

Summary of Product Characteristics

Wellinta 150 mg sustained release film coated tablets

1. Name of the medicinal product

Wellinta 150 mg sustained release film coated tablets.

2. Qualitative and quantitative composition

Each tablet contains bupropion hydrochloride 150 mg.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Sustained release film coated tablets.

Red round, film-coated, engraved (H) from one side.

4. Clinical particulars

4.1 Therapeutic indications

Wellinta tablets are indicated as an aid to smoking cessation in combination with motivational support in nicotine dependent patients.

4.2 Posology and method of administration

Posology

Use in Adults

It is recommended that treatment is started while the patient is still smoking and a "target stop date" set within the first two weeks of treatment with **Wellinta**, preferably in the second week.

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

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

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

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

Paediatric population

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

Older people

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

Patients with hepatic impairment

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

Patients with renal impairment

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

Method of administration

Wellinta should be used in accordance with smoking cessation guidelines.

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

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

Wellinta 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.

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

Discontinuing therapy

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

4.3 Contraindications

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

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

Wellinta is contraindicated in patients with a known central nervous system (CNS) tumour.

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

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

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

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

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

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

4.4 Special warnings and precautions for use

Seizures

The recommended dose of **Wellinta** must not be exceeded, since bupropion is associated with a dose-related risk of seizure. At doses up to the maximum recommended daily dose (300mg of **Wellinta** daily), the incidence of seizures is approximately 0.1% (1/1,000).

There is an increased risk of seizures occurring with the use of **Wellinta** in the presence of predisposing risk factors which lower the seizure threshold. **Wellinta** must not be used in patients with predisposing risk factors unless there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure. In these patients, a maximum dose of 150mg daily should be considered for the duration of treatment.

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

- concomitant administration of other medicinal products known to lower the seizure threshold (e.g., antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines). For patients prescribed such medicinal products whilst taking **Wellinta**, a maximum dose of 150mg daily for the remainder of their treatment should be considered.
- alcohol abuse (see also section 4.3)
- history of head trauma
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products.

Wellinta 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 metabolized by this enzyme are administered concomitantly.

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

Neuropsychiatry

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

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and behavior (including suicide attempt), has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during **Wellinta** treatment, and generally occurred early during the treatment course.

Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behaviour associated with antidepressant use compared to placebo in patients less than 25 years old.

Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly.

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

Hypersensitivity

Wellinta should be discontinued if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may progress or recur following the discontinuation of **Wellinta** 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. These symptoms may resemble serum sickness (see section 4.8). In most patients, symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and resolved over time.

Hypertension

In clinical practice, hypertension, which in some cases may be severe (see section 4.8) and require acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. This has been observed in patients with and without pre-existing hypertension. A baseline blood pressure should be obtained at the start of treatment with subsequent monitoring, especially in patients with pre-existing hypertension. Consideration should be given to discontinuation of **Wellinta** if a clinically significant increase in blood pressure is observed.

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

Specific patient groups

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

Patients with hepatic impairment - Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized. 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, **Wellinta** should be used with caution in patients with mild to moderate hepatic impairment and 150 mg once a day is the recommended dose in these patients.

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

Patients with renal impairment - Bupropion is mainly excreted into urine as its metabolites. Therefore 150 mg once a day is the recommended dose in patients with renal impairment, as bupropion and its active metabolites may accumulate to

a greater extent than usual (see sections 4.2 and 5.2). The patient should be closely monitored for possible undesirable effects that could indicate high drug or metabolite levels.

Interference with urine testing

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

Inappropriate routes of administration

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

Serotonin Syndrome

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when **Wellinta** is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin

Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.5). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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

4.5 Interaction with other medicinal products and other forms of interaction

In patients receiving medicinal products known to lower the seizure threshold, **Wellinta** must only be used if there is a compelling clinical justification for which

the potential medical benefit of smoking cessation outweighs the increased risk of seizure (see section 4.4).

The effect of bupropion on other medicinal products:

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

Concomitant therapy with medicinal products with narrow therapeutic indices that are predominantly metabolized by CYP2D6 should be initiated at the lower end of the dose range of the concomitant medicinal product. Such medicinal products include certain antidepressants (e.g. desipramine, imipramine, paroxetine), antipsychotics (e.g. risperidone, thioridazine), beta-blockers (e.g. metoprolol), and Type 1C antiarrhythmics (e.g. propafenone, flecainide). If **Wellinta** 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 **Wellinta** should be carefully considered compared with the potential risks.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when **Wellinta** is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin

Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.4).

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

Although citalopram is not primarily metabolized 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 metabolized to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6 (see section 5.2). Co-administration of medicinal products that may affect the metabolism of bupropion via CYP2B6

isoenzyme (e.g. CYP2B6 substrates: cyclophosphamide, ifosfamide, and CYP2B6 inhibitors: orphenadrine, ticlopidine, clopidogrel), may result in increased bupropion plasma levels and lower levels of active metabolite hydroxy-bupropion.

The clinical consequences of the inhibition of the metabolism of bupropion via CYP2B6 enzyme and the consequent changes in the bupropion-hydroxybupropion ratio are currently unknown.

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

In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80% (see section 5.2).

Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55% in healthy volunteers.

Patients receiving any of these drugs with bupropion may need increased doses of bupropion but the maximum recommended dose of bupropion should not be exceeded.

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

Other interactions:

Smoking is associated with an increase in CYP1A2 activity. After cessation of smoking, reduced clearance of medicinal products metabolized by this enzyme, with subsequent increases in plasma levels, may occur. This may be particularly

important for those medicinal products primarily metabolized by CYP1A2 with narrow therapeutic windows (e.g. theophylline, tacrine and clozapine). The clinical consequences of smoking cessation on other medicinal products that are partially metabolized by CYP1A2 (e.g., imipramine, olanzapine, clomipramine, and fluvoxamine) are unknown. In addition, limited data indicate that the metabolism of flecainide or pentazocine may also be induced by smoking.

Administration of **Wellinta** 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 **Wellinta** treatment. The consumption of alcohol during **Wellinta** treatment should be minimized or avoided.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of certain congenital cardiovascular malformations specifically ventricular septal defects and left outflow tract heart defects. These findings are not consistent across studies. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). **Wellinta** should not be used in

pregnancy. Pregnant women should be encouraged to quit smoking without the use of pharmacotherapy.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

As with other CNS acting drugs bupropion may affect ability to perform tasks that require judgement or motor and cognitive skills. Wellinta has also been reported to cause dizziness and lightheadedness. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain Wellinta does not adversely affect their performance.

4.8 Undesirable effects

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

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 (>1/10000, <1/1,000); very rare (<1/10000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	Not known	Anaemia, leucopenia and thrombocytopenia
Immune system disorders*	Common	Hypersensitivity reactions such as urticaria

	Rare	More severe hypersensitivity reactions including angioedema, dyspnea /bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness
Metabolism and nutrition disorders	Uncommon	Anorexia
	Rare	Blood glucose disturbances
	Not known	hyponatraemia
Psychiatric disorders	Very common	Insomnia (see section 4.2)
	Common	Depression (see section 4.4), agitation, anxiety
	Uncommon	Confusion
	Rare	Irritability, hostility, hallucinations, depersonalisation, abnormal dreams including nightmares
	Very rare	Delusions, paranoid ideation, restlessness, aggression
	Not known	Suicidal ideation and suicidal behaviour***, psychosis, dysphemia
Nervous system disorders	Common	Tremor, concentration disturbance, headache, dizziness, taste disorders
	Rare	Seizures (see below) **, dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope

	Not known	Serotonin syndrome****
Eye disorders	Uncommon	Visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Palpitations
Vascular disorders	Uncommon	Increased blood pressure (sometimes severe), flushing
	Rare	Vasodilation, postural hypotension
Gastrointestinal disorders	Common	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation
Hepatobiliary disorders	Rare	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous tissue disorders*	Common	Rash, pruritus, sweating.
	Rare	Erythema multiforme and Stevens Johnson syndrome have also been reported. Exacerbation of psoriasis
	Not known	Systemic lupus erythematosus syndrome aggravated, cutaneous lupus erythematosus, acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders	Rare	Twitching
Renal and urinary disorders	Rare	Urinary frequency and/or retention
	Very rare	Urinary incontinence
General disorders and administration site conditions	Common	Fever
	Uncommon	Chest pain, asthenia

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

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Website:

4.9 Overdose

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose has been reported. In addition to those events reported as Undesirable Effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and/or ECG changes such as conduction disturbances (including QRS prolongation), arrhythmias and tachycardia. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate. Although most patients recovered without sequelae, deaths associated with bupropion have been reported rarely in patients ingesting large overdoses of the drug. Serotonin syndrome has also been reported.

Treatment: In the event of overdose, hospitalization is advised. ECG and vital signs should be monitored.

Ensure an adequate airway, oxygenation and ventilation. The use of activated charcoal is recommended. No specific antidote for bupropion is known. Further management should be as clinically indicated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit either monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown.

However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Clinical safety

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

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

In a retrospective analysis using data from the National Birth Defects Prevention Study, a statistically significant association was observed between the occurrence of a left outflow tract heart defect in the infant and self-reported maternal bupropion use in early pregnancy. No association was observed between maternal bupropion use and any other type of cardiac defect or with all categories of heart defects combined.

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

5.2 Pharmacokinetic properties

Absorption

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

After chronic dosing with bupropion 150 mg bid, the C max of bupropion is similar to values reported after single dosing.

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

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

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 L.

Bupropion, hydroxybupropion and threohydrobupropion bind moderately to plasma proteins (84%, 77% and 42%, respectively). Bupropion and its active

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

Biotransformation

Bupropion is extensively metabolized 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 metabolized to inactive metabolites (some of which have not been fully characterized but may include conjugates) and excreted in the urine.

In vitro studies indicate that bupropion is metabolized 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 13.3 μ M, respectively (see section 4.5).

Following oral administration of a single 150-mg dose of bupropion, there was no difference in C max, half-life, T max, AUC, or clearance of bupropion or its major metabolites between smokers and non-smokers.

Bupropion has been shown to induce its own metabolism in animals following sub-chronic administration. In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion hydrochloride for 10 to 45 days.

Elimination

Following oral administration of 200mg of 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 hydrochloride is approximately 200 L/hr and the mean elimination half-life of bupropion is approximately 20 hours.

The elimination half-life of hydroxybupropion is approximately 20 hours. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively).

Special Patient 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)

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Mannitol

Hydroxy propyl methyl cellulose (HPMC K15 M)

Hydroxy propyl methyl cellulose (HPMC E5)

Colloidal sodium dioxide (Aerosil 200)

Magnesium stearate

Coating material

Hydroxy propyl methyl cellulose (HPMC E5)

Polyethylene glycol 6000

Titanium dioxide (E171)

Talc powder

Cremsoin red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Carton box contains (1,2 or 3 (AL/ Opaque white PVDC) Strips each of 10 film coated tablet with insert leaflet.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorization holder

Elixir pharma