Applicant: Teva Pharmaceuticals (Pty) Ltd	Product name: BUPYRA XL 150 & 300
Date of Registration: 24 May 2022	Dosage form & strength: Each extended release tablet contains 150 mg or 300 mg bupropion hydrochloride
Reg No: BUPYRA XL 150: 54/1.2/0026 BUPYRA XL 300: 54/1.2/0533	

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

BUPYRA XL 150, extended release tablets

BUPYRA XL 300, extended release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

BUPYRA XL 150: Each extended release tablet contains 150 mg bupropion hydrochloride.

BUPYRA XL 300: Each extended release tablet contains 300 mg bupropion hydrochloride.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Extended release tablet.

BUPYRA XL 150 is a round, biconvex creamy-white to pale yellow extended release tablet.

BUPYRA XL 300 is a creamy-white to pale yellow, round tablet printed with ‘GS2’ on one side and plain on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

BUPYRA XL is indicated for the treatment of depression as defined by DSM IV Criteria.

Following a satisfactory response, continuation with BUPYRA XL 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.

BUPYRA XL tablets should be swallowed whole. The tablets should not be cut, crushed or chewed as this may lead to an increased risk of adverse effects including seizure.

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

Insomnia is a very common adverse event which is often transient. Insomnia may be reduced by avoiding dosing at bedtime (provided there is at least 24 hours between doses) or, if clinically indicated, dose reduction.

Posology:

Initial treatment:

The initial dose of BUPYRA XL 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 (e.g. 150 mg twice daily) may be switched to extended release tablets 300 mg once daily.

Special populations:

Children and adolescents: BUPYRA XL is not indicated for use in children or adolescents aged less than 18 years (see **section 4.3**).

Elderly: Greater sensitivity of some elderly individuals to BUPYRA XL 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: BUPYRA XL 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 **section 4.4**). BUPYRA XL is contraindicated in patients with moderate to severe hepatic cirrhosis (see **section 4.3**).

4.3 Contraindications:

- Hypersensitivity to bupropion hydrochloride or to any of the excipients listed in **section 6.1**.
- Patients younger than 18 years.
- BUPYRA XL is contraindicated in patients with a seizure disorder or any history of seizures.
- BUPYRA XL is contraindicated in patients with a known central nervous system tumour.
- Patients being treated with any other preparation containing bupropion should not receive BUPYRA XL, as the incidence of seizures is dose dependent.
- Patients undergoing abrupt discontinuation of alcohol or sedatives (benzodiazepines and benzodiazepine-like medicines) should not receive BUPYRA XL.
- Patients with a current or previous diagnosis of bulimia or anorexia nervosa should not receive BUPYRA XL as a higher incidence of seizures was seen in this patient population when BUPYRA XL was administered.
- BUPYRA XL is contraindicated with concomitant administration with monoamine oxidase inhibitors (MAOIs). At least 14 days should elapse between the discontinuation of MAOIs and initiation of treatment with BUPYRA XL.
- Liver disease, Child-Pugh grades B and C, range 7-13.

- Women of child-bearing potential not using contraception.

4.4 Special warnings and precautions for use:

Seizures:

The recommended dose of BUPYRA XL should not be exceeded, since BUPYRA XL is associated with a dose-related risk of seizure.

The overall incidence of seizure with modified release bupropion tablets in clinical trials at doses up to 450 mg/day was approximately 0,1 %.

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

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

BUPYRA XL treatment should be stopped and is not recommended for patients who experience a seizure while on treatment.

Interactions (see section 4.5):

Due to pharmacokinetic interactions, plasma levels of bupropion or its metabolites may be altered, which may increase the potential for undesirable effects (e.g. dry mouth, insomnia, seizures). Therefore, care should be

taken when BUPYRA XL is given concomitantly with medicines which can induce or inhibit the metabolism of bupropion.

BUPYRA XL inhibits metabolism by cytochrome P450 2D6. Caution is advised when medicines metabolised by this enzyme are administered concurrently.

Neuropsychiatry:

Suicide/suicidal thoughts or clinical worsening:

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 medicines. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients being treated with BUPYRA XL 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 disorder: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania and mania.

A meta-analysis of placebo controlled clinical trials of antidepressant medicines in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behaviour associated with antidepressant use compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany medicine therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

It should be recognised that the onset of some neuropsychiatric symptoms could be related either to the underlying disease state or the medicine therapy and an appropriate patient assessment should be undertaken (see *Neuropsychiatric symptoms including mania and bipolar disorder* below; see **section 4.8**).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing BUPYRA XL, in patients who experience the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Neuropsychiatric symptoms including mania and bipolar disorder:

Neuropsychiatric symptoms have been reported (see **section 4.8**). In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. Aggression, rage and violent behaviour may occur. Additionally, a major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Limited clinical data on the use of bupropion in combination with mood stabilisers in patients with a history of bipolar disorder suggests a low rate of switch to mania. Prior to initiating treatment with BUYPRA XL, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

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

Hypersensitivity:

BUPYRA XL should be promptly discontinued if patients experience hypersensitivity reactions during treatment (see **section 4.3**). Healthcare providers should be aware that the symptoms may progress or recur following the discontinuation of BUPYRA XL and should ensure symptomatic treatment is administered for an adequate length of time (at least one week).

Symptoms typically include skin rash, pruritus, urticaria or chest pain, but more severe reactions may include angioedema, dyspnoea/bronchospasm, anaphylactic shock, erythema multiforme or Stevens-Johnson syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity (see **section 4.8**). In most patients symptoms improved after stopping bupropion and initiating treatment with antihistamines or corticosteroids, and resolved over time.

Cardiovascular disease:

There is limited clinical experience of the use of bupropion as contained in BUPYRA XL to treat depression in patients with cardiovascular disease. Care should be exercised if it is used in these patients. However, bupropion as contained in BUYPRA XL was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease (see **section 5.1**).

Blood pressure:

Bupropion as contained in BUPYRA XL has been shown not to induce significant increases in blood pressure in non-depressed patients with Stage I hypertension. However, in clinical practice, hypertension, which in some cases may be severe (see **section 4.8**) and require acute treatment, has been reported in patients receiving bupropion. This has been observed in patients with and without pre-existing hypertension.

A baseline blood pressure should be obtained at the start of treatment, with subsequent monitoring especially in patients with pre-existing hypertension.

Consideration should be given to discontinuation of BUPYRA XL if a clinically significant increase in blood pressure is observed.

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

Hepatic impairment:

Bupropion as contained in BUPYRA XL is extensively metabolised in the liver to active metabolites, which are further metabolised. No statistically significant differences in the pharmacokinetics of bupropion were observed in patients with mild to moderate hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients.

Therefore, BUPYRA XL should be used with caution in patients with mild hepatic impairment and reduced frequency of dosing should be considered (see **section 4.2**).

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

Renal impairment and elderly patients:

Bupropion in BUPYRA XL is extensively metabolised in the liver to active metabolites which are further metabolised and excreted by the kidneys. Therefore, treatment should be initiated at a reduced frequency and/or dose in patients with renal impairment, 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.

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

Interference with urine testing:

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

Serotonin syndrome:

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when BUPYRA XL, is co-administered with serotonergic medicines, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see **section 4.5**). If concomitant treatment with other serotonergic medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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

Inappropriate routes of administration:

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

Paediatric population:

The safety and efficacy with the treatment of BUPYRA XL tablets in patients under 18 years of age have not been established. Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders (see **section 4.3**).

Brugada syndrome:

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

4.5 Interaction with other medicines and other forms of interaction:

Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, concomitant use of BUPYRA XL and monoamine oxidase inhibitors (MAOIs) is contraindicated (see **section 4.3**) as there is an increased possibility of adverse reactions from their co-administration. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with BUPYRA XL. For reversible MAOIs a 24-hour period is sufficient.

The effect of bupropion on other medicines:

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

Concomitant therapy with medicines with narrow therapeutic indices that are predominantly metabolised by CYP2D6 should be initiated at the lower end of the dose range of the concomitant medicine. Such medicines include certain antidepressants (e.g. desipramine, imipramine), antipsychotics (e.g. risperidone, thioridazine), beta-blockers (e.g. metoprolol), serotonin selective reuptake inhibitors (SSRIs) and Type 1C antidysrhythmics (e.g. propafenone, flecainide). If BUPYRA XL is added to the treatment regimen of a patient already receiving such a medicine, the need to decrease the dose of the original medicine should be considered.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when bupropion is co-administered with a serotonergic medicine, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see **section 4.4**).

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

Although citalopram (a SSRI) is not primarily metabolised by CYP2D6, in one study, bupropion increased the C_{max} and AUC of citalopram by 30 % and 40 %, respectively.

Co-administration of digoxin with bupropion may decrease digoxin levels. Digoxin AUC 0–24 h was decreased and renal clearance was increased in healthy volunteers, based on a cross-study comparison.

Medical practitioners should be aware that digoxin levels may rise on discontinuation of BUPYRA XL and the patient should be monitored for possible digoxin toxicity.

The effect of other medicines on bupropion:

BUPYRA XL is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6 (**see section 5.2**). Co-administration of medicines that may affect the metabolism of bupropion via CYP2B6 isoenzyme (e.g. CYP2B6 substrates: cyclophosphamide, ifosfamide, and CYP2B6 inhibitors: orphenadrine, ticlopidine, clopidogrel), may result in increased bupropion plasma levels and lower levels of active metabolite hydroxybupropion. The clinical consequences of the inhibition of the metabolism of bupropion via CYP2B6 enzyme and the consequent changes in the bupropion-hydroxybupropion ratio are currently unknown.

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

It has been reported in a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80 % (see **section 5.2**). Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55 % in healthy volunteers. The clinical consequences of the reduced exposure are unclear but may include decreased efficacy in the treatment of major depression. Patients receiving any of these medicines with BUPYRA XL may need increased doses, but the maximum recommended dose of BUPYRA XL should not be exceeded.

Other interaction information:

Administration of BUPYRA XL to patients receiving either levodopa or amantadine concurrently should be undertaken with caution. Limited clinical data suggest a higher incidence of undesirable effects (e.g. nausea, vomiting, and neuropsychiatric events – see **section 4.8**) in patients receiving BUPYRA XL concurrently with either levodopa or amantadine.

Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. The consumption of alcohol during BUPYRA XL treatment should be minimised or avoided.

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

There has been no systematic evaluation of the combination of bupropion as contained in BUPYRA XL with antidepressants (other than desipramine and citalopram), benzodiazepines (other than diazepam), or neuroleptics. There has also been limited clinical experience with St John's Wort.

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

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety in pregnancy has not been established.

Epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of some congenital cardiovascular malformations,

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

Lactation:

Safety in lactation has not been established.

As bupropion and its metabolites are excreted in human breast milk, mothers should be advised not to breastfeed while taking BUPYRA XL.

Fertility:

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

4.7 Effects on ability to drive and use machines:

BUPYRA XL may affect the ability to perform tasks that require judgement or motor and cognitive skill. Patients should exercise caution before driving or use of any machinery until they are reasonably certain BUPYRA XL does not adversely affect their performance.

4.8 Undesirable effects:

SOC:	**FREQUENCY:**	
Blood and lymphatic system disorders:	*Frequency unknown:*	Anaemia, leukopenia and thrombocytopenia
Immune system disorders:	*Frequent:*	Hypersensitivity reactions such as urticaria

	Less frequent:	More severe hypersensitivity reactions including angioedema, dyspnoea/bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.
Metabolism and nutrition disorders:	*Frequent:*	Anorexia
	Less frequent:	Weight loss, blood glucose disturbances
	Frequency unknown:	Hyponatraemia
Psychiatric disorders:	*Frequent:*	Insomnia (see **section 4.2**), agitation, anxiety
	Less frequent:	Depression, confusion, aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including

		nightmares, delusions, depersonalisation, paranoid ideation
	Frequency unknown:	Suicidal ideation and suicidal behaviour***, psychosis
Nervous system disorders:	*Frequent:*	Headache, tremor, dizziness, taste disorders
	Less frequent:	Concentration disturbance, seizures**, dystonia, ataxia, parkinsonism, incoordination, memory impairment, paraesthesia, syncope
	Frequency unknown:	Serotonin syndrome****
Eye disorders:	*Frequent:*	Visual disturbance
Ear and labyrinth disorders:	*Frequent:*	Tinnitus
Cardiac disorders:	*Less frequent:*	Tachycardia, palpitations
Vascular disorders:	*Frequent:*	Increased blood pressure (sometimes severe), flushing
	Less frequent:	Vasodilation, postural hypotension

Gastrointestinal disorders:	*Frequent:*	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation
Hepato-biliary disorders:	*Less frequent:*	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous tissue disorders*:	*Frequent:*	Rash, pruritis, sweating
	Less frequent:	Erythema multiforme, Stevens Johnson syndrome, exacerbation of psoriasis
	Frequency unknown:	Systemic lupus erythematosus syndrome aggravated, cutaneous lupus erythematosus, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders:	*Less frequent:*	Twitching
Renal and urinary disorders:	*Less frequent:*	Urinary frequency and/or retention, urinary incontinence

General disorders and administration site conditions:	*Frequent:*	Fever, chest pain, asthenia

* Hypersensitivity may manifest as skin reactions. Refer to 'Immune system disorders' and 'Skin and subcutaneous tissue disorders'.

** The incidence of seizures is approximately 0,1 % (1/1,000). The most frequent type of seizures is generalised tonic-clonic seizures, a seizure type which can result in some cases, in postictal confusion or memory impairment (see **section 4.4**).

*** Cases of suicidal ideation and suicidal behaviour have been reported during bupropion therapy or early after treatment discontinuation (see **section 4.4**).

**** Serotonin syndrome may occur as a consequence of an interaction between BUPYRA XL and a serotonergic medicine such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see **section 4.4**).

Reporting of suspected adverse reactions:

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

4.9 Overdose:

In addition to those events reported as undesirable effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation), dysrhythmias and tachycardia. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate.

Although most patients recovered without sequelae, deaths associated with BUPYRA XL have been rarely reported in patients ingesting large overdoses of the medicine.

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose has been reported. Serotonin syndrome has also 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 recommended. No specific antidote for BUPYRA XL is known.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

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

A1.2 Psycho-analeptics

Mechanism of action:

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

The mechanism of action of bupropion as an antidepressant is unknown. It is however presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

5.2 Pharmacokinetic properties:

Absorption:

After oral administration of bupropion tablets to healthy volunteers, peak plasma concentrations for bupropion was reached within approximately 5 hours. At steady state, the C_{max} and AUC values of hydroxybupropion are approximately 3 and 14 times that of bupropion, respectively. The C_{max} of threohydrobupropion at steady state is similar to that of bupropion and the AUC is approximately 5 times higher while the plasma concentrations of erythrohydrobupropion are comparable to those of bupropion. Peak plasma levels of hydroxybupropion are reached at 7 hours while those for threohydrobupropion and erythrohydrobupropion are reached at 8 hours. The AUC and C_{max} values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion increase dose proportionally over a dose range of 50-200 mg following single doses and over a dose range of 300-450 mg/day following chronic dosing.
The absolute bioavailability of bupropion is not known; urinary excretion data, however, show that at least 87 % of the dose of bupropion is absorbed.

The absorption of bupropion is not significantly affected by food.
Bupropion and its metabolites 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 hydroxybupropion are moderately bound to plasma proteins (84 % and 77 %, respectively). The extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

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

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

Biotransformation:

Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: Hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion. All of these metabolites are of clinical importance, as their plasma concentrations are high as or even higher than those of bupropion. The active metabolites are further metabolised to inactive metabolites (some of which have not been fully characterised but may include conjugates) and excreted in the urine.

Peak plasma concentrations of hydroxybupropion occur approximately 7 hours following bupropion hydrochloride administration.

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.

According to *in vitro* studies, bupropion is metabolised to its major active metabolite hydroxybupropion primarily by CYP2B6, while CYP1A2, 2A6, 2C9, 3A4 and 2E1 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 extensive metabolisers of the CYP2D6 isoenzyme, co-administration of bupropion and desipramine has resulted in 2- and 5-fold increases in the C_{max} and AUC, respectively, of desipramine.

After 7 days this effect was still visible after one dose of bupropion.

When bupropion is administered with substrates for CYP2D6 pathway, caution is advised (see **section 4.5**).

There is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving the 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 were recovered in the urine and faeces, respectively. The fraction of the dose of bupropion excreted unchanged was only 0,5 %, a finding consistent with the extensive metabolism of bupropion.

Less than 10 % of this ^{14}C dose was accounted for in the urine as active metabolites.

The mean apparent clearance following oral administration of bupropion is approximately 200 L/hr and the mean elimination half-life of bupropion is approximately 20 hours.

The elimination half-life of hydroxybupropion is approximately 20 hours and its area under the plasma medicine concentration versus time curve (AUC) at steady state is approximately 8 and 1,6 times higher than that of bupropion, respectively. Steady-state for bupropion and its metabolites is reached within 8 days.

The insoluble shell of the modified release tablet may remain intact during gastrointestinal transit and be eliminated in the faeces.

Special patient populations:

Elderly:

Reports from pharmacokinetic studies in the elderly have shown variable results. A single dose study showed that the pharmacokinetics of bupropion and its metabolites in the elderly do not differ from those in the younger adults. Another pharmacokinetic study, single and multiple 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. Limited data in patients with end-stage renal failure or moderate to severely impaired renal function indicate that exposure to bupropion and/or its metabolites were increased (see **section 4.4**).

Patients with hepatic impairment:

The pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild cirrhosis (Child-Pugh grade A, range 5-6) when compared to healthy volunteers, although more variability was observed between individual patients. For patients with moderate to severe hepatic cirrhosis (Child Pugh grades B & C, range 7-13), a single dose of bupropion produced a C_{max} and AUC that were substantially increased (mean difference approximately 70 % and 3-fold, respectively) and more variable when compared to the values in healthy volunteers; the mean half-life was also longer (by approximately 40 %). For hydroxybupropion, the mean C_{max} was lower (by approximately 70 %), the mean AUC tended to be higher (by approximately 30 %), the median T_{max} was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 4-fold) than in healthy volunteers. For threohydrobupropion and erythrohydrobupropion, the mean C_{max} tended to be lower (by approximately 30 %), the mean AUC tended to be higher (by approximately 50 %), the median T_{max} was later (by approximately 20 hrs), and the mean half-life was longer (by approximately 2-fold) than in healthy volunteers (see **section 4.3**).

In-vitro release of bupropion with alcohol:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

BUPYRA XL 150:

Core: hydroxypropyl cellulose, magnesium stearate, silicified microcrystalline cellulose, stearic acid 50.

Extended release coating: Opadry white 29A18501 consisting of: ethyl cellulose, hydroxypropyl cellulose, titanium dioxide (E171), triethyl citrate.

Modified release coating: methacrylic acid - ethyl acrylate copolymer, talc.

BUPYRA XL 300:

Core: povidone, cysteine hydrochloride monohydrate, colloidal anhydrous silica, glycerol dibehenate, magnesium stearate.

First coating: ethyl cellulose, povidone, macrogol.

Second coating: methacrylic acid - methyl methacrylate copolymer (1:1), colloidal hydrated silica, macrogol, triethyl citrate.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

BUPYRA XL 150: Unopened: 2 years.

After first opening: 2 months.

BUPYRA XL 300: 3 years.

6.4 Special precautions for storage:

BUPYRA XL 150: Store at or below 30 °C.

BUPYRA XL 300: Store at or below 25 °C.

Store in the original container in order to protect from moisture and light. Keep the bottle tightly closed.

6.5 Nature and contents of container:

BUPYRA XL 150: White, round, 75 ml HDPE containers with desiccant in canister and closed with a child-resistant white plastic cap (PP-closure) that includes an induction heat seal membrane. The HDPE bottle will be packed in an outer carton box.

Pack sizes: 30, 60 or 90 tablets.

BUPYRA XL 300: Blister: OPA/Alu/PVC-Alu blister strips containing 7, 10, 14, 15 or 28 tablets per blister strip. The blister strips will be packed in an outer carton.

Pack sizes: 7, 28, 30, 56, 60 or 90 tablets.

HDPE bottle: White, round, 60 ml HDPE containers with a silica gel canister and closed with a child-resistant white plastic cap (PP-closure) that includes an induction sealing liner. The HDPE bottle will be packed in an outer carton box.

Pack sizes: 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

2090

8. REGISTRATION NUMBER(S):

BUPYRA XL 150: 54/1.2/0026

BUPYRA XL 300: 54/1.2/0533

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

24 May 2022

10. DATE OF REVISION OF THE TEXT:

23 May 2023