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.

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.

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 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.

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 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).

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 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.

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**.

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.

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

	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.

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, 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), 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

WAARSKUWING: SELFMOORDGEDAGTES EN -GEDRAG

SELFMOORDNEIGEND- EN ANTIDEPRESSANTE MIDDELS

Antidepressante het die risiko van selfmoordgedagtes en -gedrag by kinders, adolessente en jong volwassenes in korttermynstudies verhoog. Hierdie studies het nie 'n toename in die risiko van selfmoordgedagtes en -gedrag met antidepressante wat by proefpersone van 65 jaar en ouer gebruik is, getoon nie (sien afdeling 4.4).

Pasiënte van alle ouderdomme wat met antidepressantbehandeling begin, moet noukeurig dopgehou word vir verergering en vir die voorkoms van selfmoordgedagtes en gedrag. Gesinne en versorgers moet ingelig word oor die noodsaaklikheid van noukeurige waarneming en kommunikasie met die voorskrywer (sien afdeling 4.4).

SKEDULINGSTATUS

S5

1. EIENDOMSNAAM VAN DIE MEDISYNE

BUDEP XR 150 Verlengde-vrystelling Tablette

BUDEP XR 300 Verlengde-vrystelling Tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

BUDEP XR 150

Elke verlengde-vrystelling tablet bevat 150 mg bupropionhidrochloried.

Bevat suiker: laktosemonohidraat 4,76 mg per tablet met verlengde vrystelling.

Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

BUDEP XR 300

Elke verlengde-vrystelling tablet bevat 300 mg bupropionhidrochloried.

Bevat suiker: laktosemonohidraat 9,73 mg per tablet met verlengde vrystelling.

Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM

Verlengde-vrystelling tablette

BUDEP XR 150

Wit tot liggeel, ronde, filmomhulde tablette bedruk met “**L2**” in swart ink aan die een kant en glad aan die ander kant.

BUDEP XR 300

Wit tot liggeel, ronde, filmomhulde tablette bedruk met “**L**” in swart ink aan die een kant en glad aan die ander kant.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

BUDEP XR is aangedui vir die behandeling van depressie soos gedefinieer deur DSM V Kriteria. Na 'n bevredigende reaksie is voortsetting met **BUDEP XR**-behandeling effektief om terugval te voorkom en die herhaling van verdere depressiewe episodes te voorkom.

4.2 Dosering en metode van toediening

Behandeling moet begin word deur mediese praktisyns wat ervare is met die behandeling van depressie.

Dosis

Aanvanklike behandeling

Die aanvangsdosis van **BUDEP XR** is 150 mg as 'n enkele dosis soggens. Pasiënte wat nie voldoende reageer op 'n dosis van 150 mg / dag nie, kan voordeel trek uit 'n verhoging tot die gewone volwasse teikendosis van 300 mg / dag, wat een keer per dag gegee word.

Oorskakeling van pasiënte van tablette met langdurige vrystelling

Wanneer pasiënte van tablette met langdurige vrystelling na tablette met verlengde vrystelling oorgeskakel word; gee dieselfde daaglikse dosis indien moontlik. Pasiënte wat tans met 300 mg / dag tablette met langdurige vrystelling behandel word (byvoorbeeld 150 mg twee keer per dag), kan oorgeskakel word na tablette met verlengde vrystelling 300 mg een keer per dag.

Spesiale bevolkingsgroepe

Bejaarde bevolkingsgroep

Groter sensitiwiteit van sommige ouer persone vir bupropion kan nie uitgesluit word nie, en daarom kan 'n verminderde frekwensie en / of dosis benodig word (sien afdeling 4.4).

Nierversaking

Behandeling van pasiënte met nierversaking moet met 'n laer frekwensie en / of dosis begin word, aangesien bupropion en sy metaboliete in sulke pasiënte in 'n groter mate as gewoonlik kan ophoop (sien afdeling 4.4).

Lewerversaking

BUDEP XR moet met omsigtigheid gebruik word by pasiënte met matige lewerversaking. Vanweë verhoogde wisselvalligheid in die farmakokinetika by pasiënte met matige lewersirrose, moet 'n verminderde frekwensie van dosis oorweeg word (sien afdelings 4.8 en 4.4). **BUDEP XR** is teenaangedui by pasiënte met matige tot ernstige lewersirrose.

Pediatriese bevolking

BUDEP XR is nie aangedui vir gebruik by kinders of adolessente onder die ouderdom van 18 jaar nie (sien afdeling 4.3).

Toedieningsmetode

BUDEP XR-tablette moet heel ingesluk word en nie gesny, fyngedruk of gekou word nie, want dit kan lei tot 'n verhoogde risiko vir newe-effekte, insluitend aanvalle.
Daar moet minstens ‘n 24 uur interval tussen opeenvolgende dosisse wees.
Slapeloosheid is 'n baie algemene newe-effek wat dikwels van verbygaande aard is.
Slapeloosheid kan verminder word deur dosering voor slaaptyd te vermy (mits daar minstens 24 uur tussen dosisse is) of, indien klinies aangedui, ‘n dosisverlaging.

4.3 Kontraindikasies

BUDEP XR word teenaangedui by die volgende:

- Pasiënte onder 18 jaar.
- Hipersensitiwiteit vir bupropion of enige komponent van **BUDEP XR**. Anafilaktoïede / anafilaktiese reaksies en Stevens-Johnson-sindroom is gerapporteer.

- By pasiënte met 'n aanvalstoornis.
- **BUDEP XR** moet nie toegedien word aan pasiënte wat tans behandel word met enige ander middel wat bupropion bevat nie, omdat die voorkoms van aanvalle dosisafhanklik is.
- By pasiënte wat alkohol, bensodiasepiene, barbiturate en / of kalmeermiddels skielik staak.
- By pasiënte met 'n huidige of vorige diagnose van bulimie of anorexia nervosa, is 'n hoër voorkoms van aanvalle by hierdie pasiëntpopulasie gesien toe bupropion toegedien is.
- Gelyktydige toediening van **BUDEP XR** met monoamienoksidaseremmers (MAO-remmers) is teenaangedui. Minstens 14 dae moet verloop tussen die beëindiging van MAO-remmers en die aanvang van die behandeling met **BUDEP XR**. Die aanvang van behandeling met **BUDEP XR** by 'n pasiënt wat alreeds behandel word met omkeerbare MAO's soos linesolied of intraveneuse metileenblou, is teenaangedui.
- Lewersiekte, Child-Pugh graad B&C, reeks 7-13.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Dosisverwante risiko vir aanvalle

Die aanbevole dosis **BUDEP XR** moet nie oorskry word nie, aangesien bupropion gepaard gaan met 'n dosisverwante risiko vir aanvalle.

BUDEP XR moet gestaak word by pasiënte wat 'n aanval kry tydens behandeling (sien afdeling 4.8). Klinici moet daarop let dat die simptome kan voortduur nadat behandeling met bupropion gestaak is en dat kliniese behandeling dienooreenkomstig voorsien moet word.

Die totale voorkoms van aanvalle met bupropion is gerapporteer om 0,1% te wees.

Daar is 'n verhoogde risiko van aanvalle wat voorkom met die gebruik van bupropion in die teenwoordigheid van predisponerende risikofaktore wat die aanvaldrempel verlaag, insluitende:

- geskiedenis van koptrauma
- gewas in die sentrale senuweestelsel (SSS)

- geskiedenis van aanvalle
- gepaardgaande toediening van ander medisyne waarvan bekend is dat dit die aanvaldrempel verlaag (sien afdeling 4.5)
- oormatige gebruik van alkohol of kalmeermiddels (sien afdeling 4.3)
- diabetes behandel met hipoglukemiese middels of insulien
- gebruik van stimulante of anorektiese produkte.

BUDEP XR moet gestaak word en behoort nie aanbeveel te word vir pasiënte wat tydens die behandeling 'n aanval kry nie.

Kliniese verergering en selfmoordrisiko verbonde aan psigiatriese afwykings

Sien waarskuwing in die bostaande tabel.

Pasiënte met 'n ernstige depressieversteuring se toestand kan vererger ten opsigte van depressie en / of die voorkoms van selfmoordgedagtes en gedrag (selfmoord), ongeag die gebruik van antidepressante. Hierdie risiko kan voortduur totdat beduidende remissie plaasvind. 'n Oorsaaklike rol vir antidepressante om sulke gedrag te veroorsaak, is egter nie vasgestel nie.

Aangesien verbetering in depressie gedurende die eerste paar weke of langer nie moontlik is nie, moet pasiënte wat met bupropion behandel word, noukeurig dopgehou word vir kliniese verergering (insluitend die ontwikkeling van nuwe simptome) en selfmoordneigings. Veral aan die begin van behandeling, of ten tye van die dosisverandering, neem dit toe of neem dit af.

Pasiënte met 'n geskiedenis van selfmoordgedrag of -gedagtes, jong volwassenes en pasiënte wat 'n beduidende mate van selfmoordgedagtes het voordat die behandeling begin, loop 'n groter risiko van selfmoordgedagtes of selfmoordpogings en moet sorgvuldig gemonitor word tydens die behandeling.

Die volgende simptome is gerapporteer by pasiënte wat behandel word met antidepressante vir depressiewe orde: angs, agitasie, paniekaanvalle, slapeloosheid, geïrriteerdheid,

vyandigheid (aggressiwiteit), impulsiwiteit, akatisie (psigomotoriese rusteloosheid), hipomanie en manie.
Daarbenewens is 'n verhoogde risiko vir selfmoorddenke en gedrag geassosieer met die gebruik van antidepressante, in vergelyking met plasebo, by pasiënte jonger as 25 jaar gerapporteer by volwassenes met ernstige depressie en ander psigiatriese afwykings. Pasiënte (en versorgers van pasiënte) moet in kennis gestel word van die noodsaaklikheid om te monitor vir enige verergering van hul toestand (insluitend die ontwikkeling van nuwe simptome) en / of die voorkoms van selfmoordgedagtes / gedrag of gedagtes om hulself te benadeel en om onmiddellik mediese advies in te win as hierdie simptome voorkom.

Daar moet in gedagte gehou word dat die aanvang van sommige neuropsigiatriese simptome verband kan hou met die onderliggende siektetoestand of die medisyne (sien neuropsigiatriese simptome, insluitend manie en bipolêre versteuring hieronder, afdeling 4.8).
Daar moet oorweeg word om die terapeutiese behandeling te verander, insluitend die beëindiging van bupropion by pasiënte wat kliniese verergering ervaar (insluitend die ontwikkeling van nuwe simptome) en / of die opkoms van selfmoordgedagtes / gedrag, veral as hierdie simptome ernstig is, ‘n skielike aanvang neem, of nie deel was van die simptome van die pasiënt nie.
Alhoewel dit nie nodig is om bupropion geleidelik te verminder wanneer behandeling gestaak word nie, moet die pasiënt gemonitor word vir verergering van depressiewe simptome na staking.

Neuropsigiatriese simptome, insluitend manie en bipolêre afwykings

Neuropsigiatriese simptome is gerapporteer (sien afdeling 4.8). In die besonder is psigotiese en maniese simptomatologie gerapporteer, hoofsaaklik by pasiënte met 'n bekende geskiedenis van psigiatriese siektes. Agressie, woede en gewelddadige gedrag kan voorkom. Daarbenewens kan 'n depressiewe episode die aanvanklike aanduiding van bipolêre versteuring wees. Daar word algemeen geglo dat die behandeling van so 'n episode

met slegs 'n antidepressant, die waarskynlikheid van voorkoms van 'n gemengde / maniese episode kan verhoog by pasiënte met 'n risiko vir bipolêre versteuring. Beperkte kliniese data oor die gebruik van bupropion in kombinasie met gemoedsstabiliseerders by pasiënte met 'n geskiedenis van bipolêre versteuring, dui op 'n lae tempo van oorskakeling na manie. Voordat behandeling met bupropion ‘n aanvang neem, moet pasiënte voldoende gekeur word om vas te stel of hulle die risiko loop van bipolêre versteuring. So’n keuring moet 'n gedetailleerde psigiatriese geskiedenis insluit, insluitend 'n familiegeskiedenis van selfmoord, bipolêre versteuring en depressie.

Lewerversaking

Bupropion word breedvoerig in die lewer gemetaboliseer tot aktiewe metaboliete, wat verder gemetaboliseer word. Geen statisties beduidende verskille in die farmakokinetika van bupropion is gerapporteer by pasiënte met matige lewersirrose in vergelyking met gesonde vrywilligers nie, maar bupropion-plasmavlakke het 'n hoër wisselvalligheid getoon tussen individuele pasiënte. Daarom moet bupropion met omsigtigheid gebruik word by pasiënte met matige lewerversaking, en 'n verminderde dosis moet oorweeg word (sien afdeling 5.2 en 4.3).

Nierversaking

Bupropion word breedvoerig in die lewer gemetaboliseer tot aktiewe metaboliete, wat verder gemetaboliseer word en deur die niere uitgeskei word. Daarom moet die behandeling van pasiënte met nierversaking met 'n laer frekwensie en / of dosisse begin word, aangesien bupropion en die metaboliete daarvan by sulke pasiënte tot 'n groter mate as gewoonlik kan ophoop. Die pasiënt moet fyn dopgehou word vir moontlike nadelige effekte (bv. slapeloosheid, droë mond, aanvalle) wat kan dui op hoë bupropion- of metabolietvlakke, toksiese effekte van verhoogde bloed- en weefselvlakke van bupropion en metaboliete.

Bejaarde pasiënte

Gerapporteerde kliniese ervaring met bupropion het geen verskille in verdraagsaamheid tussen bejaarde en ander volwasse pasiënte geïdentifiseer nie. Groter sensitiwiteit van

sommige ouer persone kan egter nie uitgesluit word nie; daarom kan 'n verminderde frekwensie van dosering benodig word (sien afdeling 5.2).

Kardiovaskulêre siekte

Daar is beperkte kliniese ervaring gerapporteer oor die gebruik van bupropion om depressie te behandel by pasiënte met kardiovaskulêre siektes. ‘n Oorsaaklike verband tussen die gebruik van bupropion en skielike dood kan egter nie uitgesluit word nie. Sorg moet gedra word as dit by hierdie pasiënte gebruik word.

Kardiale geleidingsversteurings: Bupropion kan hartgeleidingsindroom ontmasker bv. Brugada-sindroom, 'n seldsame oorerflike siekte van die kardiale natriumkanaal met kenmerkende EKG-veranderinge (regter bondeltakblok en ST-segmentverhoging in regter prekordiale leidings), wat kan lei tot hartstilstand of skielike dood. Omsigtigheid word aangeraai by pasiënte met Brugada-sindroom of 'n familiegeskiedenis van hartstilstand of skielike dood.

Hipertensie

Bupropion kan bloeddruk verhoog.

Bepaal bloeddruk voordat u met bupropion begin, en monitor dit periodiek tydens die behandeling. Die risiko van hipertensie word verhoog as bupropion gelyktydig gebruik word met MAO-remmers of ander middels wat die dopaminerge of noradrenerge aktiwiteit verhoog (sien afdeling 4.3).

Hipersensitiwiteit

Bupropion moet onmiddellik gestaak word as pasiënte gedurende die behandeling hipersensitiwiteitsreaksies ervaar (sien afdeling 4.8). Genbeeskundiges moet daarop let dat die simptome kan voortduur na die staking van bupropion, en dat kliniese behandeling dienooreenkomstig voorsien moet word.

Hoeksluiting gloukoom

Hoeksluiting gloukoom het voorgekom by pasiënte met onbehandelde anatomies smal hoeke wat met antidepressante behandel is.

Kinders en adolessente jonger as 18 jaar

Die veiligheid en doeltreffendheid van bupropion by pasiënte onder 18 jaar is nie gerapporteer nie.

Behandeling met antidepressante word na bewering geassosieer met 'n verhoogde risiko vir selfmoorddenke en -gedrag by kinders en adolessente met ernstige depressie en ander psigiatriese afwykings (sien afdeling 4.3).

Laktose

BUDEP XR bevat laktose wat 'n effek kan hê op die glukemiese beheer van pasiënte met diabetes mellitus.

Pasiënte met seldsame oorerflike probleme van galaktose-intoleransie, Lapp-laktase-tekort of glukose-galaktose-wanabsorpsie, moet nie **BUDEP XR** neem nie.

4.5 Interaksie met ander medisyne en ander vorme van interaksie

Medisyne wat bekend is om die CYP2B6-iso-ensiem te beïnvloed

Bupropion word hoofsaaklik deur die sitochroom P450 IIB6 (CYP2B6) gemetaboliseer tot sy metaboliet hidroksibupropion (sien afdeling 5.2). Versigtigheid moet aan die dag gelê word wanneer bupropion toegedien word met medisyne wat die CYP2B6-iso-ensiem beïnvloed (bv. orfenadrien, siklofosfamied, ifosfamied, prasugrel, simetidien, tiklopidien en klopidogrel). Alhoewel bupropion nie deur die CYP2B6-iso-ensiem gemetaboliseer word nie, is daar wel berig dat bupropion en hidroksiebupropion inhibeerders van die CYP2D6-baan is. In 'n gerapporteerde menslike farmakokinetiese studie het toediening van bupropion plasmavlakke van desipramien verhoog. Hierdie effek was ten minste sewe dae na die laaste dosis bupropion steeds aanwesig.

Gelyktydige behandeling met medisyne wat hoofsaaklik deur hierdie iso-ensiem gemetaboliseer word [soos sekere beta-blokkers (bv. metoprolol), anti-aritmestowwe (bv. propafenon en flekainied), selektiewe serotonien-heropname-remmers (SSRIs), trisikliese antidepressante (bv. venlafaksien) , nortriptilien, imipramien, desipramien, paroksetien, fluoksetien en sertralien), antipsigotika (bv. haloperidol, risperidon en tioridasien)] moet aan die laer end van die dosisreeks van die medisyne wat gesamentlik toegedien word. As bupropion by die behandelingsregimen gevoeg word van 'n pasiënt wat reeds 'n medikasie

ontvang wat deur CYP2D6 gemetaboliseer word, moet die noodsaaklikheid om die dosis van die oorspronklike medikasie te verlaag, oorweeg word, veral vir medisyne met 'n smal terapeutiese indeks (sien afdeling 5.2).

Alhoewel sitalopram nie hoofsaaklik deur CYP2D6 gemetaboliseer word nie, is berig dat bupropion die Cmax en AUC (van sitalopram met onderskeidelik 30% en 40%) verhoog. Aangesien bupropion omvattend gemetaboliseer word, kan die toediening van medisyne waarvan bekend is dat dit metabolisme induseer (bv. karbamasepien, fenobarbitoon, fenitoïne) of die metabolisme daarvan rem wat die kliniese aktiwiteit daarvan beïnvloed.

Ritonavir en lopinavir

In 'n reeks gerapporteerde studies by gesonde vrywilligers is berig dat ritonavlr (100 mg twee keer per dag of 600 mg twee keer per dag) of ritonavir 100 mg plus lopinavir 400 mg twee keer per dag die blootstelling aan bupropion en die belangrikste metaboliete daarvan op 'n dosisafhanklike manier verminder met ongeveer 20 tot 80%. Hierdie effek is vermoedelik te wyte aan die induksie van bupropionmetabolisme. Pasiënte wat ritonavir ontvang, mag verhoogde dosisse van **BUDEP XR** benodig, maar die maksimum aanbevole dosis van **BUDEP XR** moet nie oorskry word nie.

Alkohol

Daar is verslae van nadelige neuropsigiatriese gebeure of verminderde alkoholverdraagsaamheid by pasiënte wat alkohol drink tydens bupropionbehandeling. Die verbruik van alkohol tydens die behandeling met **BUDEP XR** moet beperk word of vermy word.

Levodopa of amantadien

Beperkte gerapporteerde kliniese data dui op 'n hoër voorkoms van newe-effekte by pasiënte wat gelyktydig bupropion en levodopa toegedien word. Die toediening van bupropion aan pasiënte wat gelyktydig levodopa of amantadien ontvang, moet met omsigtigheid gedoen word.

Nikotien transdermale stelsel

Gelyktydige gebruik van bupropion en 'n nikotien-transdermale stelsel (NTS) kan bloeddruk verhoog.

MAO-remmers

Na berig word inhibeer bupropion die heropname van dopamien en norepinefrien. Gelyktydige gebruik van MAO-remmers en bupropion is teenaangedui omdat daar 'n verhoogde risiko is vir hipertensiewe reaksies as bupropion saam met MAO-remmers gebruik word.

Daar is aangemeld dat die akute toksisiteit van bupropion verhoog word deur die MAO-remmer fenelsien. Minstens 14 dae moet verloop tussen die staking van 'n MAO-remmer wat bedoel is om depressie te behandel en die aanvang van die behandeling met **BUDEP XR**. Omgekeerd, moet minstens 14 dae toegelaat word nadat behandeling met **BUDEP XR** gestaak is voordat 'n MAO-antidepressant begin word (sien afdelings 4.2 en 4.3).

4.6 Vrugbaarheid, swangerskap en laktasie

Swangerskap

Veiligheid tydens swangerskap en laktasie is nie gerapporteer nie.

Gerapporteerde epidemiologiese studies van swangerskapuitkomste na blootstelling aan moeders in die eerste trimester van bupropion, het 'n verband met 'n verhoogde risiko van aangebore kardiovaskulêre misvormings, insluitend ventrikulêre septale defekte en linker ventrikulêre uitvloeiselkanaaldefekte, gerapporteer. Hierdie bevindings is nie konsekwent in alle studies nie.

Borsvoeding

Aangesien bupropion en die metaboliete daarvan in menslike borsmelk uitgeskei word, moet moeders aangeraai word om nie te borsvoed terwyl hulle **BUDEP XR** neem nie.

Vrugbaarheid

'n Gerapporteerde vrugbaarheidstudie by rotte in dosisse tot 300 mg / kg / dag het geen bewyse van verswakte vrugbaarheid getoon nie (sien afdeling 5.3).

4.7 Effekte op die vermoë om te bestuur en masjiene te gebruik

Pasiënte moet versigtig wees voordat hulle bestuur of masjinerie gebruik totdat hulle redelik seker is dat bupropion tablette nie hul vermoëns nadelig beïnvloed nie.

4.8 Ongewenste effekte

Die newe-effekte word hieronder gelys volgens die orgaanklas en frekwensie van die stelsel.

Tabel 1: Opsomming van newe-effekte in tabelvorm

Stelsel Orgaanklas	**Frekwensie**	**Newe-effekte**
Immuunstelselafwykings *	Gereeld	Hipersensitiwiteitsreaksies soos urtikariaal.
	Minder gereeld	Ernstiger hipersensitiwiteitsreaksies, insluitend angio-oedeem, dispnee / brongospasma en anafilaktiese skok. Artralgie, mialgie en koors is ook gerapporteer in verband met uitslag en ander simptome wat dui op vertraagde hipersensitiwiteit. Hierdie simptome kan soos serumsiekte lyk. * Sien ook “Vel- en onderhuidse weefselafwykings”
Metabolisme en voedingsafwykings	Gereeld	Anoreksie, gewigstoename of gewigsverlies.
	Minder gereeld	Bloedglukose versteurings.
Psigiatriese afwykings	Gereeld	Slapeloosheid, agitasie, angs Minder gereeld: verwarring, depressie, aggressie, vyandigheid, geïrriteerdheid, rusteloosheid, hallusinasies, abnormale drome, insluitend nagmerries, depersonalisering, dwalings, paranoïese gedagtes.
	Frekwensie onbekend	Selfmoordgedagtes en selfmoordgedrag, psigose (sien afdeling 4.4)
Senuweestelselafwykings	Gereeld	Hoofpyn of migraine, bewing, duiseligheid, slaperigheid, senuweeagtigheid, smaakstoornisse

	Minder gereeld	Konsentrasieversteuring, aanvalle (sien afdeling 4.4 & 4.8), distonie, ataksie, parkinsonisme, koordinasieversteurings, geheueverswakking, parestesie, sinkopee.
Oogafwykings	Gereeld	Visuele versteuring
Oor- en labirintstoornisse	Gereeld	Tinnitus, gehoorversteuring
Hartafwykings	Minder gereeld	Tagikardie, hartkloppings, hittegloede, hartritmestoornisse, hipertensie, hipotensie
Vaatstoornisse	Gereeld	Verhoogde bloeddruk (soms erg), blos op die vel.
	Minder gereeld	Vaatverwyding, posturale hipotensie
Respiratoriese afwykings	Gereeld	Faringitis, sinusitis, verhoogde hoes
Gastro-intestinale afwykings	Gereeld	Droë mond, gastro-intestinale versteuring, insluitend naarheid en braking, buikpyn, hardlywigheid, disfagie
Hepato-bilière afwykings	Minder gereeld	Verhoogde lewerensieme, geelsug, hepatitis
Vel- en onderhuidse weefselafwykings *	Gereeld	Uitslag, pruritus, sweet Minder gereeld: Erythema multiforme, Stevens Johnson-sindroom * Sien ook “Immuunstelselafwykings”
Spier- en bindweefselaf-wyking	Minder gereeld	Ruk bewegings
Nier- en urienafwykings	Minder gereeld	Urinêre frekwensie en / of retensie, urinêre dringendheid, vaginale bloeding, urienweginfeksie
Algemene afwykings en	Gereeld	Koors, astenie, pyn op die bors, menstruele klagtes, akatisie, verminderde libido.

toestande op die toedienings-plek		

Post-bemarkingservaring

Die volgende nadelige reaksies is gerapporteer tydens die gebruik van bupropion na goedkeuring. Aangesien hierdie reaksies vrywillig gerapporteer word uit 'n populasie van 'n onseker grootte, is dit nie altyd moontlik om die frekwensie daarvan betroubaar te skat of 'n oorsaaklike verband met blootstelling aan geneesmiddels vas te stel nie.

Tabel 2: Opsomming in tabelvorm van ongewenste reaksies aangemeld ná bemarking

Stelsel Orgaanklas	**Newe-effekte**
Bloed en limfstelsels versteurings	Eggimose, bloedarmoede, leukositose, leukopenie, limfadenopatie, pansitopenie en trombositopenie. Veranderde PT en / of INR, geassosieer met hemorragiese of trombotiese komplikasies, is waargeneem toe bupropion saam met warfarin toegedien is.
Endokriene afwykings	Hiperglusemie, hipoglusemie en sindroom van onvanpaste antidiuretiese hormoonafskeiding.
Metabolisme en voedingsaf-wykings	Glukosuria.
Psigiatriese afwykings	Abnormale koördinasie, depersonalisering, emosionele labiliteit, hiperkinesie, hipertonie, hipertesie, vertigo, amnesie, ataksie, derealisering, abnormale elektroenkefalogram (EKG), aggressie, akinesie, afasie, koma, disartrie, diskinesie, distonie, euforie, ekstrapiramidiese sindroom, verhoogde libido, neuralgie, neuropatie, paranoïese idee, rusteloosheid, selfmoordpoging en ontmaskering van tardiewe diskinesie.
Oog afwykings	Akkommodasie abnormaliteit, droë oog, verhoogde intraokulêre druk, gloukoom met hoeksluiting en mydriasis.
Oor- en labirintstoornisse	Doofheid.
Hartafwykings	Beroerte, sinkopee, volledige atrioventrikulêre blok, ekstrasistole, miokardiale infarksie, flebitis.

Vaatstoornisse	Posturale hipotensie, hipertensie, longembolie, vasodilatasie.
Asemhalings-, torakale en mediastinumafwykings	Bronchospasma en longontsteking.
Gastrointestinale afwykings	Bruxisme, gastriese terugvloei, gingivitis, glossitis, verhoogde speekselafskeiding, mondsere, stomatitis, dors, oedeem van die tong, kolitis, slukderm, gastro-intestinale bloeding, tandvleisbloeding, dermperforasie en maagsweer.
Hepato-bilière afwykings	Abnormale lewerfunksie, geelsug, hepatitis, lewerskade, pankreatitis.
Vel- en onderhuidse weefselafwykings *	Makulopapulêre uitslag, alopesie, angio-oedeem, eksfoliatiewe dermatitis en hirsutisme.
Spier- en bindweefselaf-wyking	Beenkrampe, koors / rabdomiolise, en spierswakheid. Voortplantingstelsel- en borsversteurings: Impotensie, poliurie, prostaatversteuring, abnormale ejakulasie, sistitis, dispareunie, disurie, ginekomastie, menopouse, pynlike ereksie, salpingitis, urinêre inkontinensie, urinêre retensie en vaginitis.
Algemene afwykings en toestande op die toedienings-plek	Rillings, oedeem in die gesig, oedeem, perifere oedeem, spier- en skeletpyn op die bors, liggevoeligheid en malaise.

Rapportering van verwagte newe-effekte

Aanmelding van verwagte newe-effelcte na magtiging van die medisyne is belangrik. Dit laat voortgaande monitering van die voordeel/risiko-balans van die medisyne toe. Gesodheidsorgverskaffers word gevra om enige verwagte newe-effekte aan te meld aan SAHPRA via die Med Safety APP (Medsafety X SAHPRA) en e-verslaggewing platform (who-umc.org) gevind op die SAHPRA webwerf. Deur newe-effekte aan te meld, kan u help om meer inligting oor die veiligheid van **BUDEP XR** te verskaf.

As nadelige reaksies vermoed word kan die ook aan die Houer van sertifikaat van registrasie per e-pos of telefonies gerapporteer word: pharmacovigilance.africasme@sunpharma.com of tel: +27(0) 12 643 2000.

4.9 Oordosering

Bykomend tot die reaksies wat onder newe-effekte gerapporteer word, het oordosering gelei tot simptome soos slaperigheid, bewusteloosheid en EKG-veranderinge soos geleidingsversteurings (insluitend QRS-verlenging) of ritmestoornisse.

Akute inname van dosisse van meer as tien keer die maksimum terapeutiese dosis is gerapporteer.

Behandeling: In geval van oordosis, word hospitalisasie aanbeveel. EKG en vitale tekens moet gemonitor word. Verseker voldoende lugweg, suurstof en ventilasie. Die gebruik van geaktiveerde ho Verdere behandeling moet plaasvind soos klinies aangedui of soos aanbeveel deur die nasionale gifsentrum, waar beskikbaar word houtskool ook aanbeveel.

Geen spesifieke teenmiddel vir bupropion is bekend nie.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Kategorie A. 1.2. Psigo-analeptika (antidepressante).

Pharmakoterapeutiese groep: Ander antidepressante, ATC kode: N06 AX12.

Bupropion is 'n remmer van die neuronale heropname van kategolamiene (noradrenalien en dopamien) met 'n minimale effek op die heropname van indolamiene (serotonien), en rem nie monoamienoksidase nie. Die werkingsmeganisme van bupropion is onbekend.

5.2 Farmakokinetiese eienskappe

Absorpsie

Na orale toediening van bupropion verlengde vrystellingstablette aan gesonde vrywilligers, is gerapporteer dat die tyd tot die hoogste plasmakonsentrasies vir bupropion ongeveer 5 uur is.

Die opname van bupropion word na bewering nie beduidend beïnvloed as dit saam met voedsel geneem word nie. Na bewering vertoon Bupropion en sy metaboliete lineêre kinetika na chroniese toediening van 150 tot 300 mg per dag.

Verspreiding

Bupropion word wyd versprei met 'n skynbare verspreidingsvolume van ongeveer 2000 ℓ. Bupropion en hidrobupropion is matig gebind aan menslike plasmaproteïene (onderskeidelik 84% en 77%).

Die mate van proteïenbinding van die treohidrobupropionmetaboliet is na bewering ongeveer die helfte van die waarneming met bupropion.

Biotransformasie

Bupropion word breedvoerig by mense gemetaboliseer. Drie farmakologies-aktiewe metaboliete is in plasma geïdentifiseer: hidroksibupropion en die amino-alkoholisomere, treohidrobupropion en eritrohidrobupropion. Dit is klinies belangrik, aangesien die plasmakonsentrasies so hoog of hoër is as dié van bupropion. Daar is gerapporteer dat die piekplasmakonsentrasies van hidroksibupropion ongeveer 7 uur na toediening van bupropion plaasvind. Eritrohidrobupropion kan nie in die plasma gemeet word na 'n enkele dosis bupropion nie. Die aktiewe metaboliete word verder tot onaktiewe metaboliete gemetaboliseer en in die urine uitgeskei. Daar is gerapporteer dat bupropion gemetaboliseer word tot sy belangrikste aktiewe metaboliet, hidroksibupropion, hoofsaaklik deur CYP2B6, terwyl sitochroom P450-ensieme nie betrokke is by die vorming van treohidrobupropion nie (sien afdeling 4.5). Bupropion en hydroksiebupropion is albei relatief swak kompeterende remmers van die CYP2D6-iso-ensiem met Ki-waardes van onderskeidelik 21 en 13,3 M. By menslike vrywilligers waarvan bekend is dat dit omvattend gemetaboliseer word deur CYP2D6-iso-ensiem, is gelyktydig gerapporteer dat die toediening van bupropion en desipramien 'n twee- en vyfvoudige toename in die Cmax en AUC van desipramien tot gevolg het. Hierdie effek was ten minste sewe dae na die laaste dosis bupropion aanwesig. Aangesien bupropion nie deur die CYP2D6-baan gemetaboliseer word nie, word daar nie verwag dat desipramien die farmakokinetika van bupropion sal beïnvloed nie. Wees versigtig wanneer bupropion saam met substrate vir die CYP2D6-baan toegedien word (sien afdeling 4.5). By mense is geen bewyse van ensieminduksie gerapporteer vir bupropion of hydroksiebupropion by vrywilligers of pasiënte wat die aanbevole dosisse bupropion vir 10 tot 45 dae ontvang het nie.

Elliminasie

Na orale toediening van 200 mg 14C-bupropion by mense, is berig dat 87% en 10% van die radioaktiewe dosis onderskeidelik in die urine en ontlasting teruggevind is. Die fraksie van die orale dosis bupropion wat onveranderd uitgeskei word, is na bewering slegs 0,5%, 'n bevinding wat ooreenstem met die uitgebreide metabolisme van bupropion. Daar is berig dat minder as 10% van hierdie 14C dosis in die urine as aktiewe metaboliete beskou word.
Die skynbare gemiddelde opruiming na orale toediening van bupropion is gerapporteer op ongeveer 200 ℓ / uur en die gemiddelde eliminasiehalfleeftyd van bupropion is ongeveer 20 uur.
Die eliminasiehalfleeftyd van hidroksiebupropion is na bewering ongeveer 20 uur en die oppervlakte onder die plasma-geneesmiddelkonsentrasie versus tydkurwe (AUC) by bestendige toestand is ongeveer 17 keer die van bupropion. Die eliminasiehalfleeftyd vir treohidrobupropion en erithrohidrobupropion is na bewering langer (onderskeidelik 37 en 33 uur) en die bestendige AUC-waardes is onderskeidelik 8 en 1,6 keer hoër as dié van bupropion. Na bewering is bestendigheid binne 8 dae bereik vir bupropion en die metaboliete daarvan.

Spesiale pasiëntbevolkingsgroepe

Bejaardes

Gerapporteerde farmakokinetiese studies by bejaardes het wisselvallige resultate getoon. 'n Enkedosisstudie het getoon dat die farmakokinetika van bupropion en die metaboliete daarvan by bejaardes nie verskil van dié van jonger volwassenes nie. 'n Ander farmakokinetiese studie wat gerapporteer is, enkele en meervoudige dosisse, het voorgestel dat ophoping van bupropion en sy metaboliete in 'n groter mate by bejaardes kan voorkom. Kliniese ervaring het nie verskille in verdraagsaamheid tussen ouer en jonger pasiënte geïdentifiseer nie, maar groter sensitiwiteit by ouer pasiënte kan nie uitgesluit word nie.

Pasiënte met nierversaking

Die eliminasie van bupropion en die belangrikste metaboliete daarvan kan verminder word deur verswakte nierfunksie (sien afdeling 4.4).

Pasiënte met verminderde lewerfunksie

Die farmakokinetika van bupropion en die aktiewe metaboliete daarvan is na bewering nie statisties beduidend verskillend by pasiënte met ligte sirrose (Child-Pugh graad A, reeks 5-6) in vergelyking met gesonde vrywilligers nie, hoewel groter wisselvalligheid by individuele pasiënte gerapporteer is. Vir pasiënte met matige tot ernstige lewersirrose (Child-Pugh grade B & C, reeks 7-13), is berig dat 'n enkele dosis bupropion 'n Cmax en AUC lewer wat aansienlik verhoog is (gemiddelde verskil ongeveer 70% en drievoudig, onderskeidelik) en veranderliker in vergelyking met die waardes by gesonde vrywilligers, was die gemiddelde halfleeftyd ook langer (met ongeveer 40%). Vir die metaboliete is gerapporteer dat die gemiddelde Cmax laer was (met ongeveer 30 tot 70%), die gemiddelde AUC was geneig om hoër te wees (met ongeveer 30 tot 50%), die mediaan Tmax was later (ongeveer 20 uur), en die gemiddelde halfleeftye was langer (ongeveer twee- tot viervoudig) as by gesonde vrywilligers (sien afdeling 4.3).

5.3 Prekliniese veiligheidsdata

Lewenslange karsinogenisiteitsstudies is aangemeld by rotte en muise in dosisse van onderskeidelik 300 en 150 mg / kg / dag bupropionhidrochloried. Hierdie dosisse is onderskeidelik ongeveer sewe en tweemaal die maksimum aanbevole dosis vir mense (MRHD) op 'n mg / m2 basis. In die gerapporteerde rotstudie was daar 'n toename in nodulêre proliferatiewe letsels in die lewer in dosisse van 100 tot 300 mg / kg / dag van bupropionhidrochloried (ongeveer twee tot sewe keer die MRHD op 'n mg / m2 basis); laer dosisse is nie getoets nie. Die vraag of sulke letsels voorlopers van lewerneoplasmas kan wees, is tans nog nie opgelos nie. Soortgelyke lewerletsels is nie by muise gerapporteer nie, en geen toename in Daar is berig dat bupropion 'n positiewe reaksie (twee tot drie keer beheermutasiesnelheid) in twee van vyf stamme in een Ames-bakteriële mutagenisiteitstoets lewer, maar was negatief in ‘n ander. Kwaadaardige gewasse in die lewer en ander organe is nie in een van die twee studies aangemeld nie. Daar is berig dat bupropion 'n toename in chromosomale afwykings lewer in een van drie sitogenetiese studies in rotte beenmurg.

'n Gerapporteerde vrugbaarheidstudie by rotte in dosisse tot 300 mg / kg / dag het geen bewyse van verswakte vrugbaarheid getoon nie.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe

Etiel sellulose (ethocel 45 cps standaard premie), gliserielbehenaat (Compritol ATO 888),

Hidroksiepropielsellulose (HPC-L),

Hipromellose (Methocel E5 premium),

Isopropielalkohol,

Metakrielsuurkopolimeer dispersie (Eudragit L30D-55), Metileen chloride,

Opacode S-1-17823 (swart),

Poliëtileenglikool 6000,

Povidoon (plasdoon K90 D),

Silikondioksied (Syloid 244 FP),

Stariensuur,

Trietiel sitraat.

6.2 Onversoenbaarheid

Nie van toepassing nie.

6.3 Rakleeftryd

36 maande

6.4 Spesiale voorsorgmaatreëls vir opberging

HOU BUITE BEREIK VAN KINDERS

Bêre by of benede 25 ° C.

Bewaar in die oorspronklike verpakking totdat dit benodig word.

Lewer ongebruikte tablette by u apteker terug.

Moenie ongebruikte medisyne weggooi in riool of rioolstelsels nie.

6.5 Aard en inhoud van die houer

BUDEP XR 150 en **BUDEP XR 300** tablette word verpak in HDPE-bottels. Elke HDPE bottel bevat 30 tablette.

HDPE bottelverpakking:

Wit ondeursigtige HDPE-bottel met wit ondeursigtige polipropileen-kinderbestande sluiting met induksie-seëlvoering wat 1 g silikagel-droogmiddelsakkie bevat.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering

Geen spesiale vereistes vir wegdoening nie.

7. BEMARKINGSMAGTIGINGHOUER

RANBAXY PHARMACEUTICALS (EDMS) BPK

Lautreweg 14, Stormill, Uitb.1,

Roodepoort, 1724

Suid-Afrika

Tel: +27(0) 12 643 2000

8. BEMARKINGSMAGTIGINGSNOMMERS

BUDEP XR 150: 48/1.2/0114

BUDEP XR 300: 48/1.2/0115

9. DATUM VAN EERSTE GOEDKEURING/HERNUWING VAN GOEDKEURING

Datum van registrasie: 09 Feruarie 2021

10. DATUM VAN DIE TEKSHERSIENING

Oktober 2024