual urinary symptoms demonstrated that compared to placebo, terazosin hydrochloride significantly improved the symptoms of hesitancy, intermittency, impairment in size and force of urinary stream, sensation of incomplete emptying, terminal dribbling,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

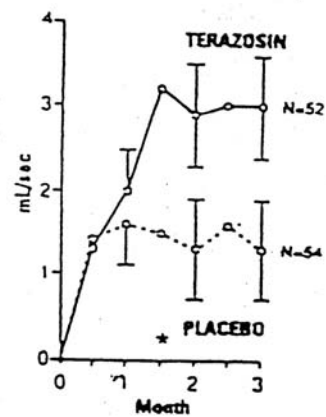
In a short-term study (Study 1), patients were randomized to either 2, 5 or 10 mg of terazosin hydrochloride or placebo. Patients randomized to the 10 mg group achieved a statistically significant response in both symptoms and peak flow rate compared to placebo. (see Figure 1).

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

Mean Change in Total Symptom Score from Baseline+



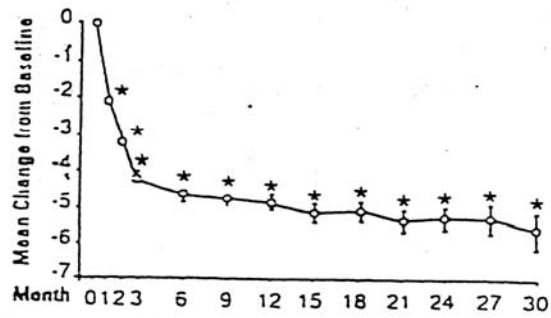
Mean Increase in Peak Flow Rate (mL/sec) from Baseline +



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

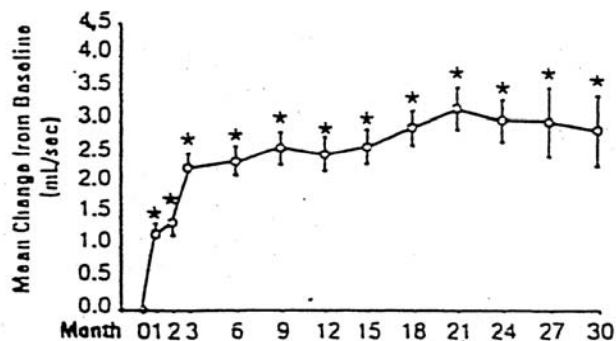
Figure 2
Mean Change in Total Symptom Score from Baseline - Long-term, Open-Label, Non-Placebo Controlled Study (N=494)



* $p \leq 0.05$ 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)



* $p \leq 0.05$ 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 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. (see Table 4).

| Table 4 | | | | | |
|--|-----------|--|--------------------|--|--------------------|
| 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 | 519 | -3.3* | 65 | -14.4* |
| DBP (mm Hg) | Placebo | 293 | +0.4 | 45 | -7.1 |
| | Terazosin | 519 | -2.2* | 65 | -15.1* |

* p ≤ 0.05 versus placebo

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 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 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 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 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 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 to 1000 ng/mL.

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

TOXICOLOGY

Acute Toxicity

| SPECIES | SEX | ROUTE | LD₅₀ RANGE mg/kg | FINDINGS |
|----------------|------------|--------------|--|---|
| Mice | F | I.V. | 264 | Decreased activity, ataxia, dyspnea, twitches and convulsions. |
| | M | I.V. | 240 | |
| | F | P.O. | 4 200 | |
| | M | P.O. | 3 700 | |
| Rat | F | I.V. | 271 | Decreased activity, dyspnea and mucoid discharges from eyes and nose. |
| | M | I.V. | 255 | |
| | F | P.O. | 6 000 | |
| | M | P.O. | 5 500 | |

Table 5 summarizes the acute toxicity results. Intravenous and oral median lethal dosages (LD50) 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.

Subacute and Chronic Toxicity

| Table 6 | | | | | |
|---|--------------|---------------------------|---------------------------------------|-----------------|---|
| 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 M | 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 F 10 M | 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 | 10 F 10 M | 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. |

Table 6 (continued)
Results of Terazosin Hydrochloride Subacute and Chronic Toxicity Studies

| SPECIES | ROUTE | DOSE mg/kg/day | ANIMALS PER DOSE LEVEL | DURATION | FINDINGS |
|---------|-------|----------------------|--|------------------------|---|
| Rat | Oral | 0 8 40 250 | 110 F (controls) 110 M (controls) 60 F (treated) 60 M (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 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 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 | 10 F 10 M | 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 kentonuria. No evidence of renal histopathology. Splenic congestion observed at 40 and 150 mg/kg. |
| Mouse | Oral | 0 2 8 32 | 110 F (controls) 110 M (controls) 50 F (treated) 50 M (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.

Table 6 (continued)
Results of Terazosin Hydrochloride Subacute and Chronic Toxicity Studies

| SPECIES | ROUTE | DOSE mg/kg/day | ANIMALS PER DOSE LEVEL | DURATION | FINDINGS |
|---------|-------|---------------------|---------------------------|----------|--|
| Dog | Oral | 0 5 40 300 | 3 F 3 M | 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 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 F 6 M | 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 | 3 F 3 M | 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 FINDING(S) |
|-----------------------------|--|--------------------------------------|---------------------|---|
| Ames Test | Salmonella-strains TA-1535, TA-1537 and TA-1538, activated and non-activated with hepatic microsomes | 50, 100 and 500 µg/plate | <i>In vitro</i> | No evidence of mutagenic potential. |
| <i>In vivo</i> Cytogenetics | Rat - bone marrow | 60, 240 and 480 mg/kg/day for 5 days | <i>In vivo</i> P.O. | No evidence of mutagenicity observed. |
| Dominant Lethal | Mouse | 50, 165 and 500 mg/kg/day | <i>In vivo</i> 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 oncogenic in mice when administered in feed for two years at a maximum tolerated dose of 32 mg/kg/day.

Teratogenicity

Teratology - Segment II

| Table 8 | | | | | |
|---|--------------|---------------------------|-----------------------------------|-----------------------|---|
| 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 F | 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 60 mg/kg. |
| Rabbit | Oral | 0 8 22 60 | 15 F | 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 60 mg/kg. No teratogenicity or embryotoxicity seen at 8 or 22 mg/kg. |

Fertility and General Reproductive Performance - Segment 1

| Table 9 | | | | | |
|--|--------------|---------------------------|---|-----------------|--|
| 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 embryoletality, 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 10 | | | | | |
|---|-------|---------------------|---------------------------|---|--|
| 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 F | 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, Halstenson CE, Matzke GR, Napier JL, Keane WF. Antihypertensive therapy with once-daily administration of terazosin, a new alpha-1 adrenergic-receptor blocker. *Pharm* 1985;5(5):285-289.
2. Abraham PA, Opsahl JA, Halstenson CE, Matzke GR, Keane WF. Prospective comparison of the renal effects of terazosin and propranolol during antihypertensive therapy. *J Hypertension* 1986;4(suppl 5):S479-S481.
3. Caine M. Clinical experience with alpha-adrenoceptor antagonists in benign prostatic hypertrophy. *Fed Proc* 1986;45:2604-2068.
4. Caine M. The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J Urol* 1986;136:1-4.
5. Caine M. Alpha-adrenergic mechanisms in dynamics of benign prostatic hypertrophy. *Urol (suppl)* 1988;32:16-20.
6. Chrysant SG, Black HR, Davidov M, *et al.* Experience with terazosin administered in combination with other antihypertensive agents. *Am J Med* 1986;80(suppl 5B):55-61.
7. Cohen A. Placebo-controlled study of once-daily administration of terazosin to patients with mild to moderate hypertension. *Curr Ther Res* 1987;41(1):105-113.
8. Dauer AD, Deger G, Fleming L. Terazosin: An effective once-a-day antihypertensive agent with an apparent beneficial effect on cholesterol. *Today's Ther Trends* 1986;4(1):1-15.
9. Dauer AD, Abraham PA, Cohen A, *et al.* Terazosin: An effective once-daily monotherapy for the treatment of hypertension. *Am J Med* 1986;80(suppl 5B):29-34.
10. Deger G. Effect of terazosin on serum lipids. *Am J Med* 1986;80 (suppl 5B):82-85.
11. Deger G, Cutler RE, Dietz AJ, Lewin AJ, Vlachakis N. Comparison of the safety and efficacy of once-daily terazosin versus twice-daily prazosin for the treatment of mild to moderate hypertension. *Am J Med* 1986;80(suppl 5B):62-67.
12. Jungers P, Ganeval D, Pertuiset N, Chauveau P. Influence of renal insufficiency on the pharmacokinetics and pharmacodynamics of terazosin. *Am J Med* 1986;80(suppl 5B):94-99.
13. Kyncl JJ. Pharmacology of terazosin. *AM J Med* 1986;80(suppl 5B):12-19.

14. Kyncl JJ, Sonders RC, Sperzel WD, Wynn M, Seely JH. Terazosin. *New Cardiovascular Drugs* 1986; Raven Press, N.Y.:1-17.
15. Luther RR, Glassman HN, Jordan DC, Sperzel WD. Efficacy of terazosin as an antihypertensive agent. *Am J Med* 1986;80(suppl 5B): 73-76.
16. Luther RR, Glassman HN, Spertzel WD, Steinberg FJ, Horton JK, Jordan DC. Terazosin: A new alpha₁-blocker for the treatment of hypertension: a review of randomized, controlled clinical trials of once-daily administration as monotherapy. *J. Hypertension* 1986;4 (suppl 5):S494-S497.
17. McNeil JJ, Drummer OH, Conway EL, Workman BS, Louis WJ. Effect of age on pharmacokinetics of and blood pressure responses to prazosin and terazosin. *J. Cardiovasc Pharmacol* 1987;10(2):168-175.
18. Mersey JH, Abraham PA, Arnold JD, *et al.* Long-term experience with terazosin for treatment of mild to moderate hypertension. *Am J Med* 1986;80(suppl 5B):68-72.
19. Rudd P, Berenson G. Brown M, *et al.* Cumulative experience with terazosin administered in combination with diuretics. *Am J Med* 1986;80(suppl 5B):49-54.
20. Ruoff G, Cohen A, Hollifield JW, McCarron DA. Comparative trials of terazosin with other antihypertensive agents. *Am J Med* 1986;80(suppl 5B):42-48.
21. Ruoff G, Dietz AJ, Keilson L, Lunn J, McCarron DA, Nash DT. Effect of withdrawal of terazosin therapy in patients with hypertension. *Am J Med* 1986; 80(suppl 5B):35-41.
22. Sonders RC. Pharmacokinetics of terazosin. *Am J Med* 1986;80(suppl 5B):20-24.
23. Sperzel WD, Glassman HN, Jordan DC, Luther RR. Overall safety of terazosin as an antihypertensive agent. *Am J Med* 1986;80(suppl 5B):77-81.
24. Titmarsh S, Monk JP. Terazosin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. *Drugs* 1987;33:461-477.

PART III: CONSUMER INFORMATION**HYTRIN[®]
terazosin hydrochloride**

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

ABOUT THIS MEDICATION**What the medication is used for:**

HYTRIN[®] is used to treat:

- Hypertension (high blood pressure)
- Benign prostatic hyperplasia (enlargement of the prostate gland)

HYTRIN[®] 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. HYTRIN[®] 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 HYTRIN[®].

What it does:

HYTRIN works by relaxing blood vessels so that blood passes through them more easily. This helps to lower blood pressure.

HYTRIN[®] 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:

HYTRIN[®] should not be used if you are allergic to any component of HYTRIN[®], including active ingredient and non-active ingredients.

What the medicinal ingredient is:

Terazosin hydrochloride

What the important nonmedicinal ingredients are:

Corn starch, lactose, magnesium stearate, povidone (for 1, 2, 5 mg only), pregelatinized starch (for 10 mg only) and talc. Also contains FD&C yellow No. 6 (for 2 mg), iron oxide (for 5 mg) and FD&C blue No. 2 (for 10 mg).

What dosage forms it comes in:

If your doctor prescribed the Starter Pack, it is important to complete the Starter Pack as indicated before starting your HYTRIN[®] prescription.

HYTRIN[®] is a tablet and is available in the following four strengths: 1 mg, 2 mg, 5 mg and 10 mg.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

- **HYTRIN[®] should not be used if you have been diagnosed with micturition syncope.**

BEFORE you use HYTRIN[®] talk to your doctor or pharmacist if:

- you have low blood pressure.
- you are using VIAGRA[®] (sildenafil), CIALIS[®] (tadalafil) or LEVITRA[®] (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.

You should not drive, operate heavy machinery, or do any hazardous task, until you are used to the effects of the medication. You should also avoid situations where injury could result should syncope occur during initiation of terazosin therapy. If you begin to feel dizzy, sit or lie down until you feel better.

INTERACTIONS WITH THIS MEDICATION

In general, you should avoid the use of phosphodiesterase (PDE5) inhibitors such as VIAGRA[®] (sildenafil), CIALIS[®] (tadalafil) or LEVITRA[®] (vardenafil) when taking HYTRIN[®] due to the risks of developing serious hypotension (low blood pressure).

Administration of HYTRIN[®] with verapamil (*i.e.*, ISOPTIN[®], TARKA[®] or CHRONOVERA[®]) to hypertensive patients may result in low blood pressure and/or a rapid heart beat.

Do not take these drugs with HYTRIN[®] without your doctor's advice.

PROPER USE OF THIS MEDICATION

Usual dose:

Follow your doctor's instructions very carefully about how to take HYTRIN[®]. 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 HYTRIN[®], you should have regular check-ups to evaluate your progress regarding your BPH and to monitor your blood pressure.

Overdose:

If you or someone you know accidentally takes more than stated dose, contact your doctor immediately or go to the nearest hospital with the tablets. Tell your doctor or hospital how much was taken. Treat even small overdoses seriously.

Missed Dose:

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

Never double-up on a missed dose.

Talk to your doctor if you have not taken HYTRIN[®] 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.

HYTRIN[®] 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 HYTRIN[®] at bedtime. If you take HYTRIN[®] 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 HYTRIN[®].

Other side effects with HYTRIN[®] include back pain, constipation, diarrhea, drowsiness or sleepiness, dry mouth, flatulence, headache, impotence, indigestion, libido decreased, nasal congestion, nausea, "puffiness" of the feet or hands, swelling, urinary frequency, urinary incontinence primarily reported in postmenopausal women, urinary tract infection, weakness or weight gain.

Discontinue your medication and inform your physician if you experience any of the following: anxiety, difficulty breathing/shortness of breath, heart palpitations, rash, drowsiness/sleepiness sweating, vomiting, blurred or hazy vision, weakness, allergic reaction, chest pain, decreased blood pressure or low blood pressure, permanent erection, unknown bruising or increased bleeding after a cut.

Check with your physician or pharmacist if you experience any unexpected effects, or are concerned by the above side effects.

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

| Symptom / effect | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|--|-------------------------------------|--------------|---|
| | Only if severe | In all cases | |
| Abnormal, Irregular or Rapid Heartbeat (Palpitation) | | | ✓ |
| Allergic Reaction | | | ✓ |
| Anxiety | | | ✓ |
| Blurred or Hazy Vision | | | ✓ |
| Chest pain | | | ✓ |
| Decreased Blood Pressure or Low Blood Pressure | | | ✓ |
| Depression | ✓ | | |
| Difficulty breathing or Shortness of Breath | | | ✓ |

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

| | | | |
|--|---|--|---|
| Drowsiness or Sleepiness | | | ✓ |
| Fainting | | | ✓ |
| Joint Inflammation or Joint Pain | ✓ | | |
| Permanent Erection | | | ✓ |
| Rash | | | ✓ |
| Sweating | | | ✓ |
| Unknown Bruising or Increased Bleeding after a Cut | | | ✓ |
| Vomiting | | | ✓ |
| Weakness | | | ✓ |

Check with your pharmacist or doctor **immediately**, if you experience any of the above symptoms of the serious side effects.

HOW TO STORE IT

Keep HYTRIN[®] and all other medicines out of reach of children.

HYTRIN[®] tablets should be stored at 15°C to 25°C.

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

It is important to keep the HYTRIN[®] in the original package.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: cadmp@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.abbott.ca>

or by contacting the sponsor, Abbott Laboratories, Limited, at: 1-800-361-7852

This leaflet was prepared by Abbott Laboratories, Limited.

Last revised: June 15, 2006.