BUDEP XR 150

BUDEP XR 300

WARNING: SUICIDAL THOUGHTS AND BEHAVIOURS

SUICIDALITY AND ANTIDEPRESSANT AGENTS

Antidepressants increased the risk of suicidal thoughts and behaviour in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behaviour with antidepressants used in subjects aged 65 and older (see section 4.4).

In patients of all ages who are started on antidepressant therapy, monitor closely for exacerbation, and for emergence of suicidal thoughts and behaviours. Advise families and caregivers of the need for close observation and communication with the prescriber (see section 4.4).

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BUDEP XR 150 Extended-Release Tablets

BUDEP XR 300 Extended-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BUDEP XR 150

Each extended release tablet contains 150 mg bupropion hydrochloride.

Contains sugar: lactose monohydrate 4,76 mg per extended release tablet.

BUDEP XR 300

Each extended release tablet contains 300 mg bupropion hydrochloride.

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Contains sugar: lactose monohydrate 9,17 mg per extended release tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablets

BUDEP XR 150

White to pale yellow, round, film-coated tablets imprinted with **'L2'** in black ink on one side and plain on the other side.

BUDEP XR 300

White to pale yellow, round, film coated tablets imprinted with '**L**' in black ink on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BUDEP XR is indicated for the treatment of depression as defined by DSM V Criteria.

Following a satisfactory response, continuation with **BUDEP XR** 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.

Posology

Initial treatment

The initial dose of **BUDEP XR** 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.

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Switching patients from sustained release tablets

When switching patients from sustained release tablets to 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 (for example, 150 mg twice daily) may be switched to extended release tablets 300 mg once daily.

Special populations

Elderly population

Greater sensitivity of some elderly individuals to bupropion cannot be ruled out, hence a reduced frequency and/or dose 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

BUDEP XR should be used with caution in patients with mild liver impairment. Because of increased variability in the pharmacokinetics in patients with mild hepatic cirrhosis, a reduced frequency of dosing should be considered (see sections 4.8 and 4.4). **BUDEP XR** is contra-indicated in patients with moderate to severe hepatic cirrhosis.

Paediatric population

BUDEP XR is not indicated for use in children or adolescents under the age of 18 years (see section 4.3).

Method of administration

BUDEP XR tablets should be swallowed whole and not cut, crushed 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 is a very common adverse event that is often transient. Insomnia may be

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reduced by avoiding dosing at bedtime (provided there is at least 24 hours between doses) or, if clinically indicated, dose reduction.

4.3 Contraindications

BUDEP XR is contra-indicated in following:

- Patients under 18 years.
- Hypersensitivity to bupropion or any component of **BUDEP XR.** Anaphylactoid/anaphylactic reactions and Stevens-Johnson Syndrome have been reported.
- In patients with a seizure disorder.
- **BUDEP XR** should not be administered to patients currently being treated with any other preparation containing bupropion, as the incidence of seizure is dose dependent.
- In patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates and/or sedatives.
- In patients with a current or previous diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was seen in this patient population when bupropion was administered.
- Concomitant administration of **BUDEP XR** with monoamine oxidase inhibitors (MAOIs) is contra-indicated. At least 14 days should elapse between the discontinuation of MAOIs and the initiation of treatment with **BUDEP XR**. Starting **BUDEP XR** in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- Liver disease, Child-Pugh grades B&C, range 7-13.

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4.4 Special warnings and precautions for use

Dose-related risk of seizure

The recommended dose of **BUDEP XR** should not be exceeded, since bupropion is associated with a dose-related risk of seizure.

BUDEP XR should be discontinued in patients who experience a seizure while on treatment (see section 4.8). Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion and clinical management should be provided accordingly.

The overall incidence of seizure with bupropion has been reported to be 0,1 %.

There is an increased risk of seizures occurring with the use of bupropion in the presence of predisposing risk factors, which lower the seizure threshold. Therefore bupropion should not be administered to patients with one or more conditions predisposing to a lowered seizure threshold including:

- history of head trauma
- central nervous system (CNS) tumour
- history of seizures
- concomitant administration of other medications known to lower the seizure threshold (see section 4.5)
- excessive use of alcohol or sedatives (see section 4.3)
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products.

BUDEP XR should be discontinued and not recommended in patients who experience a seizure while on treatment.

Clinical exacerbation and suicide risk associated with psychiatric disorders

See boxed warning.

Patients with major depressive disorder may experience worsening of their depression

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and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. As improvement in depression may not occur during the first few weeks or more of treatment, patients being treated with bupropion should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of therapy, or at the time of dose changes, either increases or decreases.

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

The following symptoms have been reported in patients being treated with antidepressants for major depressive order: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania.

In addition, an increased risk of suicidal thinking and behaviour associated with antidepressant use compared to placebo in patients less than 25 years old, has been reported in adults with major depressive disorder and other psychiatric disorders.

Patients (and caregivers of patients) should be alerted about the need to monitor for any exacerbation 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 recognized that the onset of some neuropsychiatric symptoms could be related either to the underlying disease state or the medicine therapy (see neuropsychiatric symptoms including mania and bipolar disorder below, section 4.8).

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Consideration should be given to changing the therapeutic regimen, including possibly discontinuing bupropion in patients who experience clinical exacerbation (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Although there is no need to taper bupropion upon discontinuation, the patient should be monitored for exacerbation of depressive symptoms following discontinuation.

Neuropsychiatric symptoms including mania and bipolar disorders

Neuropsychiatric symptoms 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. Aggression, rage and violent behaviour may occur. Additionally, a major depressive episode may be the initial presentation of bipolar disorder. It is generally believed 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 in combination with mood stabilizers in patients with a history of bipolar disorder, suggest a low rate of switch to mania.

Prior to initiating treatment with bupropion, patients should be adequately screened to determine if they are at risk of bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

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 has been reported in patients with mild hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients. Therefore bupropion should be used with caution in patients with mild hepatic

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impairment and reduced frequency of dosing should be considered (see section 5.2 and 4.3).

Renal Impairment

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

Elderly patients

Reported clinical experience with bupropion has not identified any differences in tolerability between elderly and other adult patients. However, greater sensitivity of some elderly individuals cannot be ruled out; hence a reduced frequency of dosing may be required (see section 5.2).

Cardiovascular disease

There is limited clinical experience reported of the use of bupropion to treat depression in patients with cardiovascular disease. A causal relationship between the use of bupropion and sudden death cannot be excluded. Care should be exercised if it is used in these patients.

Cardiac conduction disorders: Bupropion may unmask cardiac conduction syndromes e.g. 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.

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Hypertension

Bupropion can increase blood pressure.

Assess blood pressure before initiating treatment with bupropion, and monitor periodically during treatment. The risk of hypertension is increased if bupropion is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity (see section 4.3).

Hypersensitivity

Bupropion should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see section 4.8). Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion, and clinical management should be provided accordingly.

Angle-closure glaucoma

Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.

Children and adolescents younger than 18 years

The safety and efficacy of bupropion in patients under 18 years of age have not been reported. Treatment with antidepressants has been reported to be associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders (see section 4.3).

Lactose

BUDEP XR contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take **BUDEP XR**.

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4.5 Interaction with other medicines and other forms of interaction

Medicines known to affect the CYP2B6 isoenzyme

Bupropion is metabolised to its metabolite hydroxybupropion primarily by the cytochrome P450 IIB6 (CYP2B6) (see section 5.2). Care should therefore be exercised when bupropion is co-administered with medicines known to affect the CYP2B6 isoenzyme (e.g. orphenadrine, cyclophosphamide, ifosfamide, prasugrel, cimetidine, ticlopidine and clopidogrel). Although bupropion is not metabolised by the CYP2B6 isoenzyme, it has been reported that bupropion and hydroxybupropion are inhibitors of the CYP2D6 pathway. In a reported human pharmacokinetic study, administration of bupropion increased plasma levels of desipramine. This effect was present for at least seven days after the last dose of bupropion.

Concomitant therapy with medicines predominantly metabolised by this isoenzyme [such as certain beta-blockers (e.g., metoprolol), anti-dysrrhythmics (e.g., propafenone, and flecainide), selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, and thioridazine)] should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a medication metabolised by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index (see section 5.2).

Although citalopram is not primarily metabolised by CYP2D6, bupropion has been reported to increase the C_{max}, and AUC (of citalopram by 30 % and 40 %, respectively).

Since bupropion is extensively metabolised, the co-administration of medicines known to induce metabolism (e.g. carbamazepine, phenobarbitone, phenytoin) or inhibit metabolism may affect its clinical activity.

Ritonavir and lopinavir

In a series of reported studies in healthy volunteers, ritonavlr (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg twice daily has been reported to reduce the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80 %. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving ritonavir may need increased doses of **BUDEP XR** but the maximum recommended dose of **BUDEP XR** should not be exceeded.

Alcohol

There have been reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. The consumption of alcohol during **BUDEP XR** treatment should be minimised or avoided.

Levodopa or amantadine

Limited reported clinical data suggest a higher incidence of adverse events in patients receiving concurrent administration of bupropion and levodopa. Administration of bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

Nicotine transdermal system

Concomitant use of bupropion and a nicotine transdermal system (NTS) may result in elevation of blood pressure.

MAO inhibitors

Bupropion has been reported to inhibit the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. The acute toxicity of bupropion has been reported to be enhanced by the MAO inhibitor phenelzine. At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of treatment with **BUDEP XR**. Conversely, at least 14

days should be allowed after stopping **BUDEP XR** before starting an MAOI antidepressant (see sections 4.2 and 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been reported.

Reported 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

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

Fertility

A reported fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility (see section 5.3).

4.7 Effects on the ability to drive and use machines

Patients should exercise caution before driving or use of machinery until they are reasonably certain bupropion tablets do not adversely affect their performance.

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4.8 Undesirable effects

The side effects are listed below according to system organ class and frequency.

Table 1: Tabulated summary of adverse events

System Organ Class	Frequency	Adverse events
Immune system disorders*	Frequent	Hypersensitivity reactions such as urticarial.
	Less frequent	More severe hypersensitivity reactions including angio-oedema, dyspnoea/bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness. *See also "***Skin and subcutaneous tissue disorders***"
Metabolism and nutritional disorders	Frequent	Anorexia, weight gain or weight loss
	Less frequent:	Blood glucose disturbances
Psychiatric disorders	Frequent	Insomnia, agitation, anxiety *Less frequent:* Confusion, depression, aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including nightmares, depersonalisation, delusions, paranoid ideation
	Frequency unknown	Suicidal ideation and suicidal behaviour, psychosis (see section 4.4)
Nervous system disorders	Frequent:	Headache or migraine, tremor, dizziness, somnolence, nervousness, taste disorders

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	Less frequent	Concentration disturbance, seizures (see section 4.4 & 4.8), dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope
Eye disorders	Frequent	Visual disturbance
Ear and labyrinth disorders	Frequent	Tinnitus, auditory disturbance, gustatory disturbance
Cardiac disorders	Less frequent:	Tachycardia, palpitations, hot flashes, cardiac arrhythmia, hypertension, hypotension
Vascular disorders	Frequent	Increased blood pressure (sometimes severe), flushing
	Less frequent:	Vasodilation, postural hypotension
Respiratory disorders	Frequent	Pharyngitis, sinusitis, increased cough
Gastro-intestinal disorders	Frequent	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation, dysphagia
Hepato-biliary disorders	Less frequent	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous tissue disorders*	Frequent	Rash, pruritus, sweating
	Less frequent	Erythema multiforme, Stevens Johnson syndrome. *See also " **Immune system disorders**"
Musculoskeletal and connective tissue disorders	Less frequent:	Twitching
Renal and urinary disorders	Less frequent:	Urinary frequency and/or retention, urinary urgency, vaginal haemorrhage, urinary tract infection
General disorders and administration site conditions	Frequent	Fever, asthenia, chest pain, menstrual complaints, akathisia, decreased libido.

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Post marketing experience

The following adverse reactions have been reported during post-approval use of bupropion. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 2: Tabulated summary of post-marketing adverse events

System Organ Class	Adverse events
Blood and lymphatic system disorders	Ecchymosis, anaemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia and thrombocytopenia. Altered PT and/or INR, associated with haemorrhagic or thrombotic complications, were observed when bupropion was co-administered with warfarin.
Endocrine disorders	Hyperglycaemia, hypoglycaemia, and syndrome of inappropriate antidiuretic hormone secretion.
Metabolism and nutritional disorders:	Glycosuria.
Psychiatric disorders	Abnormal coordination, depersonalisation, emotional lability, hyperkinesia, hypertonia, hypersthesia, vertigo, amnesia, ataxia, derealisation, abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.
Eye disorders	Accommodation abnormality, dry eye, increased intraocular pressure, angle-closure glaucoma, and mydriasis.
Ear and labyrinth disorders	Deafness.
Cardiac disorders:	Stroke, syncope, complete atrioventricular block, extra-systoles, myocardial infarction, phlebitis.
Vascular disorders	Postural hypotension, hypertension, pulmonary embolism,

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	vasodilation.
Respiratory, thoracic and mediastinal disorders	Bronchospasm and pneumonia.
Gastrointestinal disorders	Bruxism, gastric reflux, gingivitis, glossitis, increased salivation, mouth ulcers, stomatitis, thirst, oedema of tongue, colitis, oesophagitis, gastro-intestinal haemorrhage, gum haemorrhage, intestinal perforation, and stomach ulcer.
Hepato-biliary disorders	Abnormal liver function, jaundice, hepatitis, liver damage, pancreatitis.
Skin and subcutaneous tissue disorders	Maculopapular rash, alopecia, angio-oedema, exfoliative dermatitis, and hirsutism.
Musculoskeletal and connective tissue disorders	Leg cramps, fever/rhabdomyolysis, and muscle weakness.
Reproductive system and breast disorders:	Impotence, polyuria, prostate disorder, abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.
General disorders and administration site conditions	Chills, facial oedema, oedema, peripheral oedema, musculoskeletal chest pain, photosensitivity, and malaise.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email: pharmacovigilance.africasme@sunpharma.com or Tel: +27(0) 12

643 2000.

4.9 Overdose

In addition to the events reported under side-effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or dysrhythmias.

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose has been reported.

Treatment: In the event of overdose, hospitalisation is advised. ECG and vital signs should be monitored. Ensure an adequate airway, oxygenation and ventilation. The use of activated charcoal is also recommended. No specific antidote for bupropion is known. Further management should take place as clinically indicated or as recommended by the national poison centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A. 1.2. Psycho-analeptics (antidepressants)

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

Bupropion is an inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin), and does not inhibit monoamine oxidase. The mechanism of action of bupropion is unknown.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of bupropion extended release tablets to healthy volunteers, time to peak plasma concentrations for bupropion has been reported to be approximately 5 hours.

The absorption of bupropion has been reported to be not significantly affected when

taken with food. Bupropion and its metabolites has been reported to exhibit linear kinetics following chronic administration of 150 to 300 mg per day.

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 ℓ. Bupropion and hydrobupropion are moderately bound to human plasma proteins (84 % and 77 % respectively). The extent of protein binding of the threohydrobupropion metabolite has been reported to be about half that seen with bupropion.

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 have clinical importance, as their plasma concentrations have been reported to be as high as or higher than those of bupropion. Peak plasma concentrations of hydroxybupropion has been reported to occur approximately 7 hours following administration of bupropion. Erythrohydrobupropion cannot be measured in the plasma after a single dose of bupropion. The active metabolites are further metabolised to inactive metabolites and excreted in the urine.

It has been reported that bupropion is metabolised to its major active metabolite, hydroxybupropion, primarily by CYP2B6, while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion (see section 4.5).

Bupropion and hydroxybupropion are both relatively weak competitive inhibitors of the CYP2D6 isoenzyme with K_i values of 21 and 13,3 μM, respectively. In human volunteers known to be extensively metabolised by CYP2D6 isoenzyme, co-administration of bupropion and desipramine has been respectively reported to result in a two- and fivefold increase in the C_{max} and AUC, 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 CYP2D6 pathway (see section 4.5).

In humans, no evidence of enzyme induction has been reported for bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion for 10 to 45 days.

Elimination

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87 % and 10 % of the radioactive dose has been reported to be recovered in the urine and faeces, respectively. The fraction of the oral dose of bupropion excreted unchanged has been reported to be only 0,5 %, a finding consistent with the extensive metabolism of bupropion. Less than 10 % of this ^{14}C dose has been reported to account for in the urine as active metabolites.

The mean apparent clearance following oral administration of bupropion has been reported to be approximately 200 ℓ/hr and the mean elimination half-life of bupropion is approximately 20 hours.

The elimination half-life of hydroxybupropion has been reported to be approximately 20 hours and its area under the plasma drug concentration versus time curve (AUC) at steady-state is approximately 17 times that of bupropion. The elimination half-lives for threohydrobupropion and erythrohydrobupropion have been reported to be 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 has been reported to be reached within 8 days.

Special patient populations

Elderly

Reported pharmacokinetic studies in the elderly have shown variable results. A single

dose reported 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 doses, 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.

Patients with renal impairment

The elimination of bupropion and its major metabolites may be reduced by impaired renal function (see section 4.4).

Patients with hepatic impairment

The pharmacokinetics of bupropion and its active metabolites has been reported not to be statistically significantly different in patients with mild cirrhosis (Child-Pugh grade A, range 5-6) when compared to healthy volunteers, although greater variability has been reported in individual patients. For patients with moderate to severe hepatic cirrhosis (Child-Pugh grades B & C, range 7-13), a single dose of bupropion has been reported to produce a C_{max} and AUC that were substantially increased (mean difference approximately 70 % and three-fold, respectively) and more variable when compared to the values in healthy volunteers, the mean half-life was also longer (by approximately 40 %). For the metabolites, the mean C_{max} has been reported to be lower (by approximately 30 to 70 %), the mean AUC tended to be higher (by approximately 30 to 50 %), the median T_{max} was later (by approximately 20 hours), and the mean half-lives were longer (by approximately two- to fourfold) than in healthy volunteers (see section 4.3).

5.3 Preclinical safety data

Lifetime carcinogenicity studies have been reported in rats and mice at doses up to 300 and 150 mg/kg/day bupropion hydrochloride, respectively. These doses are approximately seven and two times the maximum recommended human dose (MRHD),

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respectively, on a mg/m^2 basis. In the reported rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day of bupropion hydrochloride (approximately two to seven times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not reported in mice, and no increase in malignant tumours of the liver and other organs was reported in either study.

Bupropion was reported to produce a positive response (two to three times control mutation rate) in two of five strains in one Ames bacterial mutagenicity assay, but was negative in another. Bupropion was reported to produce an increase in chromosomal aberrations in one of three *in vivo* rat bone marrow cytogenetic studies.

A reported fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethyl cellulose (ethocel 45 cps standard premium),

Glycerylbehenate (Compritol ATO 888),

Hydroxypropyl cellulose (HPC-L),

Hypromellose (Methocel E5 premium),

Isopropyl alcohol,

Methacrylic acid copolymer dispersion (Eudragit L30D-55),

Methylene chloride,

Opacode S-1-17823 (black),

Polyethylene glycol 6000,

Povidone (plasdone K90 D),

Silicon dioxide (Syloid 244 FP),

Stearic acid,

Triethyl citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

36 months

6.4 Special precautions for storage

KEEP OUT OF REACH OF CHILDREN.

Store at or below 25 °C.

Keep in the original package until required for use.

Return all unused medicines to your pharmacist.

Do not dispose of unused medicines in drains or sewerage systems.

6.5 Nature and contents of container

BUDEP XR 150 and **BUDEP XR 300** tablets are packed in HDPE bottles. Each HDPE bottle contains 30 tablets.

HDPE bottle pack:

White opaque HDPE bottle with white opaque polypropylene child resistant closure with wad having induction sealing liner containing 1 g silica gel desiccant sachet.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

RANBAXY PHARMACEUTICALS (PTY) LTD

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

Tel: +27(0) 12 643 2000

8. MARKETING AUTHORISATION NUMBER(S)

BUDEP XR 150: 48/1.2/0114

BUDEP XR 300: 48/1.2/0115

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 09 February 2021

10. DATE OF REVISION OF THE TEXT

October 2024

Signed: PM