CATALINA
Health Resource

December 1, 2003

BY FEDERAL EXPRESS

Dockets Management Branch
(HFA - 305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 03N-0344; Request for Comment on Direct-to-Consumer Promotion of Prescription Drugs

Dear Sir/Madam:

Catalina Health Resource (CHR) submits the attached to the above docket. I made a presentation on behalf of CHR at the Food and Drug Administration's public meeting on September 23, 2003 regarding alternatives to the current brief summary requirements. During that presentation, I referenced a January issue of the TV Guide as an illustrative comparison of the requirements applicable to the print advertising of different FDA-regulated products. Those advertisements are now attached for submission to this docket.

Sincerely,

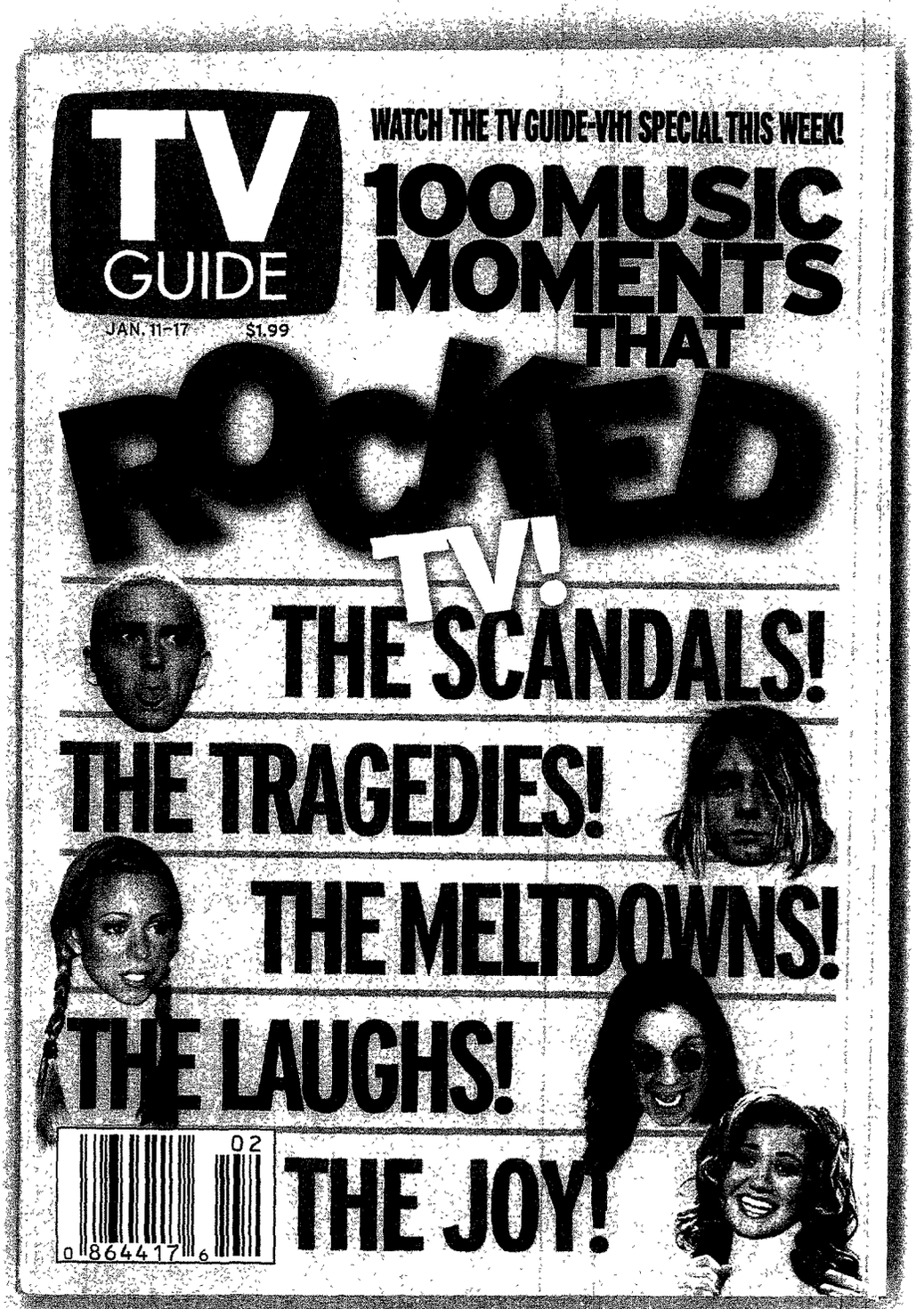
Michael Roberts/TEL

Michael Roberts
Vice President, Retail and Clinical Services
Catalina Health Resource

Attachments

03N-0344 SUP 2

515 Olive Street | Suite 1400 | St. Louis MO | 63101 | 314.613.3500 | FAX: 314.421.5036


TV GUIDE
JAN. 11-17 $1.99
WATCH THE TV GUIDE-VH1 SPECIAL THIS WEEK!
100 MUSIC MOMENTS THAT ROCKED TV!
THE SCANDALS!
THE TRAGEDIES!
THE MELTDOWNS!
THE LAUGHS!
THE JOY!
02
0 86441 7 6

NicoDerm® CQ®

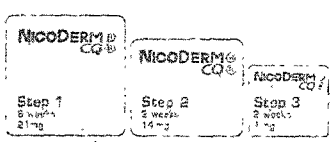
YOUR PERSONAL SUPPORT

NicoDerm CQ is available in Opaque and Clear for a more personal way to quit.

Kicking the habit can be difficult, but it's one of the most important things you'll ever do. Just planning to quit may seem daunting right now, but with a stop-smoking strategy that fits your needs, you have a greater chance of success. *NicoDerm CQ* is committed to giving you the tools to help you quit smoking and break the chain of cigarette addiction.

Step by Step

The ***NicoDerm® CQ®*** patch works by safely providing controlled doses of nicotine for 16 hours or 24 hours[1] if you need extra help fighting morning cravings. No matter how many cigarettes you smoke[2], you can use ***NicoDerm CQ's*** customized stop-smoking program to help ease the common cravings and irritability that result from withdrawal, allowing you to gradually wean yourself off nicotine entirely.



Step 1 – Initial treatment: 6 weeks with 21mg patch

Step 2 – First step-down: 2 weeks with 14mg patch

Step 3 – Final step-down: 2 weeks with 7mg patch

GlaxoSmithKline makes an annual grant to the American Cancer Society for cancer research and education in return for the use of their seal.

American Cancer Society

Ask your doctor or pharmacist, or check out **www.quit.com** for more information.

Use as directed. Individual results may vary. Support program can improve the chance of success.

NOTE: 1 When worn for 24 hours. 2 If you smoke more than 10 cigarettes a day, start with step 1. If you smoke 10 or less cigarettes a day, start with step 2.

EASY
OPENING BOX.
IT'S
CLOSING IT
THAT'S HARD.

CHEEZ-IT

GET YOUR OWN BOX

PRASHANT GUPTA/FX NETWORKS

New from Xenadrine!

Lose weight fast! One delicious bite at a time

A diet bar that works as good as it tastes? Unheard of! That's what Jacqui Davis thought until she lost 32 pounds in 5 weeks with the revolutionary new Xenadrine bar. Now she's a believer.

Xenadrine bars are unlike any other protein bar on the market because they're the only ones that contain Clarinol™ CLA (Conjugated Linoleic Acid). This naturally occurring compound is clinically proven to significantly decrease body-fat, while simultaneously increasing lean muscle. In a recent clinical study, the CLA group experienced significantly greater fat loss than the placebo group. (Just two bars per day provide more than enough CLA to yield similar results.) No other bar even comes remotely close to providing such amazing benefits.

Jacqui Davis Lost 32 Pounds in 5 Weeks!

LAURA CAVANAUGH/GLOBE PHOTOS

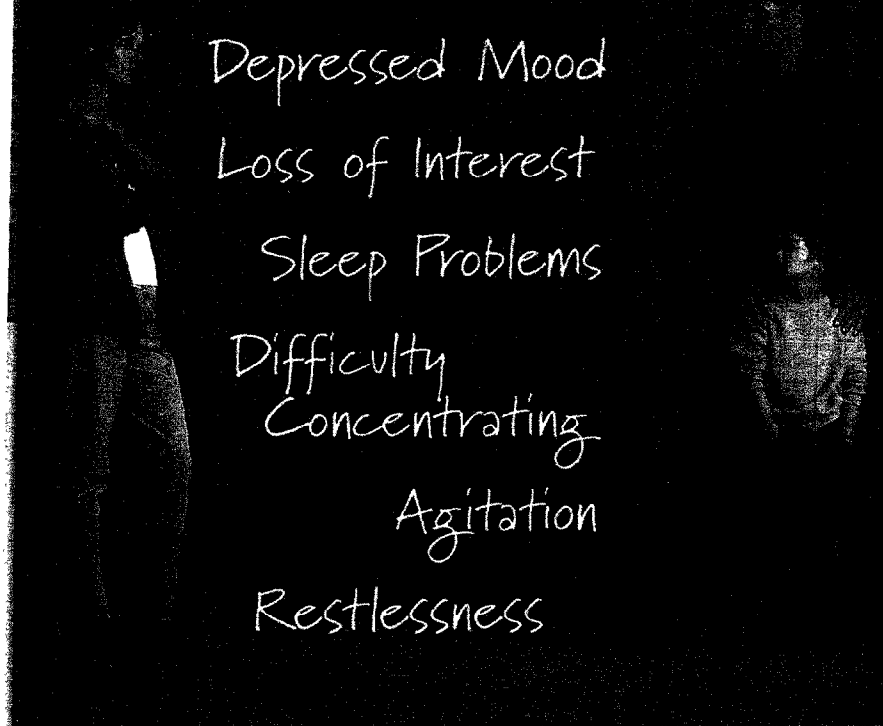
Xenadrine bars are also the only ones in the category to earn the coveted Gold Medal for flavor from the American Tasting Institute. These sensational new bars are available in four award-winning flavors: Cookies & Cream, Chocolate Peanut, Chocolate Almond and Chocolate Covered Strawberry.

Lose fat and gain muscle one delicious bite at a time with the revolutionary new Xenadrine High Protein Weight-Control Bar.

Available at GNC, Wal-Mart, Walgreens, Target and other fine health food and drug stores nationwide.

www.Xenadrine.com

What's standing between you and your life?



Life is too precious to let another day go by feeling not quite "yourself." If you've experienced some of these symptoms of depression nearly every day, for at least two weeks, a chemical imbalance could be to blame. And life can feel difficult ALL DAY. That's why you need relief ALL DAY. **NEW THERA® *PAXIL CR* CONTROLLED-RELEASE TABLETS.**

Paxil CR is a time-release tablet from the makers of *Paxil*. The CR means Controlled Release for Continuous Relief. Symptom relief usually requires two or more weeks of daily treatment. Prescription *Paxil CR* is not for everyone. Tell your doctor what medicines you're taking. People taking MAOIs or thioridazine should not take *Paxil CR*. *Paxil CR* is generally well tolerated. Side effects may include nausea, diarrhea, constipation, dizziness, sweating, tremor, sexual side effects, injury, yawn, abnormal vision or sleepiness. Patients should not stop taking *Paxil CR* before talking to their doctor. **Feeling balanced, more like "yourself," is within reach. Call 1-866-PAXIL-CR or visit www.paxilcr.com Please see product information on following page.**

PAXIL CR®
PAROXETINE HCl
CONTROLLED-RELEASE TABLETS

Your life is waiting!®

gsk GlaxoSmithKline

Advertisement

PAXIL CR™
(paroxetine hydrochloride) Controlled-Release Tablets

See complete prescribing information in GlaxoSmithKline literature. The following is a brief summary.

INDICATIONS AND USAGE: Paxil CR (paroxetine hydrochloride) is indicated for the treatment of major depressive disorder and panic disorder as defined in DSM-IV

CONTRAINDICATIONS: Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS) Contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in *Paxil CR*.

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use *Paxil CR* in combination with an MAOI, or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil CR* before starting an MAOI.

Potential Interaction with Thioridazine
Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit $P_{450}IID_6$, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine.

PRECAUTIONS: Among 760 patients with major depressive disorder or panic disorder treated with *Paxil CR* in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, use *Paxil CR* cautiously in patients with a history of mania.

Among 760 patients who received *Paxil CR* in controlled clinical trials in major depressive disorder or panic disorder, one patient (0 1%) experienced a seizure. Use *Paxil CR* cautiously in patients with a history of seizures Discontinue it in any patient who develops seizures

The possibility of suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs Close supervision of high-risk patients should accompany initial drug therapy. Write *Paxil CR* prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose Use the same precautions when treating patients with major depressive disorder as when treating patients with other psychiatric disorders

During clinical trials with immediate-release paroxetine, the following adverse events were reported at an incidence of 2% or greater for immediate-release paroxetine hydrochloride and were at least twice that reported for placebo while discontinuing therapy with *Paxil CR*: abnormal dreams, paresthesia, and dizziness In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention During marketing of immediate-release paroxetine hydrochloride, there have been spontaneous reports of similar adverse events, which may have no causal relationship to the drug, upon the discontinuation of immediate-release paroxetine hydrochloride (particularly when abrupt), including the following: dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), agitation, anxiety, nausea, and sweating. These events are generally self-limiting. Similar events have been reported for other selective serotonin reuptake inhibitors

Monitor patients for these symptoms when discontinuing treatment, regardless of the indication for which *Paxil CR* is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then consider resuming the previously prescribed dose Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION in complete prescribing information)

Reversible hyponatremia has been reported with immediate-release paroxetine hydrochloride, mainly in elderly individuals, patients taking diuretics or those who were otherwise volume depleted.

Abnormal bleeding (mostly ecchymosis and purpura) associated with immediate-release paroxetine hydrochloride treatment, including a report of impaired platelet aggregation has been reported; the relationship to paroxetine is unclear

Clinical experience with immediate-release paroxetine hydrochloride in patients with concomitant systemic illness is limited. Use *Paxil CR* cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with immediate-release paroxetine therapy have been reported As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, use caution when prescribing *Paxil CR* for these patients In patients with severe renal impairment (creatinine clearance <30 mL/min) or severe hepatic impairment, a lower starting dose (10 mg) should be used

Observe the usual cautions in cardiac patients

Paxil CR tablets should not be chewed or crushed, and should be swallowed whole

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that *Paxil CR* therapy does not affect their ability to engage in such activities.

Tell patients 1) to continue therapy as directed, 2) to inform physicians about other medications they are taking, or plan to take; 3) to avoid alcohol while taking *Paxil CR*; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy or if they are nursing

Concomitant use of *Paxil CR* with tryptophan is not recommended Use cautiously with warfarin Weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan have been rarely reported When administering *Paxil CR* with cimetidine, dosage adjustment of *Paxil CR* after the 25 mg starting dose should be guided by clinical effect

When co-administering *Paxil CR* with phenobarbital or phenytoin, no initial *Paxil CR* dosage adjustment is needed, changes should be based on clinical effect

Concomitant use of *Paxil CR* with drugs metabolized by the cytochrome $P_{450}IID_6$ (those used to treat major depressive disorder such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine, phenothiazines, Type 1C antiarrhythmics such as propafenone, fecainide and encainide) or with drugs that inhibit this isozyme (e g , quinidine) may require lower doses than usually prescribed for either *Paxil CR* or the other drug; approach concomitant use cautiously

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered.

An *in vivo* interaction study revealed that paroxetine had no effect on terfenadine pharmacokinetics. Additional *in vitro* studies showed that the inhibitory effects of paroxetine on other $IIIA_4$ substrates (astemizole, cisapride, triazolam, and cyclosporin) was at least 100 times less potent than ketoconazole, a potent $IIIA_4$ inhibitor Assuming that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's inhibition of $IIIA_4$ activity should have little clinical significance

Use caution when co-administering *Paxil CR* with tricyclic antidepressants (TCAs) TCA plasma concentrations may need monitoring, and the TCA dose may need to be reduced.

Administration of *Paxil CR* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug

Concomitant use of *Paxil CR* and alcohol in depressed patients is not advised Undertake concurrent use of *Paxil CR* and lithium or digoxin cautiously If adverse effects are seen when co-administering *Paxil CR* with procyclidine, reduce the procyclidine dose Elevated theophylline levels have been reported with immediate-release paroxetine treatment co-administration, monitoring theophylline levels is recommended

A significantly greater number of male rats in the 20 mg/kg/

day group developed reticulum cell sarcomas vs animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown There is no evidence of mutagenicity with *Paxil CR*.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) showed a reduced pregnancy rate

Pregnancy Category C: Reproduction studies performed at *doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits*, approximately 8 (rat) and 2 (rabbit) times the MRHD on a mg/m^2 basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation The cause of these deaths is not known There are no adequate and well-controlled studies in pregnant women. *Paxil CR* should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of paroxetine on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when *Paxil CR* is administered to a nursing woman. Safety and effectiveness in the pediatric population have not been established.

In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended. However, there were no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in complete prescribing information) In a controlled study focusing specifically on elderly patients with major depressive disorder, *Paxil CR was demonstrated to be* safe and effective in the treatment of elderly patients (>60 years of age) with major depressive disorder (See CLINICAL TRIALS and ADVERSE REACTIONS—Table 2 in complete prescribing information.)

ADVERSE REACTIONS: Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with *Paxil CR*: Adverse Events Associated with Discontinuation of Treatment

Ten percent (21/212) of *Paxil CR* patients discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder The most common events (≥1%) associated with discontinuation and considered to be drug related (i e , those events associated with dropout at a rate approximately twice or greater for *Paxil CR* compared to placebo) included: nausea (3.7% vs 0 5%); asthenia (1 9% vs 0 5%), dizziness (1 4% vs. 0.0%), somnolence (1.4% vs. 0.0%), respectively. In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of *Paxil CR* patients discontinued due to these adverse events. nausea (2.9% vs. 0.0%), headache (1.9% vs. 0.9%), *depression* (1.9% vs 0.0%), *LFT's abnormal* (1.9% vs. 0 0%), for *Paxil CR* and placebo, respectively. Eleven percent (50/444) of *Paxil CR* patients in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included: nausea (2 9% vs. 0 4%); insomnia (1.8% vs. 0.0%); headache (1 4% vs. 0.2%), asthenia (1.1% vs 0.0%) for *Paxil CR* and placebo, respectively.

The most commonly observed adverse events associated with *Paxil CR* in a pool of two trials for major depressive disorder (incidence of 5 0% or greater and incidence for *Paxil CR* at least twice that for placebo) were: abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning Using the same criteria, the adverse events associated with the use of *Paxil CR* in a study of elderly patients with major depressive disorder were: abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

In the pool of panic disorder studies, the adverse events meeting these criteria were: abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Incidence in Controlled Clinical Trials

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥1% of patients with major depressive disorder were: **Body as a Whole:** Headache (27% vs. 20%), asthenia (14% vs. 9%), infection (8% vs. 5%), abdominal pain (7% vs. 4%), back pain (5% vs. 3%), trauma (5% vs. 1%), pain (3% vs. 1%), allergic reaction (2% vs 1%); **Cardiovascular System:** tachycardia (1% vs. 0%), vasodilatation (2% vs 0%); **Digestive System:** Nausea (22% vs 10%), diarrhea (18% vs. 7%), dry mouth (15% vs. 8%), constipation (10% vs 4%), flatulence (6% vs. 4%), decreased appetite (4% vs. 2%), vomiting (2% vs 1%), **Nervous System:** somnolence (22% vs 8%), insomnia (17% vs. 9%), dizziness (14% vs. 4%), libido decreased (7% vs 3%), tremor (7% vs 1%), hypertonia (3% vs 1%), paresthesia (3% vs. 1%), agitation (2% vs. 1%), confusion (1% vs. 0%); **Respiratory System:** yawn (5% vs. 0%), rhinitis (4% vs 1%), cough increased (2% vs 1%), bronchitis (1% vs. 0%), **Skin and Appendages:** sweating (6% vs. 2%), photosensitivity (2% vs 0%), **Special Senses:** abnormal vision (5% vs. 1%), taste perversion (2% vs 0%); **Urogenital System:** abnormal ejaculation (26% vs 1%), female genital disorder (10% vs. <1%), impotence (5% vs. 3%), urinary tract infection (3% vs. 1%), menstrual disorder (2% vs <1%), vaginitis (2% vs 0%)

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥5% of elderly patients with major depressive disorder were· **Body as a Whole:** headache (17% vs 13%), asthenia (15% vs 14%), trauma (8% vs 5%), infection (6% vs. 2%), **Digestive System:** dry mouth (18% vs. 7%), diarrhea (15% vs. 9%), constipation (13% vs. 5%), dyspepsia (13% vs. 10%), decreased appetite (12% vs 5%), flatulence (8% vs. 7%); **Nervous System:** somnolence (21% vs. 12%), insomnia (10% vs. 8%), dizziness (9% vs. 5%), libido decreased (8% vs <1%), tremor (7% vs. 0%), **Skin and Appendages:** sweating (10% vs. <1%), **Urogenital System:** abnormal ejaculation (17% vs 3%), impotence (9% vs 3%)

The most commonly observed treatment-emergent adverse *events associated with Paxil CR, occurring in ≥1% of patients* with panic disorder were: **Body as a Whole:** asthenia (15% vs 10%), abdominal pain (6% vs 4%); trauma (5% vs. 4%), **Cardiovascular System:** vasodilation (3% vs. 2%); **Digestive System:** nausea (23% vs 17%), dry mouth (13% vs 9%), diarrhea (12% vs. 9%), constipation (9% vs. 6%), decreased appetite (8% vs 6%), **Metabolic/Nutritional Disorders:** weight loss (1% vs 0%); **Musculoskeletal System:** Myalgia (5% vs. 3%), **Nervous System:** insomnia (20% vs 11%), somnolence (20% vs 9%), libido decreased (9% vs 4%), nervousness (8% vs 7%); tremor (8% vs 2%), anxiety (5% vs 4%), agitation (3% vs. 2%), hypertonia (2% vs <1%), myoclonus (2% vs. <1%), **Respiratory System:** sinusitis (8% vs 5%), yawn (3% vs. 0%), **Skin and Appendages:** sweating (7% vs. 2%), **Special Senses:** abnormal vision (3% vs <1%); **Urogenital System:** abnormal ejaculation (27% vs 3%), impotence (10% vs. 1%), female genital disorders (7% vs 1%), urinary frequency (2% vs <1%), urination impaired (2% vs. <1%), vaginitis (1% vs <1%).

Studies in major depressive disorder show a clear dose-dependent relationship for some of the more common adverse events associated with the use of immediate-release paroxetine The percentage of patients in clinical trials reporting symptoms of sexual dysfunction in non-elderly patients with major depressive disorder and in patients with panic disorder are in males: decreased libido (10% and 9%), ejaculatory disturbance (26% and 27%), impotence (5% and 10%), in females: decreased libido (4% and 8%), orgasmic disturbance (10% and 7%).

Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with *Paxil CR*, or the immediate-release formulation, had minimal weight loss (about 1 pound)

In a study of elderly patients with major depressive disorder, three of 104 *Paxil CR* patients and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern. Two of the *Paxil CR* patients dropped out of the study due to abnormal liver function tests; the third

patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, four of 444 *Paxil CR* patients and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of *Paxil CR*. The clinical significance of these findings is unknown. In placebo-controlled clinical trials with the immediate release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients

Other Events Observed During the Clinical Development of Paroxetine: During premarketing assessment in major depressive disorder and panic disorder, multiple doses of *Paxil CR* were administered to 760 patients in phase 3 double-blind, controlled, outpatient studies. The following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and post-traumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included The extent to which these events may be associated with *Paxil CR* is unknown

Body as a Whole: Infrequent were anaphylactoid reaction, chills, flu syndrome, malaise; also observed were adrenergic syndrome, face edema, neck rigidity, sepsis. **Cardiovascular System:** Frequent were hypertension, hypotension; Infrequent were angina pectoris, bradycardia, bundle branch block, palpitation, postural hypotension, syncope; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, hematoma, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles. **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastroenteritis, gastroesophageal reflux, gingivitis, glossitis, gum hyperplasia, hemorrhoids, hepatosplenomegaly, increased salivation, intestinal obstruction, melena, pancreatitis, peptic ulcer, rectal hemorrhage, stomach ulcer, toothache, ulcerative stomatitis; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, colitis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, throat tightness, tongue discoloration, tongue edema **Endocrine System:** Infrequent were hyperthyroidism, ovarian cyst, testes pain; also observed were diabetes mellitus, goiter, hypothyroidism, thyroiditis. **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, hypochromic anemia, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia **Metabolic and Nutritional Disorders:** Infrequent were bilirubinemia, dehydration, generalized edema, hyperglycemia, hyperkalemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst, also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. **Musculoskeletal System:** Infrequent were arthritis, bursitis, myasthenia, myopathy, myositis, tendonitis, also observed were generalized spasm, osteoporosis, tenosynovitis, tetany **Nervous System:** Infrequent were amnesia, ataxia, convulsion, diplopia, dystonia, emotional lability, hallucinations, hypesthesia, hypokinesia, incoordination, neuralgia, neuropathy, nystagmus, paralysis, paranoid reaction, vertigo, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hostility, hyperalgesia, irritability, libido increased, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis, trismus. **Respiratory System:** Infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia, stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased. **Skin and Appendages:** Infrequent were acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, pruritus, seborrhea, urticaria; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. **Special Senses:** Infrequent were abnormality of accommodation, conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus, visual field defect; also observed were amblyopia, anisocoria, blepharitis, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss. **Urogenital System:** Infrequent were albuminuria, amenorrhea*, breast enlargement*, breast pain*, cystitis, dysuria, hematuria, kidney calculus, menorrhagia*, nocturia, prostatitis*, urinary incontinence, urinary retention; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, female lactation, fibrocystic breast, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, polyuria, pyuria, salpingitis, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate

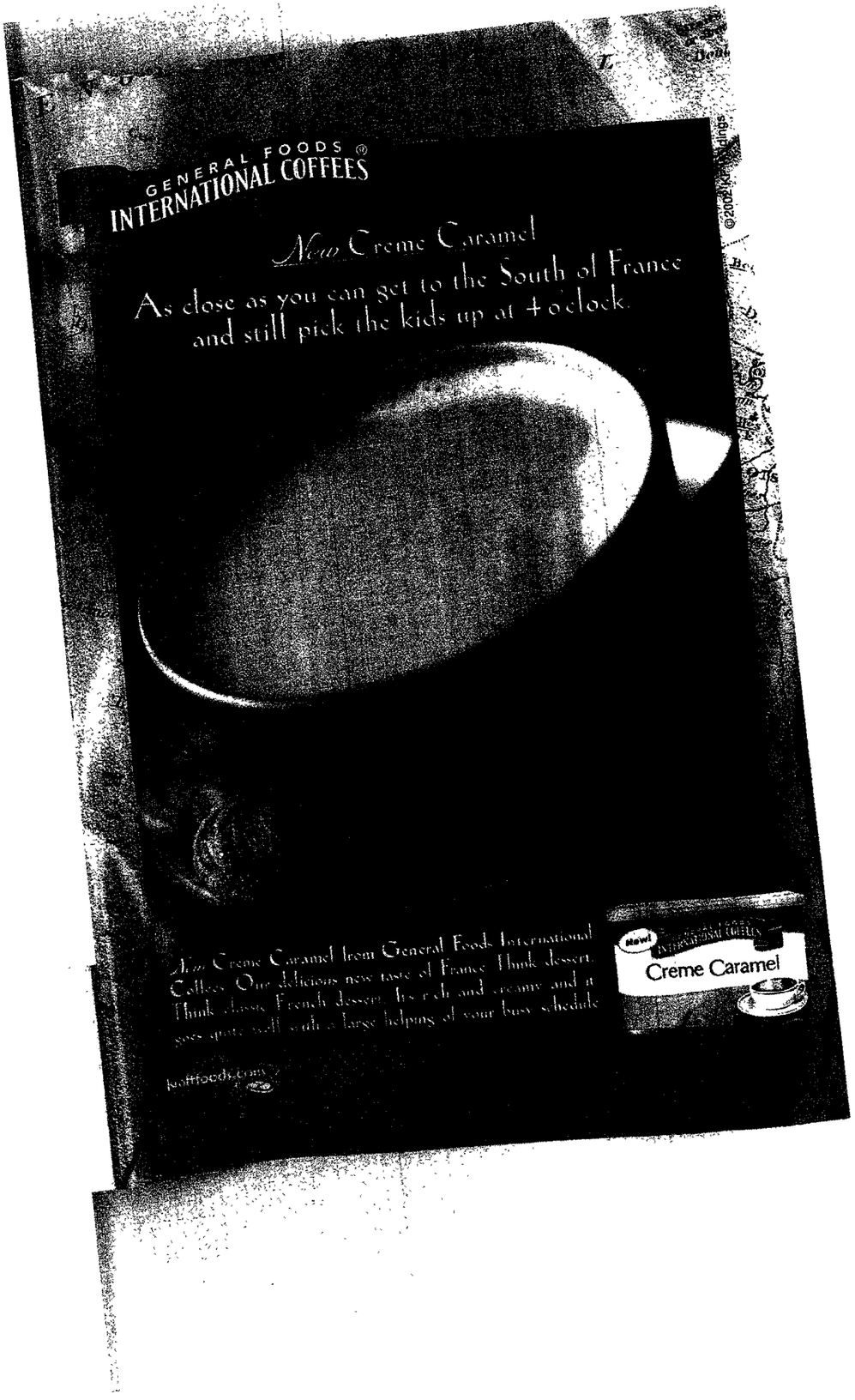
Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events, extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus, serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor); status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura) There has been a report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin co-administration. There has been a report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil CR* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil CR* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

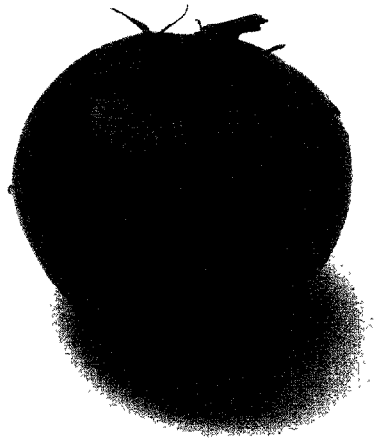
GlaxoSmithKline
Research Triangle Park, NC 27709

BRS–PC:L3

PXC159R0


GENERAL FOODS®
INTERNATIONAL COFFEES
New Creme Caramel
As close as you can get to the South of France
and still pick the kids up at 4 o'clock.
New!
Creme Caramel
kraftfoods.com

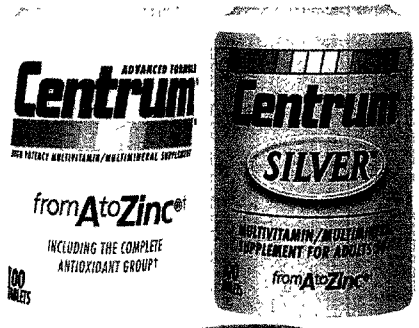
SOMETHING IN THIS TOMATO MAY HELP PROTECT AGAINST HEART DISEASE.



Emerging science suggests that a remarkable nutrient, LYCOPENE, is one of the ingredients in tomatoes that may help reduce the risk of heart disease. Now Centrum and Centrum Silver both contain lycopene‡ Another way that the advanced formulas of Centrum, combined with a healthy lifestyle, do more for your health everyday.

Centrum® and Centrum® Silver®

Now More Complete With Lycopene



THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THESE PRODUCTS ARE NOT INTENDED TO DIAGNOSE, TREAT, CURE, OR PREVENT ANY DISEASE.

Take along with a healthy diet. †Contains all nutrients with an RDI (except iron in Centrum Silver). ‡Not intended to provide your daily intake of Lycopene. Choose a diet rich in tomatoes and other fruits and vegetables.

Wyeth®

www.centrum.com