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ZYBAN TABLETS 150 mg

WARNING
Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking ZYBAN for smoking cessation.
(see Warnings and Precautions> **Neuropsychiatric symptoms)**

TITLE

Bupropion hydrochloride.

SCOPE

Trade Name

ZYBAN™

Formulation and Strength

– film-coated tablets containing 150 mg of bupropion hydrochloride.

Sustained release film-coated tablet.

Excipients

Cellulose, Microcrystalline
Hypromellose
Cysteine hydrochloride Monohydrate
Magnesium Stearate
Purified Water
White colour concentrate
Carnauba Wax
White colour concentrate:
(Opadry OY-7300 White or
Opadry YS-1-18202-A White)

CLINICAL INFORMATION

Indications

Bupropion tablets are indicated as an aid to smoking cessation - in combination with motivational support.

Dosage and Administration

It is recommended that treatment is started while the patient is still smoking and a "target stop date" set within the first two weeks of treatment with Bupropion, preferably in the second week.

Patients should be treated for at least 7 weeks.

Discontinuation should be considered if the patient has not made significant progress towards abstinence by the seventh week of therapy, since it is unlikely that they will stop smoking during that attempt.

Systematic evaluation of Bupropion 300 mg/day for the prevention of relapse demonstrated that treatment for up to one year was well tolerated and efficacious in preventing relapse.

As many patients attempting to stop smoking experience multiple relapses, whether treatment with bupropion should be continued for longer periods should be determined on an individual basis.

The recommended posology does not require modification if Bupropion is used in combination with Nicotine Transdermal Systems (*See Warnings And Precautions*).

Sustained release Bupropion tablets should be swallowed whole. The tablets should not be crushed or chewed as this may lead to an increased risk of adverse effects including seizures.

Studies suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food (see *Pharmacokinetics*).

Populations

- **Adults**

The initial dose is 150mg to be taken daily for three days, increasing to 150mg twice daily. There should be an interval of at least 8 hours between successive doses.

The maximum single dose should not exceed 150mg and the total daily dose should not exceed 300mg.

Insomnia is a very common adverse event which is often transient. Insomnia may be reduced by avoiding dosing at bedtime (provided there is at least 8 hours between doses) or, if clinically indicated, dose reduction.

- **Children and Adolescents**

The safety and efficacy of Bupropion tablets in patients under 18 years of age have not been established.

- **Elderly**

Greater sensitivity of some elderly individuals to bupropion cannot be ruled out, hence a reduced frequency and/or dose may be required (See *Warnings And Precautions*).

- **Renal impairment**

Treatment of patients with renal impairment should be initiated at reduced frequency and/or dose, as bupropion and its metabolites may accumulate in such patients to a greater extent than usual (*See Warnings And Precautions*).

- **Hepatic impairment**

Bupropion should be used with caution in patients with liver impairment. Because of increased variability in the pharmacokinetics in patients with mild to moderate hepatic cirrhosis, a reduced frequency of dosing should be considered (*See Warnings And Precautions*).

Sustained release Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150mg on alternate days in these patients (*See Warnings And Precautions*).

Contraindications

- Bupropion is contraindicated in patients with hypersensitivity to bupropion or any of the other components of the preparation.

- Bupropion is contraindicated in patients with seizure disorder.

- Bupropion is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives.

- Bupropion Tablets should not be administered to patients currently being treated with any other preparation containing bupropion as the incidence of seizures is dose dependent.

- Bupropion is contraindicated in patients with a current or previous diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was seen in this patient population when bupropion was administered.

- Concomitant use of Bupropion and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with Bupropion Tablets.

Warnings and Precautions

Seizures

The recommended dose of Bupropion tablets should not be exceeded (maximum daily dose of 150 mg twice daily), since bupropion is associated with a dose-related risk of seizure. The incidence of seizures at doses of sustained release bupropion tablets up to 400 mg/day is approximately 0.1% (1/1,000).

The risk of seizures occurring with the use of Bupropion, which appears to be strongly associated with the presence of predisposing risk factors. Therefore Bupropion should be administered with extreme caution to patients with one or more conditions predisposing to a lowered seizure threshold. These include:

- history of head trauma
- central nervous system (CNS) tumour
- history of seizures
- concomitant administration of other medications known to lower the seizure threshold.

In addition, caution should be used in those clinical circumstances associated with an increased risk of seizures. These include excessive use of alcohol or sedatives, (see *Contraindications*), diabetes treated with hypoglycaemics or insulin and use of stimulants or anorectic products.

Bupropion should be discontinued and not recommenced in patients who experience a seizure while on treatment.

Hypersensitivity
Bupropion should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see *Adverse Reactions*). Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion, and clinical management should be provided accordingly.

Hepatic impairment
Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised. No statistically significant differences in the pharmacokinetics of bupropion were observed in patients with mild to moderate hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients. Therefore Bupropion should be used with caution in patients with hepatic impairment and reduced frequency of dosing should be considered in patients with mild to moderate hepatic cirrhosis. (*see Dosage and Administration and Pharmacokinetics*).

Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency of dosing is required, as peak bupropion levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual (*see Dosage and Administration and Pharmacokinetics*)

All patients with hepatic impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

Renal impairment and elderly patients
Bupropion is extensively metabolised in the liver to active metabolites which are further metabolised and excreted by the kidneys. Therefore treatment of patients with renal impairment should be initiated at reduced frequency and/or dose as bupropion and its metabolites may accumulate in such patients to a greater extent than usual (see Pharmacokinetics). The patient should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

Clinical experience with bupropion has not identified any differences in tolerability between elderly and other adult patients. However, greater sensitivity of some elderly individuals to bupropion cannot be ruled out; hence a reduced frequency and/or dose may be required *(see Pharmacokinetics).*

Neuropsychiatric symptoms
Neuropsychiatric symptoms have been reported (see *Adverse Reactions*). Psychotic and manic symptomatology has been observed, mainly in patients with a history of psychiatric illness. Additionally, bupropion may precipitate a manic episode in patients with bipolar disorder.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and behaviour (including suicide attempt), has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during bupropion treatment, and generally occurred during the early stages of treatment.

Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behaviour associated with antidepressant use compared to placebo in patients less than 25 years old.

When treating with bupropion, clinicians should monitor for the emergence of significant neuropsychiatric symptoms (including changes in behaviour, hostility, agitation, depressed mood, and suicide-related events, including ideation, behaviour, and attempted suicide) or for worsening of pre-existing psychiatric illness.

Clinicians should advise patients and caregivers that the patient should contact a healthcare provider immediately if neuropsychiatric symptoms not typical for the patient are observed.

Cardiovascular disease
Bupropion was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease (see Clinical pharmacology and Clinical Studies).

In a study in non-depressed subjects (including both smokers and non-smokers) with untreated Stage I hypertension, bupropion did not produce a statistically significant effect on blood pressure. However, spontaneous reports of increased blood pressure (sometimes severe) have been received (see *Adverse Reactions*). Prior to initiation of combination therapy with a Nicotine Transdermal System (NTS), prescribers should consult the prescribing information of the relevant NTS. If combination therapy is used, monitoring for treatment-emergent elevations of blood pressure is recommended. (See *Adverse Reactions*).

Interactions

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 IIB6 (CYP2B6) (see Pharmacokinetics). Care should therefore be exercised when Bupropion is co-administered with drugs known to affect the CYP2B6 isoenzyme (e.g.: orphenadrine, cyclophosphamide, ifosfamide, ticlopidine, clopidogrel).

Although bupropion is not metabolised by the CYP2D6 isoenzyme, *in vitro* human P450 studies have shown that bupropion and hydroxybupropion are inhibitors of the CYP2D6 pathway. In a human pharmacokinetic study, administration of bupropion increased plasma levels of desipramine. This effect was present for at least 7 days after the last dose of bupropion. Concomitant therapy with drugs predominantly metabolised by this isoenzyme (such as certain beta-blockers, antiarrhythmics, SSRIs, TCAs, antipsychotics) should be initiated at the lower end of the dose range of the concomitant medication. If Bupropion is added to the treatment regimen of a patient already receiving a medication metabolised by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index (see *Pharmacokinetics*).

Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g. tamoxifen), may have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion.

Although citalopram is not primarily metabolised by CYP2D6, in one study, bupropion increased the Cmax and AUC of citalopram by 30% and 40%, respectively.

Since bupropion is extensively metabolised, the co-administration of drugs known to induce metabolism (e.g. carbamazepine, phenobarbital, phenytoin, ritonavir, efavirenz) or inhibit metabolism may affect its clinical activity.

In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg (Kaletra) twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80%. Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55% in healthy volunteers Patients receiving any of these drugs with bupropion may need increased doses of bupropion but the maximum recommended dose of bupropion should not be exceeded.

Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during Bupropion treatment. The consumption of alcohol during Bupropion treatment should be minimised or avoided.

Limited clinical data suggest a higher incidence of neuropsychiatric adverse events in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

Studies suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food (see *Pharmacokinetics*).

Physiological changes resulting from smoking cessation itself, with or without treatment with Bupropion, may alter the pharmacokinetics of some medications taken concomitantly.

Pregnancy and Lactation

Fertility
A fertility study in rats revealed no evidence of impaired fertility.

Pregnancy
The safety of Bupropion for use in human pregnancy has not been established.

Administration of bupropion should only be considered during pregnancy if the expected benefits are greater than the potential risks.

In a retrospective, managed-care database study (n=7,005 infants), there was no greater proportion of congenital malformations (2.3%) or cardiovascular malformations (1.1%) associated with first trimester exposure to bupropion (n=1,213 infants) compared with the use of other antidepressants in the first trimester (n=4,743 infants; 2.3% and 1.1% for congenital and cardiovascular malformations, respectively) or bupropion use outside the first trimester (n=1,049 infants; 2.2% and 1.0%, respectively).

Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri-natal or post-natal development.

Lactation
As bupropion and its metabolites are excreted in human breast milk mothers should be advised not to breast feed while taking Bupropion tablets.

Ability to perform tasks that require judgement, motor or cognitive skills

As with other drugs which act on the central nervous system (CNS) bupropion may affect ability to perform tasks that require judgement or motor and cognitive skills. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain Bupropion tablets do not adversely affect their performance.

Adverse Reactions

The list below provides information on the undesirable effects identified from clinical experience, categorised by System Organ Class. It is important to note that smoking cessation is often associated with nicotine withdrawal symptoms some of which are also recognised as adverse events associated with Bupropion.

Undesirable effects are ranked under headings of frequency using the following convention; very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000), very rare (<1/10,000).

Immune system disorders*

Common	Hypersensitivity reactions such as urticaria
Very Rare:	More severe hypersensitivity reactions including angioedema, dyspnoea/bronchospasm and anaphylactic shock Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.

* See also "Skin and subcutaneous tissue disorders".

Metabolism and nutrition disorders

Common:	Anorexia
Very Rare:	Blood glucose disturbances

Psychiatric disorders

Very Common:	Insomnia
Common:	Agitation, anxiety, depression
Uncommon:	Confusion
Very Rare:	Aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams, depersonalisation, delusions, paranoid ideation.
Not known:	Suicidal ideation and suicidal behaviour***.

***Cases of suicidal ideation and suicidal behaviour have been reported during bupropion therapy (See *Warnings and Precautions)*

Nervous system disorders

Very Common:	Headache
Common:	Tremor, dizziness, taste disorders, concentration disturbance.
Rare:	Seizures (see Warnings and Precautions)
Very Rare:	Dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope.

Eye disorders

Common:	Visual disturbance

Ear and labyrinth disorders

Uncommon:	Tinnitus

Cardiac disorders

Uncommon:	Tachycardia
Very Rare:	Palpitations

Vascular disorders

Uncommon:	Increased blood pressure (sometimes severe), flushing
Very Rare:	Vasodilation, postural hypotension

Gastrointestinal disorders

Very Common:	Dry mouth, gastrointestinal disturbance including nausea and vomiting
Common:	Abdominal pain, constipation

Hepatobiliary disorders
Very Rare: Elevated liver enzymes, jaundice, hepatitis

Skin and subcutaneous tissue disorders*
Common: Rash, pruritus, sweating
Very Rare: Erythema multiforme, Stevens Johnson syndrome
* See also "Immune system disorders".

Musculoskeletal and connective tissue disorders
Very Rare: Twitching

Renal and urinary disorders
Very Rare: Urinary frequency and/or retention

General disorders and administration site conditions
Common: Fever, asthenia
Uncommon Chest pain

Overdosage

Symptoms and Signs
In addition to those events reported under Adverse Reactions, overdose has resulted in symptoms including drowsiness, and loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias.

Acute ingestion of doses of bupropion in excess of 10 times the maximum therapeutic dose has been reported.

Treatment
In the event of overdose, hospitalisation is advised. ECG and vital signs should be monitored.

Ensure an adequate airway, oxygenation and ventilation. The use of activated charcoal is recommended. No specific antidote for bupropion is known. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmacotherapeutic group: Other antidepressants, ATC code: N06 AX12

Mechanism of Action
Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin), and does not inhibit monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics

Absorption

Following oral administration of sustained release bupropion tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours.

Three studies suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food. When taken following food, peak plasma concentration of bupropion (Cmax) increased by 11%, 16% and 35% in the three studies. The overall exposure to bupropion (AUC) increased by 17%, 17% and 19% in the three studies (see *Interactions*).

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg per day.

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 L.
Bupropion and hydroxybupropion are moderately bound to plasma proteins (84% and 77%, respectively). The extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion. These may have clinical importance, as their plasma concentrations are as high or higher than those of bupropion.
Erythrohydrobupropion cannot be measured in the plasma after a single dose of Bupropion. The active metabolites are further metabolised to inactive metabolites and excreted in the urine.

In vitro studies indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the CYP2B6, while cytochrome P450s are not involved in the formation of threohydrobupropion (see *Interactions*).

Bupropion and hydroxybupropion are both relatively weak competitive inhibitors of the CYP2D6 isoenzyme with K_i values of 21 and 13.3μM, respectivelyin vitro. In human volunteers known to be extensive metabolisers of the CYP2D6 isoenzyme, co-administration of bupropion and desipramine has resulted in 2- and 5-fold increases in the Cmax and AUC, respectively, of desipramine. This effect was present for at least 7 days after the last dose of bupropion. Since bupropion is not metabolised by CYP2D6, desipramine is not anticipated to affect the pharmacokinetics of bupropion. Caution is advised when Bupropion is administered with substrates for the CYP2D6 pathway. (See *Interactions*).

Bupropion has been shown to induce its own metabolism in animals following sub-chronic administration. In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion hydrochloride for 10 to 45 days.

Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite.

In a healthy volunteer study, ritonavir at a dose of 100 mg twice daily reduced the AUC and C_{max} of bupropion by 22% and 21%, respectively. The AUC and C_{max} of the metabolites of bupropion were decreased by 0 to 44%. In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the AUC and the C_{max} of bupropion by 66% and 62%, respectively. The AUC and C_{max} of the metabolites of bupropion were decreased by 42 to 78%.

In another healthy volunteer study, Kaletra® (lopinavir 400 mg/ritonavir 100 mg twice daily) decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion were decreased by 50% and 31%, respectively.

Peak plasma concentrations of hydroxybupropion and threohydrobupropion are achieved approximately 6 hours following administration of a single dose of sustained release Bupropion.

Following oral administration of a single 150-mg dose of sustained release bupropion, there was no difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and non-smokers.

Elimination

Following oral administration of 200mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and faeces, respectively. The fraction of the dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion. Less than 10% of this ^{14}C dose was accounted for in the urine as active metabolites.

The mean apparent clearance following oral administration of bupropion hydrochloride is approximately 200 L/hr and the mean elimination half-life of bupropion is approximately 20 hours.

The elimination half-life of hydroxybupropion is approximately 20 hours and its area under the plasma drug concentration versus time curve (AUC) at steady state is approximately 17 times that of bupropion. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively) and steady-state AUC values are 8 and 1.6 times higher than that of bupropion, respectively. Steady-state for bupropion and its metabolites is reached within 8 days.

Special Patient Populations

- **Elderly**

Pharmacokinetic studies in the elderly have shown variable results. A single dose study showed that the pharmacokinetics of bupropion and its metabolites in the elderly do not differ from those in the younger adults. Another pharmacokinetic study, single and multiple dose, has suggested that accumulation of bupropion and its metabolites may occur to a greater extent in the elderly. Clinical experience has not identified differences in tolerability between elderly and younger patients, but greater sensitivity in older patients cannot be ruled out.

- **Renal impairment**

The elimination of bupropion and its major metabolites may be reduced by impaired renal function (see *Warnings and Precautions*). In subjects with end stage renal failure or moderate to severely impaired renal function, exposure to bupropion and/or its metabolites was increased.

- **Hepatic impairment**

The pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild to moderate cirrhosis when compared to healthy volunteers, although more variability was observed between individual patients. For patients with severe hepatic cirrhosis, the bupropion Cmax and AUC were substantially increased (mean difference approximately 70% and 3-fold, respectively) and more variable when compared to the values in healthy volunteers; the mean half-life was also longer (by approximately 40%). For the metabolites, the mean Cmax was lower (by approximately 30 to 70%), the mean AUC tended to be higher (by approximately 30 to 50%), the median Tmax was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 2 to 4-fold) than in healthy volunteers. (See *Warnings and Precautions).*

Clinical Studies

In clinical trials, treatment with bupropion reduced withdrawal symptoms compared to placebo and also showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

Three studies (Studies 403, 405 and ZYB40017) demonstrated efficacy in a population of smokers motivated to quit. Study 403 was a dose-ranging study that indicated that bupropion was efficacious and that 300mg was the most effective dose. Study 405 demonstrated that bupropion SR was more effective than a nicotine transdermal system (NTS) and that a combination of bupropion SR and NTS led to numerically greater efficacy than either treatment alone. Study ZYB40017 further confirmed the efficacy of bupropion SR in a large population of smokers. The primary efficacy measure in each of these studies was continuous abstinence from smoking for a four-week period (beginning of Week 4 through end of Week 7 of the treatment phase). This efficacy measure is the generally accepted international regulatory criterion for approval of an aid to smoking cessation. Long term treatment with bupropion SR has been shown to prevent relapse to smoking. Study 406 demonstrated that patients randomised to Zyban for up to 52 weeks had a longer median time to relapse compared with patients randomised to placebo.

Studies AK1A4013 and ZYB40014 demonstrated the benefit of bupropion SR as an aid to smoking cessation in populations of smokers with COPD and stable cardiovascular disease. In study ZYB40014 subjects had at least one of the following conditions either with or without controlled hypertension: history of myocardial infarction, history of interventional cardiac procedure, stable angina, peripheral vascular disease, or congestive heart failure class I or II. Although these patients were older, less healthy, and had smoked more cigarettes for longer, the efficacy of bupropion SR in these medically compromised patients was largely comparable to that seen in the earlier studies with bupropion SR in the general smoking population. Significantly more patients with cardiovascular disease on bupropion SR compared with placebo remained continuously abstinent during weeks 4 to 7 of treatment and through to 12 months, while almost twice as many patients with COPD receiving bupropion SR achieved continuous abstinence during weeks 4 to 7 of treatment and through to the 6-month follow-up than those on placebo.

In a randomized double-blind placebo-controlled study of bupropion SR in adult smokers hospitalized with acute cardiovascular disease bupropion SR improved short-term but not long--term smoking cessation rates over that achieved with a counseling programme alone. Bupropion SR appeared to be well tolerated during the treatment period in hospitalized smokers with acute cardiovascular disease.

Bupropion SR is equally effective in prior NRT users versus those who have not used NRT, and efficacy has been demonstrated in smokers who have used bupropion SR for a previous quit attempt. A retrospective analysis of a placebo-controlled study suggests that bupropion shows efficacy rates that are equivalent in smokers who have previously used NRT, and those who have not. Two studies (ZYB40003 and ZYB40001) have demonstrated the long term efficacy of bupropion in smokers who had previously used bupropion in an attempt to stop smoking.

NON-CLINICAL INFORMATION

The oncogenicity studies in the mouse and rat confirm the absence of carcinogenicity in these species. Liver changes are seen in animal studies but these reflect the action of a hepatic enzyme inducer. At clinical doses in man there is no evidence of any enzyme induction, which suggests that the hepatic findings in the laboratory animals have only limited importance in the evaluation and risk assessment of bupropion.

PHARMACEUTICAL INFORMATION

Shelf Life

24 months.

Special Precautions for Storage

Store below 25°C.

Nature and Contents of Container

Bupropion Hydrochoride Sustained-release Tablets, 150mg are packed into cold form foil / foil blister.The foil / foil blister is comprised of a polyamide / aluminium foil / polyvinyl chloride blister forming material and lidding material of aluminium foil with heat-seal lacquer on the inner surface.

Incompatibilities

None reported.

Use and Handling

None

Manufacturer

SmithKline Beecham Corporation, USA

License Holder

GlaxoSmithKline (Israel) Ltd.
25 Basel St., PETAH-TIKVA 49002

License Number: 118-33-29919-00

Zyb DR v2