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BUPROPION XL AURO P1537848

BUPROPION XL AURO P1537848

Professional Information for Medicines for Human Use
SCHEDULING STATUS
S5

1. NAME OF THE MEDICINE
BUPROPION XL 150 mg AURO
BUPROPION XL 300 mg AURO

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each **BUPROPION XL 150 mg AURO** tablet contains 150mg of bupropion hydrochloride.
Each **BUPROPION XL 300 mg AURO** tablet contains 300mg of bupropion hydrochloride.

Sugar free
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
BUPROPION XL 150 mg AURO, off-white to pale yellow, circular, biconvex, film-coated extended-release tablets imprinted with 'B 150' on one side and plain on the other side.
BUPROPION XL 300 mg AURO, Off-white to pale yellow, circular, biconvex, film-coated extended-release tablets imprinted with 'B 300' on one side and plain on the other side.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
BUPROPION XL AURO is indicated for the treatment of depression as defined by DSM IV Criteria.
Following a satisfactory response, continuation with **BUPROPION XL AURO** 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 a medical practitioner experienced in the treatment of depression.

Initial treatment:
The initial dose of **BUPROPION XL 150 mg AURO** is 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 300mg/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 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 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.

Renal impairment:
The elimination of bupropion and its major metabolites may be reduced by impaired renal function (see section 4.4).

Hepatic impairment:
BUPROPION XL AURO should be used with caution in patients with mild hepatic impairment. A reduction in the frequency of **BUPROPION XL AURO** dosing should be considered due to the increased variability in the pharmacokinetics in patients with mild hepatic cirrhosis (see section 4.4). **BUPROPION XL AURO** is contraindicated in patients with moderate to severe hepatic cirrhosis (see section 4.3).

Paediatric population
BUPROPION XL AURO is not indicated for use in children or adolescents younger than 18 years (see section 4.3).

Method of administration
BUPROPION XL AURO 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.
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.

4.3. Contraindications
- Hypersensitivity to bupropion or any other component of the preparation.
- Patients under 18 years.
- **BUPROPION XL AURO** is contra-indicated in patients with a seizure disorder.
- **BUPROPION XL AURO** 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 AURO** is contra-indicated in patients undergoing abrupt discontinuation of alcohol or sedatives.
- **BUPROPION XL AURO** 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 AURO** 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 AURO.**
- Liver disease, Child-Pugh grades B and C, range 7-13.
- **BUPROPION XL AURO** is contraindicated in patients with known Central Nervous System (CNS) tumour.

4.4. Special warnings and precautions for use
Seizures
The recommended dose of modified release bupropion tablets should not be exceeded, since bupropion 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 **BUPROPION XL AURO** in the presence of predisposing risk factors which lower the seizure threshold. Therefore, **BUPROPION XL AURO** should be administered with caution to patients with one or more conditions predisposing to a lowered seizure threshold.
All patients should be assessed for predisposing risk factors, which include:
- Concomitant administration of other medicinal products known to lower the seizure threshold (e.g.antipsychotics, antidepressants, antimalarial, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines)
- Alcohol abuse (see also section 4.3)
- History of head trauma
- Diabetes treated with hypoglycaemics or insulin
- Use of stimulants or anorectic products

BUPROPION XL AURO should be discontinued and not recommenced in 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 bupropion is given concomitantly with medicinal products which can induce or inhibit the metabolism of bupropion. Bupropion inhibits metabolism by cytochrome P450 2D6. Caution is advised when medicinal products metabolised by this enzyme are administered concurrently. In the literature it has been shown that medications that inhibit CYP2D6 may lead to reduced concentrations of endoxifen which is the active metabolite of tamoxifen. Therefore, the use of bupropion, which is an inhibitor of CYP2D6, should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Neuropsychiatry
Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.
A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug 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 drug therapy (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 the medicinal product, 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. If the decision is made to discontinue **BUPROPION XL AURO** a tapering off period may be considered. Bupropion is selective inhibitor of the neuronal re-uptake of catecholamines, and a rebound effect or discontinuation reactions cannot be ruled out. Decrease a daily dose of 300 mg to 150 mg prior to 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. 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 an antidepressant, 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. Data in animals suggest a potential for seizure. However, studies on abuse liability in humans and extensive clinical experience show that bupropion has low abuse potential. 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
BUPROPION XL AURO should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may progress or recur following the discontinuation of **BUPROPION XL AURO** and should ensure symptomatic treatment is administered for an adequate length of time (at least one week). Symptoms typically include skin rash, pruritus, urticaria, 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 antihistamine or corticosteroids and resolved over time.

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 AURO** and sudden death cannot be excluded. Care should be exercised if it is used in these patients. However, bupropion was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease (see section 5.1).

Blood pressure
Bupropion 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 **BUPROPION XL AURO** if a clinically significant increase in blood pressure is observed.
Concomitant use of bupropion and a nicotine transdermal system may result in elevations of blood pressure.

Angle-closure glaucoma
Bupropion as found in **BUPROPION XL AURO** may cause pupillary dilation which could trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Brugada syndrome
Bupropion 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.

Specific patient groups
Paediatric population - 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).
Patients with 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 AURO** should be used with caution in patients with moderate hepatic impairment and reduced frequency of dosing should be considered.

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

Patients with renal impairment- Bupropion is mainly excreted into the urine as its metabolites. Therefore, in patients with renal impairment, bupropion and its active metabolites may accumulate to a greater extent than usual. The patient should be closely monitored for possible undesirable effects (e.g. insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels (see section 4.2).

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 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.

Inappropriate routes of administration
BUPROPION XL AURO 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 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 AURO** is co-administered with a serotonergic medicinal product, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.5). If concomitant treatment with other serotonergic medicinal product 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.

Porphyria
Bupropion as in **BUPROPION XL AURO** is classified as possibly porphyrinogenic. It should only be used when no safer alternative is available, and precautions should be considered in vulnerable patients.

4.5. Interaction with other medicines and other forms of interaction
Since MAOIs also enhance the catecholaminergic pathways, by a different mechanism from bupropion, concomitant use of **BUPROPION XL AURO** and 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 **BUPROPION XL AURO.** For reversible MAOIs a 24-hour period is sufficient.

The effect of bupropion on other medicinal products
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 medicinal products with narrow therapeutic indices that are predominantly metabolised by CYP2D6 should be initiated at the lower end of the dose range of the concomitant medicinal product. Such medicinal products include certain antidepressants (e.g. desipramine, imipramine), antipsychotics (e.g. risperidone, thioridazine), beta-blockers (e.g. metoprolol), SSRIs and Type 1C antidysrhythmic (e.g. propafenone, flecainide). If **BUPROPION XL AURO** is added to the treatment regimen of a patient already receiving such a medicinal product, the need to decrease the dose of the original medicinal product should be considered. In these cases, the expected benefit of treatment with **BUPROPION XL AURO** should be carefully compared with the potential risks.
There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when **BUPROPION XL AURO** is co-administered with a serotonergic agent, such as SSRIs or SNRIs (see section 4.4).
Medicinal products 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 (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. Clinicians should be aware that digoxin levels may rise on discontinuation of bupropion and the patient should be monitored for possible digoxin toxicity.

The effect of other medicinal products on bupropion
Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6 (see section 5.2). Co-administration of medicinal products 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 is extensively metabolised, caution is advised when bupropion is coadministered with medicinal products 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.
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 medicinal products with bupropion may need increased doses of bupropion, but the maximum recommended dose of bupropion should not be exceeded.

Other interaction information
Administration of **BUPROPION XL AURO** 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 bupropion 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 **BUPROPION XL AURO** treatment should be minimised or avoided.
There have been no pharmacokinetic studies with bupropion and co-administered benzodiazepines. Based on in vitro metabolic pathways, there is no basis for such an interaction. After coadministration of bupropion with diazepam in healthy volunteers, there was less sedation than when diazepam was administered alone.

SCHEDULING STATUS
S5

PATIENT INFORMATION LEAFLET
BUPROPION XL AURO tablets
(bupropion hydrochloride)
(Sugar free)

Read all of this leaflet carefully before you take BUPROPION XL AURO.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist, nurse or other healthcare professional.
- **BUPROPION XL AURO** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What **BUPROPION XL AURO** is and what it is used for
2. What you need to know before you take **BUPROPION XL AURO**
3. How to take **BUPROPION XL AURO**
4. Possible side effects
5. How to store **BUPROPION XL AURO**
6. Contents of the pack and other information

1. What BUPROPION XL AURO is and what it is used for
BUPROPION XL AURO contains a medicine given orally by your doctor to treat depression. It belongs to a medicine group called antidepressants. It works in the brain called noradrenaline and dopamine, which are linked with depression.
It may take a while before you start feeling better. It takes time for **BUPROPION XL AURO** to have its full effect, sometimes weeks or months. Follow your doctor's instructions carefully and continue to take your tablets **BUPROPION XL AURO** to prevent depression coming back.

2. What you need to know before you take BUPROPION XL AURO
Do not take BUPROPION XL AURO
- If you are hypersensitive (allergic) to bupropion hydrochloride or any of the ingredients of **BUPROPION XL AURO** (listed in section 6)
- If you are taking any other medicines which contain bupropion
- If you have had a seizure (fit)
- If you have an existing condition or history of eating disorders (such as anorexia nervosa, a condition where people become very thin due to the fear of weight gain, which leads to extreme dieting) or bulimia (an emotional disorder characterised by an obsessive desire to lose weight, in which bouts of extreme overeating are followed by fasting or other methods to lose weight)
- If you are undergoing abrupt discontinuation of alcohol, sedatives (medicines used for sleeping), or medicines to treat anxiety (especially benzodiazepines) or benzodiazepine-like medicines (if you are going to stop them while you are taking **BUPROPION XL AURO**)
- If you recently stopped taking tranquillisers or sedatives, or if you are going to stop them while you're taking **BUPROPION XL AURO**
- If you have a tumour of the brain called a cranial tumour
- If you are taking monoamine oxidase inhibitors (MAOIs) in the last 14 days
- if you are pregnant or breastfeeding
- if you are less than 18 years of age. There is an increased risk of suicidal thoughts and behaviour in children under 18 years of age are treated with antidepressants
- if you have moderate to severe liver disease including cirrhosis.

Warnings and precautions
Tell your doctor or healthcare professional before being given **BUPROPION XL AURO** if:
- if you've ever had any fits or seizures in the past
- if you have had a serious head injury or a history of head trauma
- if you have a tumour in the brain
- if you have had any mental illness
- if you have diabetes for which you use insulin or tablets
- if you have had any mental illness other than depression
- if you have had a serious head injury
- if you are over 65 years of age
- if you are pregnant or plan to become pregnant soon
- if you have a brain tumour
- if you are taking any medicines that can cause fits (see 'Other medicines and **BUPROPION XL AURO**' below)
- if you take medicines used for sleeping (sedatives)
- if you are using any stimulants or medicine to help you lose weight.

Special care should be taken with BUPROPION XL AURO and let your doctor know if:
If you are depressed, you can sometimes have thoughts of harming or killing yourself. These thoughts may be increased when first starting antidepressants. These medicines all take time to work - usually about two weeks but sometimes longer.
You may be more likely to think like this:
- if you have previously had thoughts about killing or harming yourself
- if you are a young adult
- if you experience a big change in your depression and/or have thoughts of harming or killing yourself, whether or not you are taking antidepressant medicines contact your doctor or go to the hospital immediately.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before being given **BUPROPION XL AURO**.

Children and adolescents
BUPROPION XL AURO should not be used to treat children under 18 years of age. There is an increased risk of suicidal thoughts and behaviour when children under 18 years of age are treated with antidepressants.

Other medicine and BUPROPION XL AURO:
Always tell your healthcare professional if you are taking any other medicines, including those obtained without a prescription.
If you have been taking other antidepressants called monoamine oxidase inhibitors (MAOIs) in the last 14 days, tell your doctor before taking **BUPROPION XL AURO** (see also 'Do not take **BUPROPION XL AURO**' in section 2).
BUPROPION XL AURO might have interactions with other medicines which include the following. Tell your doctor if you are taking:
- If you take steroids (by mouth or injection)
- If you take medicines for diabetes
- If you take some types of anti-histamines that can cause sleepiness
- If you take medicines for diabetes

Tell your doctor before you take **BUPROPION XL AURO** if any of the above applies to you.
There may be an increase of side effects of other medicines when taken together with **BUPROPION XL AURO**.
- if you take other medicines for depression (such as nortriptyline, imipramine, desipramine, venlafaxine, paroxetine, sertraline, fluoxetine, fluvoxamine) or other mental illness (such as haloperidol, risperidone or thioridazine)
- if you take beta-blockers (such as metoprolol)
- if you take medicines for irregular heart rhythm (such as propafenone or flecainide)
- if you take medicines for Parkinson's disease (such as levodopa, amantadine or orphenadrine)
- if you take ifosfamide or ifosfamide, mainly used to treat cancer
- if you take valproate, medicine to treat epilepsy
- if you take tidogrelone or clopidogrel, mainly used to prevent stroke
- if you take orphenadrine used to treat muscle spasms
- if you take nicotine patches to help you stop smoking

If any of these applies to you, talk to your doctor immediately, before taking **BUPROPION XL AURO**. Your doctor may need to adjust your dose or recommend an alternative
The effect of **BUPROPION XL AURO** may be weakened:
- **BUPROPION XL AURO** (such as carbamazepine, phenytoin or phenobarbital (used to treat epilepsy) and medicines to treat HIV infection (such as efavirenz)

If you are taking any of these medicines, your doctor may need to adjust your dose of **BUPROPION XL AURO**.
BUPROPION XL AURO may weaken the effect of tamoxifen, medicine used to treat breast cancer. Tell your doctor if this applies to you.
BUPROPION XL AURO may cause a false-positive urine test for amphetamines. Tell your doctor that you are taking **BUPROPION XL AURO** if you require a urine test.
If you take digoxin for your heart, **BUPROPION XL AURO** may reduce its level in your blood, weakening the effect of digoxin. Your doctor might need to adjust the dose of digoxin and continue to monitor its level in your blood.

Pregnancy, breastfeeding and fertility
If you are pregnant or think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking **BUPROPION XL AURO**.
Do not take **BUPROPION XL AURO** if you are pregnant or breastfeeding unless your doctor has told you to take it.
If you are taking **BUPROPION XL AURO**, use effective contraception to avoid falling pregnant.

Driving and using machines
BUPROPION XL AURO might cause drowsiness and dizziness. Do not drive or operate tools or machines if you experience such side effects.
It is not always possible to predict to what extent **BUPROPION XL AURO** will affect your ability to drive or operate machinery. You should also bear in mind that they do not engage in the above activities until they are aware of the measure to which **BUPROPION XL AURO** affects them.

3. How to take BUPROPION XL AURO
Do not share medicines prescribed for you with any other person. Always take **BUPROPION XL AURO** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
The usual dose is one 150 mg tablet taken once each day.
Your doctor may increase your dose to 300 mg once a day if your depression does not improve after several weeks.
Take your dose of **BUPROPION XL AURO** early in the morning.
Do not take **BUPROPION XL AURO** more than once each day.
Swallow the tablets whole. Do not chew them, crush them or split them – this may lead to too much medicine being released into your body. If this happens you may be more likely to get side effects including seizures (fits).
Your doctor will tell you how long your treatment with **BUPROPION XL AURO** will last.
If you have the impression that the effect of **BUPROPION XL AURO** is too strong or too weak, tell your doctor or pharmacist.

If you take more BUPROPION XL AURO than you should
If you take too many tablets, contact your doctor or hospital immediately. If neither is available, contact the nearest hospital or poison centre.
When you take a dose which is too high of **BUPROPION XL AURO**, you may increase the risk of a seizure (fit). Other serious effects may also happen. Contact your doctor immediately or go to the hospital emergency.

If you forget to take BUPROPION XL AURO
Do not take a double dose to make up for forgotten individual doses.

4. Possible side effects
Like all medicines, **BUPROPION XL AURO** can have side effects.
Not all side effects reported for **BUPROPION XL AURO** are included in this leaflet. Should any unexpected effects occur or if you experience an untoward effects while taking **BUPROPION XL AURO**, please consult your doctor, pharmacist or other healthcare professional for advice.
If any of the following happens, stop taking **BUPROPION XL AURO** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- allergic reactions presenting as red skin or rash (like nettle rash) with difficulty in breathing or swallowing
- if you have had any mental illness other than depression
- fits (seizures or convulsions), the chance of this happening is higher if you take too much **BUPROPION XL AURO**. If you take certain medicines, or if you are at higher than usual risk of fits; talk to your doctor before taking this medicine
- allergic reactions presenting as blisters and peeling skin, unusual wheezing or difficulty in breathing, swollen eyelids, lips or tongue, pains in muscles or joints, collapse or blackout.

The following side effects may happen with these, you may have had a serious reaction to **BUPROPION XL AURO**. You may need urgent medical attention or hospitalisation.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- changes in the way your heart beats, for example if you notice it beating faster or irregular.
- thoughts of harming or killing themselves while taking **BUPROPION XL AURO**. Should any unexpected effects occur (see 'Take special care with **BUPROPION XL AURO**' in section 2).

These are all serious side effects. You may need urgent medical attention.
Tell your doctor if you notice any of the following:

Frequent side effects:
- difficulty in sleeping (make sure you take **BUPROPION XL AURO** in the morning)
- headache
- dry mouth, feeling sick, vomiting, tummy pain or other upsets (constipation)
- skin reactions, itching, sweating and skin rash (sometimes due to an allergic reaction)
- shakiness, tremor, weakness, tiredness
- feeling dizzy or fainting
- changes in the taste of food, loss of appetite (anorexia)
- increase in blood pressure sometimes severe, flushing
- ringing in the ears, visual disturbances.

Less frequent side effects:
- fits (seizures) (see 'Take special care with **BUPROPION XL AURO**' in section 2).

Rare side effects:
- difficulty concentrating, feeling confused, restless, irritable, hostile, aggressive, strange dreams, tingling or numbness, loss of memory, weight loss, changes in blood sugar levels
- twitching, muscle stiffness, uncontrolled movements, problems with co-ordination or balance
- yellowing of skin or the whites of your eyes (jaundice) which may be caused by raised liver enzymes, hepatitis
- unusual bruising or purple patches of red skin)
- feeling unreal or strange (depersonalisation); seeing or hearing things that are not there (hallucinations), sensing or believing things that are not true (delusions), suspicious feelings (paranoia)
- feeling dizzy or fainting when getting up quickly.

Side effects with unknown frequency:
- loss of contact with reality and unable to think or judge clearly (psychosis), other symptoms may include hallucinations and/or delusions.
- Hot flushes, sweating

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for quality-problem-reporting-form/. By reporting side effects, you can help provide more information on the safety of **BUPROPION XL AURO**.

5. How to store BUPROPION XL AURO
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
Store **BUPROPION XL AURO** at or below 25 °C.
- Do not use this medicine after the expiry date stated on the carton.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information
What BUPROPION XL AURO contains
The active substance is bupropion hydrochloride
Each USP-150 tablet contains bupropion hydrochloride extended release tablets USP-150 mg
Each film-coated tablet contains bupropion hydrochloride extended release tablets USP 300 mg
The other ingredients of **BUPROPION XL AURO** are Microcrystalline cellulose NF; Hydroxypropyl cellulose NF; Hypromellose USP; Lactose monohydrate USP; Glycerol Dibehenate USNF; Ethyl cellulose USNF; Povidone USP; Polyethylene Glycol USNF; Alcohol USP; Methacrylic acid and Ethyl Acrylate copolymer dispersion USNF; Triethyl citrate USNF; Polyethylene Glycol USNF; Hydroxypropyl cellulose NF; Titanium dioxide IP; Opadry Clear 03F28920 IH; Opacode Black S-1-17823 and Isopropyl Alcohol USP.

What BUPROPION XL AURO looks like and contents of the pack
BUPROPION XL 150 mg AURO, off-white to pale yellow, circular, biconvex, film-coated extended release tablets imprinted with 'B 150' on one side and plain on the other side.
BUPROPION XL 300 mg AURO, off-white to pale yellow, circular, biconvex, film-coated extended release tablets imprinted with 'B 300' on one side and plain on the other side.
BUPROPION XL AURO are marketed in round wide mouth white opaque colour HDPE containers closed with white opaque 33 mm - 400 polypropylene screw caps with tamper evident and pilfer proof heat seal liner. The HDPE container also contains one No. of 1 g 2 in 1 silica gel sachet (150 mg) or one No. of 1 g 2 in 1 silica gel sachet (300 mg). This is a non-sterile product. Other pack sizes may be available.
Pack sizes: 30's One container enclosed in carton with package leaflet.

NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE PERSON RESPONSIBLE FOR PLACING ON THE MARKET OR IMPORTATION
AUROGEN SA (PTY) LTD
Woodhill Office Park, Building 1, First Floor
Woodhill Road, Glenanda
Menlyn Ext. 12, 1448
Johannesburg
South Africa

This leaflet was last revised in
02 December 2024

REGISTRATION NUMBER
BUPROPION XL 150 mg AURO: 56/1.2/0751
BUPROPION XL 300 mg AURO: 56/1.2/0752

There has been no systematic evaluation of the combination of bupropion 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 **BUPROPION XL AURO** and a nicotine transdermal system (NTS) may result in elevations of blood pressure.

4.6 Fertility, pregnancy and lactation
Pregnancy
Some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of certain congenital cardiovascular malformations specifically ventricular septal defects and left outflow tract heart defects. These findings are not consistent across studies. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). **BUPROPION XL AURO** should not be used during pregnancy unless the clinical condition of the woman requires treatment with bupropion and alternative treatments are not an option.

Breastfeeding
The safety of **BUPROPION XL AURO** 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 **BUPROPION XL AURO**.

4.7. Effects on ability to drive and use machines
As with other CNS acting drugs bupropion may affect ability to perform tasks that require judgement or motor and cognitive skill. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain **BUPROPION XL AURO** does not adversely affect their performance.

4.8. Undesirable effects
The frequencies are defined as follows:
frequent, less frequent
Not known cannot be estimated from the available data

System Organ Class	Frequency	Event
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia Anaemia, leukopenia
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
	Less Frequent	Agitation, anxiety, depression, aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including nightmares, depersonalisation, delusions, 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	Frequent	Tachycardia
	Less Frequent	Palpitations
Vascular disorders	Frequent	Increased blood pressure (sometimes severe), flushing
	Less Frequent	Vasodilation, postural hypotension
Gastrointestinal disorder	Frequent	Drymouth, gastrointestinal disturbance including nausea, and vomiting, abdominal pain, constipation
Hepatobiliary disorders	Less Frequent	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, sweating
	Less Frequent	Erythema multiforme, Stevens-Johnson Syndrome, exacerbation of psoriasis
	Frequency unknown	Systemic Lupus Erythematosus Syndrome aggravated, cutaneous lupus erythematosus
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

f. 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 Reactions Reporting Form'. Found under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

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 electrocardiogram (ECG) changes such as conduction disturbances (including QRS prolongation),dysrrhythmias 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 medicinal product. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacological class: A.1.2: Psycho-analeptics (Antidepressant)
Pharmacotherapeutic group: Other antidepressants, ATC code: N06 AX12

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:
Maximum plasma concentrations (C_{max}) of approximately 160 ng/mL have been reported in healthy volunteers approximately 5 hours after oral administration of 300 mg bupropion hydrochloride as in **BUPROPION XL AURO.**
At steady state, the C_{max} and AUC values of hydroxybupropion have been reported to be approximately 3 and 14 times that of bupropion, respectively. The C_{max} of threohydrobupropion at steady state was found to be similar to that of bupropion and the AUC approximately 5 times higher, while the plasma concentrations of erythrohydrobupropion was comparable to those of bupropion.

Peak plasma levels of hydroxybupropion was reached at 7 hours while those for threohydrobupropion and erythrohydrobupropion were reached at 8 hours.

The AUC and C_{max} values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion have been reported to increase proportionally with the dose.

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 influenced when taken with food.

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 AURO.** 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 Ki 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 14C-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 14C 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 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).

Environmental Risk Assessment
BUPROPION XL AURO is a well-established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites are expected to be very limited. The use of **BUPROPION XL AURO** is not considered warranting any environmental concerns or requiring any special product labelling.

6.1. PHARMACEUTICAL PARTICULARS
Inner core
Microcrystalline cellulose USNF
Hydrochloric acid USNF Sodium
Stearyl Fumurate USNF
Povidone USP Glyceryl
Dibehenate USNF

Stage I (Extended Release) Coating
Ethyl cellulose USNF
Povidone USP
Polyethylene Glycol USNF
Alcohol USP [Ethanol 96 % v/v]

Stage II (Delayed Release) Coating
Methacrylic acid and Ethyl Acrylate copolymer dispersion USNF
Triethyl citrate USNF
Polyethylene Glycol USNF
Silicon Dioxide USNF (Syloid AL-1-FP)

Stage III (Film) coating
Opadry AMB white OY-B-28920 IH

Final Coated Tablet weight (Stage III)
Opacode Black S-1-17823
Isopropyl Alcohol USP

6.2. **Incompatibilities**
Not applicable

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at or below 25 °C.
Keep in original packaging until required for use.
KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container
BUPROPION XL 150 mg AURO are marketed in round wide mouth white opaque colour HDPE containers closed with white opaque 33 mm - 400 polypropylene child resistant closure with wad having an induction sealing liner. The HDPE container also contains one No. of 1 g 2 in 1 silica gel sachet. This HDPE container is further packed in pre-printed carton with package leaflet.

Pack size: 30s - One HDPE container contains 30 tablets.

BUPROPION XL 300 mg AURO are marketed in round wide mouth white opaque colour HDPE containers closed with white opaque 33 mm - 400 polypropylene child resistant closure with wad having an induction sealing liner. The HDPE container also contains one No. of 1 g 2 in 1 silica gel sachet. This HDPE container is further packed in pre-printed carton with package leaflet.

Pack size: 30s - One HDPE container contains 30 tablets.

6.6 Special precautions for disposal
No special requirements for disposal.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
AUROGEN SA (PTY) LTD
Woodhill Office Park, Building 1,
First Floor
53 Phillip Engelbrecht Avenue
Meyersdal, Ext. 12, 1448
Johannesburg
South Africa

8. REGISTRATION NUMBER
BUPROPION XL 150 mg AURO: 56/1.2/0751
BUPROPION XL 300 mg AURO: 56/1.2/0752

9. DATE OF FIRST AUTHORISATION
16 July 2024

10. DATE OF REVISION OF THE TEXT
03 December 2024

P1537848

DETACH BEFORE DISPENSING

AUROBINDO Packaging Development	Product Name: BUPROPION XL AURO	Component: Leaflet	Item Code: P1537848	Date & Time: 06.03.2025 & 03:43 PM
	Customer / Country: APL-South Africa APLHC Unit-4	Version No.: 06	Reason of Issue: New	No. of Colours : 1 — Black
Team Leader: Kiran Kumar; Initiator: Bhogeswara Rao	Dimensions: 360 x 660 mm	Font Type: Arial	Font Size: 7 pt	
Design Agency: vakils PREMEDIA; APL_LN: 3062	Pharmacode: 37848			

Date - Designer - Run:
1. 18-SEP-2024 (Dipali) - FR
2. 04-OCT-2024 (Dipali) - FR1
3. 14-OCT-2024 (Satish) - RR1
4. 19-OCT-2024 (Adi) - RR2
5. 05-DEC-2024 (Dipali) - RR3
6. 05-MAR-2025 (Adi) - FR2
7. 06-MAR-2025 (Adi) - RR4
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Reviewed / Approved by

Sign / Date

Additional Information: Supercede Item Code: NA