Versión GDSv34-IPIv18

Wellbutrin XL

Bupropion hydrochloride

Qualitative and Quantitative Composition

WELLBUTRIN XL is available as:

- tablets containing 150 mg of bupropion hydrochloride
- tablets containing 300 mg of bupropion hydrochloride

Clinical Information

Indications

WELLBUTRIN XL is indicated for the treatment of major depressive episodes. Following satisfactory response, continuation with *WELLBUTRIN XL* therapy is effective in preventing relapse.

Dosage and Administration

Pharmaceutical form: Extended release (XL) film-coated tablet.

WELLBUTRIN XL 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.

WELLBUTRIN XL tablets can be taken with or without food.

Use in Adults

The maximum single dose of *WELLBUTRIN XL* is 300 mg.

There should be an interval of at least 24 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 24 hours between doses) or if clinically indicated, dose reduction.

Initial Treatment

The initial dose of WELLBUTRIN XL tablets is 150 mg taken as a single daily dose in the morning. Patients who are not responding adequately to a dose of 150 mg/day may benefit from an increase to the usual adult target dose of 300 mg/day, given once daily

The onset of action with bupropion has been noted as early as 14 days after starting therapy. As with all antidepressants the full antidepressant effect of *WELLBUTRIN XL* may not be evident until after several weeks of treatment.

Switching PATIENTS from *WELLBUTRIN SR* Tablets

When switching patients from *WELLBUTRIN SR* (sustained release) tablets to *WELLBUTRIN XL* tablets, give the same total daily dose when possible. Patients who are currently being treated with *WELLBUTRIN SR* tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to *WELLBUTRIN XL* 300 mg once daily.

Maintenance therapy

It is generally agreed that acute episodes of depression require 6 months or longer of antidepressant drug treatment. Bupropion (300 mg/day) was shown to be efficacious during long-term (up to 1 year) treatment.

Use in Children and Adolescents

WELLBUTRIN XL is not indicated for use in children or adolescents aged less than 18 years (*see Warnings and Precautions*). The safety and efficacy of *WELLBUTRIN XL* 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 hepatic Impairment

WELLBUTRIN XL 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 XL 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 active metabolites may accumulate in such patients to a greater extent than usual (*see Warnings and Precautions*).

Contraindications

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

WELLBUTRIN XL is contraindicated in patients with a seizure disorder.

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

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

Warnings and Precautions

Seizures

The recommended dose of *WELLBUTRIN XL* should not be exceeded, since bupropion is associated with a dose-related risk of seizure. The overall incidence of seizure with *WELLBUTRIN XL* in clinical trials at doses up to 450 mg/day was 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 XL* should be administered with extreme caution to patients with one or more conditions pre disposing to a lowered seizure threshold. These include:

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

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

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

Hypersensitivity Reactions

WELLBUTRIN XL 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 XL* 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 XL 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. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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.

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 XL* is used in these patients. However, bupropion was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease (*see Pharmacological Properties and Clinical Studies*).

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*).

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 intra-nasally or by parenteral injection.

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*).

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 XL* is co-administered with drugs known to affect the CYP2B6 isoenzyme (e.g. orphenadrine, cyclophosphamide, ifosfamide, ticlopidine, clopidogrel).

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

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

Coadministration 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.

Interactions Involving Laboratory Tests

WELLBUTRIN XL 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 XL* 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: 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.

Lactation

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

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 XL* tablets do not adversely affect their performance.

Adverse Reactions

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

Body (general):

Fever, chest pain, asthenia.

Cardiovascular:

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

CNS:

Seizures (*see Warnings and Precautions*), insomnia, tremor, dystonia, ataxia, Parkinsonism, twitching, incoordination, concentration disturbance, headache, dizziness, depression, confusion, delusions, paranoid ideation, panic attack, hallucinations, agitation, restlessness, anxiety, irritability, hostility, aggression, depersonalisation, abnormal dreams, memory impairment, paraesthesia, dysphemia.

Endocrine and Metabolic:

Anorexia, weight loss, blood glucose disturbances, hyponatraemia

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, systemic lupus erythematosus syndrome aggravated and cutaneous lupus erythematosus, acute generalised exanthematous pustulosis and alopecia have also been rarely reported.

Special Senses:

Tinnitus, visual disturbance, taste disorders.

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.

In a study in healthy volunteers, no clinically significant effect of extended release bupropion tablets (450 mg/day) compared with placebo was observed on QTcF interval after 14 days of dosing to steady state.

Pharmacokinetics

Absorption

Following oral administration of *WELLBUTRIN XL* to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours.

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

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

Distribution

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

The extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion. These may have clinical importance, as their plasma concentrations are as high or higher than those of bupropion.

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

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

In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours after administration of extended release bupropion.

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 14C-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 14C 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.

The insoluble shell of the extended release tablet may remain intact during gastrointestinal transit and be eliminated in the faeces.

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 hours), 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.

Clinical Studies

The efficacy and tolerability of *WELLBUTRIN XL* has been examined in 7 double blind studies.

In one of two identical flexible-dose studies (WXL101497, n=576) *WELLBUTRIN XL* (150 to 300 mg/day) was statistically significantly superior to placebo on the primary parameter, change from baseline in Montgomery-Asberg Depression Rating Scale the (MADRS) total score (p=0.006). Statistically significant effects were also found for a number of secondary endpoints including MADRS responders and remitters, Clinical Global Impressions (CGI) severity and global improvement, Sheehan Disability Scale, MEI and Q-LES-Q. The efficacy of *WELLBUTRIN XL* in this study was broadly similar to that of the comparator, venlafaxine. In the second study (AK130939, n=591), *WELLBUTRIN XL* did not separate significantly from placebo for the primary parameter, change from baseline in MADRS total score (p=0.146) although statistically significant effects were seen for venlafaxine (p<0.001 versus placebo).

WELLBUTRIN XL was shown to be of benefit in elderly patients in a placebo controlled flexible dose design study (AK130940, n=420) conducted over the dose range 150-300 mg/day. Statistically significant effects were shown for MADRS responders, CGI global improvement, Sheehan Disability Scale, MEI and Q-LES-Q although only a trend was seen on the primary parameter, change from baseline in MADRS total score (p=0.085).

Two placebo and escitalopram controlled studies (AK130926, n=424 and AK130927, n=425) over the *WELLBUTRIN XL* dose range of 300-450 mg/day were conducted in adults. After 8 weeks of treatment, *WELLBUTRIN XL* subjects reported significantly less orgasm dysfunction than escitalopram treated subjects in each study (p=0.014 and p<0.001 versus escitalopram) although statistical significance for *WELLBUTRIN XL* versus placebo was not shown for either study on the co-primary parameter, change from baseline in Hamilton Depression Rating Scale (HAMD) total score (p=0.179 and p=0.184 versus placebo, respectively). *WELLBUTRIN XL* separated from placebo on a number of secondary endpoints: mean change from randomisation in Hospital Anxiety and Depression scale total score in the individual studies; HAMD-17 remission rates in study 1; and CGI-S mean change from randomisation and CGI-I responder rates in study 2.

In an 8-week study of adult patients with major depressive disorder (MDD) and reduced levels of pleasure, interest and energy (AK130931, n=274), *WELLBUTRIN XL* showed statistically significantly greater improvement over placebo for the primary parameter, change from baseline in IDS self-rated scale (p=0.018). Statistical significance was also shown for a number of secondary endpoints including the clinician rated IDS, CGI severity of illness and CGI improvement.

In an active controlled 12-week study of *WELLBUTRIN XL* (300-450 mg/day) versus venlafaxine in adult patients with MDD (WXL100368, n=348), *WELLBUTRIN XL* showed significantly less negative impact on sexual functioning (the primary parameter; p=0.005) and an overall efficacy similar to that of venlafaxine. *WELLBUTRIN XL* and venlafaxine were comparable as evaluated by the HAMD-17 total score, the depressed mood item, Bech melancholia subscale, HAMD-17 responder rates and the change from randomisation in the CGI-S. Statistical significance in favour of *WELLBUTRIN XL* over venlafaxine was shown for the proportion of HAMD remitters and CGI-I responders.

Non-Clinical Information

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.

Pharmaceutical Information

List of Excipients

Tablet Core

Polyvinyl alcohol

Glyceryl behenate

Tablet Coat

Ethylcellulose 100

Polyethylene glycol 1450

Povidone

Methacrylic Acid Copolymer Dispersion (Eudragit L30 D-55)

Silicon dioxide

Triethyl citrate

Edible black ink (for printing)

Shelf-Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Nature and Contents of Container

HDPE bottles with a child-resistant closure.

Incompatibilities

None reported.

Use and Handling

None.

Not all presentations are available in every country.

Version number: GDSv34-IPIv18
Date of issue: 03 November 2023