

DATA SHEET

ZYBAN[®] Tablets

Bupropion hydrochloride tablets 150mg

Pharmaceutical form

Modified release film-coated tablet.

Clinical particulars

Therapeutic Indications

Zyban tablets are indicated for the treatment of nicotine dependence as an aid to smoking cessation.

Posology and Method of Administration

Zyban tablets should be swallowed whole and not be cut, crushed or chewed as this may lead to an increased risk of adverse effects including seizures.

Use in Adults

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 Zyban, preferably in the second week.

The initial dose is 150mg 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.

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 hydrochloride 300mg/day for the prevention of relapse demonstrated that treatment for up to 1 year was well tolerated and efficacious in preventing relapse.

- As many patients attempting to stop smoking experience multiple relapses, whether treatment with Zyban should be continued for longer periods should be determined on an individual basis.
- The recommended posology does not require modification if Zyban is used in combination with Nicotine Transdermal Systems for nicotine dependence. (See Special Warnings And Special Precautions for Use).

Use in Children and Adolescents.

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

Use in patients with liver impairment

Zyban 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 Special Warnings and Special Precautions for Use).

Zyban 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 Special Warnings and Special Precautions for Use).

Contra-indications

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

Zyban is contraindicated in patients with a current seizure disorder or any history of seizures.

Zyban is contraindicated in patients with a known central nervous system (CNS) tumour.

Zyban is contraindicated in patients undergoing abrupt withdrawal from alcohol or sedatives.

Zyban 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 an immediate release form of bupropion was administered.

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

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

Special Warnings and Special Precautions for Use

The recommended dose of Zyban must not be exceeded, since bupropion is associated with a dose-related risk of seizure. The incidence of seizure at doses of sustained release bupropion tablets up to 300mg/day is approximately 0.1% (1/1,000).

There is an increased risk of seizures occurring with the use of Zyban in the presence of predisposing risk factors which lower the seizure threshold. Zyban must not be used in patients with predisposing risk factors unless there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure. In these patients, a maximum dose of 150mg daily should be considered for the duration of treatment.

All patients should be assessed for predisposing risk factors, which include:

- concomitant administration of other medicinal products known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines).
- excessive use of alcohol or sedatives (see also Contra-indications)
- history of head trauma
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products

Zyban should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see Undesirable Effects). Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion, and clinical management should be provided accordingly. 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 Zyban 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 Posology and Method of Administration and Pharmacokinetic Properties)

Zyban 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 Posology and Method of Administration and Pharmacokinetic Properties)

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.

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. 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 cannot be ruled out; hence a reduced frequency and/or dose may be required. (See Pharmacokinetic properties)

The pharmacology of bupropion resembles that of some antidepressants. Neuropsychiatric symptoms have been reported (see Undesirable Effects). In particular, psychotic and manic symptomatology has been observed, mainly in patients with a history of psychiatric illness. Additionally, Zyban may precipitate a manic episode in patients with bipolar disorder.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during Zyban 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.

Clinicians should be aware of the possible emergence of significant depressive symptoms or suicidal ideation in patients being treated with bupropion, and should advise and monitor patients accordingly.

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 Undesirable Effects).

Interaction with Other Medicinal Products and Other Forms of Interaction

In patients receiving medicinal products known to lower the seizure threshold, Zyban must only be used if there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure (See Special Warnings and Special Precautions for Use).

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

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 2B6 (CYP2B6) (see Pharmacokinetic Properties). Care should therefore be exercised when Zyban 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, bupropion and its main metabolite, hydroxybupropion, inhibit the CYP2D6 pathway, as shown by *in vitro* studies and an *in vivo* study. In a human pharmacokinetic study, co-administration of bupropion hydrochloride and desipramine to healthy volunteers known to be extensive metabolisers of the CYP2D6 isoenzyme resulted in a five-fold increase in AUC and a two-fold increase in C_{max} of desipramine. Inhibition of CYP2D6 was present for at least 7 days after the last dose of bupropion hydrochloride.

Concomitant therapy with medicinal products predominantly metabolised by this isoenzyme with narrow therapeutic indices including certain antidepressants (e.g. desipramine, imipramine, paroxetine), antipsychotics (e.g. risperidone, thioridazine), beta-blockers (e.g. metoprolol), and Type 1C antiarrhythmics (e.g. propafenone, flecainide) should be initiated at the lower end of the dose range of the concomitant medicinal product. If Zyban is added to the treatment regimen of a patient already receiving a medicinal product metabolised by CYP2D6, the need to decrease the dose of the original medicinal product should be considered, particularly for those concomitant medicinal products with a narrow therapeutic index. In these cases the expected benefit of treatment with Zyban should be carefully considered compared with the potential risks.

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 C_{max} 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, phenobarbitone, 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 lopinavir 400 mg/ritonavir 100 mg 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%. This effect of ritonavir/Kaletra[®] and efavirenz is thought to be due to the induction of

bupropion metabolism. 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 Zyban treatment. The consumption of alcohol during Zyban 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 Zyban 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.

Use During Pregnancy and Lactation

The safety of Zyban 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.

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

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

Effects on Ability to Drive and Use Machines

As with other CNS acting drugs 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 Zyban tablets do not adversely affect their performance.

Effects on Laboratory Tests

Zyban has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for amphetamines. A more specific alternative chemical method should be considered to confirm a positive result.

Undesirable Effects

The list below provides information on the undesirable effects identified from clinical experience, categorised by body system. 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 Zyban.

Body (general)

Fever, chest pain, asthenia.

Cardiovascular

Tachycardia, palpitations, vasodilation, postural hypotension, increased blood pressure (in some cases severe), flushing, syncope.

CNS

Seizures (See Special Warnings And Special Precautions For Use), insomnia, tremor, dystonia, ataxia, Parkinsonism, twitching, incoordination, concentration disturbance, headache, dizziness, depression, confusion, hallucinations, agitation, anxiety, irritability, hostility, depersonalisation, abnormal dreams, memory impairment, paraesthesia, aggression, restlessness, delusions, paranoid ideation.

Endocrine and metabolic

Anorexia, blood glucose disturbances.

Gastrointestinal

Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation.

Genitourinary

Urinary frequency and/or retention.

Hepatobiliary

Elevated liver enzymes, jaundice, hepatitis.

Skin / Hypersensitivity

Rash, pruritus, sweating.

Hypersensitivity reactions ranging in severity from urticaria to angioedema, dyspnoea/bronchospasm and rarely 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.

Erythema multiforme and Stevens Johnson syndrome have also been rarely reported.

Special Senses

Tinnitus, visual disturbance, taste disorders.

Overdose

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose has been reported. In addition to those events reported as Undesirable Effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias.

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 also 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.

Pharmacological properties

Pharmacodynamic Properties

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.

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.

Pharmacokinetic Properties

Absorption

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

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

The absorption of bupropion is not significantly affected when taken with food.

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000L. 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. Peak plasma concentrations of hydroxybupropion and threohydrobupropion are achieved approximately 6 hours following administration of a single dose of Zyban. Erythrohydrobupropion cannot be measured in the plasma after a single dose of Zyban. 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 CYP2B6, while cytochrome P450s are not involved in the formation of threohydrobupropion. (See Interactions with Other Medicinal Products and Other Forms of Interaction)

Bupropion and hydroxybupropion are both relatively weak inhibitors of the CYP2D6 isoenzyme with K_i values of 21 and 13.3 μ M, respectively. 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 C_{max} 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 the CYP2D6 pathway, desipramine is not anticipated to affect the pharmacokinetics of bupropion. Caution is advised when Zyban is administered with substrates for the CYP2D6 pathway. (See Interactions with Other Medicinal Products and Other Forms of Interaction)

Following oral administration of a single 150mg dose of 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.

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 for 10 to 45 days.

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, 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.

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 is approximately 200L/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.

Patients with renal impairment

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

Patients with 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 C_{max} 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 C_{max} was lower (by approximately 30 to 70%), the mean AUC tended to be higher (by approximately 30 to 50%), the median T_{max} was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 2 to 4-fold) than in healthy volunteers (See Special Warnings And Special Precautions for Use).

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.

Preclinical Safety Data

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 particulars

List of Excipients

Tablet core	Film coat
Microcrystalline cellulose	Hydroxypropyl methylcellulose
Hydroxypropyl methylcellulose	Titanium dioxide
Cysteine hydrochloride	Polyethylene glycol
Magnesium stearate	Carnauba wax (as polish)
	Edible black ink (for printing)

Incompatibilities

None reported.

Shelf Life

30 months.

Special Precautions for Storage

Do not store above 25°C.

Medicines classification

Prescription Medicine

Name and address

GlaxoSmithKline NZ Limited

Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900

Facsimilie: (09) 367 2910

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