32.5 mm

32.5 mm

Pharmacode

1. **NAME OF THE MEDICINAL PRODUCT**

Zymon MR Tablets 150 mg
(Bupropion Hydrochloride Modified Release Tablets 150 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablets contains: Bupropion hydrochloride 150 mg
Excipients: For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablets.
White to pale yellow, round, biconvex tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zymon is indicated for the treatment of major depressive episodes.

4.2 Posology and method of administration

Use in Adults

The recommended starting dose is 150 mg, given once daily. An optimal dose was not established in clinical studies. If no improvement is seen after 4 weeks treatment at 150 mg, the dose may be increased to 300 mg, given once daily. There should be an interval of at least 24 hours between successive doses.

The onset of action of bupropion has been noted 14 days after starting therapy. As with all antidepressants the full antidepressant effect of Zymon, may not be evident until after several weeks of treatment.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

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).

Switching patients from bupropion prolonged –release tablets

When switching patients from the twice-daily prolonged release bupropion tablet to Zymon tablets, the same total daily dose should be given when possible.

Paediatric population

Zymon is not indicated for use in children or adolescents aged less than 18 years (see section 4.4).The safety and efficacy of Zymon in patients under 18 years of age have not been established.

Elderly people

Efficacy has not been clearly demonstrated in elderly people. In a clinical study, elderly people were treated with the same dosage regimen as described in the section "Use in adults". Increased sensitivity cannot be ruled out in some elderly people.

Patients with hepatic impairment

Zymon should be used with caution in patients with hepatic impairment (see section 4.4), Because of increased variability in the pharmacokinetics in patients with mild to moderate impairment, the recommended dose in these patients is 150 mg once a day.

Patients with renal impairment

The recommended dose in these patients is 150mg once a day, as bupropion and its active metabolites may accumulate in such patients to a greater extent than usual (see section 4.4).

Method of administration

For oral use.

Zymon 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.

Zymon can be taken with or without food.

Discontinuing therapy

Although no withdrawal symptoms were observed in clinical studies with bupropion, which were recorded spontaneously rather than systematically, a tapering therapy may be considered.

Bupropion selectively inhibits the neuronal re uptake of catecholamines. A rebound effect or withdrawal symptoms cannot therefore be ruled out.

4.3 Contraindications

Zymon is contraindicated in patients with hypersensitivity to bupropion or any of the excipients listed in section 6.1.

Zymon is contraindicated in patients taking any other medicinal product containing bupropion, as the incidence of seizures (epileptic fits) is dose-dependent and to avoid overdose.

Zymon is contraindicated in patients who currently suffer from seizures (epileptic fits) or have ever suffered from seizures in the past.

Zymon is contraindicated in patients with a tumour of the central nervous system (CNS)

Zymon is contraindicated in patients who undergo abrupt withdrawal from alcohol or any other medicine known to be associated with a risk of seizures (in particular benzodiazepines or benzodiazepine-like medicines) at any time during treatment.

Zymon is contraindicated for use in patients with severe hepatic cirrhosis.

Zymon is contraindicated in patients with a current or previous diagnosis of bulimia or anorexia nervosa.

Concomitant use of Zymon and Monoamine Oxidase Inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with Zymon. For reversible MAOIs a 24-hour period is sufficient.

4.4 Special warnings and precautions for use

Suicidality in Children and Adolescents

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- The indication(s) approved in paediatric for the particular drug should be clearly stated / included.

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 in the presence of predisposing risk factors, which lower the seizure threshold. Therefore, bupropion should be used 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 a use of other medicinal 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 traumatic brain injury
- Diabetes treated with antiglycaemic or insulin
- Treatment with stimulants or appetite suppressants

Patients who experience a seizure during treatment with Zymon must discontinue Zymon and must not restart 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).

Neuropsychiatric Disorders

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 drugs in adult patients with psychiatric disorder 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 this symptoms present.

It should be recognised that either the onset of some neuropsychiatric symptoms could be related 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 patients presenting symptoms.

Neuropsychiatric symptoms including mania episodes 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 abuse. 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

Zymon should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Clinician should be aware that symptoms may progress or recur following the discontinuation of Zymon and should ensure symptomatic treatment is administered for an adequate length of time (at least one week). Symptoms typically include skin rash, pruritus, urticaria or chest pain, but more severe reactions may include angioedema, dyspnoea/ bronchospasm, anaphylactic shock, erythema multiforme or Stevens-Johnson syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity (see section 4.8). In most patients, symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and eventually disappeared completely.

Cardiovascular disease

There is limited clinical experience of the use of bupropion to treat depression in patients with cardiovascular disease. Care should be exercised if 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 immediate treatment, has been reported in patients receiving bupropion. This has been observed in patients with and without pre-exiting hypertension.

Baseline blood pressure should be determined at the start of treatment and monitored thereafter, particularly in patients with pre-existing hypertension. If a clinically significant increase in blood pressure occurs, discontinuation of Zymon should be considered.

The simultaneous use of bupropion and a transdermal nicotine delivery system may lead to an increase in blood pressure.

Brugada syndrome

Bupropion may unmask Brugada syndrome, a rare hereditary disorder of the cardiac sodium channel with characteristic ECG changes (ST segment elevation and abnormal T waves in the right chest wall lead), which can 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.

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 disorder.

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 to moderate hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients. Therefore, Zymon should be used with caution in patients with mild to moderate hepatic impairment (see section 4.2).

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

Elderly People

Efficacy has not been clearly demonstrated in the elderly people. In a clinical study, elderly people were treated with the same dosing regimen as adults (see section 4.2 under "Use in Adults"and section 5.2). Increased sensitivity cannot be excluded in some elderly people.

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

Zymon is for oral use only. Inhalation of crushed tablets or injection of dissolved bupropion has been reported and may result in rapid release, faster absorption, and possible overdose. Seizures and/or death have been reported when bupropion was administered intranasal or by parenteral injection.

Serotonin syndrome

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when bupropion was co-administered with a serotonergic agent such as the selective serotonin reuptake inhibitors (SSRIs) or the serotonin noradrenaline reuptake inhibitors (SNRIs) (see section 4.5). If concomitant treatment with other serotonergic agents is clinically indicated, careful observation of the patient is recommended, particularly during treatment initiation and when the dose is increased.

Serotonin syndrome may include mood 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, diarrhea). If serotonin syndrome is suspected, a dose reduction or discontinuation of treatment should be considered depending on the severity of the symptoms.

4.5 Interaction with other medicinal products and other forms Interaction

Monoamine oxidase A and B inhibitors also enhance the catecholaminergic metabolic pathways through a different mechanism than bupropion. Therefore, the concomitant use of Zymon and monoamine oxidase inhibitors (MAO inhibitors) is contraindicated (see section 4.3) as there is an increased potential for side effects from their combination. At least 14 days must elapse between the end of treatment with irreversible MAO inhibitors and the start of treatment with Zymon. For reversible MAO inhibitors, a period of 24 hours is sufficient.

Effect of bupropion on other medicinal products

Although not metabolised by the CYP2D6 isoenzyme, bupropion and its main metabolite, hydroxy bupropion 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 Cmax and AUC of desipramine. Inhibition of CYP206 was present for at least 7 days after the last dose of bupropion.

Concomitant treatment with medicinal products that are predominantly metabolised via CYP2D6 and have a narrow therapeutic index should be started at their lower dose range. These include certain antidepressants (e.g. desipramine, imipramine), antipsychotics (e.g. risperidone, thioridazine), betablockers (e.g. metoprolol), selective serotonin reuptake inhibitors (SSRIs) and type 1C antiarrhythmics (e.g. propafenone, flecainide). If Zymon is used in addition to a treatment in which the patient is already receiving such a medicinal product, a reduction in the dosage of the medicinal product already being used must be considered. In these cases, the expected benefit of treatment with Zymon must be carefully weighed against the possible risks.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when Zymon was co-administered with a serotonergic agent such as the selective serotonin reuptake inhibitors (SSRIs) or the serotonin noradrenaline reuptake inhibitors (SNRIs) (see section 4.4).

Medicines that require metabolic activation by CYP2D6 to be effective (e.g. tamoxifen) may have reduced efficacy when co-administered with CYP2D6 inhibitors such as bupropion (see section 4.4).

Although citalopram (a SSRI) is not primarily metabolised by CYP2D6, in one study, bupropion increased the Cmax 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. Clinician should be aware that digoxin levels may rise on discontinuation of bupropion and the patient should be monitored for possible digoxin toxicity.

Effect of other medicinal products on bupropion

Bupropion is metabolised to its major active metabolite hydroxy bupropion 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 co administered 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 safely.

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 ones daily for two weeks reduced the exposure of bupropion by approximately 55% in heathy 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 drugs with bupropion may need increased doses of bupropion but the maximum recommended dose of bupropion should not be exceeded.

Other interaction information

Administration of Zymon 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 amantadine.

Although clinical data do not identify a pharmacokinetics 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 Zymon treatment should be minimised or avoided.

There have been no pharmacokinetics studies with bupropion and co-administered benzodiazepines. Based on *in vitro* metabolic pathways, there is no basis for such an interaction. After co-administration of bupropion with diazepam in healthy volunteers, there was less sedation than when diazepam was administered alone. There has been no systematic evaluation of the combination of bupropion 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 Zymon 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. Zymon should not be used during pregnancy unless the clinical condition of the woman requires treatment with bupropion and alternative treatments are not an option.

Breast-feeding

Bupropion and its metabolites are excreted in human breast milk. A decision on whether to abstein from breast-feeding or to abstein from therapy with Zymon should be made taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Zymon therapy to the mother.

Fertility

There are no data on the effect of bupropion on fertility in humans. A reproduction study in rats showed no evidence of impaired fertility (see section 5.3).

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, motor and cognitive skill. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain Zymon does not adversely affect their performance.

4.8 Side effects

The following list provides information on undesirable effects based on clinical experience, classified by frequency and system organ class.

The following categories are used to indicate the frequency of side effects: 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); not known (frequency cannot be estimated from the available data).

Diseases of the blood and lymphatic system	Not known	Anaemia, leukopenia and thrombocytopenia
Diseases of the immune system*	Frequently	Hypersensitivity reactions such as urticaria
	Very rare	More serious hypersensitivity reactions including angioedema, dyspnea/bronchospasm, and anaphylactic shock. Arthralgia, myalgia, and fever have also been reported in association with rash and other symptoms suggestive of a delayed hypersensitivity reaction. These symptoms may resemble serum sickness.

Pharmacode

520 mm

150 mm
Front Side

Alembic Pharmaceuticals Limited	Alembic
Product: Zymon MR Tablets 150 mg	Black
Type: Packinsert	
Size: 150 x 520 mm	
Folded Size: 150 x 32.5 mm	
Date: 26-02-2026	
	DieLine Not to be Printed

Metabolism and nutrition disorders	Frequently	Loss of appetite
	Occasionally	Weight loss
	Very rare	Fluctuations in blood sugar levels
	Not known	Hyponatraemia
Psychiatric disorders	Very common	Insomnia (see section 4.2)
	Frequently	Agitation, anxiety
	Occasionally	Depression (see section 4.4), confusion
	Very rare	Aggression, hostile behavior, irritability, restlessness, hallucinations, unusual dreams including nightmares, depersonalization, delusions, paranoid ideas
	Not known	Suicidal thoughts, suicidal behavior***, psychosis, dysphemia
Diseases of the nervous system	Very common	Headache
	Frequently	Tremors, dizziness, taste disorders
	Occasionally	Concentration problems
	Rarely	Seizures (see section below)**
	Very rare	Dystonia, ataxia, parkinsonism, coordination disorders, memory impairment, paraesthesia, syncope
	Not known	serotonin syndrome****
Eye diseases	Frequently	Visual disturbances
Diseases of the ear and labyrinth	Frequently	Tinnitus
Heart disease	Occasionally	Tachycardia
	Very rare	Palpitations
Vascular disorders	Frequently	Increased blood pressure (sometimes severe), flushing
	Very rare	Vasodilation, orthostatic hypotension
Diseases of the gastrointestinal tract	Very common	Dry mouth, gastrointestinal disturbance including nausea and vomiting
	Frequently	Abdominal pain, constipation
Liver and gallbladder diseases	Very rare	Elevated liver enzymes, jaundice, hepatitis
Diseases of the skin and subcutaneous tissue*	Frequently	Rash, pruritus, sweating
	Very rare	Erythema multiforme, Stevens Johnson syndrome, exacerbation of psoriasis
	Not known	Exacerbation of systemic lupus erythematosus, cutaneous lupus erythematosus, acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders	Very rare	Muscle twitching
Diseases of the kidneys and urinary tract	Very rare	Changes in micturition frequency and/or urinary retention, urinary incontinence
General disorders and administration site conditions	Frequently	Fever, chest pain, asthenia

*Hypersensitivity may manifest itself in skin reactions. See "Disorders of the immune system" and "diseases of the skin and subcutaneous tissue".

**The frequency of seizures is approximately 0.1% (1/1,000). The most common seizure type is generalised tonic-clonic seizure, a type of seizure which may in some cases lead to postictal confusion or memory impairment (see section 4.4).

***Cases of suicidal thoughts or suicidal behavior during therapy with Bupropion or shortly after discontinuation of treatment have been reported (see section 4.4).

****Serotonin syndrome may occur as a result of an interaction between bupropion and a serotonergic medicinal product such as the selective serotonin reuptake inhibitors (SSRIs) or the serotonin noradrenaline reuptake inhibitors (SNRIs) (see section 4.4).

4.9 Overdose

Acute overdoses exceeding 10 times the maximum therapeutic dose have been reported. In addition to the adverse reactions listed above, overdose has resulted in symptoms such as drowsiness, loss of consciousness and/or electrocardiogram (ECG) changes such as conduction disturbances (including QRS complex widening), arrhythmias and tachycardias. QTc prolongation has also been reported, but has generally been noted in association with QRS complex widening and increased heart rate. Although most patients recovered without sequelae, rare deaths have been reported in association with bupropion overdose in patients taking large overdoses of the drug. 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

Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX12.

Mechanism of action

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit either monoamine oxidase. The mechanism of action of bupropion as an antidepressant is unknown. However, it is presumed that this action is mediated by noredrenergic and/or dopaminergic mechanisms.

Clinical efficacy

The antidepressant effect of bupropion was investigated in a clinical trial program that included a total of 1,155 patients treated with modified-release bupropion tablets and 1,868 patients with major depressive disorder (MDD) treated with bupropion extended-release tablets. The efficacy of modified release bupropion tablets was investigated in seven studies: three studies in the EU were conducted with doses of up to 300 mg/day and four studies in the US were conducted in a flexible dose range of up to 450 mg/day. In addition, 9 studies with bupropion extended-release tablets in patients with major depressive disorder can be considered supportive due to the bioequivalence of modified-release bupropion tablets (once daily) and bupropion extended-release tablets (twice daily).

Modified-release bupropion tablets demonstrated statistical superiority over placebo as measured by improvement in the Montgomery-Asberg Depression Scale (MADRS) total score in one of two identical studies using doses between 150 to 300 mg/day. Response and remission rates were also statistically significantly higher with modified-release bupropion tablets compared with placebo. In a third study in elderly patients, statistical superiority over placebo was not achieved in the primary parameter, the mean change from baseline in the MADRS (last observation carried forward endpoint), but statistically significant effects were seen in a secondary analysis (observed case).

In two of four studies conducted in the United States with modified-release bupropion tablets (300 to 450 mg/day), a significant benefit was shown in the primary endpoint. One of the two positive studies conducted in patients with major depression was placebo-controlled, the other was drug controlled.

In a relapse prevention study, patients who responded to an 8-week open-label acute treatment phase with bupropion extended-release tablets (300 mg/day) were randomized to either a bupropion extended-release tablet or a placebo treatment arm for a further 44 weeks. Bupropion extended release tablets demonstrated statistically significant superiority over placebo in the primary endpoint ($p < 0.05$). The incidence of maintenance of effect during the 44-week double-blind follow-up phase was 64% with bupropion extended-release tablets and 48% with placebo.

Clinical safety

The prospectively observed rate of cardiovascular birth defects in pregnancies with prenatal exposure to bupropion in the first trimester in the International Pregnancy Registry was 9/675 (1.3%).

In a retrospective study, there was no higher rate of congenital or cardiovascular malformations in the newborns of more than a thousand patients who took bupropion in the first trimester compared with the use of other antidepressants.

In a retrospective analysis using data from the National Birth Defects Prevention Study, there was a statistically significant association between the occurrence of left out flow tract heart defects in the newborn and self-reported maternal use of bupropion in early pregnancy. No association was found between maternal use of bupropion and other types of heart defects, or all categories of heart defects combined.

Another analysis of data from the Slone Epidemiology Centre Birth Defects Study showed no statistically significant increase in left outflow tract heart defects with maternal use of bupropion. However, there was a statistically significant association for ventricular septal defects after the use of bupropion alone in the first trimester.

In a study in healthy volunteers, no clinically significant effect of bupropion modified-release tablets (450 mg/day) on the QTcF interval was observed compared with placebo after 14 days of steady state dosing.

5.2 Pharmacokinetic properties

Absorption

After oral administration of 300 mg bupropion hydrochloride once daily as the modified release tablet to healthy volunteers, maximum plasma concentrations (Cmax) of approximately 160 ng/ml are observed at approximately 5 hours. At steady state, the Cmax and AUC values of hydroxybupropion are approximately 3 and 14 times that of bupropion, respectively. The Cmax of threohydrobupropion at steady state is similar to that of bupropion and the AUC is approximately 5 times higher while the plasma concentrations of erythrohydrobupropion are comparable to those of bupropion. Peak plasma levels of hydroxybupropion are reached at 7 hours while those for threohydrobupropion and erythrohydrobupropion are reached at 8 hours. The AUC and Cmax values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion increase dose proportionally over a dose range of 50-200mg following single doses and over a dose range of 300-450mg/day following chronic dosing.

The absolute bioavailability of bupropion is not known; urinary excretion data, however, show that at least 87% of the dose of bupropion is absorbed.

The absorption of bupropion modified release tablets is not significantly influenced when taken concurrently with food.

Distribution

Bupropion is widely distributed with an apparent volume of distribution at approximately 2000 L.

Bupropion, hydroxybupropion and threohydrobupropion bind moderately to plasma proteins (84%, 77% and 42%, respectively).

Bupropion and its active metabolites are excreted in breast milk. Animal studies have shown that bupropion and its active metabolites cross the blood-brain barrier and the placenta. Positron emission tomography studies in healthy volunteers have shown that bupropion passes into the central nervous system and binds to the dopamine reuptake transporter in the striatum (approximately 25% at 150 mg twice daily).

Biotransformation

Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino alcohol isomer, threohydrobupropion and erythrohydrobupropion. These may have clinical importance, as their plasma on central ions are as high or higher than those of bupropion. The active metabolites are further metabolised to inactive metabolites (some of which have not been fully characterised but may include conjugates) end excreted in the urine.

In vitro studies show that bupropion is metabolized primarily by CYP2B6 to its major active metabolite, hydroxybupropion, with less involvement of CYP1A2, 2A6, 2C9, 3A4 and 2E1. In contrast, the formation of threohydrobupropion proceeds via carbonyl reduction without involvement of cytochrome P450 isoenzymes (see section 4.5).

The potential of threohydrobupropion and erythrohydrobupropion to inhibit the cytochrome P450 system has not been studied.

Bupropion and hydroxybupropion are both inhibitors of the CYP2D6 isoenzyme with Ki values of 21 and 13.3μM, respectively (see section 4.5).

Bupropion has been shown to induce its own metabolism in animals following multiple administration. In humans, no enzyme induction of bupropion or hydroxybupropion has been demonstrated in volunteers or patients receiving the recommended dose of bupropion hydrochloride for 10 to 45 days.

Elimination

After oral administration of 200 mg 14C-bupropion to humans, 87% and 10% of the radioactive dose was recovered in urine and feces, respectively. The proportion of bupropion excreted unchanged was only 0.5% of the dose; this finding is consistent with the extensive metabolism of bupropion. Less than 10% of this 14C dose was recovered in the urine as active metabolites.

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

The elimination half-life of hydroxybupropion is approximately 20 hours, the elimination half-lives of threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively), and the steady-state AUC values are 8 and 1.6 times higher than those of bupropion, respectively. Steadystate for bupropion and its metabolites is reached within 8 days.

The insoluble shell of the modified-release tablet may remain intact during gastrointestinal transit and be excreted in the feces.

Special Patient Group:

Patients with renal impairment

The elimination of bupropion and its major active metabolites may be reduced in patients with impaired renal function. Limited data from patients with end-stage renal disease or moderate to severe renal impairment indicate that the available concentration of bupropion and/or its metabolites was increased (see section 4.4).

Patients with hepatic impairment

The pharmacokinetics of bupropion and its active metabolites were not statistically significantly altered in patients with mild to moderate liver cirrhosis compared to healthy subjects, although greater inter-patient variability was observed (see section 4.4). In patients with severe liver cirrhosis, the Cmax and AUC of bupropion were substantially increased (mean difference approximately 70% and 3-fold, respectively) and varied more compared to those in healthy subjects; the mean halflife was also longer (by approximately 40%). In the case of hydroxybupropion, the mean Cmax was lower (by approximately 70%), the mean AUC tended to be higher (by approximately 30%), the median Tmax was later (by approximately 20 hours), and the mean half-lives were longer (by approximately 4-fold) than in healthy subjects. In the case of threohydrobupropion and erythrohydrobupropion, the mean Cmax tended to be lower (by approximately 30%), the mean AUC tended to be higher (by approximately 50%), the median Tmax later (by approximately 20 hours) and the mean half-life longer (by approximately 2-fold) than in healthy subjects (see section 4.3).

Elderly people

Pharmacokinetic studies in elderly patients have shown mixed results. A single dose study has shown that the pharmacokinetics of bupropion and its metabolites in elderly and younger adults are no different. Another single and multiple dose pharmacokinetic study suggests that bupropion and its metabolites may accumulate to a greater extent in elderly patients. Clinical experience has shown no differences in tolerability between elderly and younger patients, but greater sensitivity in elderly patients cannot be excluded (see section 4.4).

In vitro release of bupropion with alcohol

In vitro studies have shown that bupropion is released more rapidly from the modified release formulation at high alcohol concentrations (up to 40%) (up to 20% dissolved after 2 hours) (see section 4.5).

5.3 Preclinical safety data

Reproductive toxicity studies in rats at exposures similar to those obtained at the maximum recommended human dose (based on systemic exposure data) showed no adverse effects on fertility, pregnancy and fetal development. In rabbits, reproductive toxicity studies at doses up to 7 times the maximum recommended human dose (measured on a mg/m2 basis; no systemic exposure data are available) showed only a small increase in skeletal changes (increased occurrence of a common anatomical variant of an accessory thoracic rib and delayed ossification of the phalanges). In addition, reductions in fetal weight were reported in rabbits at maternally toxic doses.

In animal studies, bupropion caused the following dose-dependent symptoms at doses several times higher than the therapeutic dose in humans:

Ataxia and convulsions in rats, general weakness, tremors and vomiting in dogs, and increased lethality in both species. Due to enzyme induction occurring in animals but not in humans, the systemic exposure achieved in the animal studies was approximately the same as the systemic exposure in humans at the maximum recommended dose.

The animal studies showed liver changes that reflect the effect of hepatic enzyme induction. In humans, bupropion does not induce its own metabolism at the recommended doses. This indicates that the liver findings in laboratory animals have only limited significance in the evaluation and risk assessment of bupropion.

Genotoxicity data show that bupropion is weakly mutagenic in bacteria but not in mammals. Therefore, it is not considered genotoxic to humans. Studies in mice and rats confirm that bupropion is not carcinogenic in these species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet Core:

Povidone
Hydrochloric Acid
Ethyl Alcohol Anhydrous
Sodium Stearyl Fumarate
Ethyl Cellulose
Hydroxy Propylcellulose
Meth Acrylic Acid- Ethyl Acrylate Copolymer (1 :1) Type A
Colloidal Anhydrous Silica
Macrogols 1500
Triethyl Citrate
Isopropyl Alcohol
Purified Water
Opadry Clear YS-1-7006

6.2 Incompatibilities

Not applicable

6.3 Nature and contents of container

30 & 60 modified release tablets in a white opaque HDPE bottle. Not all pack sizes may be marketed.

6.4 Special precautions for disposal

No special requirement for disposal.

6.5 Storage

Store below 30ºC. Store in the original package.

7. MANUFACTURED BY:

Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P.O. Tajpura, Near Baska,
Taluka Halol, Panchmahal, Gujarat-389350 India.

Product Registration Holder in MY:

GENPHARMA SDN. BHD.
Lot 5016, Jalan Teratai,
5 ½ Mile Off Jalan Meru,
41050 Klang, Selangor, Malaysia

8. DATE OF REVISION

26.02.2026

200XXXXX

520 mm

150 mm

Back Side