

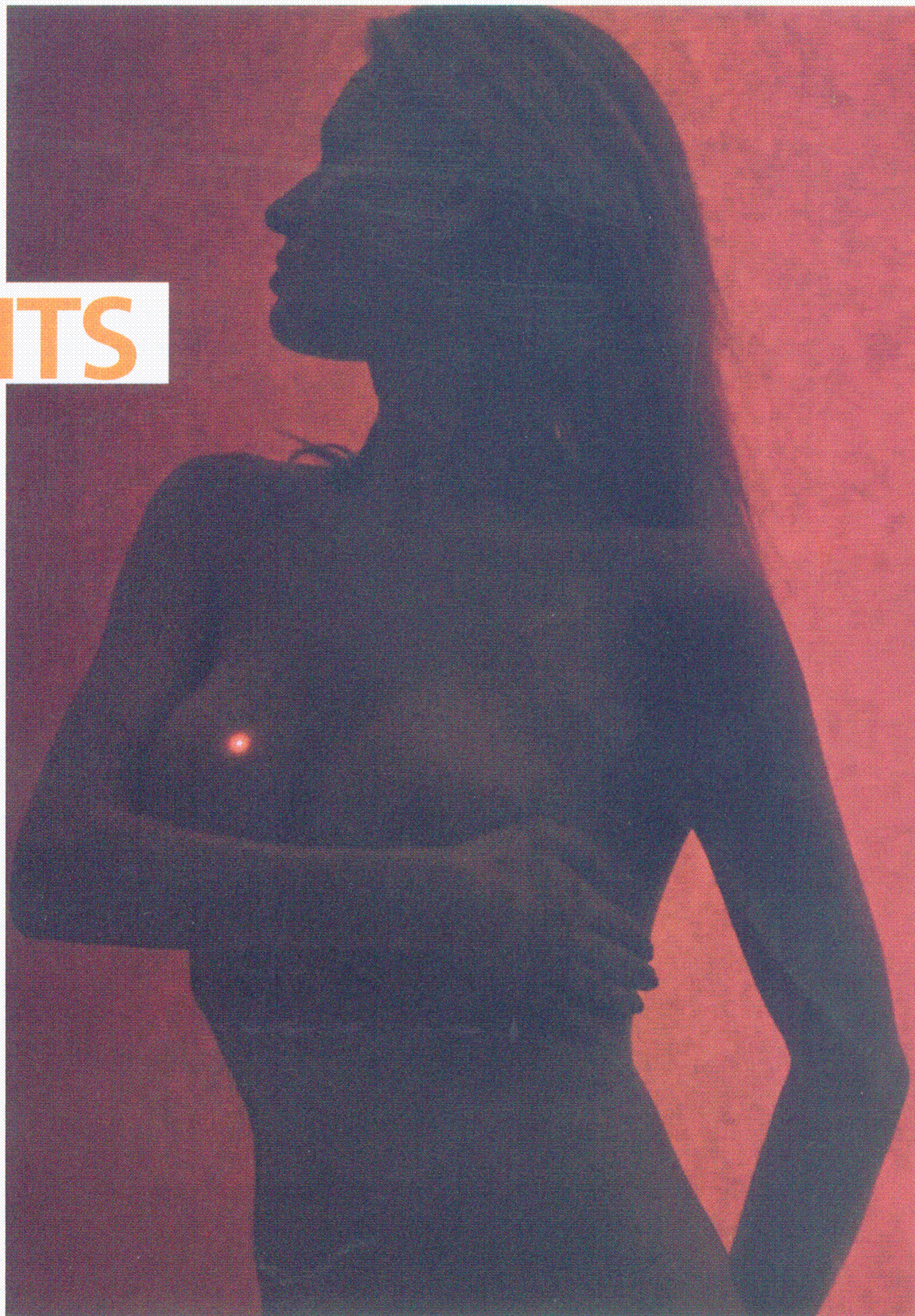
KINDER, GENTLER TREATMENTS FOR BREAST CANCER

Doctors are on the verge of determining which localized tumors will remain slow-growing, and which will become aggressive killers—and treatment will be revolutionized
By Kathleen McAuliffe

The days when mastectomies were routine are mercifully gone. But breast-cancer therapy can still be painful, protracted and disfiguring—and more doctors are acknowledging that, for many women, the cure can sometimes be worse than the disease.

This can be true for some breast cancers caught at the localized stage (meaning they have not broached the lymph nodes, a sign they have spread). These now constitute the majority—62 percent—of the estimated 203,000 breast-cancer cases diagnosed last year. It's even more poignant for the additional 54,000 women whose malignancies were caught so early that the minute cluster of cancerous cells had yet to break through the milk duct, a condition known as ductal-cell carcinoma in situ, or DCIS. Doctors widely acknowledge that some localized cancers might be cured with surgery alone, sparing women radiation and chemotherapy; it might be possible one day to leave certain cases of DCIS in a woman's breast without endangering her. "In general, more women die *with* DCIS rather than because of it," says Julie Gralow, M.D., associate professor of medical oncology at the University of Washington in Seattle.

The problem is that, right now, no one knows which patients will be fine with less treatment. In



fact, new data suggests that tumor size and lymph-node involvement are not as powerful prognostic indicators as once thought. Small tumors can spread and kill, while large ones may stay localized. And left untreated, DCIS may evolve into an invasive cancer that can spread. Lacking a crystal ball, doctors must treat all cancers, no matter how tiny, as if they have the potential to be lethal. After surgery to remove the tumor, radiation is often recommended to reduce the risk of recurrence. If tests give any hint the cancer may behave more aggressively, surgery is typically followed by chemotherapy or other drug regimens notorious for their debilitating side effects.

But that could soon change. Now available, or in advanced testing, are treatments that promise to be less lengthy and minimize scarring. Better yet, medical

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researchers are rapidly developing molecular tools for predicting which tumors are likely to spread—which means doctors may one day be able to reserve the heavy artillery for more dangerous tumors, sparing many women harsh interventions. To be sure, more research is needed on these approaches, but experts are hopeful that better treatment options and easier choices for women are on the horizon.

MINIMALLY INVASIVE BIOPSIES

Seventy to eighty percent of biopsies come back benign. But all too often, finding out whether a suspicious lump is cancer has meant in-hospital surgery and a one- to two-inch scar. Now, a less invasive outpatient procedure, available at many teaching hospitals, cancer-care and breast-care centers and large private hospitals, allows women to obtain accurate results without general anesthesia or stitches. The new approach replaces

the scalpel with either a fine needle, core biopsy needle or a thin vacuum probe no bigger than a pencil. Using X rays or ultrasound for guidance, the instrument is inserted into the suspicious site and tissue removed by either a spring-loaded device or a vacuum-assisted apparatus called a Mammotome. The latter is typically recommended if the



Within five years, genetic tests will transform cancer diagnosis and management.

target is not a clearly defined mass or consists of calcifications, as several samples can be acquired with a single insertion.

Numerous studies show that the core-needle and Mammotome yield diagnoses just as accurate as a surgical biopsy, but with less scarring. The only thing left behind is a small puncture, reports Joshua Gross, M.D., chief of the division of breast imaging at Beth Israel Medical Center in New York City. If a woman has cystic breasts, calcifications or other conditions that may necessitate multiple biopsies, the advantage of a slim probe over the scalpel mounts. “I frequently see women whose breasts are distorted and crisscrossed with scars from surgical biopsies, and yet they didn’t even have cancer,” Gross says. “With the tools now available, detecting disease doesn’t have to be so damaging.”

GENETIC FINGERPRINTING OF TUMORS

In what scientists hailed as a landmark study last December in *The New England Journal of Medicine*, Dutch researchers reported exciting progress toward developing a test to predict which breast cancers will spread. Using microarrays (specialized chips that bind to genetic material), they screened breast tumors for activity of multiple genes and uncovered 70 genes

that looked promising for predicting patient outcomes. They then examined breast tumors from 295 mostly middle-aged women whose disease was confined to the breast or had spread no farther than the underarm lymph nodes. Among patients for whom the genetic test predicted a good prognosis, 85.2 percent remained cancer-free ten years later, as compared to 50.6 percent of women given a poor prognosis by the test.

The genetic signature appeared to be superior to traditional criteria for predicting outcomes, such as the size of the tumor, how it looks under a microscope, number of lymph nodes affected and estrogen receptors. Indeed, small tumors often had bad prognoses and large tumors good prognoses.

“The hope is this kind of molecular fingerprinting of tumors will help us identify who needs much less aggressive treatment,” says Todd Golub, M.D., who directs cancer genomics research at the Whitehead Institute/MIT Center for Genome Research in Cambridge, Massachusetts. “It may be that some tumors we’re currently treating with chemotherapy or radiation could be cured with surgery alone.” In the case of DCIS, he says, it may even be possible to do nothing at all for carefully selected patients.

He and other scientists caution that the prognostic accuracy of genetic fingerprinting is not yet powerful enough for doctors to recommend withholding therapy. But with many pharmaceutical companies and academics studying the technology, rapid advances are widely anticipated.

“In the next four to five years, these arrays will be in wide clinical use and will transform cancer diagnosis and management,” says Marc Lippman, M.D., a breast-cancer expert and chair of the department of internal medicine at the University of Michigan Medical School. Another way the technology might potentially

be deployed, he says, is for women at high risk for recurrence to get treatment tailored to the genetic underpinnings of their disease. “We have about one hundred anti-cancer agents that all affect different tumor-growth pathways,” he says. “These arrays should enable us to go straight to the drug, or combination of drugs, that will be most effective.”

NONSURGICAL LUMPECTOMIES

Using radio-frequency energy, lasers and freezing methods, it’s possible to destroy tumors from the inside, without cutting open the breast. This promises far superior cosmetic results and faster recuperation times. These slice-free techniques are still in clinical testing, but if successful, could be offered on an outpatient basis to many women who currently qualify for a surgical lumpectomy.

Some of these methods could be clinically available as soon as five years from now, says Eva Singletary, M.D., professor of surgical oncology at Houston’s University of Texas MD Anderson Cancer Center, which recently participated in a multi-center trial of radio-frequency energy. In the study, doctors used ultrasound to guide a needle into the tumors of 30 patients. Once it’s properly inserted, prongs splay out from

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the tip of the needle and begin vibrating, causing frictional heat that cooks the tumor from the inside. To test the effectiveness of the procedure, all the patients then received either a lumpectomy or a mastectomy, and the tissue was examined for signs of cancer. Except for four patients (including two in whom the probe could not be accurately placed), "We're seeing one hundred percent destruction of the cancer cells," says Singletary. "There's a lot of enthusiasm about this." In her next trial, women treated by the technique will be able to forego a lumpectomy or mastectomy afterward, but multiple needle biopsies will monitor for the presence of cancer cells.

Meanwhile, at Rush-Presbyterian-St. Luke's Medical Center in Chicago, similar advances are being reported by Kambiz Dowlat, M.D., and colleagues using a thin fiber-optic cable inserted into the breast to zap tumors targeted with a laser. Still another group is making progress using a pencil-thin probe to pierce the breast and freeze the tumor with argon gas.

To date, these methods have produced almost no side effects, save for one minor skin burn. Nonetheless, not all women will be good candidates. In general, experts say nonsurgical approaches work best with small tumors that can be seen clearly on a mammogram; when heating methods are used, tumors cannot be close to the surface of the skin or chest muscle.

RADIATION: SHORT AND SWEET

Radiation after a lumpectomy reduces the risk of a local recurrence by 10–30 percent, but it can be an ordeal. Five days a week, for six and a half consecutive weeks, women must go to the hospital—a big inconvenience for working women and those who have to drive long distances to obtain treatment. That drawback sent doctors looking for a swifter way to achieve the same outcome, and new findings suggest they're succeeding. In patients who had small tumors that were completely removed, early data indicates that radiation can be compressed into less than a week without increasing the risk of relapse. What's more, these patients are less likely to suffer such common side effects as fatigue, redness and unwanted radiation exposure to healthy surrounding tissues.

"The vast majority of tumors come back right where they used to be," says Robert Kuske, M.D., professor of human oncology at the University of Wisconsin in Madison. By focusing radiation only at the site where the risk of recurrence is greatest, he says, it's possible to shorten treatment.

Using a treatment similar to brachytherapy for prostate-cancer patients, Kuske numbs the breast with local anesthesia and then guides 12–30 thin catheters around the lumpectomy site. A tiny radioactive seed is run down into the tip of each and treatment delivered for ten to fifteen minutes twice daily for a total of four to five days. (The catheters remain in place during this time.) For nearly twelve years, Kuske has used this procedure to treat approximately 350 patients—so far, with excellent results. After an average of six years, his patients have actually had a slightly lower rate of recurrence of cancer than would be expected in the same period with standard radiation. Most local recurrences appear within the first five years; Kuske plans to track all patients for a full ten years. ►

Brief Summary of Prescribing Information as of November 2000

ALLEGRA® (fexofenadine hydrochloride) Capsules and Tablets

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis

ALLEGRA is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

Chronic Idiopathic Urticaria

ALLEGRA is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.

CONTRAINDICATIONS

ALLEGRA is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Drug Interaction with Erythromycin and Ketoconazole

Fexofenadine hydrochloride has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine hydrochloride with ketoconazole and erythromycin led to increased plasma levels of fexofenadine hydrochloride. Fexofenadine hydrochloride had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine hydrochloride 120 mg twice daily (two times the recommended twice daily dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when patients were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table.

Effects on steady-state fexofenadine hydrochloride pharmacokinetics after 7 days of co-administration with fexofenadine hydrochloride 120 mg every 12 hours (two times the recommended twice daily dose) in normal volunteers (n=24)

Concomitant Drug	C _{max,SS} (Peak plasma concentration)	AUC _{0-12h} (Extent of systemic exposure)
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated *in vitro*, *in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. *In vivo* animal studies also suggest that in addition to increasing absorption, ketoconazole decreases fexofenadine hydrochloride gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Drug Interactions with Antacids

Administration of 120 mg of fexofenadine hydrochloride (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox[®]) decreased fexofenadine AUC by 41% and C_{max} by 43%. ALLEGRA should not be taken closely in time with aluminum and magnesium containing antacids.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine hydrochloride exposure (based on plasma area-under-the-concentration vs. time [AUC] values). No evidence of carcinogenicity was observed in an 18-month study in mice and in a 24-month study in rats at oral doses up to 150 mg/kg of terfenadine (which led to fexofenadine exposures that were respectively approximately 3 and 5 times the exposure from the maximum recommended daily oral dose of fexofenadine hydrochloride in adults and children).

In vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at an oral dose of 150 mg/kg of terfenadine (which led to fexofenadine hydrochloride exposures that were approximately 3 times the exposure of the maximum recommended daily oral dose of fexofenadine hydrochloride in adults).

Pregnancy

Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral doses of terfenadine up to 300 mg/kg (which led to fexofenadine exposures that were approximately 4 and 31 times, respectively, the exposure from the maximum recommended daily oral dose of fexofenadine in adults). There are no adequate and well controlled studies in pregnant women. Fexofenadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine (approximately 3 times the maximum recommended daily oral dose of fexofenadine hydrochloride in adults based on comparison of fexofenadine hydrochloride AUCs).

Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

The recommended dose in patients 6 to 11 years of age is based on cross-study comparison of the pharmacokinetics of ALLEGRA in adults and pediatric patients and on the safety profile of fexofenadine hydrochloride in both adult and pediatric patients at doses equal to or higher than the recommended doses.

The safety of ALLEGRA tablets at a dose of 30 mg twice daily has been demonstrated in 438 pediatric patients 6 to 11 years of age in two placebo-controlled 2-week seasonal allergic rhinitis trials. The safety of ALLEGRA for the treatment of chronic idiopathic urticaria in patients 6 to 11 years of age is based on cross-study comparison of the pharmacokinetics of ALLEGRA in adult and pediatric patients and on the safety profile of fexofenadine in both adult and pediatric patients at doses equal to or higher than the recommended dose.

The effectiveness of ALLEGRA for the treatment of seasonal allergic rhinitis in patients 6 to 11 years of age was demonstrated in one trial (n=411) in which ALLEGRA tablets 30 mg twice daily significantly reduced total symptom scores compared to placebo, along with extrapolation of demonstrated efficacy in patients ages 12 years and above, and the pharmacokinetic comparisons in adults and children. The effectiveness of ALLEGRA for the treatment of chronic idiopathic urticaria in patients 6 to 11 years of age is based on an extrapolation of the demonstrated efficacy of ALLEGRA in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar in children to that of adult patients.

The safety and effectiveness of ALLEGRA in pediatric patients under 6 years of age have not been established.

Geriatric Use

Clinical studies of ALLEGRA tablets and capsules did not include sufficient numbers of subjects aged 65 years and over to determine whether this population responds differently from younger patients. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Seasonal Allergic Rhinitis

Adults. In placebo-controlled seasonal allergic rhinitis clinical trials in patients 12 years of age and older, which included 2461 patients receiving fexofenadine hydrochloride capsules at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of fexofenadine hydrochloride (60 mg capsules twice daily), and that were more common with fexofenadine hydrochloride than placebo, are listed in Table 1.

In a placebo-controlled clinical study in the United States, which included 570 patients aged 12 years and older receiving fexofenadine hydrochloride tablets at doses of 120 or 180 mg once daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. Table 1 also lists adverse experiences that were reported by greater than 2% of patients treated with fexofenadine hydrochloride tablets at doses of 180 mg once daily and that were more common with fexofenadine hydrochloride than placebo. The incidence of adverse events, including drowsiness, was not dose-related and was similar across subgroups defined by age, gender, and race.

Table 1
Adverse experiences in patients ages 12 years and older reported in placebo-controlled seasonal allergic rhinitis clinical trials in the United States
Twice daily dosing with fexofenadine capsules
at rates of greater than 1%

Adverse experience	Fexofenadine 60 mg Twice Daily (n=679)	Placebo Twice Daily (n=671)
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Table 2
Once daily dosing with fexofenadine hydrochloride tablets
at rates of greater than 2%

Adverse experience	Fexofenadine 180 mg once daily (n=283)	Placebo (n=293)
Headache	10.6%	7.5%
Upper Respiratory Tract Infection	3.2%	3.1%
Back Pain	2.8%	1.4%

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride and placebo-treated patients.

Pediatric. Table 2 lists adverse experiences in patients aged 6 to 11 years of age which were reported by greater than 2% of patients treated with fexofenadine hydrochloride tablets at a dose of 30 mg twice daily in placebo-controlled seasonal allergic rhinitis studies in the United States and Canada that were more common with fexofenadine hydrochloride than placebo.

Table 2
Adverse experiences reported in placebo-controlled seasonal allergic rhinitis studies in pediatric patients ages 6 to 11 in the United States and Canada at rates of greater than 2%

Adverse experience	Fexofenadine 30 mg twice daily (n=209)	Placebo (n=229)
Headache	7.2%	6.6%
Accidental Injury	2.9%	1.3%
Coughing	3.6%	1.3%
Fever	2.4%	0.9%
Pain	2.4%	0.4%
Otitis Media	2.4%	0.0%
Upper Respiratory Tract Infection	4.3%	1.7%

Chronic Idiopathic Urticaria

Adverse events reported by patients 12 years of age and older in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies. In placebo-controlled chronic idiopathic urticaria clinical trials, which included 726 patients 12 years of age and older receiving fexofenadine hydrochloride tablets at doses of 20 to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. Table 3 lists adverse experiences in patients aged 12 years and older which were reported by greater than 2% of patients treated with fexofenadine hydrochloride 60 mg tablets twice daily in controlled clinical studies in the United States and Canada and that were more common with fexofenadine hydrochloride than placebo. The safety of fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria in pediatric patients 6 to 11 years of age is based on the safety profile of fexofenadine hydrochloride in adults and adolescent patients at doses equal to or higher than the recommended dose (see Pediatric Use).

Table 3
Adverse experiences reported in patients 12 years and older in placebo-controlled chronic idiopathic urticaria studies in the United States and Canada at rates of greater than 2%

Adverse experience	Fexofenadine 60 mg twice daily (n=186)	Placebo (n=178)
Back Pain	2.2%	1.1%
Sinusitis	2.2%	1.1%
Dizziness	2.2%	0.6%
Drowsiness	2.2%	0.0%

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or parosmia. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

OVERDOSAGE

Reports of fexofenadine hydrochloride overdose have been infrequent and contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg (six normal volunteers at this dose level), and doses up to 690 mg twice daily for 1 month (three normal volunteers at this dose level) or 240 mg once daily for 1 year (234 normal volunteers at this dose level) were administered without the development of clinically significant adverse events as compared to placebo.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine hydrochloride from blood (1.7% removed) following terfenadine administration. No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (110 times the maximum recommended daily oral dose in adults and 200 times the maximum recommended daily oral dose in children based on mg/m²) and up to 5000 mg/kg in rats (230 times the maximum recommended daily oral dose in adults and 400 times the maximum recommended daily oral dose in children based on mg/m²). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (300 times the maximum recommended daily oral dose in adults and 530 times the maximum recommended daily oral dose in children based on mg/m²).

Prescribing Information as of November 2000

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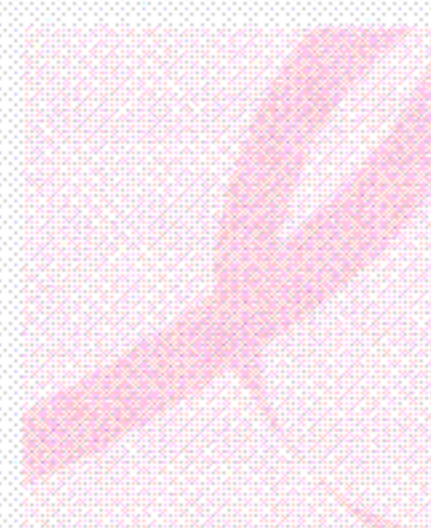
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Prevention and

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To deliver brachytherapy to the breast more efficiently, Kuske and other doctors are now employing a recently approved device called MammoSite. It consists of a single catheter tipped by a balloon that holds the radioactive seed. For appropriate patients, say experts, the device is a lot easier to insert than multiple catheters, and requires a single small incision; treatment lasts about the same amount of time. So far, however, MammoSite patients have only been followed for two and a half years.

Another timesaving alternative to the standard six-and-a-half-week radiation regimen—and one that has the further advantage of being totally noninvasive—is being developed by Silvia Formenti, professor and chairman of radiology oncology at New York University School of Medicine. With her approach, the patient is placed on her stomach on a table with a hole through which the breast drops down. Instead of radiating the whole breast, a higher than normal dose of radiation is focused only on the area at highest risk of a recurrence. In this way, treatment can be completed in five 15-minute sessions given every other day.

Ideally, women who get partial breast radiation with seeds or an external beam should enroll in clinical trials, says Formenti, and have a tumor no bigger than three centimeters in diameter and no or minimal lymph node involvement.

Until further studies are completed, however, the treatment's long-term effectiveness cannot be guaranteed. Indeed, there are concerns that the strategy would not protect women with unsuspected multifocal disease, or clusters of cancer cells in more than one part of the breast, reports LaMar McGinnis, M.D., senior medical consultant at the American Cancer Society.

The hope is that genetic science will one day identify cancers likely to be multifocal, enabling doctors to select patients most likely to benefit from shorter, more focused regimens. "Currently, many women who are ideal candidates for a breast-conserving lumpectomy are instead choosing a mastectomy owing to the time and hardship of getting conventional radiation," says McGinnis. "Faster, more convenient treatment would likely change their choice." ■