The content of this leaflet was updated according to the guidelines of the Ministry of Health in November 2017

WELLBUTRIN XR

1. NAME OF THE MEDICINAL PRODUCT

WELLBUTRIN XR 150 mg.

WELLBUTRIN XR 300 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bupropion hydrochloride 150 mg or 300 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablet.

150 mg tablet: Creamy white to pale yellow round tablet imprinted with "GS5FV" in black ink on one side and the other side plain.

300 mg tablet: Creamy white to pale yellow round tablet imprinted with "GS5YZ" in black ink on one side and the other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Following satisfactory response, continuation with WELLBUTRIN XR therapy is effective in preventing relapse.

4.2 Posology and method of administration

Posology

Use in Adults

The recommended starting dose is 150 mg, given once daily. An optimal dose was not established in clinical studies. If no improvement is seen after 4 weeks treatment at 150 mg, the dose may be increased to 300 mg, given once daily. There should be an interval of at least 24 hours between successive doses.

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

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

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).

Pediatric Population

WELLBUTRIN XR is not indicated for use in children or adolescents aged less than 18 years (see section 4.4). The safety and efficacy of WELLBUTRIN XR in patients under 18 years of age have not been established.

Older people

Efficacy has been shown equivocally in older people. In a clinical trial, older people followed the same dose regimen as for the adults (see Use in Adults). Greater sensitivity in some older individuals cannot be ruled out.

Patients with hepatic impairment

WELLBUTRIN XR should be used with caution in patients with hepatic impairment (see section 4.4). 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.

Patients with renal impairment

The recommended dose in these patients is 150mg once a day, as bupropion and its active metabolites may accumulate in such patients to a greater extent than usual (see section 4.4).

Method of administration

WELLBUTRIN XR 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 XR tablets can be taken with or without food.

Discontinuing therapy

Although discontinuation reactions (measured as spontaneously reported events rather than on rating scales) were not observed in clinical studies with WELLBUTRIN XR, a tapering off period may be considered. Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines and a rebound effect or discontinuation reactions cannot be ruled out.

4.3 Contraindications

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

WELLBUTRIN XR is contraindicated in patients taking any other medicinal product containing bupropion, as the incidence of seizures is dose dependent and to avoid overdosage.

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

WELLBUTRIN XR is contraindicated in patients with a known central nervous system tumour.

WELLBUTRIN XR 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 a risk of seizures on withdrawal (in particular benzodiazepines and benzodiazepine-like agents).

WELLBUTRIN XR is contraindicated for use in patients with severe hepatic cirrhosis.

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

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

4.4 Special warnings and precautions for use

Seizures

The recommended dose of modified release bupropion tablets should not be exceeded, since bupropion is associated with a dose-related risk of seizure. The overall incidence of seizure with modified release bupropion tablets in clinical trials at doses up to 450 mg/day was approximately 0.1%.

There is an increased risk of seizures occurring with the use of WELLBUTRIN XR in the presence of predisposing risk factors which lower the seizure threshold. Therefore WELLBUTRIN XR should be administered with caution to patients with one or more conditions predisposing to a lowered seizure threshold.

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

- Concomitant administration of other medicinal products known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines)
- Alcohol abuse (see also section 4.3)
- History of head trauma
- Diabetes treated with hypoglycaemics or insulin
- Use of stimulants or anorectic products

WELLBUTRIN XR 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 concurrently.

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

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). 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 until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour 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; see section 4.8).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medicinal product, in patients who experience 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 section 4.8). In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known 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.

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

Clinical experience with bupropion in patients receiving electroconvulsive therapy (ECT) is limited. Caution should be exercised in patients receiving ECT therapy concomitantly with bupropion treatment.

<u>Hypersensitivity</u>

WELLBUTRIN XR should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may progress or recur following the discontinuation of WELLBUTRIN XR 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, erythema multiforme or Stevens - Johnson syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and

other symptoms suggestive of delayed hypersensitivity (see section 4.8). In most patients symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and resolved over time.

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 it is used in these patients. However, bupropion was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease (see section 5.1).

Blood pressure

Bupropion has been shown not to induce significant increases in blood pressure in non-depressed patients with Stage I hypertension. However, 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. 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 WELLBUTRIN XR if a clinically significant increase in blood pressure is observed.

Concomitant use of bupropion and a nicotine transdermal system may result in elevations of blood pressure.

Specific patient groups

Pediatric population - 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.

Patients with 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 XR should be used with caution in patients with mild to moderate hepatic impairment (see section 4.2).

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

Patients with renal impairment– Bupropion is mainly excreted into the urine as its metabolites. Therefore in patients with renal impairment, bupropion and its active metabolites may accumulate to a greater extent than usual. The patient should be closely monitored for possible undesirable effects (e.g. insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels (see section 4.2).

Older people – Efficacy has been shown equivocally in older people. In a clinical trial, older people followed the same dose regimen as for the adults (see sections 4.2 Use in Adults and 5.2). Greater sensitivity in some older individuals cannot be ruled out.

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

WELLBUTRIN XR 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.

4.5 Interaction with other medicinal products and other forms of interaction

Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, concomitant use of WELLBUTRIN XR 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 WELLBUTRIN XR. For reversible MAOIs a 24 hour period is sufficient.

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 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.

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), antipsychotics (e.g. risperidone, thioridazine), beta-blockers (e.g. metoprolol), serotonin selective reuptake inhibitors (SSRIs) and Type 1C antiarrhythmics (e.g. propafenone, flecainide). If WELLBUTRIN XR 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 WELLBUTRIN XR should be carefully compared with the potential risks.

Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g. tamoxifen), may have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion (see section 4.4).

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.

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, clopidogrel), may result in increased bupropion plasma levels and lower levels of active metabolite hydroxybupropion. 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 coadministered 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. The clinical consequences of the reduced exposure are unclear, but may include decreased efficacy in the treatment of major depression. 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.

Other interaction information

Administration of WELLBUTRIN XR 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 bupropion treatment. The consumption of alcohol during WELLBUTRIN XR treatment should be minimised or avoided.

There have been no pharmacokinetic studies with bupropion and co-administered benzodiazepines. Based on *in vitro* metabolic pathways, there is no basis for such an interaction. After coadministration of bupropion with diazepam in healthy volunteers, there was less sedation than when diazepam was administered alone.

There has been no systematic evaluation of the combination of bupropion with antidepressants (other than desipramine and citalopram), benzodiazepines (other than diazepam), or neuroleptics. There has also been limited clinical experience with St Johns Wort.

Concomitant use of WELLBUTRIN XR and a nicotine transdermal system (NTS) may result in elevations of blood pressure.

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). WELLBUTRIN XR should not be used during pregnancy unless the clinical condition of the woman requires treatment with bupropion and alternative treatments are not an option.

Breastfeeding

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 WELLBUTRIN XR should be made taking into account the benefit of breast-feeding to the newborn/infant and the benefit of WELLBUTRIN XR 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 skill. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain WELLBUTRIN XR 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.

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, leukopenia and thrombocytopenia
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.
Metabolism and nutrition disorders	Common	Anorexia
	Uncommon	Weight loss
	Very Rare	Blood glucose disturbances
	Not Known	hyponatraemia
Psychiatric disorders	Very common	Insomnia (see section 4.2)
	Common	Agitation, anxiety
	Uncommon	Depression (see section 4.4), confusion
	Very rare	Aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including nightmares, depersonalisation, delusions, paranoid ideation

	Not known	Suicidal ideation and suicidal behaviour***, psychosis
Nervous system disorders	Very Common	Headache
	Common	Tremor, dizziness, taste disorders
	Uncommon	Concentration disturbance
	Rare	Seizures (see below)**
	Very Rare	Dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope
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, exacerbation of psoriasis
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

* 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 or early after treatment discontinuation (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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

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 electrocardiogram (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.

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 of action of bupropion as an antidepressant is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Clinical efficacy

The antidepressant activity of bupropion was studied in a clinical programme involving a total of 1155 WELLBUTRIN XR patients and 1868 WELLBUTRIN SR patients with Major Depressive Disorder (MDD). Seven of the studies examined the efficacy of WELLBUTRIN XR: 3 were conducted in the EU at doses up to 300 mg/day and 4 were conducted in the US over a flexible dose range of up to 450 mg/day. In addition, 9 studies in MDD with WELLBUTRIN SR are considered to be supportive based on the bioequivalence of WELLBUTRIN XR (once daily) to the SR (twice daily) tablet.

WELLBUTRIN XR demonstrated statistical superiority over placebo as measured by improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score in 1 of 2 identical studies utilising doses in the range 150-300 mg. Response and remission rates were also statistically significantly higher with WELLBUTRIN XR compared to placebo. In a third study in elderly patients, statistical superiority over placebo was not achieved on the primary parameter, mean change from baseline in MADRS (Last Observation Carried Forward endpoint) although statistically significant effects were seen on a secondary (Observed Case) analysis.

Significant benefit was shown on the primary endpoint in 2 of 4 US studies with WELLBUTRIN XR (300-450 mg). Of the 2 positive studies, one was a placebo controlled study in patients with MDD and one was an active controlled study in patients with MDD.

In a relapse prevention study, patients responding to 8 weeks of acute treatment with open-label WELLBUTRIN SR (300 mg/day) were randomised to either WELLBUTRIN SR or placebo for a further 44 weeks. WELLBUTRIN SR demonstrated a statistically significant superiority compared to placebo ($P < 0.05$) on the primary outcome measure. The incidence of maintenance of effect during the 44 week double blind follow-up period was 64% and 48% for WELLBUTRIN SR and placebo, respectively.

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.

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

5.2 Pharmacokinetic properties

Absorption

After oral administration of 300 mg bupropion hydrochloride once daily as the modified release tablet to healthy volunteers, maximum plasma concentrations (Cmax) of approximately 160 ng/ml are observed at approximately 5 hours. At steady state, the Cmax and AUC values of hydroxybupropion are approximately 3 and 14 times that of bupropion, respectively. The Cmax of threohydrobupropion at steady state is similar to that of bupropion and the AUC is approximately 5 times higher while the plasma concentrations of erythrohydrobupropion are comparable to those of bupropion. Peak plasma levels of hydroxybupropion are reached at 7 hours while those for threohydrobupropion and erythrohydrobupropion are reached at 8 hours. The AUC and Cmax values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion increase dose proportionally over a dose range of 50-200 mg following single doses and over a dose range of 300-450 mg/day following chronic dosing.

The absolute bioavailability of bupropion is not known; urinary excretion data, however, show that at least 87% of the dose of bupropion is absorbed.

The absorption of bupropion modified release tablets is not significantly influenced when taken concurrently with food.

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. Positron Emision Tomography studies in healthy volunteers demonstrate that bupropion penetrates the CNS and binds to the striatal dopamine reuptake transporter (approximately 25% at 150 mg twice daily).

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).

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) 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 modified release tablet may remain intact during gastrointestinal transit and be eliminated in the faeces.

Special Patient Groups:

Patients with 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).

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 (see section 4.4). 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 hydroxybupropion, the mean C_{max} was lower (by approximately 70%), the mean AUC tended to be higher (by approximately 30%), the median T_{max} 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 C_{max} tended to be lower (by approximately 30%), the mean AUC tended to be higher (by approximately 50%), the median T_{max} 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).

Older people

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).

In-vitro release of bupropion with alcohol

In-vitro tests showed that at high alcohol concentrations (up to 40%), bupropion is released more rapidly from the modified release formulation (up to 20% dissolved at 2 hours) (see section 4.5).

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/m2 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

Tablet Core:

Polyvinyl Alcohol
Glyceryl Dibehenate

Tablet Coating:

First Coating:	Second Coating:
Ethyl Cellulose	Macrogol 1450
Povidone K-90	Methacrylic Acid Ethyl Ecrylate Copolymer Dispersion (Eudragit L30 D-55)
Macrogol 1450	Silicon Dioxide
	Triethyl Citrate

Printing Ink:

Black Printing Ink (Opacode S-1-17823).
Opacode S-1-17823 consists of Shellac Glaze ~45% (20% Esterified), Iron Oxide Black (E172), and Ammonium Hydroxide 28%.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging.

6.4 Special precautions for storage

Store below 25°C.

Store in the original package in order to protect from moisture and light.

Use within 30 days after opening.

6.5 Nature and contents of container

White opaque high density polyethylene (HDPE) bottles containing a combination charcoal/silica gel desiccant canister and closed with a child-resistant closure that includes an induction heat seal membrane.

150 mg: 7, 30 and 90 (3X30) tablets.

300 mg: 7, 30 and 90 (3X30) tablets.

Not all pack sizes may be marketed.

7. Manufacturer: Aspen Bad Oldesloe GmbH, Bad Oldsloe, Germany.

8. License Holder: GlaxoSmithKline (Israel) Ltd, 25 Basel St., Petach Tikva.

9. License number: Wellbutrin XR 150mg tablets 140-05-31653
Wellbutrin XR 300mg tablets 140-06-31654

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Well DR v7