In the study of up to 1 year’s treatment duration, patients treated with ZYBAN® demonstrated significantly less weight gain (p = 0.05) than those patients treated with placebo throughout the study (8 lb versus 13 lb, respectively, at Week 52).

Cardiovascular Effects: In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have occurred in patients with and without evidence of preexisting hypertension.

Data from a comparative study of ZYBAN®, nicotine transdermal system (NTS), the combination of sustained-release bupropion hydrochloride and placebo, and placebo alone, as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of ZYBAN® and NTS compared to patients treated with ZYBAN® and placebo. In this study, 2.5% of patients treated with the combination of ZYBAN® and NTS had treatment-emergent hypertension compared to 2.5%, 1.6% and 3.1% of patients treated with ZYBAN®, placebo, and NTS, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN® and NTS and four patients (1.7%) treated with ZYBAN® alone had hypertension. Monitoring of blood pressure is recommended in all patients receiving the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of ZYBAN® in patients with a recent history of myocardial infarction or other cardiac event. Caution should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension or syncope, including those taking antidepressants, and was also generally well tolerated in a group of 36 depressed individuals with stable heart failure. However, lower blood pressure in the study of patients with stable heart failure, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

Renal Impairment: In clinical practice, the safety of ZYBAN® in patients with renal impairment has not been established. Bupropion is extensively metabolized in the liver to active metabolites, which are largely further metabolized. Therefore, caution is needed when bupropion is used with caution in patients with renal impairment and a reduced frequency of dosing should be considered as appropriate. The use of ZYBAN® in patients with mild to moderate hepatic impairment should be initiated at 100 mg of bupropion. Bupropion is not recommended in patients with severe hepatic impairment (see Warnings, and also Dosage and Administration).

Hepatic Impairment: Based on the variability reported for individual pharmacokinetic (PK) values of patients with mild hepatic impairment, it is recommended that the pharmacokinetics of bupropion be monitored for patients with mild or moderate hepatic impairment should be initiated at 100 mg of bupropion. Bupropion is not recommended in patients with severe hepatic impairment (see Warnings, and also Dosage and Administration).

All patients with hepatic impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug and metabolite levels. These adverse effects were generally well tolerated in a group of 36 depressed individuals with stable heart failure. However, lower blood pressure in the study of patients with stable heart failure, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.
Dosage and Administration

Dosage in special populations:

- Pregnancy: Teratogenic Effects: Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a mg/m² basis). There is no evidence of impaired fertility or harm to the fetus due to ZYBAN in rats. However, adequate and well-controlled studies in pregnant women are not available. Because animal reproduction studies are not always predictive of human response, ZYBAN should be given to pregnant women only if clearly needed.

- Nursing Mothers: Bupropion and its metabolites are secreted in human milk. Based on studies of healthy human volunteers, up to 6% of the bupropion dose and 1% of the bupropion metabolites are found in human milk. Because of the potential for serious adverse reactions in nursing infants from ZYBAN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

- Children: The safety and efficacy of ZYBAN in children under 18 years of age have not been established. There are no adequate and well-controlled studies in pregnant women. It is also not known whether ZYBAN can cause fetal harm when administered to a pregnant woman. The effects of ZYBAN on labor and delivery are unknown.

- Precautions: ZYBAN is well tolerated. Adverse events were minimally associated with the use of ZYBAN and its metabolites. None of the adverse events were related to the dose of ZYBAN.

- Adverse reactions:

- Gastrointestinal: Diarrhea, constipation, abdominal pain, nausea, vomiting, flatulence, anorexia.

- Central Nervous System: Headache, dizziness, tremor, somnolence.

- Special Senses: Tinnitus.

- Other: Rash, pruritus, urticaria.

- Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion:

- Gastrointestinal: Nausea, vomiting, diarrhea, constipation, abdominal pain, flatulence, anorexia, eructation, ankyloglossia.

- Cardiovascular: Hypertension, hypotension, tachycardia, vasodilation.

- Central Nervous System: Headache, dizziness, tremor, somnolence, thinking abnormality.

- Special Senses: Tinnitus.

- Other: Rash, pruritus, urticaria.

- Adverse Reactions Associated with Discontinuation of Treatment:


- Other: Rash, pruritus, urticaria.

- Special Senses: Tinnitus.

- Other: Rash, pruritus, urticaria.

- Adverse Reactions Associated with Discontinuation of Treatment Due to Drug Interactions:


- Other: Rash, pruritus, urticaria.

- Special Senses: Tinnitus.

- Other: Rash, pruritus, urticaria.

- Other Events Observed During the Clinical Development and Postmarketing Experience of Drug Interactions:

- Gastrointestinal: Nausea, vomiting, diarrhea, constipation, abdominal pain, flatulence, anorexia, eructation, ankyloglossia.

- Cardiovascular: Hypertension, hypotension, tachycardia, vasodilation.

- Central Nervous System: Headache, dizziness, tremor, somnolence, thinking abnormality.

- Special Senses: Tinnitus.

- Other: Rash, pruritus, urticaria.

- Other Events Observed During the Clinical Development and Postmarketing Experience of Drug Interactions Due to Postmarketing Experience:

- Gastrointestinal: Nausea, vomiting, diarrhea, constipation, abdominal pain, flatulence, anorexia, eructation, ankyloglossia.

- Cardiovascular: Hypertension, hypotension, tachycardia, vasodilation.

- Central Nervous System: Headache, dizziness, tremor, somnolence, thinking abnormality.

- Special Senses: Tinnitus.

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- Cardiovascular: Hypertension, hypotension, tachycardia, vasodilation.

- Central Nervous System: Headache, dizziness, tremor, somnolence, thinking abnormality.

- Special Senses: Tinnitus.

- Other: Rash, pruritus, urticaria.

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- Other: Rash, pruritus, urticaria.
Digestive: Frequent were dyspepsia, flatulence, and vomiting. Infrequent were abnormal liver function, bruxism, dyspepsia, gastric reflux, gingivitis, glossitis, jaundice, and stomatitis. Rare was edema of tongue. Also observed were colitis, constipation, coprolexia, diarrhea, dyspepsia, edema ascites, edema leg, gastritis, hepatitis, increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool abnormality.

Endocrine: Also observed were hyperglycemia, hypoglycemia, obesity, and trichomoniasis. Also, decreased sex drive and decreased libido were reported.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukemia, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.

Musculoskeletal: Infrequent were leg cramps and twisting. Also observed were edema, increased weight, and peripheral edema. Also observed was glossalgia.

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Nervous System: Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS status postictal, confusional state, dizziness, decreased memory, depersonalization, emotional lability, hostility, hyperkinnesia, hypotonia, hyperesthesia, paresis, suicidal ideation and verify. Rare were amnesia, ataxia, derealization, hypomania and hypophonia, incoordination, loosening of associations, and Stevens-Johnson syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms of delayed hypersensitivity. These symptoms may resemble serum sickness.

Skin/Hypersensitivity: Frequent was angioedema. Infrequent were acne, angioneurotic edema, bullous eruption, contact dermatitis, exfoliative dermatitis, fixed drug eruption, hair loss, itching, keratoderma blennorrhagicum, lichen planus, lip swelling, maculopapular rash, orofacial granulomatosis, pruritus, pemphigus, pemphigoid, purpuric eruption, rash, and urticaria. Rare was pemphigus vulgaris. Very rare was erythema nodosum. Also observed were alopecia, angioedema, erythema multiforme, erythema nodosum, erythema simplex, erythema, extravascularized gland, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking of tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

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Respiratory: Rare was bronchospasm. Also observed was pneumonia.
Combination Treatment With Bupropion and a NTS: ZYBAN® may be prescribed in combination with NTS for smoking cessation. The prescriber should review the complete prescribing information for both ZYBAN® and NTS before using combination therapy. Treatment is initiated at 150 mg/day while the patient is still smoking and increased after 3 days to 300 mg/day given at 150 mg twice daily (nicotine transdermal system (NTS)) (150 mg twice daily). This treatment with ZYBAN® after approximately 1 week when the patient has reached the target quit date. During weeks 8 and 9, and vital signs should be obtained. Avoid combining ZYBAN® and NTS in patients to prevent emergence of hypertension in patients treated with the combination of ZYBAN® and NTS is recommended.

OVERDOSAGE Human Overdose Experience: In addition to those events reported under Adverse Reactions, overdose has resulted in symptoms including drowsiness, loss of consciousness and EEG changes such as coiling waves (including QRS prolongation) or arrhythmias. There has been limited experience with overdose of the sustained-release formulation of bupropion; three such cases have been reported during clinical trials with fewer patients. One patient ingested 3000 mg of bupropion sustained-release tablets and vomited quickly after the overdose; the patient was treated with activated charcoal and lightheadedness. A second patient ingested a “handful” of bupropion sustained-release tablets and experienced confusion, lethargy, nausea, and muscle rigidity. A third patient ingested 800 mg of bupropion sustained-release tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and “grogginess”. None of the patients experienced further adverse effects.

There has been extensive experience with overdoses of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials in depressed patients. Treatment consisted of supportive care provided without significant sequelae. Another patient who ingested 9000 mg of immediate-release bupropion and 300 mg of tetracyclic, selective serotonin re-uptake inhibitors or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines.

Pharmacokinetics: Following oral administration of ZYBAN® Tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased Cmax and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect. In vivo tests indicate that bupropion is 84% bound to human serum protein. The major metabolic pathways of ZYBAN® involve oxidation and conjugation. Bupropion and its metabolites are excreted in the urine. The mean elimination half-life of ZYBAN® after chronic dosing is 21 (± 9) hours, and steady-state plasma concentrations of bupropion are reached within 5 days (See Pharmacology, Human Pharmacokinetics).

Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, visual hallucinations, and “grogginess”. None of the patients experienced further adverse effects.

Table IV Comparative Trial: Quit Rates by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Abstinence From Week 4 Placebo</th>
<th>NTX</th>
<th>ZYBAN 300 mg/day</th>
<th>Placebo</th>
<th>NTS</th>
<th>ZYBAN 300 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>Placebo (n = 151)</td>
<td>(n = 244)</td>
<td>(n = 244)</td>
<td>(n = 245)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 7</td>
<td>17% (95% CI)</td>
<td>23% (11-34)</td>
<td>36% (27-46)</td>
<td>21 mg/day (n = 245)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4-week quit)</td>
<td>12% (9-19)</td>
<td>29% (23-35)</td>
<td>41% (34-47)</td>
<td>29% (23-35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 26</td>
<td>13% (10-18)</td>
<td>18% (13-24)</td>
<td>30% (23-37)</td>
<td>12% (8-16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8% (4-13)</td>
<td>12% (8-16)</td>
<td>23% (16-29)</td>
<td>8% (4-13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1% (0.0-6)</td>
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The treatment combination of ZYBAN® and NTS displayed the highest rates of continuous abstinence throughout the study, the quit rates for the combination were significantly higher than other formulations. Nicotine replacement therapy was used after the treatment period. The combination treatment of ZYBAN® and NTS was associated with significantly higher quit rates than placebo alone. Quit rates for ZYBAN® are similar in patients with and without prior quit attempts using nicotine replacement therapy.

The study was a long-term relapse prevention trial conducted at five clinical centers. Patients in this study received open-label ZYBAN®300mg/day for 7 weeks. Patients who quit smoking while receiving ZYBAN® were then randomized to ZYBAN® 300 mg/day or placebo for a total study duration of 1 year. Abstinence from smoking was determined by patient self-report and verified by expired air carbon monoxide levels.

Results of this 1-year trial demonstrated statistically significantly less relapse to smoking for those patients taking ZYBAN® compared to those taking placebo. The time for 50% of patients randomized to smoking was significantly longer than for patients randomized to ZYBAN® compared to placebo (32 weeks versus 20 weeks). Continuous abstinence rates were greater for those patients randomized to ZYBAN® as compared to placebo through 5 months (P = 0.05; 55% versus 44%). At 1 year, point prevalence abstinence rates only (abstinence for the 7 consecutive days preceding the clinic visit) were significantly higher for patients treated with ZYBAN® compared to placebo-treated patients (P < 0.01; 55% versus 42%). Treatment with ZYBAN® reduced some of the withdrawal symptoms compared to placebo: irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending on the study and the phase, use of ZYBAN® showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

STORAGE AND STABILITY
Store at 15 to 25°C. Store in a dry place, protected from light.

I N C O M B I N A T I O N T R E A T M E N T G R O U P S

<table>
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**STORAGE AND STABILITY**

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**DOSE FORMS, COMPOSITION AND PACKAGING**

ZYBAN® sustained-release 150 mg tablets are supplied as round, purple, biconvex, film-coated tablets printed with ZYBAN® trademark.

Each 150 mg tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: caibauna wax, cellulose hydrochloride, edible black ink, FD&C Blue No. 2 Lake, FD&C Red No. 5, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide.

**ZYBAN® 150 mg tablets are supplied in blister packs of 60 tablets.**