PROFESSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BUPROPION 300 ACCORD (Modified release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains 300 mg bupropion hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablet.

BUPROPION 300 ACCORD modified release tablets are creamy-white to pale yellow, round, tablets printed with "GS2" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BUPROPION 300 ACCORD is indicated for the treatment of depression as defined by DSM IV Criteria. Following a satisfactory response, continuation with BUPROPION 300 ACCORD therapy is effective in preventing relapse and preventing recurrence of further depressive episodes.

4.2 Posology and method of administration

Therapy should be initiated by medical practitioners experienced in the treatment of depression.

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Posology

Initial treatment

The initial dose of bupropion hydrochloride modified release is 150 mg taken as a single dose in the morning. Patients who are not responding adequately to a dose of 150 mg/day may benefit from an increase to the usual adult target dose of 300 mg/day, given once daily. There should be an interval of at least 24 hours between successive doses. Insomnia is a very common adverse event which is often transient. Insomnia may be reduced by avoiding dosing at bedtime (provided there is at least 24 hours between doses) or, if clinically indicated, dose reduction.

Switching patients from sustained release tablets

When switching patients from sustained release tablets to extended release tablets; give the same total daily dose when possible. Patients who are currently being treated with sustained release tablets at 300 mg/day (e.g. 150 mg twice daily) may be switched to extended release tablets 300 mg once daily.

Special populations

Renal impairment

Treatment of patients with renal impairment should be initiated at a reduced frequency and/or dose, as bupropion and its metabolites may accumulate in such patients to a greater extent than usual (see section 4.4.)

Hepatic impairment:

BUPROPION 300 ACCORD should be used with caution in patients with mild liver impairment. Because of increased variability in the pharmacokinetics in patients with mild hepatic cirrhosis, a reduced frequency of dosing should be considered (see sections 4.8 and 4.4.). BUPROPION 300 ACCORD is contra-indicated in patients with moderate to severe hepatic cirrhosis.

Elderly

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Greater sensitivity of some elderly individuals to BUPROPION 300 ACCORD cannot be ruled out, hence a reduced frequency and/or dose may be required (see section 4.4.).

Paediatric population

BUPROPION 300 ACCORD is not indicated for use in children or adolescents aged less than 18 years (see section 4.3).

Method of administration

For oral use.

BUPROPION 300 ACCORD tablets should be swallowed whole. The tablets should not be cut, crushed or chewed as this may lead to an increased risk of adverse effects including seizures.

4.3 Contraindications

- Hypersensitivity to the active substance, bupropion hydrochloride, or to any of the excipients listed in section 6.1.
- Patients under 18 years.
- Patients with a seizure disorder or any history of seizures.
- BUPROPION 300 ACCORD should not be administered to patients currently being treated with any other preparation containing bupropion, as the incidence of seizures is dose dependent.
- Patients with a known central nervous system tumour.
- Patients undergoing abrupt discontinuation of alcohol or sedatives.
- 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 300 ACCORD with monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.5). At least 14 days should elapse between the discontinuation of MAOIs and initiation of treatment with BUPROPION 300 ACCORD.
- Liver disease, Child-Pugh grades B and C, range 7-13.

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- BUPROPION 300 ACCORD is contraindicated in patients with a history of bipolar disorder as it may precipitate a manic episode during the depressed phase of their illness.

4.4 Special warnings and precautions for use

The recommended dose of BUPROPION 300 ACCORD should not be exceeded, as bupropion is associated with a dose-related risk of seizure.

BUPROPION 300 ACCORD should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see section 4.8). Medical practitioners should be aware that symptoms may persist beyond the discontinuation of BUPROPION 300 ACCORD and clinical management should be provided accordingly.

At doses up to the maximum recommended daily dose (300mg of bupropion daily), the incidence of seizures is approximately 0,1 % (1/1000). There is an increased risk of seizures occurring with the use of BUPROPION 300 ACCORD in the presence of predisposing risk factors, which lower the seizure threshold. Therefore, BUPROPION 300 ACCORD should not be administered to patients with one or more conditions predisposing to a lowered seizure threshold, which include:

- History of head trauma
- Central nervous system (CNS) tumour
- History of seizures
- Concomitant administration of other medicines known to lower the seizure threshold, e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines
- Excessive use of alcohol or sedatives (see section 4.3), diabetes treated with hypoglycaemics or insulin and use of stimulants or anorectic products.

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BUPROPION 300 ACCORD should be discontinued and not recommenced in patients who experience a seizure while on treatment.

Clinical worsening and suicide risk in adults associated with psychiatric disorders

Patients with major depressive disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medicines. This risk may persist until significant remission

occurs. A causal role, however, for antidepressant medicines in inducing such behaviour

has not been established. As improvement may not occur during the first few weeks or more of treatment, patients being treated with BUPROPION 300 ACCORD should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of therapy, or at the time of dose changes, either increases or decreases.

Patients with a history of suicidal behaviour or thoughts, young adults and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

The following symptoms have been reported in patients being treated with antidepressants or major depressive order: anxiety, agitation, panic attacks, insomnia, irritability, hostility aggressiveness), impulsivity, akathisia, hypomania and mania.

In addition, clinical trials of antidepressant medicine in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behaviour associated with antidepressant use in patients less than 25 years old.

Patients (and caregivers of patients) should be alerted about the need to monitor for any

worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek
medical advice immediately if these symptoms present. It should be recognised that the
onset of neuropsychiatric symptoms could be related either to the underlying disease state or the medicine therapy and an appropriate patient assessment should be undertaken (see Neuropsychiatric symptoms including mania and bipolar disorder below; section 4.8.).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing BUPROPION 300 ACCORD, in patients who experience clinical worsening (including
development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's
presenting symptoms. Although there is no need to taper BUPROPION 300 ACCORD upon discontinuation, the patient should be monitored for worsening of depressive symptoms following discontinuation.

Neuropsychiatric symptoms including mania and bipolar disorder

Neuropsychiatric symptoms have been reported (see section 4.8). In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. Aggression, rage and violent behaviour may occur.

Additionally, a major depressive episode may be the initial presentation of 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.

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Prior to initiating treatment with BUPROPION 300 ACCORD, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Hepatic impairment

Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised. No statistically significant differences in the pharmacokinetics of bupropion were observed in patients with mild hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients.

Therefore, BUPROPION 300 ACCORD should be used with caution in patients with mild hepatic impairment and reduced frequency of dosing should be considered (see sections 5.2. and 4.3.).

Renal impairment and elderly patients

Bupropion is extensively metabolised in the liver to active metabolites which are further metabolised and excreted by the kidneys. Therefore treatment of patients with renal impairment should be initiated at reduced frequency and/or dose as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects (e.g. insomnia, dry mouth, seizures) that could indicate high bupropion or metabolite levels, toxic effects of elevated blood and tissue levels of bupropion and metabolites.

Clinical experience with bupropion has not identified any differences in tolerability between elderly and other adult patients. However, greater sensitivity of some elderly individuals cannot be ruled out, hence a reduced frequency and/or dose may be required (see section 5.2.).

Cardiovascular disease

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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 and sudden death cannot be excluded. Care should be exercised if BUPROPION 300 ACCORD is used in these patients.

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

Interference with urine testing

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

Children and adolescents younger than 18 years

The safety and efficacy of treatment with bupropion in patients under 18 years of age has not been established. Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major
depressive disorder and other psychiatric disorders (see section 4.3.).

Inappropriate routes of administration

BUPROPION 300 ACCORD 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.

4.5 Interaction with other medicines and other forms of interaction

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Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 IIB6 (CYP2B6) (see section 5.2.). Care should therefore be exercised when BUPROPION 300 ACCORD is co-administered with medicines known to affect the CYP2B6 isoenzyme (e.g. orphenadrine, cyclophosphamide, ifosfamide, ticlopidine, clopidogrel).

Although bupropion is not metabolised by the CYP2D6 isoenzyme, *in vitro* human P450 studies have shown that bupropion and hydroxybupropion are inhibitors of the CYP2D6
pathway. In a human pharmacokinetic study, administration of bupropion increased plasma levels of desipramine. This effect was present for at least 7 days after the last dose of bupropion.

Concomitant therapy with medicines predominantly metabolised by this isoenzyme (such as certain beta-blockers, anti-dysrhythmics, selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antipsychotics) should be initiated at the lower end of the dose range of the concomitant medicine. If bupropion hydrochloride is added to the treatment regimen of a patient already receiving a medicine metabolised by CYP2D6, the need to decrease the dose of the original medicine should be considered, particularly for those concomitant medications with a narrow therapeutic index (see section 5.2.).

Medicines which require metabolic activation by CYP2D6 in order to be effective (e.g. tamoxifen), may have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion.

Although citalopram is not primarily metabolised by CYP2D6, in one study, bupropion increased the C_{max} and AUC of citalopram by 30 % and 40 %, respectively.

Since bupropion is extensively metabolised, the co-administration of medicines known to induce metabolism (e.g. carbamazepine, phenobarbitone, phenytoin) or inhibit metabolism may affect its clinical activity.

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In clinical studies, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80 %. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving ritonavir may need increased doses of bupropion hydrochloride but the maximum recommended dose of BUPROPION 300 ACCORD should not be exceeded.

There have been reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. The consumption of alcohol during BUPROPION 300 ACCORD treatment should be minimised or avoided.

Limited clinical data suggest a higher incidence of adverse events (e.g. nausea, vomiting and neuropsychiatric events) in patients receiving concurrent administration of bupropion and levodopa or amantadine. Administration of BUPROPION 300 ACCORD to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

Concomitant use of BUPROPION 300 ACCORD and a Nicotine Transdermal System (NTS) may result in elevations of blood pressure.

Co-administration of digoxin with BUPROPION 300 ACCORD may decrease digoxin levels. Medical practitioners should be aware that digoxin levels may rise on discontinuation of BUPROPION 300 ACCORD and the patient should be monitored for possible digoxin toxicity.

Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, concomitant use of bupropion and monoamine oxidase inhibitors (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 300 ACCORD. For reversible MAOIs, a 24-hour period is sufficient.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of some congenital cardiovascular malformations, including ventricular septal defects and left ventricular outflow tract defects. These findings are not consistent across studies.

Breastfeeding

As bupropion and its metabolites are excreted in human breast milk, mothers should be advised not to breastfeed while taking BUPROPION 300 ACCORD.

Fertility

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

4.7 Effects on ability to drive and use machines

Bupropion has been reported to cause dizziness and light headedness. Patients should exercise caution before driving or using machinery until they are reasonably certain BUPROPION 300 ACCORD tablets do not adversely affect their performance.

4.8 Undesirable effects

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION

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Blood and lymphatic system disorders	Frequency unknown	Anaemia, leucopenia, thrombocytopaenia
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, agitation, anxiety
	Less frequent	Depression, irritability, hostility, hallucinations, depersonalisation, abnormal dreams including nightmares Delusions, paranoid ideation, restlessness, aggression

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	Frequency unknown	Suicidal ideation and suicidal behaviour***, psychosis
Nervous system disorders	Frequent	Tremor, headache, dizziness, taste disorders
	Less frequent	Concentration disturbance, seizures**, dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope
Eye disorders	Frequent	Visual disturbance
Ear and labyrinth disorders	Frequent	Tinnitus
Cardiac disorders	Less frequent	Tachycardia, palpitations
Vascular disorders	Frequent	Increased blood pressure (sometimes severe), flushing
	Less frequent	Vasodilation, postural hypotension
Gastrointestinal disorders	Frequent	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation
Hepato-biliary disorders	Less frequent	Elevated liver enzymes, jaundice, hepatitis
Skin and subcutaneous	Frequent	Rash, pruritus, sweating

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tissue disorders*	Less frequent	Erythema multiforme and Stevens Johnson syndrome have also been reported. Exacerbation of psoriasis
Musculoskeletal, connective tissue and bone 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

*Hypersensitivity may manifest as skin reactions. See “Immune system disorders” and “Skin and subcutaneous tissue disorders”.

**The most common type of seizures is generalised tonic clonic seizures, a seizure type which can result in some cases in post-ictal confusion or memory impairment.
(see section 4.4).

***Cases of suicidal ideation and suicidal behaviour have been reported during bupropion therapy (see section 4.4).

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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In addition to those events reported under section 4.8, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or dysrhythmias.

Treatment

In the event of overdose, hospitalisation is advised.

ECG and vital signs should be monitored.

Ensure an adequate airway, oxygenation and ventilation. The use of activated charcoal is recommended. No specific antidote for bupropion is known.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects

Bupropion is an inhibitor of the neuronal re-uptake of catecholamines (noradrenaline (norepinephrine) and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit monoamine oxidase.

The mechanism of action of bupropion is unknown.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of bupropion tablets to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours. The absorption of bupropion is not significantly affected when taken with food.

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Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg per day.

Distribution

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 L. Bupropion and hydroxybupropion are moderately bound to plasma proteins (84 % and 77 %, respectively). The extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

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.

Erythrohydrobupropion cannot be measured in the plasma after a single dose of bupropion. The active metabolites are further metabolised to inactive metabolites and excreted in the urine.

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

Bupropion and hydroxybupropion are both relatively weak competitive inhibitors of the CYP2D6 isoenzyme with 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. Interactions with other medicines and other forms of interaction).

In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion for 10 to 45 days.

Elimination

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87 % and 10 % of the radioactive dose were recovered in the urine and faeces, respectively. The fraction of the dose of bupropion excreted unchanged was only 0,5 %, a finding consistent with the extensive metabolism of bupropion. Less than 10 % of this ^{14}C dose was accounted for in the urine as active metabolites.

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

The elimination half-life of hydroxybupropion is approximately 20 hours and its area under the plasma drug concentration versus time curve (AUC) at steady state is approximately 17 times that of bupropion. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively) and steady-state AUC values are 8 and 1,6 times higher than that of bupropion, respectively. Steady-state for bupropion and its metabolites is reached within 8 days.

Special 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.

Renal impairment

The elimination of bupropion and its major metabolites may be reduced by impaired renal function (see section 4.4. Special warnings and precautions for use).

Hepatic impairment

The pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild cirrhosis (Child-Pugh grade A, range 5-6) when compared to healthy volunteers, although more variability was observed between individual patients. For patients with moderate to severe hepatic cirrhosis (Child Pugh grades B & C, range 7-13), a single dose of bupropion produced a C_{max} and AUC that were substantially increased (mean difference approximately 70 % and 3-fold, respectively) and more variable when compared to the values in healthy volunteers; the mean half-life was also longer (by approximately 40 %). For the metabolites, the mean C_{max} was lower (by approximately 30 to 70 %), the mean AUC tended to be higher (by approximately 30 to 50 %), the median T_{max} was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 2 to 4-fold) than in healthy volunteers (see section 4.3. Contraindications).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K90

Cysteine hydrochloride monohydrate

Colloidal anhydrous silica

Glycerol dibehenate

Magnesium stearate

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Functional coating

Ethyl cellulose 100 mPas

Povidone K90

Macrogol 1450

Enteric coating

Methacrylic acid-ethyl acrylate copolymer

Colloidal hydrated silica

Macrogol 1450

Triethyl citrate

Printing

Opacode Black S-1 - 17823

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

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BUPROPION 300 ACCORD modified release tablets are packed in Alu-Alu blisters consisting of a cold formable aluminium film (25 µOPA/45 µ Alu foil/60µ PVC) and 0,025 mm aluminium foil hard tempered with HSL coating on bright side. The blisters are packed in cardboard cartons in packs of 30s.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

55/1.2/0778

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 March 2025

10. DATE OF REVISION OF THE TEXT