WELLBUTRIN SR
Bupropion hydrochloride

Qualitative and Quantitative Composition

WELLBUTRIN SR is available as sustained-release, film-coated tablet each containing 150 mg of bupropion hydrochloride.

CLINICAL INFORMATION

Indications

WELLBUTRIN SR is indicated for the treatment of major depressive episodes.

Dosage and Administration

Pharmaceutical form: Sustained-release (SR) film-coated tablet.

WELLBUTRIN SR 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.

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

Use in adults

The maximum single dose of *WELLBUTRIN SR* is 150 mg.

WELLBUTRIN SR tablets should be taken twice daily with an interval of at least 8 hours between successive doses.

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 may be considered.

Initial treatment
Dosing with *WELLBUTRIN SR* tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150 mg initial dose is adequately tolerated, patients who are not responding adequately may benefit from an increase to 300 mg/day, given as 150 mg twice daily, after an interval of at least one week. There should be an interval of at least 8 hours between successive doses.

The maximum daily dose should not exceed 300 mg/day.

Maintenance therapy

It is generally agreed that acute episodes of depression require 6 months or longer of antidepressant drug treatment.

Use in children and adolescents

WELLBUTRIN SR is not indicated for use in children or adolescents aged less than 18 years (see *Warnings and Precautions*). The safety and efficacy of *WELLBUTRIN SR* tablets in patients under 18 years of age have not been established.

Use in elderly

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

Use in patients with liver impairment

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

WELLBUTRIN SR 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 *Warnings and Precautions*).

Use in patients with renal impairment

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

Contraindications

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

WELLBUTRIN SR is contraindicated in patients with a seizure disorder.

WELLBUTRIN SR is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives.

WELLBUTRIN SR 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.

WELLBUTRIN SR 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 *WELLBUTRIN SR* and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with *WELLBUTRIN SR* tablets.

Warnings and Precautions

Seizures

The recommended dose of *WELLBUTRIN SR* should not be exceeded, since bupropion is associated with a dose-related risk of seizure. The incidence of seizure with *WELLBUTRIN SR* at doses up to 300 mg/day is approximately 0.1%.

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

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

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

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

Hypersensitivity reactions

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

Hepatic impairment

Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised. No statistically significant differences in the pharmacokinetics of bupropion

were observed in patients with mild to moderate hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients. Therefore, *WELLBUTRIN SR* should be used with caution in patients with hepatic impairment and reduced frequency of dosing should be considered in patients with mild to moderate hepatic cirrhosis (see *Dosage and Administration* and *Pharmacokinetics*).

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

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

Renal impairment

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

Elderly patients

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

Children and adolescents <18 years

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

Clinical worsening and suicide risk in adults with psychiatric disorders

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening (including development of new

symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

Patients with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

In addition, 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.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some neuropsychiatric symptoms could be related either to the underlying disease state or the drug therapy (see *Neuropsychiatric symptoms including mania and bipolar disorder* below; *Adverse Reactions*).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Neuropsychiatric symptoms including mania and bipolar disorder

Neuropsychiatric symptoms have been reported (see *Adverse Reactions*). In particular, psychotic and manic symptomatology has been observed, mainly in patients with a history of psychiatric illness. Additionally, a major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Limited clinical data on use of bupropion in combination with mood stabilisers in patients with a history of bipolar disorder suggests a low rate of switch to mania. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that *WELLBUTRIN SR* is not approved for use in treating bipolar depression.

Cardiovascular disease

There is limited clinical experience of the use of bupropion to treat depression in patients with cardiovascular disease. Care should be exercised if *WELLBUTRIN SR* is used in these patients. However, bupropion was generally shown to be well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease.

Blood pressure

In a study in non-depressed subjects (including both smokers and non-smokers) with untreated Stage I hypertension, bupropion did not produce a statistically significant effect on blood pressure. However, spontaneous reports of increased blood pressure (sometimes severe) have been received (see *Adverse Reactions*), and concomitant use of bupropion and a Nicotine Transdermal System may result in elevations of blood pressure (see *Interactions*).

Serotonin syndrome

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 *Interactions*).

Serotonin syndrome has also been reported with bupropion-only overdose (see *Overdose*).

Inappropriate routes of administration

Bupropion 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 intranasally or by parenteral injection.

Interactions

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

Although bupropion is not metabolised by the CYP2D6 isoenzyme, *in vitro* human P450 studies have shown that bupropion and hydroxybupropion are inhibitors of the CYP2D6 pathway. In a human pharmacokinetic study, administration of bupropion increased plasma levels of desipramine. This effect was present for at least 7 days after the last dose of bupropion. Therefore, concomitant therapy with drugs predominantly metabolised by this isoenzyme (such as certain beta-blockers, antiarrhythmics, selective serotonin

reuptake inhibitors (SSRIs), tricyclic antidepressants, antipsychotics) should be initiated at the lower end of the dose range of the concomitant medication. If *WELLBUTRIN SR* is added to the treatment regimen of a patient already receiving a medication metabolised by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index (see *Pharmacokinetics*).

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

Although citalopram is not primarily metabolised by CYP2D6, in one study, bupropion increased the 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 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%. 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 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 bupropion treatment. The consumption of alcohol during *WELLBUTRIN SR* 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 *Warnings and Precautions*).

Limited clinical data suggest a higher incidence of neuropsychiatric adverse events in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of *WELLBUTRIN SR* to patients receiving either levodopa or amantadine concurrently should be undertaken with caution using small initial doses and gradual dose increases.

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.

Concomitant use of *WELLBUTRIN SR* and a Nicotine Transdermal System (NTS) may result in elevations of blood pressure.

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

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

Interactions involving laboratory tests

WELLBUTRIN SR 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.

Pregnancy and Lactation

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 *Non-Clinical Information*).

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 prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe *WELLBUTRIN SR* 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%).

A retrospective, managed-care database study (n=7,005 infants) using United Healthcare data showed that infants exposed to bupropion during the first trimester (n=1,213) were at no greater risk for congenital malformations overall (prevalence 23.1/1,000 vs 23.2/1,000; adjusted OR = 0.95; 95% CI 0.62, 1.45) or cardiovascular malformations (prevalence 10.7/1,000 vs 10.8/1,000; adjusted OR = 0.97; 95% CI 0.52, 1.80) when compared to infants exposed to other antidepressants (n=4,743) during the first trimester. There were also no increased risk observed for either congenital malformations overall (prevalence 23.1/1,000 vs 21.9/1,000; adjusted OR = 1.00; 95% CI 0.57, 1.73) or cardiovascular malformations (prevalence 10.7/1,000 vs 9.5/1,000; adjusted OR = 1.07;

95% CI 0.48, 2.40) in infants exposed to bupropion during the first trimester as compared to those exposed to bupropion outside the first trimester (n=1,049).

In a retrospective case-control analysis using data from the National Birth Defects Prevention Study, there were 12,383 case infants and 5,869 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 7,913 infant cases of cardiac defects and 8,611 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.

Lactation

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

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

The list below provides information on the undesirable effects identified from clinical experience, categorised by System Organ Class.

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

Immune system disorders*

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

**** See also "Skin and subcutaneous tissue disorders".***

Metabolism and nutrition disorders

Common:	Anorexia
Uncommon:	Weight loss
Very Rare:	Blood glucose disturbances, hyponatraemia.

Psychiatric disorders

Very Common:	Insomnia
Common:	Agitation, anxiety
Uncommon:	Depression, confusion
Very Rare:	Aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams, depersonalisation, delusions, paranoid ideation, panic attack.

Nervous system disorders

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

Eye disorders

Common:	Visual disturbance.

Ear and labyrinth disorders

Common:	Tinnitus.

Cardiac disorders

Uncommon:	Tachycardia
Very Rare:	Palpitations.

Vascular disorders

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

Gastrointestinal disorders

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

Hepatobiliary disorders

Very Rare:	Elevated liver enzymes, jaundice, hepatitis.

Skin and subcutaneous tissue disorders*

Common:	Rash, pruritus, sweating
Very Rare:	Erythema multiforme, Stevens-Johnson syndrome, systemic lupus erythematosus syndrome aggravated, cutaneous lupus erythematosus, acute generalised exanthematous pustulosis.

**** See also "Immune system disorders".***

Musculoskeletal and connective tissue disorders

Very Rare:	Twitching.

Renal and urinary disorders

Very Rare:	Urinary frequency and/or retention, urinary incontinence.

General disorders and administration site conditions

Common:	Fever, chest pain, asthenia.

Overdose

Symptoms and Signs

In addition to those events reported under *Adverse Reactions*, 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 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

Pharmacodynamics

ATC Code

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

Mechanism of Action

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin), and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics

Absorption

Following oral administration of *WELLBUTRIN SR* to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 3 hours. Three studies suggest that exposure to bupropion may be increased when sustained-release bupropion tablets are taken with food. When taken following food, peak plasma concentration of bupropion (C_{max}) increased by 11%, 16% and 35% in the three studies. The overall exposure to bupropion (AUC) increased by 17%, 17% and 19% in the three studies.

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

Distribution

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

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 *WELLBUTRIN SR*. Erythrohydrobupropion cannot be measured in the plasma after a single dose of *WELLBUTRIN SR*. 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*).

Bupropion and hydroxybupropion are both relatively weak competitive 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 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 *WELLBUTRIN SR* is administered with substrates for the CYP2D6 pathway (see *Interactions*).

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

Patients with renal impairment

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

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 *Warnings and Precautions*).

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.

Non-Clinical Information

Carcinogenesis/mutagenesis

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

Reproductive toxicology

A two-generation reproductive and fertility study in Long Evans rats receiving 100, 200, 300 mg/kg bupropion daily by gavage revealed no treatment or compound related effects observed on mating or fertility performance. No compound related effects were observed in reproductive ability, fertility, gross anatomic abnormalities, foetal deaths or pup survival and growth during lactation. In F1 generation females, no compound related effects were observed on lactation, body weight at sacrifice, reproduction performance and post-mortem findings. Similarly, no compound related findings were observed in the

clinical condition, reproductive performance or necropsy of the F1 males. In F2 generation, no compound related effects were observed on the male:female ratio of pups, survival or body weight. No compound related effects were observed on necropsy.

In studies conducted in rats and rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of foetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased foetal weights were seen at 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

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 man there is no evidence of any enzyme induction, which suggests that the hepatic findings in the laboratory animals have only limited importance in the evaluation and risk assessment of bupropion.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet Core
Microcrystalline cellulose, Hypromellose, Cysteine hydrochloride, Magnesium stearate, Purified water

Film Coat
White colour concentrate (Opadry OY-7300 White or Opadry YS-1-18202-A White), Carnauba wax, Purified water

Storage

The storage conditions are detailed on the packaging.

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