Early detection of stage A prostate carcinoma: Combined use of prostate-specific antigen and transrectal ultrasonography

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We prospectively studied 103 men who had normal results on digital prostate examinations but had bladder outlet obstruction secondary to prostatic hypertrophy and needed transurethral prostatectomy. All men underwent a preoperative transrectal ultrasonographic examination of the prostate and prostate-specific antigen (PSA) level determination. A total of 30 cancers were ultimately detected, 22 (73%) of which were detected preoperatively by either an abnormal ultrasonogram or elevated PSA levels (or both). Eight of these men were spared transurethral prostatectomy and had definitive treatment based on transrectal biopsy and appropriate staging evaluation. For PSA and ultrasonography combined, the sensitivities and negative predictive values for cancer (92% and 94%, respectively) were superior to the specificities and positive predictive values (71% and 64%, respectively). The combined use of both studies is recommended to rule out cancer in candidates for prostatectomy

but not to routinely screen the general male population older than 40 years.

(Key words: Prostate, prostate carcinoma, prostate-specific antigen, transrectal ultrasonography of the prostate)

Prostate cancer is the most common tumor in men and is the third leading cause of cancer death in American men.¹ Historically, the diagnosis has relied on palpation of an abnormal gland or unexpected discovery after simple prostatectomy (suprapubic or transurethral) for supposedly benign prostatic hypertrophy. This latter category has represented stage A prostate cancer. In 1965, Denton and coauthors² suggested that approximately 20% of prostates removed for benign disease would have carcinoma. If one considers the many transurethral prostatectomies performed in the United States alone, 20% represents a significant number of newly diagnosed malignancies.

Since the development of transrectal ultrasonography, Lee and associates³⁻⁵ have implied a possible role for this modality in detecting nonpalpable prostate cancer. Others have relegated its use to staging local disease and monitoring responses to various forms of treatments.⁶ The same controversies appear to exist for prostate-specific antigen (PSA) deter-

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mination. Stamey and colleagues^{7,8} have very nicely documented the role of PSA determination in follow-up to treatment in many situations. However, PSA alone may not be a highly reliable marker to detect prostate cancer, because elevations can occur with prostatitis and even enlarged benign glands.

The availability of transrectal ultrasonography and PSA has prompted others to study their usefulness in detecting nonpalpable prostate cancer.^{4,9,10} These studies base the accuracy of both modalities on tissue obtained merely from transrectal or transperineal biopsy. None have used the final tissue diagnosis of prostatectomy specimens in patients with glands normal to palpation. As a result, we have tried to resolve some of the controversies by combining PSA values with transrectal ultrasonography results before prostatectomy and clinically correlate these data with the presence or absence of carcinoma not only in the biopsy tissue but also in the prostatectomy specimens. In so doing, we believe that a more accurate assessment of the specificity and sensitivity of these two modalities in the early detection of stage A prostate cancer can be made.

Materials and methods

Participants in this prospective study were selected from more than 500 eligible patients. The 103 men chosen, who were between the ages of 54 and 89 (mean, 71) years, were those whose prostates were judged normal on digital examination by at least two of us. All men were also candidates for transurethral resection of the prostate (TURP) because of outlet obstruction secondary to prostatic hypertrophy. These conclusions were decided by history, urine flowmetry, postvoid residual volume determinations, and cystoscopy in selected patients. Others were excluded because of urinary tract infection, prostates suspected to be abnormal, or clinical evidence of prostatitis.

Before digital rectal examination or urethral manipulation, a serum PSA level was obtained. The PSA value was determined by the Tandem-R assay (Hybritech Inc, San Diego, Calif). A urinalysis and digital rectal examination were subsequently performed.

Once the PSA results were reported, the patients were scheduled to undergo transrectal ultrasonographic examinations of the prostate. All studies were performed on an outpatient basis. The men were

instructed to take a Fleet enema the night before the examination.

Ultrasonography was performed in real time with the Brüel and Kjaer type 1846 scanner and independent transaxial and sagittal probes. Transaxial scanning was done with a type 1850 7 MHz probe (focal range 2 to 5 cm, 90-degree angle) beginning at the seminal vesicles and proceeding to the prostatic apex. Sagittal scanning was performed with a type 8537 section scanning probe. The prostate was first viewed in the midsagittal plane; thereafter, each side was viewed independently with and without magnification on the ultrasound monitor.

If the PSA value was elevated or if the ultrasonogram was suggestive of carcinoma (hypoechoic or mixed), the patient underwent a transrectal biopsy of the prostate.

The ultrasound-guided biopsy was done with a needle guide attached to the sagittal probe between two condoms. Prostatic core biopsy specimens were obtained with an 18-gauge Biopsy needle (Bard Urological Division, C. R. Bard, Inc., Covington, Ga) with the assistance of a Biopsy gun (Uppsala, Sweden). When the ultrasonogram showed an abnormality, the biopsy was performed in the region suspected to be abnormal. If only the PSA level was elevated (>4 ng/mL), two random biopsy specimens were taken from each side of the gland. Before the biopsy, patients received 500 mg of ciprofloxacin orally and were instructed to take two additional doses at 12-hour intervals after biopsy.

Patients whose biopsy results indicated malignancy underwent staging evaluation (bone scan, computed tomography, magnetic resonance imaging of the pelvis). Treatment was then based on the results of this evaluation. All other patients underwent transurethral prostatectomies as planned using the usual modern fiberoptic resection equipment. In cases where carcinoma was detected on TURP specimens and missed on biopsy, the patients were staged and treated accordingly.

The staging system for ultrasound-diagnosed malignancies was the modification of the Whitmore system proposed by Lee and co-worker.⁴ Conventional staging of TURP specimens was done by the Jewitt-Whitmore system.¹¹

The equations used to calculate sensitivity, specificity, positive predictive value, and negative predictive value,⁴ as well as accuracy were the following:

$\text{Sensitivity} = \frac{\text{true-positive results}}{\text{true-positive results} + \text{false-negative results}}$

$\text{Specificity} = \frac{\text{true-negative results}}{\text{true-negative results} + \text{false-positive results}}$

Table 1
Summary of All 30 Cancers Discovered

Stage of carcinoma*	Patients		PSA† range, ng/mL	Gleason score range
	No.	Age range, yr		
A1	9	66 to 85	1.9 to 7.9	4 to 6
A2	8	62 to 80	2.9 to 106.0	4 to 8
uA	7	66 to 79	6.4 to 50.0	4 to 7
D1	4	68 to 83	21.2 to 125.0	5 to 9
D2	2	79 to 81	54.0 to 4400.0	7 to 9

*Jewitt-Whitmore¹¹ and Lee⁴ staging systems.
†PSA = prostate-specific antigen.

Table 2
Ultrasound Features of All Carcinomas (n = 30)

Stage of carcinoma*	Hypoechoic	Mixed	Isoechoic
A1	5	2	2
A2	6	0	2
uA	6	1	0
D1	3	1	0
D2	1	1	0

*Jewitt-Whitmore¹¹ and Lee⁴ staging systems.

tal biopsy in 22 men. Ultimately, 30 cancers were detected in the biopsy and prostatectomy specimens. The cancer stages and ranges of patient ages, PSA values, and Gleason scores are summarized in Table 1. In this group, there were only four patients with normal PSA values (three stage A1 and one stage A2). No direct

Positive predictive value = true-positive results/(true-positive results + false-positive results).

Negative predictive value = true-negative results/(true-negative results + false-negative results).

Accuracy = (true-positive results + true-negative results)/(true-positive results + true-negative results + false-positive results + false-negative results).

All data were then calculated as percentages by multiplying each score by 100.

Results

A total of 71 (68.9%) patients underwent a transrectal biopsy because of an abnormal ultrasonogram or elevated PSA value (or both). Cancer was detected preoperatively by transrec-

correlation existed between stage of cancer, Gleason score, and PSA values. The widest variation in PSA values (2.9 ng/ml to 106 ng/mL) seemed to be in the stage A2 carcinomas rather than stage A1 because none of the patients with stage A1 disease had PSA values above 8 ng/mL.

The ultrasonographic features of these cancers are depicted according to stage in Table 2. Only four (13%) malignant lesions were isoechoic (two stage A1 and two stage A2). Five (17%) had mixed echoic patterns, and the remaining 21 (70%) were hypoechoic. In three patients with purely hyperechoic glands considered normal, no cancer was detected on TURP.

Figure. Percentage of patients with an abnormality on ultrasonographic study or prostate-specific antigen assay and percentage of cancers detected by each test alone and combined.

Table 3
Treatment and Stage of Nine Carcinomas
Diagnosed by Transrectal Biopsy
(No Transurethral Resection
of Prostate Performed)

Age of patient	Stage of carcinoma*	Treatment
67	uA	Surveillance
62	uA	External beam radiation therapy
70	uA	Radical prostatectomy
79	uA	External beam radiation therapy
78	uA	External beam radiation therapy
75	uA	External beam radiation therapy
84	uA	External beam radiation therapy
79	D2	Orchiectomy
81	D2	Orchiectomy + flutamide

*Jewitt-Whitmore¹¹ and Lee⁴ staging systems.

Overall, 51 patients had ultrasonograms showing abnormality, and 26 of these had cancer. Of the 54 patients with elevated PSA values, 26 had cancer. Only 36 patients had both an ultrasonogram showing abnormality and an elevated PSA value; of these, 23 ultimately had cancer detected. The relative yield of each test alone and combined are graphically illustrated in the Figure.

Of these 36 patients, nine could have their cancer staged and be treated on the basis of biopsy results, thereby avoiding TURP. Only one of these nine patients refused treatment and TURP after his staging evaluation. Table 3 demonstrates the stages and treatment offered to these nine patients who did not require immediate TURP for obstructive symptoms. The other cancer patients who were subjected to TURP subsequently underwent staging and were treated accordingly (surveillance or external beam radiation therapy).

A total of 34 patients had ultrasonograms showing normal results (isoechoic) and normal PSA values. Only two (6%) of these patients had cancer noted on TURP (stage A1). The overall true- and false-positive and true- and false-negative results are listed in Table 4. These

results are based on biopsy results alone. Table 5 reviews the true- and false-positive and true- and false-negative results for transrectal ultrasonography and PSA alone and combined based on tissue results from the needle biopsy and TURP specimens.

The sensitivities, specificities, positive and negative predictive values, and accuracy of ultrasonography and PSA values alone and in combination were then calculated and are listed in Table 6. Calculations were performed on the basis of values reported in Tables 4 and 5.

The patients had no major complications from the transrectal needle biopsies. No urinary tract infections nor urosepsis developed. Only 15 patients reported having transient hematuria or rectal bleeding, which resolved spontaneously within 24 hours. Two patients had hemospermia, which was also self-limited in each case.

As for the patients who were treated for cancer on the basis of biopsy, primary fibrinolysis developed in one patient after orchiectomy for treatment of stage D2 cancer, which was discovered by transrectal ultrasonographic examination and elevated PSA (4400 ng/mL). Scrotal hematoma also developed. The patient was treated conservatively with aminocaproic acid (to reverse the coagulopathy), scrotal elevation,

Table 4 Correlation of All True- and False-Positive and True- and False-Negative Values for Prostate-Specific Antigen and Ultrasound Study Results With Pathologic Results From Needle Biopsy Specimens Alone (n = 71)		
Value	Prostate-specific antigen	Ultrasound Study
True-positive*	21	22
True-negative†	16	19
False-positive‡	33	29
False-negatives§	1	1
*Abnormal study with cancer detected. †Normal study with no cancer detected. ‡Abnormal study with no cancer detected. §Normal study with cancer detected.		

and ice. The coagulopathy and hematoma resolved within 10 days.

To date, no complications from the TURP, radiation therapy, and radical prostatectomy have been reported.

Discussion

The incidental discovery of a small amount of cancer in the prostate after suprapubic or transurethral resection (stage A1) was once considered insignificant. Follow-up usually in-

Table 5 Correlation of All True- and False-Positive and True- and False-Negative Values for Prostate-Specific Antigen and Ultrasound Study (or Both) With Pathologic Results From Transurethral Resection of the Prostate and Needle Biopsy Specimens Combined			
Value	Prostate-specific antigen (n = 103)	Ultrasound study (n = 103)	Combined modalities (n = 70)
True-positive*	26	26	23
True-negative†	45	48	32
False-positive‡	28	25	13
False-negatives§	4	4	2
*Abnormal study with cancer detected. †Normal study with no cancer detected. ‡Abnormal study with no cancer detected. §Normal study with cancer detected.			

Table 6
Calculated Sensitivities, Specificities, Positive and Negative Predictive Values, and Accuracy for Biopsy Specimens Alone (B) and Final Tissue from Transurethral Resection of Prostate and Biopsy (TURP + B)*

Value	Prostate-specific antigen (PSA)		Ultrasound study (US)		PSA + US
	B	TURP + B	B	TURP + B	TURP + B
Sensitivity, %	95	87	96	87	92
Specificity, %	33	62	40	66	71
Positive predictive value, %	39	48	43	51	64
Negative predictive value, %	94	92	95	92	94
Accuracy, %	52	69	58	72	79

*Based on data from Tables 4 and 5.

cluded a second or "staging" TURP. Recently, Epstein and associates¹² reported that 18 (86%) of 21 of their younger patients with stage A1 disease who were treated by radical prostatectomy had residual tumor. Another concern is whether TURP can cause dissemination of local disease.^{13,14} Because of these issues, it may be prudent to diagnose occult stage A adenocarcinoma of the prostate before performing simple prostatectomy so that a more definitive treatment plan may be substituted.

Also, if McNeal¹⁵ is correct that only cancers attaining a critical volume of 1 mL or 9 mm in diameter are clinically significant and since ultrasonography can usually only detect lesions larger than 9 to 10 mm in diameter, perhaps only those clinically significant cancers worthy of treatment would be detected. Currently, the only method other than ultrasonography that seems reasonable to use for searching for occult prostate cancer is serum PSA determination. Although neither procedure can be advocated as all-sufficient for the early diagnosis of prostate cancer, it may be postulated that a combination of both studies can detect a majority of early, unsuspected cancers before simple prostatectomy.

Because Lee and associates¹⁶ have demonstrated that most cancers of the prostate are hypoechoic, we used this criterion in our search for occult prostate cancer. In our series, 21 out of 30 cancers did indeed appear as hy-

poechoic. The remainder were either of mixed (5) echogenicity or isoechoic (4). However, we had 25 ultrasonograms that showed no abnormality, in which cases no cancer was detected on biopsy or TURP. This finding accounts for the difference in specificities noted by Lee and coworkers⁴ and those noted by us. Table 7 directly compares their data with ours.

It is difficult to account for the major disparity between specificities (94% vs 40%) other than to state that performance of transrectal ultrasonography is operator-dependent and judgment on areas of altered echogenicity may vary between observers. This view has been shared by Gluck and coauthors,¹⁷ who thereby accounted for the 40% specificity with ultrasonographic examination in their patients. Because of the discrepancy in specificities, we believed that combining results of ultrasonography with a more objective value (PSA) could generate a greater accuracy in detecting nonpalpable prostate cancer. As noted in Table 6, we were able to gain modest improvement in our accuracy and positive predictive value by using the combination of tests.

Also, the specificities for PSA and ultrasonography were greatly improved by reviewing all tissue (TURP as well as biopsy specimen) rather than biopsy alone. In a recent study of 1035 men with PSA and transrectal ultrasonography used as a screen for occult prostate cancer, Cooner and associates¹⁰ reported

a 35.2% chance of having adenocarcinoma of the prostate with an abnormal finding on ultrasonography and elevated PSA. Positive predictive values were lower when either PSA determination or ultrasonography was used alone: 18.2% and 19.6%, respectively. These data, however, did not include pathologic abnormalities on prostatectomy specimens because no patients with negative findings on biopsy or an ultrasonographic study showing no abnormality had a TURP performed. If they did, we can only speculate that their reported values might have been higher.

In our series, we were able to improve our positive predictive value by 13% with a combination of tests rather than ultrasonography alone (64% vs 51%) as judged by final pathologic study. We similarly observed a 16% improvement in positive predictive value by combining the PSA determinations and ultrasonography results rather than using PSA values alone (64% vs 48%).

The major problem with PSA determinations in our study occurred in cases where the ultrasonographic finding was considered normal but the PSA level was elevated. No discrete region in the prostate can be targeted for biopsy; therefore, random biopsy was performed from each side of the gland. Overall, 28 PSA values were elevated when no cancer was detectable on biopsy or TURP. The highest PSA value for benign disease was 53.8 ng/mL noted with a 110-g TURP specimen.

In a fairly recent report, Agatstein and colleagues¹⁸ have advocated the routine use of needle aspiration of the prostate to detect stage A cancer. They found that the technique was simple and without complications. It was of greater value in detecting stage A2 versus A1 cancer. However, rather than subject every man to biopsy before TURP, we recommend biopsy for patients at greater risk of having carcinoma (elevated PSA value or abnormality on ultrasonogram). In our patients, we used prophylactic antibiotics as well as the Biopsy gun, which resulted in minimal patient discomfort and no significant complications. This technique also provides a better sample of tissue for pathologic examination rather than cytologic study alone.

Table 7
Comparison of Sensitivity, Specificity, and Predictive Values for Ultrasound Study for Lee and Associates⁴ and Fiorelli and Colleagues

Value	Lee and associates ⁴ (n = 784)	Fiorelli and colleagues (n = 103)
Sensitivity, %	91	96
Specificity, %	94	40
Positive predictive value, %	31	43
Negative predictive value, %	100	95

As previously stated, we were unable to find any direct relationship between the PSA values, stages of disease, and Gleason scores. However, we use PSA values posttreatment to monitor response to therapy or progression of disease. Stamey and coauthors^{7,8,19} documented these advantages in their reviews of patients treated by radical prostatectomy, radiation therapy, and orchiectomy.

A final issue is whether it is prudent to evaluate all men and detect early-stage prostate cancer. Although a majority of men with adenocarcinoma of the prostate usually die of other causes, younger men may die of metastatic cancer.¹⁰ Until we are able to predict the exact biologic activity of certain subsets of tumor cells, can we choose to ignore occult malignancies, especially in younger, healthy men? Now that we have developed transrectal ultrasonography and discovered PSA, how do we use them?

Conclusion

With the foregoing difficult questions in mind and in keeping with the data we have presented, we believe that transrectal ultrasonography and PSA determinations should not be used as a generalized screen for men older than 40 years. However, both studies should be conducted on patients before prostatectomy for supposedly benign disease.

Most patients who are medical candidates for TURP are capable of undergoing treatment for localized prostate cancer if it is diagnosed.

Therefore, patients at high risk of having carcinoma (elevated PSA level or abnormality on ultrasonogram [or both]) should then routinely undergo biopsy as no major complications have occurred to date. In so doing, a more definitive treatment plan can be formulated in patients with carcinoma, a few of whom may even be spared simple prostatectomy. However, until more experience is gained in ultrasonographic interpretation and perhaps more refined limits on PSA values predictive of carcinoma, there will still be a certain percentage of unnecessary biopsies performed and even a few missed carcinomas. The likelihood of having prostate cancer with normal results on the ultrasonogram and normal PSA values would seem to be very low, as evidenced by our series (2 of 34 patients).

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Information for patients: Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Drug Interactions: Preliminary evidence exists that concurrent ketoconazole or macrolide administration significantly alters the metabolism of terfenadine. Concurrent use of Seldane with ketoconazole or troleandomycin is not recommended. Concurrent use of other macrolides should be approached with caution.

Carcinogenesis, mutagenesis, impairment of fertility: Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies: In rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C: There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use: Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting			
	Controlled Studies* Seldane Placebo N=781 N=665		All Clinical Studies** Seldane Placebo N=2462 N=1478	
Central Nervous System				
Drowsiness	9.0	8.1	18.1	8.5
Headache	6.3	7.4	3.8	15.8
Fatigue	2.9	0.9	5.8	4.5
Dizziness	1.4	1.1	1.0	1.5
Nervousness	0.9	0.2	0.6	1.7
Weakness	0.9	0.6	0.2	0.6
Appetite Increase	0.6	0.0	0.0	0.5
Gastrointestinal System				
Distress (Abdominal)				
Nausea				
Vomiting, Change in Bowel Habits	4.6	3.0	2.7	7.6
Eye, Ear, Nose, and Throat				
Dry Mouth/Nose/Throat	2.3	1.8	3.5	4.8
Cough	0.9	0.2	0.5	2.5
Sore Throat	0.5	0.3	0.5	3.2
Epistaxis	0.0	0.8	0.2	0.7
Skin				
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 days.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

Rare reports of severe cardiovascular adverse effects have been received which include arrhythmias (ventricular tachycardia, torsades de pointes, ventricular fibrillation), hypotension, palpitations, and syncope. In controlled clinical trials in otherwise normal patients with rhinitis, at doses of 60 mg b.i.d., small increases in QTc interval were observed. Changes of this magnitude in a normal population are of doubtful clinical significance. However, in another study (N=20 patients) at 300 mg b.i.d., a mean increase in QTc of 10% (range -4% to +30%) (mean increase of 46 msec) was observed without clinical signs or symptoms.

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia (hair loss or thinning), anaphylaxis, angioedema, bronchospasm, confusion, depression, galactorrhea, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, paresthesia, photosensitivity, seizures, sinus tachycardia, sweating, tremor, urinary frequency, and visual disturbance.

In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis. In most cases available information is incomplete.

OVERDOSSAGE

Information concerning possible overdose and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

One tablet (60 mg) twice daily for adults and children 12 years and older. Product Information as of July, 1990. MARION MERRELL DOW INC. Prescription Products Division Kansas City, MO 64114

Impairment-free relief from the first dose through the season

SELDANE®

(terfenadine) 60 mg tablets bid for seasonal allergic rhinitis

Starts fast and lasts

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