SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zyban 150 mg prolonged release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bupropion hydrochloride 150 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release 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 as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients.

4.2 Posology and method of administration

Posology

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 to be taken daily for six days, increasing on day seven to 150 mg twice daily.

There should be an interval of at least 8 hours between successive doses.

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

Insomnia is a very common adverse event which can be reduced by avoiding bedtime doses of Zyban (provided there is at least 8 hours between doses).

Paediatric population

Use in patients under 18 years of age is not recommended as the safety and efficacy of Zyban tablets have not been evaluated in these patients.

Elderly

Zyban should be used with caution in older people. Greater sensitivity in some older individuals cannot be ruled out. The recommended dose in older people is 150 mg once a day (see section 4.4).

Hepatic impairment

Zyban should be used with caution in patients with hepatic impairment. Because of increased variability in the pharmacokinetics in patients with mild to moderate impairment the recommended dose in these patients is 150 mg once a day.

Renal impairment

Zyban should be used with caution in patients with renal insufficiency. The recommended dose in these patients is 150 mg once a day (see section 4.4).

Method of administration

Zyban should be used in accordance with smoking cessation guidelines.

Prescribers should assess the patient's motivation to quit. Smoking cessation therapies are more likely to succeed in those patients whom are motivated to quit and have motivational support.

Patients should be treated for 7-9 weeks. If at seven weeks no effect is seen, treatment should be discontinued.

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

Zyban can be taken with or without food (see sections 4.5 and 5.2.).

Discontinuing therapy

Although discontinuation reactions are not expected with Zyban, a tapering-off period may be considered.

4.3 Contraindications

Zyban is contraindicated in patients with hypersensitivity to bupropion or any of the excipients listed in section 6.1.

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 who, at any time during treatment, are undergoing abrupt withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal (in particular benzodiazepines and benzodiazepine-like agents).

Zyban is contraindicated in patients with a current or previous diagnosis of bulimia or anorexia nervosa.

Zyban is contraindicated for use in patients with severe hepatic cirrhosis.

Concomitant use of Zyban and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with Zyban. For reversible MAOIs, a 24 hour period is sufficient.

Zyban is contraindicated in patients with a history of bipolar disorder as it may precipitate a manic episode during the depressed phase of their illness.

Zyban should not be administered to patients being treated with any other medicinal product containing bupropion as the incidence of seizures is dose dependent and to avoid overdosage.

4.4 Special warnings and precautions for use

Seizures

The recommended dose of Zyban must not be exceeded, since bupropion is associated with a dose-related risk of seizure. At doses up to the maximum recommended daily dose (300 mg of Zyban daily), the incidence of seizures 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:

1. 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). For patients prescribed such medicinal products whilst taking Zyban, a maximum dose of 150 mg daily for the remainder of their treatment should be considered.
2. alcohol abuse (see also section 4.3)
3. history of head trauma
4. diabetes treated with hypoglycaemics or insulin
5. use of stimulants or anorectic products.

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

Interactions (see section 4.5)

Due to pharmacokinetic interactions plasma levels of bupropion or its metabolites may be altered, which may increase the potential for undesirable effects (e.g. dry mouth, insomnia, seizures). Therefore care should be taken when bupropion is given concomitantly with medicinal products which can induce or inhibit the metabolism of bupropion.

Bupropion inhibits metabolism by cytochrome P450 2D6. Caution is advised when medicinal products metabolised by this enzyme are administered concomitantly.

In the literature it has been shown that medications that inhibit CYP2D6 may lead to reduced concentrations of endoxifen which is the active metabolite of tamoxifen. Therefore the use of bupropion, which is an inhibitor of CYP2D6, should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Neuropsychiatry

Zyban is a centrally-acting noradrenaline/dopamine reuptake inhibitor. Neuropsychiatric reactions have been reported (see section 4.8). In particular, psychotic and manic symptomatology have been reported mainly in patients with a known history of psychiatric illness.

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 Zyban treatment, and generally occurred early during the treatment course.

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 symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly.

Data in animals suggest a potential for drug abuse. However, studies on abuse liability in humans and extensive clinical experience show that bupropion has low abuse potential.

Hypersensitivity

Zyban should be discontinued if patients experience hypersensitivity reactions during treatment.

Clinicians should be aware that symptoms may progress or recur following the discontinuation of Zyban and should ensure symptomatic treatment is administered for an adequate length of time (at least one week). Symptoms typically include skin rash, pruritus, urticaria or chest pain but more severe reactions may include angioedema, dyspnoea/bronchospasm, anaphylactic shock and erythema multiforme. 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 section 4.8). In most patients symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and resolved over time.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with bupropion treatment (see section 4.8).

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, bupropion should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS, TEN, AGEP, or DRESS with the use of bupropion, the treatment must not be restarted in this patient at any time.

Hypertension

In clinical practice, hypertension, which in some cases may be severe (see section 4.8) 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. A baseline blood pressure should be obtained at the start of treatment with subsequent monitoring, especially in patients with 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.

Brugada syndrome

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.

Specific patient groups

Elderly – Clinical experience with bupropion has not identified any differences in tolerability between older and other adult patients. However, greater sensitivity of some older individuals cannot be ruled out; hence 150 mg once a day is the recommended dose in these patients (see sections 4.2 and 5.2).

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 Zyban should be used with caution in patients with mild to moderate hepatic impairment and 150 mg once a day is the recommended dose in these patients.

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

Renal impairment - Bupropion is mainly excreted into urine as its metabolites. Therefore 150 mg once a day is the recommended dose in patients with renal impairment, as bupropion and its active metabolites may accumulate to a greater extent than usual (see sections 4.2 and 5.2). The patient should be closely monitored for possible undesirable effects that could indicate high drug or metabolite levels.

Interference with urine testing

Having an amphetamine-like chemical structure, bupropion interferes with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for amphetamines. A positive result should usually be confirmed with a more specific method.

Inappropriate routes of administration

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.

Serotonin Syndrome

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when Zyban is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.5). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

4.5 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 increased risk of seizure (see section 4.4).

The effect of bupropion on other medicinal products:

Although not metabolised by the CYP2D6 isoenzyme, bupropion and its main metabolite, hydroxybupropion, inhibit the CYP2D6 pathway. Co-administration of bupropion hydrochloride and desipramine to healthy volunteers known to be extensive metabolisers of the CYP2D6 isoenzyme resulted in large (2- to 5-fold) increases in the C_{max} and AUC of desipramine. Inhibition of CYP2D6 was present for at least 7 days after the last dose of bupropion hydrochloride.

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

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when Zyban is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.4).

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 (see section 4.4).

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

Co-administration of digoxin with bupropion may decrease digoxin levels. Digoxin AUC 0–24 h was decreased and renal clearance was increased in healthy volunteers, based on a cross-study comparison. Clinicians should be aware that digoxin levels may rise on discontinuation of bupropion and the patient should be monitored for possible digoxin toxicity.

The effect of other medicinal products on bupropion:

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6 (see section 5.2). Co-administration of medicinal products that may affect the metabolism of bupropion via CYP2B6 isoenzyme (e.g. CYP2B6 substrates: cyclophosphamide, ifosfamide, and CYP2B6 inhibitors: orphenadrine, ticlopidine, clopidogrel), may result in increased bupropion plasma levels and lower levels of active metabolite hydroxy-bupropion. The clinical consequences of the inhibition of the metabolism of bupropion via CYP2B6 enzyme and the consequent changes in the bupropion-hydroxybupropion ratio are currently unknown.

Since bupropion is extensively metabolised, caution is advised when bupropion is co-administered with medicinal products known to induce metabolism (e.g. carbamazepine, phenytoin, ritonavir, efavirenz) or inhibit metabolism (e.g. valproate), as these may affect its clinical efficacy and safety.

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 twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80% (see section 5.2). 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.

Nicotine, administered transdermally by patches, did not affect the pharmacokinetics of bupropion and its metabolites.

Other interactions:

Smoking is associated with an increase in CYP1A2 activity. After cessation of smoking, reduced clearance of medicinal products metabolised by this enzyme, with subsequent increases in plasma levels, may occur. This may be particularly important for those medicinal products primarily metabolised by CYP1A2 with narrow therapeutic windows (e.g. theophylline, tacrine and clozapine).

The clinical consequences of smoking cessation on other medicinal products that are partially metabolised by CYP1A2 (e.g., imipramine, olanzapine, clomipramine, and fluvoxamine) are unknown. In addition, limited data indicate that the metabolism of flecainide or pentazocine may also be induced by smoking.

Administration of Zyban to patients receiving either levodopa or amantadine concurrently should be undertaken with caution. Limited clinical data suggest a higher incidence of undesirable effects (e.g. nausea, vomiting, and neuropsychiatric events – see section 4.8) in patients receiving bupropion concurrently with either levodopa or amantadine.

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.

Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, concomitant use of Zyban and monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.3) as there is an increased possibility of adverse reactions

from their co-administration. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with Zyban. For reversible MAOIs, a 24 hour period is sufficient.

Studies suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with a high fat meal (see section 5.2).

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 certain congenital cardiovascular malformations specifically ventricular septal defects and left outflow tract heart defects. These findings are not consistent across studies. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Zyban should not be used in pregnancy. Pregnant women should be encouraged to quit smoking without the use of pharmacotherapy.

Breast-feeding

Bupropion and its metabolites are excreted in human breast milk. A decision on whether to abstain from breast-feeding or to abstain from therapy with Zyban should be made taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Zyban therapy to the mother.

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).

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. Zyban has also been reported to cause dizziness and lightheadedness. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain Zyban does not adversely affect their performance.

4.8 Undesirable effects

The list below provides information on the undesirable effects identified from clinical experience, categorised by incidence and System Organ Class body system. It is important to note that smoking cessation is often associated with nicotine withdrawal symptoms (e.g. agitation, insomnia, tremor, sweating), some of which are also recognised as adverse events associated with Zyban.

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); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	Not known	Anaemia, leucopenia and thrombocytopenia
Immune system disorders*	Common	Hypersensitivity reactions such as urticaria
	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.
Metabolism and nutrition disorders	Uncommon	Anorexia
	Rare	Blood glucose disturbances
	Not known	Hyponatraemia
Psychiatric disorders	Very common	Insomnia (see section 4.2)
	Common	Depression (see section 4.4), agitation, anxiety
	Uncommon	Confusion
	Rare	Irritability, hostility, hallucinations, depersonalisation, abnormal dreams including nightmares
	Very rare	Delusions, paranoid ideation, restlessness, aggression
	Not known	Suicidal ideation and suicidal behaviour***, psychosis, dysphemia, panic attack
Nervous system disorders	Common	Tremor, concentration disturbance, headache, dizziness, taste disorders
	Rare	Seizures (see below)**, dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope
	Not known	Serotonin syndrome****
Eye disorders	Uncommon	Visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Palpitations
Vascular disorders	Uncommon	Increased blood pressure (sometimes severe), flushing
	Rare	Vasodilation, postural hypotension
Gastrointestinal disorders	Common	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation

Hepatobiliary disorders	Rare	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous tissue disorders*	Common	Rash, pruritus, sweating.
	Rare	Erythema multiforme and Stevens Johnson syndrome have also been reported. Exacerbation of psoriasis
	Not known	Systemic lupus erythematosus syndrome aggravated, cutaneous lupus erythematosus, acute generalised exanthematous pustulosis, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms
	Very Rare	Alopecia
Musculoskeletal and connective tissue disorders	Rare	Twitching
Renal and urinary disorders	Rare	Urinary frequency and/or retention
	Very rare	Urinary incontinence
General disorders and administration site conditions	Common	Fever
	Uncommon	Chest pain, asthenia

*Hypersensitivity may manifest as skin reactions. See “Immune system disorders” and “Skin and subcutaneous tissue disorders”.

**The incidence of seizures is approximately 0.1% (1/1,000). The most common type of seizures is generalised tonic-clonic seizures, a seizure type which can result in some cases in post-ictal confusion or memory impairment. (see section 4.4).

***Cases of suicidal ideation and suicidal behaviour have been reported during bupropion therapy (see section 4.4).

****Serotonin syndrome may occur as a consequence of an interaction between bupropion and a serotonergic medicinal product such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRI) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 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/or ECG changes such as conduction disturbances (including QRS prolongation), arrhythmias and tachycardia. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate. Although most patients recovered without sequelae, deaths associated with bupropion have been reported rarely in patients ingesting large overdoses of the drug. 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 recommended. No specific antidote for bupropion is known. Further management should be as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 either 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.

Clinical safety

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 study there was no greater proportion of congenital malformations or cardiovascular malformations amongst more than a thousand first trimester exposures to bupropion compared with the use of other antidepressants.

In a retrospective analysis using data from the National Birth Defects Prevention Study, 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. 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 analysis of data from the Slone Epidemiology Center Birth Defects Study found no statistically significant increase of left outflow tract heart defects with maternal bupropion use. However, a statistically significant association was observed for ventricular septal defects following the use of bupropion alone during the first trimester.

5.2 Pharmacokinetic properties

Absorption

After oral administration of 150 mg bupropion hydrochloride as a prolonged release tablet to healthy volunteers, maximum plasma concentrations (C_{max}) of approximately 100 nanograms per ml are observed after about 2.5 to 3 hours. The AUC and C_{max} values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion increase dose proportionally over a dose range of 50-200 mg following single dosing and over a dose range of 300-450 mg/day following chronic dosing. The C_{max} and AUC values of hydroxybupropion are approximately 3 and 14 times higher, respectively, than bupropion C_{max} and AUC values. The C_{max} of threohydrobupropion is comparable with the C_{max} of bupropion, while the AUC of threohydrobupropion is approximately 5 times higher than that of bupropion. Peak plasma levels of hydroxybupropion and threohydrobupropion are reached after about 6 hours following administration of a single dose of bupropion. Plasma levels of erythrohydrobupropion (an isomer of threohydrobupropion, which is also active) are not quantifiable after single dosing with bupropion.

After chronic dosing with bupropion 150 mg bid, the C_{max} of bupropion is similar to values reported after single dosing. For hydroxybupropion and threohydrobupropion, the C_{max} values are higher (about 4 and 7 times respectively) at steady-state than after a single dosing. Plasma levels of erythrohydrobupropion are comparable to steady-state plasma levels of bupropion. Steady-state of bupropion and its metabolites is reached within 5-8 days. The absolute bioavailability of bupropion is not known; excretion data in urine, however, show that at least 87% of the dose of bupropion is absorbed.

Two studies with bupropion SR 150 mg tablets in healthy volunteers suggest that exposure to bupropion may be increased when Zyban tablets are taken with food. When taken following a high fat breakfast, peak plasma concentration of bupropion (C_{max}) increased by 11% and 35% in the two studies, while the overall exposure to bupropion (AUC) increased by 16% and 19%.

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 L. Bupropion, hydroxybupropion and threohydrobupropion bind moderately to plasma proteins (84%, 77% and 42%, respectively).

Bupropion and its active metabolites are excreted in human breast milk. Animal studies show that bupropion and its active metabolites pass the blood-brain barrier and the placenta.

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. The active metabolites are further metabolised to inactive metabolites (some of which have not been fully characterised but may include conjugates) and excreted in the urine.

In vitro studies indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the CYP2B6, while CYP1A2, 2A6, 2C9, 3A4 and 2E1 are less involved. In contrast, formation of threohydrobupropion involves carbonyl reduction but does not involve cytochrome P450 isoenzymes. (see section 4.5)

The inhibition potential of threohydrobupropion and erythrohydrobupropion towards cytochrome P450 has not been studied.

Bupropion and hydroxybupropion are both inhibitors of the CYP2D6 isoenzyme with K_i values of 21 and 13.3µM, respectively (see section 4.5).

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 hydrochloride for 10 to 45 days.

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. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively).

Special patient population:

Renal impairment

The elimination of bupropion and its active major metabolites may be reduced in patients with impaired renal function. Limited data in patients with end-stage renal failure or moderate to severely impaired renal function indicate that exposure to bupropion and/or its metabolites was increased (see section 4.4).

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. (see section 4.4) 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 hydroxybupropion, the mean Cmax was lower (by approximately 70%), the mean AUC tended to be higher (by approximately 30%), the median Tmax was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 4-fold) than in healthy volunteers. For threohydrobupropion and erythrohydrobupropion, the mean Cmax tended to be lower (by approximately 30%), the mean AUC tended to be higher (by approximately 50%), the median Tmax was later (by approximately 20 hrs), and the mean half-life was longer (by approximately 2-fold) than in healthy volunteers. (see section 4.3)

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 older and younger patients, but greater sensitivity in older patients cannot be ruled out. (see section 4.4)

5.3 Preclinical safety data

Reproduction toxicity studies conducted in rats at exposures similar to those obtained at the maximum recommended human dose (based on systemic data on exposure) revealed no adverse effects on fertility, pregnancy and foetal development. Reproduction toxicity studies conducted in rabbits treated with doses up to 7 times the maximum recommended human dose based on a mg/m^2 basis (no systemic data on exposures are available) only revealed a slight increase in skeletal variations (increased incidence of common anatomical variation of an accessory thoracic rib and delayed ossification of phalanges). Moreover at maternally toxic doses, a decrease of rabbits foetal weight was reported.

In animal experiments bupropion doses several times higher than therapeutic doses in humans caused, amongst others, the following dose-related symptoms: ataxia and convulsions in rats, general weakness, trembling and emesis in dogs and increased lethality in both species. Due to enzyme induction in animals but not in humans, systemic exposures in animals were similar to the systemic exposures seen in humans at the maximum recommended dose.

Liver changes are seen in animal studies but these reflect the action of a hepatic enzyme inducer. At recommended doses in humans, bupropion does not induce its own metabolism. This suggests that the hepatic findings in laboratory animals have only limited importance in the evaluation and risk assessment of bupropion.

Genotoxicity data indicate that bupropion is a weak bacterial mutagen, but not a mammalian mutagen, and therefore is of no concern as a human genotoxic agent. Mouse and rat studies confirm the absence of carcinogenicity in these species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Tablet core</u>

Microcrystalline cellulose
Hypromellose
Cysteine hydrochloride monohydrate
Magnesium stearate

<u>Film coat</u>

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Carnauba wax

Printing ink

Iron oxide black (E172)
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Cartons containing cold form foil / foil child-resistant blister packs (PA-Alu-PVC / Paper-Alu)

30, 40, 50, 60 or 100 tablets are supplied in each pack. Each blister strip contains 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Glaxo SmithKline (Ireland) Ltd
12 Riverwalk,
Citywest Business Campus,
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER

PA1077/17/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 01 December 2009

10. DATE OF REVISION OF THE TEXT

23 July 2026