SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

WELLBUTRIN XL 150 extended-release tablets

WELLBUTRIN XL 300 extended-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each WELLBUTRIN XL 150 tablet contains 150 mg of bupropion hydrochloride.

Each WELLBUTRIN XL 300 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.

WELLBUTRIN XL 150: Creamy white to pale yellow, round tablet, imprinted with 'GS 5FV 150' in black ink on one side and the other side plain.

WELLBUTRIN XL 300: Creamy white to pale yellow, round tablet, imprinted with 'GS 5YZ 300' in black ink on one side and the other side plain.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

Following a satisfactory response, continuation with WELLBUTRIN 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.

Posology:

Initial treatment:

The initial dose of WELLBUTRIN 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.

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: WELLBUTRIN 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 WELLBUTRIN 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).

Liver impairment: WELLBUTRIN XL should be used with caution in patients with mild liver impairment. Because of increased variability in WELLBUTRIN XL's pharmacokinetics in patients with mild hepatic cirrhosis, a reduced frequency of dosing should be considered (see sections 4.8 and 4.4). WELLBUTRIN XL is contraindicated in patients with moderate to severe hepatic cirrhosis.

Method of administration:

WELLBUTRIN 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 seizures.

4.3 Contraindications:

- Hypersensitivity to bupropion hydrochloride or to any of the components of WELLBUTRIN XL listed in section 6.1.
- Patients under 18 years.
- WELLBUTRIN XL is contraindicated in patients with a seizure disorder.
- WELLBUTRIN XL should not be administered to patients currently being treated with any other preparation containing bupropion, as the incidence of seizures is dose dependent.
- WELLBUTRIN XL is contraindicated in patients with a known central nervous system tumour.
- WELLBUTRIN XL is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives.
- WELLBUTRIN XL is contraindicated 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 WELLBUTRIN XL with monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between the discontinuation of MAOIs and initiation of treatment with WELLBUTRIN XL.
- WELLBUTRIN XL is contraindicated for use in patients with 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 WELLBUTRIN XL should not be exceeded, since bupropion is associated with a dose-related risk of seizure.

WELLBUTRIN XL 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 WELLBUTRIN XL and clinical management should be provided accordingly.

The overall incidence of seizure with WELLBUTRIN XL in clinical trials was approximately 0,1 %.

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

WELLBUTRIN XL should be discontinued and is 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 WELLBUTRIN 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.

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).

Consideration should be given to changing the therapeutic regimen, including discontinuing WELLBUTRIN XL, 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 WELLBUTRIN XL 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). 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 a 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 WELLBUTRIN 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.

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, WELLBUTRIN XL should be used with caution in patients with mild hepatic impairment and reduced frequency of dosing should be considered (see sections 5.2 and 4.3).

Renal impairment and elderly patients:

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.

Clinical experience with WELLBUTRIN XL 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).

Cardiovascular disease:

There is insufficient clinical experience of the use of WELLBUTRIN XL to treat depression in patients with cardiovascular disease.

Care should be exercised if WELLBUTRIN XL is used in these patients.

Hypertension has been reported to be severe and may require acute treatment in patients receiving WELLBUTRIN XL. This has been observed in patients with and without pre-existing hypertension.

In cardiac conduction disorders, Bupropion 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.

Children and adolescents < 18 years:

The safety and efficacy with the treatment of WELLBUTRIN 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).

Inappropriate routes of administration:

WELLBUTRIN 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 WELLBUTRIN XL 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 WELLBUTRIN XL is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.5). 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 also been reported with bupropion-only overdose (see section 4.9).

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).

Care should therefore be exercised when WELLBUTRIN XL 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 betablockers, anti-dysrhythmics, selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and antipsychotics, should be initiated at the lower end of the dose range of the concomitant medication. If WELLBUTRIN XL 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).

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 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 % up to 80 %. Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55 %. This effect of ritonavir and efavirenz is thought to be due to the induction of bupropion metabolism. Patients receiving efavirenz with WELLBUTRIN XL may need increased doses of WELLBUTRIN XL, but the maximum recommended dose of WELLBUTRIN XL should not be exceeded.
There have been reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during WELLBUTRIN XL treatment. The consumption of alcohol during WELLBUTRIN XL treatment should be avoided.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when WELLBUTRIN XL is co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.4). Clinical data suggest a higher incidence of adverse events in patients receiving concurrent administration of bupropion and levodopa. Administration of WELLBUTRIN XL to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

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

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

Interactions involving laboratory tests:

WELLBUTRIN XL has been reported to interfere 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:

Pregnancy:

Safety in pregnancy and lactation has not been established.

WELLBUTRIN XL should not be used during pregnancy unless the clinical condition of the woman requires treatment with bupropion and alternative treatments are not an option.

Women of child-bearing potential must use reliable contraception. Studies of pregnancy outcomes following maternal exposure to bupropion in pregnancy have reported an increased risk of congenital cardiovascular malformations including ventricular septal defects and left outflow tract defects.

Breastfeeding:

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 WELLBUTRIN 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:

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

4.8 Undesirable effects:

The list below provides information on the undesirable effects identified from clinical experience, categorised by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (≥ 1/10 000).

Immune system disorders*	Common	Hypersensitivity reactions such as urticaria
	Very rare	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. * See also 'Skin and subcutaneous tissue disorders.'
Metabolism and nutritional disorders	Common	Anorexia
	Uncommon	Weight loss
	Very rare	Blood glucose disturbances
	Not known	Hyponatremia
Psychiatric disorders	Very common	Insomnia
	Common	Agitation, anxiety
	Uncommon	Confusion, depression
	Very rare	Aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams, depersonalisation, delusions, paranoid ideation
	Not known	Suicidal ideation, suicidal behaviour, psychosis, dysphemia, panic attack

Nervous system disorders	Very common	Headache
	Common	Tremor, dizziness, taste disorders
	Uncommon	Concentration disturbance
	Rare	Seizures (see section 4.4.)
	Very rare	Dystonia, ataxia, parkinsonism, incoordination, memory impairment, paraesthesia, syncope.
Eye disorders	Common	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Very rare	Palpitations
Vascular disorders	Common	Increased blood pressure (sometimes severe), flushing
	Very rare	Vasodilation, postural hypotension
Gastrointestinal disorders	Very common	Dry mouth, gastrointestinal disturbance including nausea and vomiting
	Common	Abdominal pain, constipation

Hepatobiliary disorders	Rare	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous tissue disorders*	Common	Rash, pruritus, sweating
	Very rare	Erythema multiforme and Stevens-Johnson syndrome, systemic lupus erythematosus syndrome aggravated, cutaneous lupus erythematosus, acute generalised exanthematous pustulosis, exacerbation of psoriasis. * See also 'Immune system disorders.
Musculoskeletal and connective tissue disorders	Very rare	Twitching
Renal and urinary disorders	Very rare	Urinary frequency and/or retention, urinary incontinence
General disorders and administration site conditions	Common	Fever, asthenia, chest pain

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of WELLBUTRIN XL is important. It allows continued monitoring of the benefit/risk balance of WELLBUTRIN XL. Healthcare providers 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 under Side effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or dysrrhythmias – cases of fatal outcome have been reported. Serotonin syndrome has also been reported.

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 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:

5.1 Pharmacodynamic properties:

Category and class: A 1.2 Psycho-analeptics (antidepressants)

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 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.

Metabolism: 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 WELLBUTRIN XL.

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).

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).

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.

The insoluble shell of the extended-release tablets may remain intact during gastrointestinal transit and be eliminated in the faeces.

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).

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).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

Polyvinyl alcohol

Glyceryl behenate.

Film coat*:*

Ethylcellulose 100

Povidone

Polyethylene glycol 1450

Methacrylic acid copolymer dispersion (Eudragit L30 D-55)

Silicon dioxide

Triethyl citrate

Edible black ink (for printing) (containing Shellac glaze, isopropyl alcohol, Iron Oxide black (E172), n-butyl alcohol, propylene glycol and ammonium hydroxide).

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in the original container in order to protect from humidity and light.

Keep well closed.

6.5 Nature and contents of container:

WELLBUTRIN XL 150: White opaque plastic HDPE bottles with white polypropylene plastic child-resistance closures, containing 30 tablets.

WELLBUTRIN XL 300: White opaque plastic HDPE bottles with white polypropylene plastic child-resistance closures, containing 30 tablets.

6.6 Special precautions for disposal and other handling:

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

WELLBUTRIN XL 150: 41/1.2/0371

WELLBUTRIN XL 300: 41/1.2/0372

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

15 August 2008

10. DATE OF REVISION OF THE TEXT:

23 April 2024

GDSv 33

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