SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BUPROPION XR 150 ADCO 150 mg extended-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bupropion hydrochloride 150 mg.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablets.

White to pale yellow, round, biconvex tablets, plain on both the sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BUPROPION XR 150 ADCO is indicated for the treatment of depression as defined by DSM IV criteria.

Following a satisfactory response, continuation with BUPROPION XR 150 ADCO therapy is effective in preventing relapse and preventing recurrence of further depressive episodes.

4.2 Posology and method of administration

Therapy should be initiated by medical practitioners experienced in the treatment of depression.

BUPROPION XR 150 ADCO should be swallowed whole. The tablets must not be crushed, cut or chewed as this may lead to an increased risk of adverse effects including seizures.

There should be an interval of at least 24 hours between successive doses.

Insomnia which is a very common transient side effect of BUPROPION XR 150 ADCO may be reduced by avoiding dosing at bedtime (provided there is at least 24 hours between doses) or, if clinically indicated, by dose reduction.

Initial treatment

The initial dose of BUPROPION XR 150 ADCO 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.

Switching patients from sustained-release tablets

When switching patients from sustained-release tablets to BUPROPION XR 150 ADCO extended-release tablets: give the same total daily dose when possible.

Patients who are currently being treated with sustained-release tablets at 300 mg/day (e.g. 150 mg twice daily) may be switched to BUPROPION XR 150 ADCO extended-release tablets, two tablets (300 mg) once daily.

Special populations

Elderly: Greater sensitivity of some elderly individuals to BUPROPION XR 150 ADCO cannot be ruled out, therefore, a reduced frequency and/or dose of BUPROPION XR 150 ADCO may be required (see section 4.4).

Renal impairment: Treatment of patients with renal impairment should be initiated at a reduced frequency and/or dose, as bupropion and its metabolites may accumulate in such patients to a greater extent than usual (see section 4.4).

Hepatic impairment: BUPROPION XR 150 ADCO should be used with caution in patients with mild hepatic impairment. A reduction in the frequency of BUPROPION XR 150 ADCO dosing should be considered due to the increased variability in the pharmacokinetics in patients with mild hepatic cirrhosis (see section 4.4). BUPROPION XR 150 ADCO is contraindicated in patients with moderate to severe hepatic cirrhosis (see section 4.3).

Paediatric population

BUPROPION XR 150 ADCO is not indicated for use in children or adolescents younger than 18 years (see section 4.3).

Method of administration

BUPROPION XR 150 ADCO is for oral use.

BUPROPION XR 150 ADCO should be swallowed whole. The tablets must not be crushed, cut or chewed.

4.3 Contraindications

- Patients under the age of 18 years.
- Hypersensitivity to bupropion or any of the excipients of BUPROPION XR 150 ADCO
- Patients with a seizure disorder or history of seizures.
- Patients currently being treated with any other medicines containing bupropion, as the incidence of seizures is dose dependent.
- Patients with a known central nervous system (CNS) tumour.
- Patients undergoing abrupt discontinuation of alcohol, sedatives or any medicine known to be associated with a risk of seizures on withdrawal (in particular benzodiazepines and benzodiazepine-like agents).
- Patients with a current or previous diagnosis of bulimia or anorexia nervosa, as a higher incidence of seizures were seen in this patient population when bupropion was administered.
- Concomitant administration of BUPROPION XR 150 ADCO with monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with BUPROPION XR 150 ADCO.
- Patients with liver disease (Child-Pugh grades B and C, range 7-13) including severe hepatic cirrhosis.

4.4 Special warnings and precautions for use

Seizures

The recommended dose of BUPROPION XR 150 ADCO should not be exceeded, since bupropion is associated with a dose-related risk of seizures. There is an increased risk of seizures occurring with the use of BUPROPION XR 150 ADCO in the presence of predisposing risk factors which lower the seizure threshold.

Therefore, BUPROPION XR 150 ADCO should not be administered to patients with one or more conditions predisposing to a lowered seizure threshold, which include:

- history of head trauma;
- history of seizures (see section 4.3); central nervous system (CNS) tumour (see section 4.3);
- Concomitant administration of medicines known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines);
- excessive use of alcohol or sedatives (see section 4.3);
- diabetes treated with hypoglycaemics or insulin;
- use of stimulants or anorectic products.

BUPROPION XR 150 ADCO should be discontinued and not recommenced in patients who experience a seizure while on treatment.

Interactions

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 XR 150 ADCO is given concomitantly with medicines which can induce or inhibit the metabolism of bupropion.

Bupropion inhibits metabolism by cytochrome P450 2D6. Caution is advised when medicines metabolised by this enzyme are administered concurrently with BUPROPION XR 150 ADCO. See section 4.5.

Neuropsychiatry

Clinical worsening and suicide risk in adults associated with psychiatric disorders:

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviours (suicidality), whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs.

A causal role, however, for antidepressant medicines in inducing such behaviour has not been established.

Patients being treated with BUPROPION XR 150 ADCO should, nevertheless, be observed closely for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

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

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania, and mania.

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 medicine therapy and an appropriate patient assessment should be undertaken (see Neuropsychiatric symptoms including mania and bipolar disorder below; see section 4.8).

Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing BUPROPION XR 150 ADCO, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue BUPROPION XR 150 ADCO 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. Decrease a daily dose of 300 mg to 150 mg prior to discontinuation.

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. Aggression, rage and violent behaviour may occur. 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 the use of bupropion as in BUPROPION XR 150 ADCO 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 BUPROPION XR 150 ADCO, 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.

Clinical experience with bupropion as in BUPROPION XR 150 ADCO in patients receiving electroconvulsive therapy (ECT) is limited. Caution should be exercised in patients receiving ECT therapy concomitantly with BUPROPION XR 150 ADCO treatment.

Hypersensitivity

BUPROPION XR 150 ADCO should be discontinued immediately if patients experience hypersensitivity reactions during treatment (see section 4.8). 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). These symptoms may progress or recur even after discontinuation of BUPROPION XR 150 ADCO and may require appropriate clinical intervention.

Cardiovascular disease

There is limited clinical experience of the use of bupropion as in BUPROPION XR 150 ADCO to treat depression in patients with cardiovascular disease. A causal relationship between the use of bupropion as in BUPROPION XR 150 ADCO and sudden death cannot be excluded. Care should be exercised if it is used in these patients. It should be used cautiously in patients with a recent history of myocardial infarction or unstable heart disease.

Blood pressure:

Treatment with BUPROPION XR 150 ADCO can result in elevated blood pressure and hypertension. The risk of hypertension is increased if bupropion as in BUPROPION XR 150 ADCO is used concomitantly with MAOIs or other medicines that increase dopaminergic or noradrenergic activity (see section 4.3 and 4.5).

Reportedly, bupropion as in BUPROPION XR 150 ADCO has been shown not to induce significant increases in blood pressure in non-depressed patients with Stage I hypertension. However, in reported clinical cases, hypertension, which in some instances may be severe (see section 4.8) and require acute treatment, has been reported in patients receiving bupropion. This is reported to have 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 BUPROPION XR 150 ADCO if a clinically significant increase in blood pressure is observed.

Concomitant use of bupropion as in BUPROPION XR 150 ADCO and a nicotine transdermal system may result in elevations of blood pressure. Monitoring of blood pressure is recommended in these patients. See section 4.5.

Angle-closure glaucoma

Bupropion as in BUPROPION XR 150 ADCO may cause pupillary dilation which could trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Brugada syndrome

Bupropion may unmask Brugada syndrome, a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Caution is advised in patients with Brugada syndrome or a family history of cardiac arrest or sudden death

Special patient populations

Children and Adolescents < 18 years:

The safety and efficacy of bupropion as in BUPROPION XR 150 ADCO has not been established in patients under 18 years of age. Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents (< 18 years) with major depressive disorder and other psychiatric disorders (see section 4.3).

Hepatic impairment:

Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised. Although statistically significant differences in the pharmacokinetics of bupropion in patients with mild hepatic cirrhosis compared to healthy individuals, were not observed, higher variability between individual patients have been reported. Therefore, BUPROPION XR 150 ADCO should be used with caution in patients with mild hepatic impairment, and reduced frequency of dosing should be considered (see sections 5.2 and 4.3). Patients should be monitored closely for possible side effects (e.g., insomnia, dry mouth, seizures) that could indicate high bupropion or metabolite levels.

BUPROPION XR 150 ADCO is contraindicated in patients with moderate to severe hepatic impairment including cirrhosis (see section 4.3).

Renal impairment:

Bupropion is extensively metabolised in the liver to active metabolites which are further metabolised and excreted into the urine as its metabolites. Therefore, treatment with bupropion as in BUPROPION XR 150 ADCO in patients with renal impairment should be initiated at reduced frequency and/or dose as bupropion and its active metabolites may accumulate to a greater extent than usual. Patients should be closely monitored for possible undesirable effects (e.g. insomnia, dry mouth, seizures) that could indicate high bupropion or metabolite levels (see section 4.2), toxic effects of elevated blood and tissue levels of bupropion and metabolites.

Elderly:

Differences in the tolerability of bupropion as in BUPROPION XR 150 ADCO between elderly and other adult patients have not been reported in clinical experience. However, greater sensitivity of some elderly individuals cannot be ruled out; hence a reduced frequency and/or dose may be required (see section 5.2).

Porphyria:

Bupropion as in BUPROPION XR 150 ADCO is classified as possibly porphyrinogenic. It should only be used when no safer alternative is available, and precautions should be considered in vulnerable patients.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

The concomitant use of BUPROPION XR 150 ADCO and monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.3). Although by different mechanisms, both bupropion and MAOIs enhance catecholaminergic pathways; this increases the possibility of adverse reactions, including the risk for hypertensive reactions, when administered concomitantly. At least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with BUPROPION XR 150 ADCO.

Medicines that lower the seizure threshold

The concomitant use of BUPROPION XR 150 ADCO and medicines known to lower the seizure threshold is contraindicated e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines (see section 4.3 and 4.4).

The effect of other medicines on BUPROPION XR 150 ADCO

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by cytochrome P450 CYP2B6 (see section 5.2).

The plasma levels of bupropion and its active metabolite hydroxybupropion may be increased or decreased when administered concomitantly with medicines known to affect the CYP2B6 isoenzyme e.g.:

- CYP2B6 substrates: cyclophosphamide, ifosfamide, prasugrel
- CYP2B6 inducers: ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, phenytoin
- CYP2B6 inhibitors: orphenadrine, ticlopidine, clopidogrel, valproate

It has been reported that the co-administration of bupropion with ritonavir/lopinavir reduced bupropion exposure to 20-80 %, and with efavirenz it was reduced to 55 %. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving ritonavir may need increased doses of BUPROPION XR 150 ADCO but the maximum recommended dose of BUPROPION XR 150 ADCO should not be exceeded.

Since bupropion is extensively metabolised, caution is advised when bupropion as in BUPROPION XR 150 ADCO is co-administered with medicines known to induce metabolism (i.e. decrease the exposure to bupropion and its active metabolite) or inhibit metabolism (i.e. increase the exposure to bupropion) as these may affect its clinical efficacy and safety.

Dosage increase or reduction of BUPROPION XR 150 ADCO may be considered, however, the maximum recommended dose should not be exceeded (see section 4.2).

The effect of BUPROPION XR 150 ADCO on other medicines

Although not metabolised by CYP2D6, it has been reported that in vitro human P450 studies have shown that bupropion and its main metabolite, hydroxybupropion, are known inhibitors of the CYP2D6 pathway.

Concomitant therapy with bupropion as in BUPROPION XR 150 ADCO and medicines that are predominantly metabolised by CYP2D6, especially medicines with narrow therapeutic indices, should be initiated at the lower end of the dose range of the concomitant medicine.

CYP2D6 substrates include:

- tricyclic antidepressants (e.g. nortriptyline, imipramine, desipramine)
- antipsychotics (e.g. haloperidol, risperidone, thioridazine)
- beta-blockers (e.g. metoprolol)
- serotonin selective reuptake inhibitors (SSRIs e.g. venlafaxine, paroxetine, sertraline, fluoxetine, fluvoxamine)
- Type 1C antidysrhythmics (e.g. propafenone, flecainide).

It has been reported that the co-administration of bupropion and desipramine, a medicine metabolised by CYP2D6, resulted in a 2-5 fold increase of desipramine plasma levels; this effect lasted for at least 7 days after the last dose of bupropion.

Although citalopram (a SSRI) is not primarily metabolised by CYP2D6, it has been reported that in one study, that the Cmax and AUC of citalopram were increased by 30 % and 40 %, respectively, when co-administered with bupropion. If bupropion as in BUPROPION XR 150 ADCO is added to the treatment regimen of a patient already receiving a medicine metabolised by CYP2D6, the need to decrease the dose of the original medicine should be considered, especially for those concomitant medicines with narrow therapeutic indices (see section 5.2).

The efficacy of medicines that require activation by CYP2D6 to be effective (e.g. tamoxifen), may be reduced by the concomitant administration of bupropion as in BUPROPION XR 150 ADCO; dosage increases may be required for such medicines.

Other interactions

Dopaminergic medicine interactions

Care should be taken with the co-administration of bupropion as in BUPROPION XR 150 ADCO and levodopa or amantadine. Bupropion, levodopa, and amantadine have dopamine agonist effects. The incidence of CNS adverse effects e.g. nausea, vomiting and neuropsychiatric events, may be higher with concomitant use due to cumulative dopamine agonist effects (see section 4.8).

Alcohol consumption

There have been reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion as in BUPROPION XR 150 ADCO. The consumption of alcohol during treatment with BUPROPION XR 150 ADCO should be minimised or avoided (see section 4.3 and 4.4).

Nicotine transdermal system

Concomitant use of bupropion as in BUPROPION XR 150 ADCO and a nicotine transdermal system may result in elevations of blood pressure (see section 4.4).

Medicine-Laboratory test interaction

There have been reports of false-positive urine immunoassay screening tests for amphetamines in patients taking bupropion as in BUPROPION XR 150 ADCO. This is due to a lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion as in BUPROPION XR 150 ADCO. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

Digoxin

Co-administration of digoxin with bupropion as in BUPROPION XR 150 ADCO may decrease digoxin levels. Clinicians should be aware that digoxin levels may rise on discontinuation of BUPROPION XR 150 ADCO and the patient should be monitored for possible digoxin toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of bupropion as in BUPROPION XR 150 ADCO in pregnancy has not been established.

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, including ventricular septal defects and left ventricular outflow tract defects. These findings are not consistent across studies.

Breastfeeding

The safety of BUPROPION XR 150 ADCO in lactation has not been established.

As bupropion and its metabolites are excreted in human breast milk, mothers should be advised not to breastfeed while taking BUPROPION XR 150 ADCO.

4.7 Effects on ability to drive and use machines

BUPROPION XR 150 ADCO may cause dizziness, impair the ability to perform tasks requiring judgement or motor and cognitive skills. Patients should refrain from driving or operating machinery until they are reasonably certain that BUPROPION XR 150 ADCO does not adversely affect their performance.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions by system organ class and frequency

Immune system disorders *	Frequent	Hypersensitivity reactions such as urticaria.
	Less frequent	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	Frequent	Anorexia.
	Less frequent	Weight loss, blood glucose disturbances.
	Frequency unknown	Hyponatremia
Psychiatric disorders	Frequent	Insomnia (see section 4.2), agitation, anxiety.
	Less frequent	Depression (see section 4.4), confusion, aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including nightmares, depersonalisation, delusions, paranoid ideation.
	Unknown	Suicidal ideation and suicidal behaviour ***, psychosis.
Nervous system disorders	Frequent	Headache, tremor, dizziness, taste disorders.
	Less frequent	Concentration disturbance, seizures (see below) **, dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope.

Eye disorders	Frequent	Visual disturbance.
Ear and labyrinth disorders	Frequent	Tinnitus.
Cardiac disorders	Less frequent	Tachycardia, palpitations.
Vascular disorders	Frequent	Increased blood pressure (sometimes severe), flushing.
	Less frequent	Vasodilation, postural hypotension.
Gastrointestinal disorders	Frequent	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation.
Hepatobiliary disorders	Less frequent	Elevated liver enzymes, jaundice, hepatitis.
Skin and subcutaneous tissue disorders *	Frequent	Rash, pruritus, sweating.
	Less frequent	Erythema multiforme, Stevens-Johnson syndrome, exacerbation of psoriasis.
Musculoskeletal and connective tissue disorders	Less frequent	Twitching.
Renal and urinary disorders	Less frequent	Urinary frequency and/or retention, urinary incontinence.
General disorders and	Frequent	Fever, chest pain, asthenia.

administration site conditions		

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

** 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **“6.04 Adverse Drug Reaction Reporting Form”**, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose of bupropion 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), dyshythmias 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 in patients ingesting large overdoses of BUPROPION XR 150 ADCO.

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, if patients present within 1 hour of ingestion and provided the airway can be protected. Treatment is supportive. No specific antidote for bupropion is known. Further management should be as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.1.2 Psycho-analeptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX12

Bupropion is an antidepressant of the aminoketone class.

It is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines.

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (norepinephrine (noradrenaline) and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit either monoamine oxidase.

Mechanism of action

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.

It has been reported that no clinically significant effect of modified release bupropion tablets (450 mg/day) was observed on QTcF interval after 14 days of dosing to steady state.

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations (Cmax) of approximately 160 ng/mL have been reported in healthy volunteers approximately 5 hours after oral administration of 300 mg bupropion hydrochloride as in BUPROPION XR 150 ADCO.

At steady state, the Cmax and AUC values of hydroxybupropion have been reported to be approximately 3 and 14 times that of bupropion, respectively. The Cmax of threohydrobupropion at steady state was found to be similar to that of bupropion and the AUC approximately 5 times higher, while the plasma concentrations of erythrohydrobupropion was comparable to those of bupropion.

Peak plasma levels of hydroxybupropion was reached at 7 hours while those for threohydrobupropion and erythrohydrobupropion were reached at 8 hours.

The AUC and Cmax values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion have been reported to increase proportionally with the dose.

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 is not significantly influenced when taken 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). The extent of protein binding of threohydrobupropion metabolite is about half that seen with bupropion.

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. It has been reported that bupropion penetrates the CNS and binds to the striatal dopamine reuptake transporter.

Biotransformation

Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion which are formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. These may have clinical importance, as their plasma concentrations are as high or higher than those of bupropion. Peak plasma concentrations of hydroxybupropion occur approximately 7 hours following administration of bupropion as in BUPROPION XR 150 ADCO. Erythrohydrobupropion cannot be measured in the plasma after a single dose of absorption. 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.

Reported 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 relatively weak inhibitors of the CYP2D6 isoenzyme with Ki values of 21 and 13,3 μM, respectively (see section 4.5). It has been reported that 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 Cmax and AUC, respectively, of desipramine. This effect was present for at least seven 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 bupropion is administered with substrates for the CYP1D6 (see section 4.5).

Bupropion has been shown to induce its own metabolism in animals following sub-chronic administration. As per reported clinical investigations 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 200 mg of 14C-bupropion in humans, 87 % and 10 % of the radioactive dose were reportedly 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 and its area under the plasma 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.

Special patient populations

Factors or conditions altering metabolic capacity (e.g. liver disease, congestive heart failure [CHF], age, concomitant medicines, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function, because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Patients with renal impairment:

Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised and subsequently excreted by the kidneys.

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). Therefore, treatment of patients with renal impairment should be initiated at a reduced frequency and/or dose, as bupropion and its metabolites may accumulate in such patients to a greater extent than usual (see section 4.2).

Patients with hepatic impairment:

Reportedly, the pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild cirrhosis (Child Pugh grade A, range 5-6) when compared to healthy volunteers, although more variability was observed between individual

patients (see section 4.4). For patients with moderate to severe hepatic cirrhosis (Child-Pugh grades B&C, range 7-13), a single dose of bupropion produced a Cmax and AUC that were substantially increased (mean difference approximately 70 % and 3-fold, respectively) and more variable when compared to the values in healthy volunteers; the mean half-life was also longer (by approximately 40 %). For hydroxybupropion, the mean Cmax was lower (by approximately 70 %), the mean AUC tended to be higher (by approximately 30 %), the median Tmax was later (by approximately 20 hours), and the mean half-lives were longer (by approximately 4-fold) than in healthy volunteers. For threohydrobupropion and erythrohydrobupropion, the mean Cmax tended to be lower (by approximately 30 %), the mean AUC tended to be higher (by approximately 50 %), the median Tmax was later (by approximately 20 hours), and the mean half-life was longer (by approximately 2-fold) than in healthy volunteers (see section 4.3).

Elderly patients:

It has been reported that 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 reported 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 (see section 4.4).

In-vitro release of bupropion with alcohol:

It has been reported that in-vitro at high alcohol concentrations (up to 40 %), bupropion is released more rapidly from the modified release formulation such as BUPROPION XR 150 ADCO (up to 20 % dissolved at 2 hours) (see section 4.5).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone

Sodium stearyl fumarate

Tablet coating:

Ethyl cellulose

Hydroxy propyl cellulose

Methacrylic acid - Ethyl acrylate copolymer (1:1) Type A

Silica, colloidal anhydrous

Macrogols 1500

Triethyl citrate

Opadry Clear YS-1-7006 (HPMC 2910/Hypromellose, Macrogol/PEG (MW 400), Macrogol/PEG (MW 8000)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years (24 months)

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging.

Store in a cool, dry place.

Protect from moisture and light.

6.5 Nature and contents of container

White opaque HDPE bottle sealed with induction seal and child resistant cap (along with silica gel and activated carbon pillow pack, and oxygen and moisture absorber).

Pack sizes: 28 and 30 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road, Erand Gardens

Midrand, 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

50/1.2/0967.965

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 January 2021

10. DATE OF REVISION OF THE TEXT

07 June 2023