NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ZYBAN bupropion hydrochloride 150 mg modified release film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 150 mg bupropion hydrochloride.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Modified release film coated tablet.

White, film-coated, biconvex, round tablet printed on one side with GX CH7 and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYBAN tablets are indicated for the treatment of nicotine dependence in adults aged 18 and older as an aid to smoking cessation.

4.2 Dose and method of administration

Dose

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 150 mg taken daily for three days increasing to 150 mg twice daily. There should be an interval of at least eight hours between successive doses.

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

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 300 mg/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 section 4.4 Special warnings and precautions for use).

Special Populations

Hepatic 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 section 4.4 Special warnings and precautions for use).

ZYBAN should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg on alternate days in these patients (see section 4.4 Special warnings and precautions for use).

Paediatric population

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

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.

4.3 Contraindications

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.

4.4 Special warnings and 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 300 mg/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 150 mg 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 section 4.3 Contraindications)
- history of head trauma
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products.

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

ZYBAN should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see section 4.8 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 section 4.2 Dose and method of administration and section 5.2 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 section 4.2 Dose and method of administration and section 5.2 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 section 5.2 Pharmacokinetic properties).

ZYBAN is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported, and may lead to a rapid release, faster absorption and a potential overdose. Seizures and/or cases of death have been reported when bupropion has been administered intra-nasally or by parenteral injection.

The pharmacology of bupropion resembles that of some antidepressants. Neuropsychiatric symptoms have been reported (see section 4.8 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.

In clinical practice, hypertension, which in some cases may be severe and require acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. This has been observed in patients with and without pre-existing hypertension. Consideration should be given to discontinuation of ZYBAN if a clinically significant increase in blood pressure is observed.

Limited clinical trial data suggest that higher smoking cessation rates may be achieved by the combination use of ZYBAN together with Nicotine Transdermal System (NTS). However, a higher rate of treatment-emergent hypertension was noted in the combination therapy group. If combination therapy with a NTS is used, caution must be exercised and weekly monitoring of blood pressure is recommended. Prior to initiation of combination therapy prescribers should consult the prescribing information of the relevant NTS.

There is limited clinical experience establishing the safety of ZYBAN in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Serotonin syndrome has been reported when bupropion is co-administered with drugs known to be associated with serotonin syndrome, including selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see section 4.5 Interaction with other medicines and other forms of interaction).

Serotonin syndrome has also been reported with bupropion-only overdose (see section 4.9 Overdosage).

Bupropion may unmask Brugada syndrome, a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (ST segment elevation and T wave abnormalities in the right precordial leads), which may lead to cardiac arrest and/or sudden death. Caution is advised in patients with Brugada syndrome or risk factors such as a family history of cardiac arrest or sudden death.

4.5 Interaction with other medicines 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 section 4.4 Special warnings and 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 IIB6 (CYP2B6) (see section 5.2 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 antiarrythmics (e.g. propafanone, 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 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, 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/ ritonavir plus lopinavir and efivirenz 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.

Post-marketing data show a possible pharmacodynamic interaction between bupropion and SSRIs and SNRIs resulting in an increased risk of serotonin syndrome (see section 4.4 Special warnings and precautions for use).

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.

Co-administration of digoxin with bupropion may decrease digoxin levels. Digoxin AUC 0-24 h was decreased 1.6-fold and renal clearance was increased 1.8-fold in a healthy volunteer study.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of some congenital cardiovascular malformations. These findings are not consistent across studies. The authorised prescriber will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe bupropion if the expected benefits are greater than the potential risks.

The prospectively observed proportion of cardiac birth defects in pregnancies with prenatal exposure to bupropion in the first trimester in the international Pregnancy Registry was 9/675 (1.3%).

In a retrospective, managed-care database study (n=7005 infants), there was no greater proportion of congenital malformations (2.3%) or cardiovascular malformations (1.1%) associated with first trimester exposure to bupropion (n=1213 infants) compared with the use of other antidepressants in the first trimester (n=4743 infants; 2.3% and 1.1% for congenital and cardiovascular malformations, respectively) or bupropion use outside the first trimester (n=1049 infants; 2.2% and 1.0%, respectively).

In a retrospective case-control analysis using data from the National Birth Defects Prevention Study, there were 12383 case infants and 5869 control infants. A statistically significant association was observed between the occurrence of a left outflow tract heart defect in the infant and self-reported maternal bupropion use in early pregnancy (n=10; adjusted OR=2.6; 95% CI 1.2, 5.7). No association was observed between maternal bupropion use and any other type of cardiac defect or with all categories of heart defects combined.

A further case-control analysis of data from the Slone Epidemiology Center Birth Defects Study included 7913 infant cases of cardiac defects and 8611 controls. This found no statistically significant increase of left outflow tract heart defects with maternal bupropion use (n=2; adjusted OR= 0.4; 95% CI 0.1, 1.6). However, a statistically significant association was observed for ventricular septal defects (n=17; adjusted OR=2.5; 95% CI 1.3, 5.0) following the use of bupropion alone during the first trimester.

Breast-feeding

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

Fertility

There are no data on the effect of bupropion on human fertility. A reproductive study in rats revealed no evidence of impaired fertility (see section 5.3 Preclinical safety data).

4.7 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.

4.8 Undesirable effects

Tabulated list of adverse reactions

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 section 4.4 Special warnings and 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, dysphemia, aggression, restlessness, delusions, paranoid ideation, panic attack.

Endocrine and metabolic

Anorexia, blood glucose disturbances.

Hyponatraemia has also been reported very rarely.

Gastrointestinal

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

Genitourinary

Urinary frequency and/or retention, urinary incontinence.

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, Stevens-Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus syndrome aggravated, cutaneous lupus erythematosus, acute generalised exanthematous pustulosis and alopecia have also been very rarely reported.

Special Senses

Tinnitus, visual disturbance, taste disorders.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

In addition to those events reported as Adverse Effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias; cases of fatal outcome have been reported. Serotonin syndrome has also 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 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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants, ATC code: N06 AX12.

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.

5.2 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 300 mg per day.

Studies suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food.

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2,000 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.

Biotransformation

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 section 4.5 Interaction with other medicines 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 μM, 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 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 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 section 4.5 Interaction with other medicines and other forms of interaction).

Following oral administration of a single 150 mg 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 200 mg 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 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 populations

Renal impairment

The elimination of bupropion and its major metabolites may be affected by impaired renal function (see section 4.4 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.

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 section 4.4 Special warnings and 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.

5.3 Preclinical safety data

Carcinogenesis/mutagenesis

The oncogenicity studies in the mouse and rat confirm the absence of carcinogenicity in these species.

Reproductive toxicology

Fertility

There was no evidence of impaired fertility in rats at doses up to approximately 7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

Pregnancy

There was no evidence of teratogenicity in rats or rabbits at doses up to approximately 11 and 7 times the MRHD, respectively, based on a mg/m^2 basis (the exposure at the high dose in one of the rat studies, 300 mg/kg/day, was 1.7-fold that in humans based on AUC values at steady state). In rabbits, a slight increase in skeletal variations (increased incidence of common anatomical variation of an accessory thoracic rib and delayed ossification of phalanges) was seen at doses approximately equal to the maximum human dose and above, and foetal weight was decreased at maternally toxic doses. At exposures up to approximately 7 times the MRHD on a mg/m^2 basis no adverse effects were seen in offspring of rats administered bupropion prior to mating and throughout pregnancy and lactation.

Animal toxicology and/or pharmacology

Liver changes are seen in animal studies but these reflect the action of a hepatic enzyme inducer. At clinical doses in human 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Hydroxypropyl methylcellulose
Cysteine hydrochloride
Magnesium stearate.

Film coat:

Hydroxypropyl methycellulose
Titanium dioxide
Polyethylene glycol
Carnauba wax (as polish)
Edible black ink (for printing).

6.2 Incompatibilities

None reported.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polyamide (PA)/aluminium (Al)/polyvinyl chloride (PVC) blister pack or PA/Al/PVC/paper child resistant blister pack containing 30 film coated tablets.

Not all packs may be distributed in New Zealand.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
18 May 2000

10. DATE OF REVISION OF THE TEXT

23 December 2025

Summary table of changes:

Section changed	Summary of new information
4.8	Addition of toxic epidermal necrolysis as a very rare side effect.

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