PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1 NAME OF THE MEDICINE

BUPROPION 150 XL DRL

BUPROPION 300 XL DRL

Extended-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BUPROPION 150 XL DRL tablet contains 150 mg of bupropion hydrochloride.

Each BUPROPION 300 XL DRL tablet contains 300 mg of bupropion hydrochloride.

Sugar-free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Extended-release tablets

BUPROPION 150 XL DRL: White to pale yellow, round, biconvex film-coated tab debossed with '144' on one side and plain on the other side.

BUPROPION 300 XL DRL: White to pale yellow, modified capsule shape, biconvex, film-coated tablet, debossed with '145' on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Following a satisfactory response, continuation with BUPROPION XL DRL 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 BUPROPION XL DRL 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.

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.

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: BUPROPION XL DRL is not indicated for use in children or adolescents aged less than 18 years (see section 4.3 Contraindications).

Elderly: Greater sensitivity of some elderly individuals to BUPROPION XL DRL cannot be ruled out, hence a reduced frequency and/or dose may be required (see section 4.4 Special warnings and precautions for use).

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. Special warnings and precautions for use).

Liver Impairment: BUPROPION XL DRL 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 Undesirable effects and 4.4. Special warnings and precautions for use).

BUPROPION XL DRL is contra-indicated in patients with moderate to severe hepatic cirrhosis.

Method of administration

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

4.3 Contraindications

- Patients under 18 years.

- Hypersensitivity to bupropion or any components of the preparation listed in section 6.1.
- BUPROPION XL DRL is contra-indicated in patients with a seizure disorder.
- BUPROPION XL DRL should not be administered to patients currently being treated with any other preparation containing bupropion, as the incidence of seizures is dose dependent.
- BUPROPION XL DRL is contraindicated in patients with a known central nervous system tumour.
- BUPROPION XL DRL is contra-indicated in patients undergoing abrupt discontinuation of alcohol or sedatives.
- BUPROPION XL DRL is contra-indicated 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 BUPROPION XL DRL with monoamine oxidase inhibitors (MAOIs) is contra-indicated. At least 14 days should elapse between the discontinuation of MAOIs and initiation of treatment with BUPROPION XL DRL.
- 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

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

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

There is an increased risk of seizures occurring with the use of BUPROPION XL DRL in the presence of predisposing risk factors, which lower the seizure threshold. Therefore, BUPROPION XL DRL 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, excessive use of alcohol or sedatives (see section 4.3 Contraindications), diabetes treated with hypoglycaemics or insulin and use of stimulants or anorectic products.

BUPROPION XL DRL should be discontinued and not recommenced in patients who experience a seizure while on treatment.

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

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 may not occur during the first few weeks or more of treatment, patients being treated with BUPROPION XL DRL 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.

In addition, 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.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of 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, section 4.8. Undesirable effects).
Consideration should be given to changing the therapeutic regimen, including possibly discontinuing BUPROPION XL DRL, in patients who experience clinical worsening (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 XL DRL upon discontinuation, the patient should be monitored for worsening of depressive symptoms following discontinuation.

Neuropsychiatric symptoms including mania and bipolar disorder:

Neuropsychiatric symptoms have been reported (see section 4.8 Undesirable effects). 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 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 BUPROPION XL DRL, 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.

Brugada syndrome:

BUPROPION XL DRL may unmask Brugada syndrome, a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (ST segment elevation and T wave abnormalities in the right precordial leads), which may lead to cardiac arrest and/or sudden death. Caution is advised in patients with Brugada syndrome or risk factors such as a family history of cardiac arrest or sudden death.

Special patient groups

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 were observed in patients with mild hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients.

Therefore, BUPROPION XL DRL should be used with caution in patients with mild hepatic impairment and reduced frequency of dosing should be considered (see sections 5.2 Pharmacokinetic properties and 4.3 Contraindications).

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 population:

Clinical experience 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 and/or dose may be required (see section 5.2 Pharmacokinetic properties).

Cardiovascular disease:

There is limited clinical experience of the use of bupropion to treat depression in patients with cardiovascular disease. A causal relationship between the use of BUPROPION XL DRL and sudden death cannot be excluded. Care should be exercised if BUPROPION XL DRL is used in these patients. Hypertension has been reported to be severe and may require acute treatment, in patients receiving BUPROPION XL DRL. This has been observed in patients with and without pre-existing hypertension.

Children and Adolescents < 18 years:

The safety and efficacy with the treatment of BUPROPION XL DRL 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. Contraindications).

Inappropriate routes of administration:

BUPROPION XL DRL 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 XL DRL has been administered intra-nasally or by parenteral injection.

Serotonin Syndrome:

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when BUPROPION XL DRL is co-administered with a serotonergic agent, such as Selective

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

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular

abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Serotonin syndrome has been reported in association with overdose (see section 4.9 Overdose).

4.5 Interaction with other medicines and other forms of interaction

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 IIB6 (CYP2B6) (see section 5.2 Pharmacokinetic properties).

Care should therefore be exercised when BUPROPION XL DRL is co-administered with medicines known to affect the CYP2B6 isoenzyme (e.g. orphenadrine, cyclophosphamide, ifosfamide, ticlopidine, clopidogrel).

Although bupropion is not metabolised by the CYP2D6 isoenzyme, *in vitro* human P450 studies have shown that bupropion and hydroxybupropion are inhibitors of the CYP2D6 pathway.

In a human pharmacokinetic study, administration of bupropion increased plasma levels of desipramine. This effect was present for at least 7 days after the last dose of bupropion.

Concomitant therapy with medicines predominantly metabolised by this isoenzyme (such as certain beta-blockers, anti-dysrrhythmics, selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antipsychotics) should be initiated at the lower end of the dose range of the concomitant medication. If BUPROPION XL DRL 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. Pharmacokinetic properties).

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 bupropion.

Although citalopram is not primarily metabolised by CYP2D6, in one study,

bupropion increased 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, ritonavir, efavirenz) or inhibit metabolism (e.g. valproate) may affect its clinical activity.

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 %. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving ritonavir may need increased doses of BUPROPION XL DRL but the maximum recommended dose of BUPROPION XL DRL should not be exceeded.

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

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

Limited clinical data suggest a higher incidence of adverse events in patients receiving concurrent administration of bupropion and levodopa.

Administration of BUPROPION XL DRL to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

Concomitant use of BUPROPION XL DRL and a Nicotine Transdermal System (NTS) may result in elevations of blood pressure.

Co-administration of digoxin with BUPROPION XL DRL may decrease digoxin levels. Clinicians should be aware that digoxin levels may rise on discontinuation of BUPROPION XL DRL and the patient should be monitored for possible digoxin toxicity.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when BUPROPION XL DRL is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.4 Special warnings and precautions for use).

Interactions involving laboratory tests:

BUPROPION XL DRL interferes with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for amphetamines. A more specific alternative chemical method should be considered to confirm a positive result.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

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.

Breast-feeding

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

Fertility

There are no data on the effect of bupropion in human fertility.

A reproductive study in rats revealed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

Immune system disorders *See also 'Skin and subcutaneous tissue disorders'*	
Frequent:	hypersensitivity reactions such as urticaria
Less frequent:	more severe hypersensitivity reactions including angioedema, dyspnoea / bronchospasm and anaphylactic shock arthralgia, myalgia and fever in association with rash and other symptoms of delayed hypersensitivity; these symptoms may resemble serum sickness
Metabolism and nutrition disorders	
Frequent:	anorexia
Less frequent:	blood glucose disturbances weight loss
Frequency unknown:	Hyponatremia

Psychiatric disorders	
Frequent:	insomnia, agitation, anxiety
Less frequent:	confusion, depression; aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams, depersonalisation, delusions, paranoid ideation
Frequency unknown:	suicidal ideation, suicidal behaviour, psychosis
Nervous system disorders	
Frequent:	Headache, tremor, dizziness, taste disorders
Less frequent:	concentration disturbance seizures (see section 4.4. Warnings and special precautions) 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, pruritus, sweating
Less frequent:	erythema multiforme and Stevens-Johnson syndrome, exacerbation of psoriasis **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 incontinence
General disorders and administration site conditions	
Frequent:	fever, asthenia, chest pain

**Serotonin syndrome may occur as a consequence of an interaction between bupropion and a serotonergic medicine such as Selective Serotonin Reuptake

Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.4 Special warnings and precautions for use).

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found on-line under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

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

5 PHARMACOLOGICAL PROPERTIES

Category A. 1.2. Psycho-analeptics (antidepressants).

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

5.1 Pharmacodynamic properties

Mechanism of action

Bupropion is an inhibitor of the neuronal re-uptake of catecholamines (noradrenaline (norepinephrine) 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 tablets to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours.

The absorption of bupropion is not significantly affected when taken with 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 2 000 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.

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 are as high as or higher than those of bupropion.

Peak plasma concentrations of hydroxybupropion occur approximately 7 hours following administration of BUPROPION XL DRL.

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.

In vitro studies indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by CYP2B6, while cytochrome P450s are not involved in the formation of threohydrobupropion (see section 4.5. Interactions with other medicines and other forms of interaction).

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. This effect was present for at least 7 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 Interactions with other medicines and other forms of interaction).

In humans, there is no evidence of enzyme induction of 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 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 drug concentration versus time curve (AUC) at steady state is approximately 17 times that of bupropion. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively) and steady-state AUC values are 8 and 1,6 times higher than that of bupropion, respectively.

Steady-state for bupropion and its metabolites is reached within 8 days.

Special Patient Populations:

Elderly: 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 (see section 4.4 Special warnings and precautions for use).

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 the metabolites, the mean C_{max} was 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 hrs), and the mean half-lives were longer (by approximately 2 to 4-fold) than in healthy volunteers (see section 4.3 Contraindications).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Copovidone, microcrystalline cellulose, hypromellose, hydrochloric

acid, colloidal silicon dioxide, talc, magnesium stearate

Film-coat: Opadry II, methacrylic acid copolymer dispersion (Eudragit L30 D-55), silicon dioxide, triethyl citrate

Opadry II Clear: Polyvinyl alcohol, talc, macrogol/PEG polysorbate 80

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep well closed.

Keep out of reach of children.

6.5 Nature and contents of container

BUPROPION XL DRL 150 mg: White HDPE bottles with white polypropylene child-resistant closure and a desiccant, containing 30 tablets.

BUPROPION XL DRL 300 mg: White HDPE bottles with white polypropylene child-resistant closure and a desiccant, containing 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Ltd

Block B

204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

BUPROPION 150 XL DRL: 56/1.2/0292

BUPROPION 300 XL DRL: 56/1.2/0293

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 13 February 2024

10 DATE OF REVISION OF TEXT

Not applicable.