VOXRA XL
Professional Information
Proposed PI (reformatted) compliant

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE:

VOXRA XL 150 mg Extended-Release Tablets

VOXRA XL 300 mg Extended-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Each VOXRA XL 300 tablet contains 300 mg of bupropion hydrochloride.

Sugar-free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended release tablets

VOXRA XL 150: Creamy white to pale yellow, round tablet, imprinted with ‘GS5FV’ in black ink on one side and the other side plain.

VOXRA XL 300: Creamy white to pale yellow, round tablet, imprinted with ‘GS5YZ’ in black ink on one side and the other side plain.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

VOXRA XL is indicated for the treatment of depression as defined by DSM IV Criteria. Following a satisfactory response, continuation with VOXRA 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 VOXRA 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: VOXRA XL 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 VOXRA XL 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: VOXRA 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 sections 4.8 Undesirable effects and 4.4. Special warnings and precautions for use). VOXRA XL is contra-indicated in patients with moderate to severe hepatic cirrhosis.

Method of administration

VOXRA 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:

- Patients under 18 years.
- Hypersensitivity to any component of the preparation.
- VOXRA XL is contra-indicated in patients with a seizure disorder.
- VOXRA XL should not be administered to patients currently being treated with any other preparation containing bupropion, as the incidence of seizures is dose dependent.
- Voxra XL is contraindicated in patients with a known central nervous system tumour.
- VOXRA XL is contra-indicated in patients undergoing abrupt discontinuation of alcohol or sedatives.
- VOXRA XL 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 VOXRA XL with monoamine oxidase inhibitors (MAOIs) is contra-indicated. At least 14 days should elapse between the discontinuation of MAOIs and initiation of treatment with VOXRA XL.
- Liver disease, Child-Pugh grades B and C, range 7-13.

4.4. Special warnings and precautions for use:

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

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

The overall incidence of seizure with VOXRA XL in clinical trials was approximately 0,1 %. There is an increased risk of seizures occurring with the use of VOXRA XL in the presence of predisposing risk factors, which lower the seizure threshold. Therefore, VOXRA 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. Contraindications), diabetes treated with hypoglycaemics or insulin and use of stimulants or anorectic products.

VOXRA XL 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 VOXRA 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 order: 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 below; section 4.8. Undesirable effects).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing VOXRA 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 VOXRA 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 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 VOXRA 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, VOXRA XL 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 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 VOXRA 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. Pharmacokinetic properties).

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

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

VOXRA XL 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.

Children and Adolescents < 18 years:

The safety and efficacy with the treatment of VOXRA 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. Contraindications).

4.5. Interactions 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 VOXRA 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 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 VOXRA 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. Pharmacokinetic properties).

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) 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 to 80 %. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving ritonavir may need increased doses of VOXRA XL but the maximum recommended dose of VOXRA XL should not be exceeded.

There have been reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during VOXRA XL treatment. The consumption of alcohol during VOXRA XL 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 VOXRA XL to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

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

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

4.6. Fertility, pregnancy and lactation:

Pregnancy:

Safety in pregnancy and lactation 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:

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

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 VOXRA 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, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 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.

Nervous system disorders:

Very Common: headache

Common: tremor, dizziness, taste disorders

Uncommon: concentration disturbance

Rare: seizures (see section 4.4. Warnings and special precautions)

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: errythema multiforme and Stevens-Johnson syndrome, 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 events:

Reporting suspected adverse events 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 on line under SAHPRA 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.

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:

Category A. 1.2. Psycho-analeptics (antidepressants)

5.1. Pharmacodynamic properties:

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 VOXRA 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. 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: 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).

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

18 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:

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

VOXRA XL 150: 41/1.2/0373

VOXRA XL 300: 41/1.2/0374

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

Date of Registration: 17 April 2009

10. DATE OF REVISION OF TEXT:

Date of most recent revision: 24 October 2019

GDS-17+22

AMENDMENT HISTORY

Proposed: May 2006
Amended: 16 August 2007 (in response to CC Recommendations dated 23/02/07)
Amended: 14 February 2008 (in line with CCC recommendations dated 14/12/2007)
Amended: 22 April 2008 (In response to P&A recommendations dated 28/02/2008) – Registered 17/04/09
Amended: 26 February 2009 (Proprietary name change to approved name Voxra XL)
Amended: 17 May 2012 (applicant address to CT)
Amended: 25 October 2012 (USRN to include pregnancy data) – annotated
Amended: 24 January 2013 (USRN: Compliant response to CCC recommendations dated 22/11/12, in line with VOXRA XL pi) – approved 2013.03.01
Amended: 8 May 2018 (Notification to bring in line with Regulation 9 of Act 101/1965 as amended). Implemented 9 May 2018
Amended: 22 August 2019 (reformat of compliant response submitted 22/08/2019, requested by SAHPRA backlog project)
Amended: 15 October 2019)(compliant response submitted in response to CCCR received 04.10.2019