PRODUCT INFORMATION

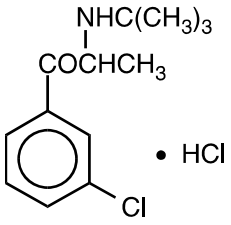
BUPROPION-RL™ SUSTAINED RELEASE TABLETS

NAME OF THE MEDICINE: bupropion hydrochloride (also known as amfebutamone hydrochloride)

DESCRIPTION: The chemical name of bupropion is (±) -1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride

Bupropion-RL tablets also contain the following excipients: cellulose – microcrystalline, hypromellose, cysteine hydrochloride, magnesium stearate, carnauba wax, titanium dioxide (E171), edible black ink.

STRUCTURE:



Molecular weight: 276.2
CAS: 31677-93-7

PHARMACOLOGY:

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 no inhibitory effect on monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

In clinical trials, treatment with bupropion reduced withdrawal symptoms compared to placebo and there was evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

Pharmacokinetics:

Absorption
Following oral administration of bupropion hydrochloride tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300mg/day. The absorption of bupropion is not significantly affected when taken with food.

Distribution
Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 L. Bupropion and its major active metabolite, hydroxybupropion, are moderately bound to plasma proteins (84% and 77%, respectively).

The extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism
Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion. These may have clinical importance, as their plasma concentrations are as high or higher than those of bupropion. Peak plasma concentrations of hydroxybupropion and threohydrobupropion are achieved approximately 6 hours following administration of a single dose 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 the cytochrome P450 IIB6 (CYP2B6), while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion (See 'INTERACTIONS').

Following oral administration of a single 150-mg dose of bupropion, there was no difference in C_{max} half-life, T_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and non-smokers.

Bupropion has been shown to induce its own metabolism in animals following sub-chronic administration. In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion hydrochloride for 10 to 45 days.

Elimination
Following oral administration of 200mg 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 hydrochloride 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 14 to 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.

Patients with renal impairment
There is inadequate information on the pharmacokinetics of bupropion in patients with renal disease. The elimination of the major metabolites of bupropion may be affected by reduced renal function (See ' PRECAUTIONS').

Patients with hepatic impairment
The pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild to moderate cirrhosis when compared to healthy volunteers, although more variability was observed between individual patients. For patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC 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 hours), and the mean half-lives were longer (by approximately 2 to 4-fold) than in healthy volunteers (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Elderly
Pharmacokinetics 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 dose, 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.

CLINICAL TRIALS:

The clinical efficacy of bupropion was demonstrated in three pivotal efficacy studies (403, 405 and 406) in chronic cigarette smokers (>15 cigarettes per day). Participants were ≥18 years of age, motivated to quit smoking, and had a history of not quitting for more than 3 months of the year. Patients received individual smoking cessation counselling in conjunction with treatment.

The primary endpoint in all studies was total abstinence during a specified 4 week time interval, and patients who had just a single inhalation during the observation period were classified as treatment failures. Abstinence was confirmed biologically by measuring exhaled carbon monoxide levels. Secondary end points included 1 week point prevalence measures of abstinence (smoking status for a 7 day period prior to each clinic visit), duration of continuous abstinence, and reported cigarette craving or nicotine withdrawal symptoms.

Studies 403 and 405 were multicentre, double-blind, placebo-controlled, parallel, randomised trials, in which the primary efficacy measure was abstinence for a 4 week period during therapy (weeks 4-7). Study 403 was a dose-response trial in which 613 patients were randomised to 7 weeks treatment with placebo, bupropion 100mg/day (50mg bd), bupropion 150mg once daily or bupropion 300mg/day (150mg bd). There was a dose-dependent increase in the percentage of patients able to achieve 4 week abstinence rates (weeks 4 to 7) across the bupropion groups. Treatment with bupropion 150mg/day and 300mg/day was significantly more effective compared with placebo, with 27% and 36% of patients abstaining respectively ($p \leq 0.05$, placebo 17%). In addition, treatment with bupropion 300mg/day was more effective than placebo in helping patients maintain continuous abstinence through to week 26 (6 months) of the study (19%, $p \leq 0.05$). At week 52, there was no significant difference in continuous abstinence rates between bupropion 300mg/day and placebo, however weekly point-prevalence abstinence demonstrated statistical significance in favour of bupropion ($p<0.05$).

Study 405 was a comparative trial, consisting of a 1-2 week baseline period, a 7 week treatment period (weeks 1-7), a 2 week tapering of therapy (weeks 8-9), and a 1 year follow up (weeks 10-52). 893 patients were randomised to placebo, bupropion 150mg bd (300mg/day), nicotine transdermal system (NTS, 21mg/day) or bupropion/NTS combination. The 4 week abstinence rates for all active therapies were significantly higher ($p \leq 0.01$) than placebo: 36%, 49% and 58% for NTS, bupropion 150mg bd, and combination treatment respectively versus 23% for placebo. The effect of bupropion was significantly higher ($p \leq 0.01$) than the effect of NTS. The comparison of the effect of bupropion/NTS vs bupropion alone did not reach statistical significance ($p=0.06$).

During the follow-up phase, continuous abstinence rates following cessation of treatment were significantly superior compared to placebo at weeks 10 and 12 for the NTS group, and from week 3 to week 52 for the bupropion alone and bupropion/NTS groups ($p \leq 0.05$). Though the bupropion/NTS treatment group consistently displayed the highest continuous abstinence rate throughout the study, no statistically significant differences were observed between bupropion alone and bupropion/NTS. Statistical significance in favour of the bupropion alone and bupropion/NTS groups versus NTS alone was demonstrated from weeks 10 through 52. bupropion demonstrated a positive effect on subjective symptoms (ie. a reduction in cigarette craving and nicotine withdrawal symptoms).

Study 406 was a multicentre, randomised, double-blind placebo-controlled comparison of bupropion for the treatment of relapse in patients who achieved abstinence from smoking while on bupropion. The study consisted of a baseline phase, a 7 week open-label phase in which 784 patients were treated with bupropion 150mg bd (300mg/day), and a 45 week double-blind phase in which patients who achieved abstinence in the open label phase were randomised to placebo or bupropion 150mg bd under double-blind conditions for a further 45 weeks. Additional primary end points in this study were time to relapse and continuous abstinence at weeks 12, 24, 36 and 52. Secondary end-points included one week point prevalence abstinence.
Four week abstinence from smoking was achieved in 48.5% of patients. Median time to relapse was 20 weeks for placebo and 32 weeks for the bupropion treatment group ($p=0.03$). Continuous abstinence rates showed no significant difference between bupropion and placebo at weeks 36 and 52. Significant point prevalence abstinence ($p<0.05$) was consistently seen at all time points except week 40 ($p=0.07$).

In all three pivotal efficacy studies (403, 405 and 406), changes in pulse rate and blood pressure were minor and there were no clinically significant differences between treatment groups. No consistent differences in body weight changes between treatment groups were observed for studies 403 and 405. In study 406, weight gain was statistically greater for placebo-treated patients than for bupropion-treated patients at every time point examined. Cessation of smoking was associated with an increase in body weight after both placebo and active treatment. All three studies suggested this effect was attenuated while taking bupropion.

INDICATIONS:

Bupropion-RL tablets are indicated as a short-term adjunctive therapy for the treatment of nicotine dependence in those who are committed to quitting smoking, when used in conjunction with counselling for smoking cessation/abstinence.

CONTRAINDICATIONS:

Bupropion-RL is contraindicated in patients with hypersensitivity to bupropion (also known as amfebutamone hydrochloride) or any of the other components of the preparation.

Bupropion-RL is contraindicated in patients with a current seizure disorder or any history of seizures.

Bupropion-RL is contraindicated in patients with a known central nervous system (CNS) tumour.

Bupropion-RL is contraindicated in patients undergoing abrupt withdrawal from alcohol or benzodiazepines.

Bupropion-RL is contraindicated in patients with a current or previous diagnosis of bulimia or anorexia nervosa.

Concomitant use of Bupropion-RL and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with Bupropion-RL tablets.

PRECAUTIONS:

Risk of seizures

Bupropion is associated with a dose-related risk of seizures, therefore the recommended dose of Bupropion-RL must not be exceeded. The incidence of seizure at doses of sustained release bupropion tablets up to 300 mg/day is approximately 0.1% (1/1,000)

There is an increased risk of seizures occurring with the use of Bupropion-RL in the presence of predisposing risk factors which lower the seizure threshold. Bupropion-RL must not be used in patients with predisposing risk factors unless there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure.

All patients should be assessed for predisposing risk factors, which include:

- concomitant administration of other medicinal products known to lower the seizure threshold for example:
  - antipsychotics
  - antidepressants (including SSRIs and tricyclic antidepressants)
  - antimalarials
  - tramadol
  - theophylline
  - systemic steroids
  - quinolones
  - sedating antihistamines
- excessive use of alcohol or sedatives (see CONTRAINDICATIONS)
- history of head trauma
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products.

Bupropion-RL should be discontinued and not recommenced in patients who experience a seizure while on treatment.

Other

Bupropion-RL should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see ADVERSE REACTIONS). Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion, and clinical management should be provided accordingly.

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 Bupropion-RL should be used with caution in patients with hepatic impairment and reduced frequency of dosing should be considered in patients with mild to moderate hepatic cirrhosis (see DOSAGE AND ADMINISTRATION and PHARMACOKINETICS).

Bupropion-RL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency of dosing is required, as peak bupropion levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual (see DOSAGE AND ADMINISTRATION and PHARMACOKINETICS).

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

The active metabolites of bupropion 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 drug or metabolite levels.

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. Elderly patients are more likely to have decreased renal function, hence a reduced frequency and/or dose may be required.

The pharmacology of bupropion resembles that of some antidepressants. Neuropsychiatric symptoms have been reported (see ADVERSE REACTIONS). In particular, psychotic and manic symptomatology has been observed, mainly in patients with a history of psychiatric illness. Additionally, Bupropion-RL may precipitate a manic episode in patients with bipolar disorder.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during bupropion treatment, and generally occurred during the early stages of treatment.

Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behaviour associated with antidepressant use compared to placebo in patients less than 25 years old.

Clinicians should be aware of the possible emergence of significant depressive symptoms or suicidal ideation in patients being treated with bupropion, and should advise and monitor patients accordingly.

Prior to initiation of combination therapy with a Nicotine Transdermal System (NTS), prescribers should consult the prescribing information of the relevant NTS. If combination nicotine replacement therapy is used, monitoring for potential treatment-emergent elevations of blood pressure is recommended (see ADVERSE REACTIONS).

Effects on ability to drive and use machinery:
As with other CNS acting drugs, Bupropion-RL may affect the ability to perform tasks that require judgement or motor and cognitive skills. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain Bupropion-RL tablets do not adversely affect their performance.

Carcinogenicity, mutagenicity and impairment of fertility:
Lifetime carcinogenicity studies were performed in rats and mice at oral doses up to 300 and 150 mg/kg/day, respectively. In male rats and male and female mice, systemic exposure (based on AUC) to bupropion and its metabolites at these dose levels in repeat dose studies

was less than in humans at the maximum recommended therapeutic dose. In female rats exposure to bupropion was up to approximately 4 fold, and to its metabolites was less than, human exposure. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day and this may be secondary to hepatic enzyme induction. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumours of the liver and other organs was seen in either study.
Genotoxicity tests showed that bupropion did not cause gene mutations in bacterial or mammalian cells *in vitro*, chromosomal damage *in vitro* or DNA damage *in vivo*. An increase in chromosomal aberrations was observed in one of three *in vivo* rat bone marrow cytogenetic studies.

A fertility study in rats at oral doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

Use in Pregnancy: Pregnancy Category B2.
The safety of bupropion for use in human pregnancy has not been established. Pregnant women should be encouraged to quit smoking without the use of pharmacotherapy.

Studies in pregnant mice, rats and rabbits showed no evidence of adverse effects on embryofetal development at oral doses up to 100, 450 and 150 mg/kg/day, respectively. In mice and rats, administration of bupropion in late gestation had no effects on parturition. In mice and rabbits, systemic exposure (based on AUC) to bupropion and its metabolites at these dose levels in repeat dose studies was less than in humans at the maximum recommended therapeutic dose. In rats, exposure to bupropion in reproduction studies was up to approximately twice, and to its metabolites was less than, human exposure.

In an additional study in pregnant rats, no adverse effects on perinatal development were observed at oral doses up to 150 mg/kg/day.

As animal studies are not always predictive of the human response, administration of Bupropion-RL should only be considered during pregnancy if the expected benefits are greater than the potential risks.

Use in Lactation:
In rats, no adverse effects on postnatal development were observed at oral doses up to 150 mg/kg/day. Plasma concentrations of bupropion were greater than, and of its metabolites were less than, human plasma concentrations at the maximum recommended therapeutic dose.

As bupropion and its metabolites are excreted in human breast milk, mothers should be advised not to breast feed while taking Bupropion-RL.

INTERACTIONS:

It is important to be aware of all medicines which patients are taking when considering their suitability for Bupropion-RL treatment. Bupropion-RL may interact with a number of medicines by lowering the seizure threshold (see PRECAUTIONS) or through other mechanisms.

In patients receiving medicinal products known to lower the seizure threshold, Bupropion-RL must only be used if there is a compelling clinical justification for which potential medical benefit of smoking cessation outweighs the potential increased risk of seizure (see PRECAUTIONS).

Physiological changes resulting from smoking cessation itself, with or without treatment with Bupropion-RL, may alter the pharmacokinetics of some medications taken concomitantly.

In vitro findings indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 IIB6 (CYP2B6) (see 'Pharmacokinetics'). Care should therefore be exercised when Bupropion-RL is co-administered with drugs 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 hydrochloride increased plasma levels of desipramine. This effect was present for at least 7 days after the last dose of bupropion hydrochloride. Concomitant use of Bupropion-RL with other drugs metabolised by the CYP2D6 isoenzyme has not been formally studied. Therefore, concomitant therapy with drugs predominantly metabolised by this isoenzyme (such as certain beta-blockers (eg metoprolol), antiarrhythmics (eg flecainide), SSRIs, TCAs, antipsychotics) should be initiated at the lower end of the dose range of the concomitant medication. If Bupropion-RL is added to the treatment regimen of a patient already receiving a medication metabolised by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index (See PHARMACOKINETICS).

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

In two studies in health volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20-80%. In another healthy volunteer study, ritonavir 100 mg plus lopinavir 400 mg twice daily decreased bupropion exposure by at least as much as 600mg twice daily ritonavir alone.

This effect is thought to be due to the induction of metabolism of bupropion and its metabolites. Patients receiving ritonavir, alone or in combination with lopinavir, may need increased doses of bupropion but the maximum recommended does of bupropion should not be exceeded.

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-RL treatment. The consumption of alcohol during Bupropion-RL treatment should be minimised or avoided.

Limited clinical data suggest a higher incidence of neuropsychiatric adverse events in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Bupropion-RL to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

Although there is no clear evidence, it is possible that an interaction may occur between bupropion and the herbal remedy St John’s Wort (hypericum perforatum), which may result in an increase in undesirable effects.

ADVERSE EFFECTS:

Clinical Trial Information

Bupropion was generally well tolerated when used to treat nicotine dependence as an aid to smoking cessation. In Table 1, the frequency of AEs reported in the treatment phase of the pivotal comparative trial (Study 405) is presented. AEs are shown if they occurred at an

incidence of 1% or more and if the AE was reported more frequently in patients treated with bupropion, nicotine transdermal system (NTS) or bupropion plus NTS when compared to patients treated with placebo.

Table 1: Incidence of adverse events reported during the treatment phase of study 405 [#]

Adverse event	Bupropion 300mg/day (n=243)	Nicotine Transdermal System (NTS) 21mg/day (n=243)	Bupropion and NTS (n=244)	Placebo (n=159)
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	< 1	1	3	1
Neck Pain	2	1	< 1	0
Facial oedema	< 1	0	1	0
Cardiovascular				
Hypertension	1	< 1	2	0
Palpitations	2	0	1	0
Digestive				
Nausea	9	7	11	4
Dry Mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhoea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	< 1	< 1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous System				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	< 1	2	2
Tremor	1	< 1	2	0
Dysphoria	< 1	1	2	1
Respiratory				
Rhinitis	12	11	9	8
Increased cough	3	5	< 1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction	11	17	15	7
Rash	4	3	3	2
Pruritus	3	1	5	1
Urticaria	2	0	2	0

Special Senses				
Taste perversion	3	1	3	2
Tinnitus	1	0	< 1	0

Selected adverse events with an incidence of at least 1 % of patients treated with BUPROPION, NTS, or the combination of BUPROPION and NTS and more frequent than in the placebo group.

Adverse Reactions Observed During Clinical Practice:
The list below provides information on the undesirable effects of bupropion identified from clinical trials and post-marketing clinical experience for which a possible casual relationship with bupropion has been established. Adverse reactions are categorised by body system and listed according to frequency. Common adverse reactions are defined as those occurring in at least 1% of patients. Uncommon adverse reactions are those occurring in 0.1% to 1% of patients. Rare adverse reactions are those occurring in less than 0.1% of patients. It is important to note that smoking cessation is often associated with nicotine withdrawal symptoms, some of which are also recognised as adverse events associated with bupropion.

Body (general)
Common: fever, asthenia. *Uncommon:* chest pain. *Rare:* malaise.

Cardiovascular
Uncommon: Flushing, tachycardia, increased blood pressure (in some cases severe).
Rare: postural hypotension, vasodilation, syncope, hypotension, palpitations.

CNS
Very Common: insomnia, headache. *Common:* dizziness, agitation, anxiety, tremor, concentration disturbance, depression. *Uncommon:* confusion. *Rare:* hallucinations, irritability, hostility, seizures (see PRECAUTIONS), depersonalisation, parkinsonism, dystonia, ataxia, inco-ordination, twitching, abnormal dreams, memory impairment, paraesthesia, delusions, paranoid ideation, aggression and restlessness.

Endocrine and metabolic
Common: anorexia. *Rare:* blood glucose disturbances.

Gastrointestinal
Common: dry mouth, nausea, constipation, gastrointestinal disturbance including abdominal pain and vomiting.

Skin / Hypersensitivity
Common: rash, pruritus, sweating. Hypersensitivity reactions ranging in severity from urticaria (*common)* to (*rarely)* angioedema, dyspnoea/bronchospasm, anaphylactic shock. *Rare*: 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. Erythema multiforme and Stevens Johnson syndrome have also been reported.

Special Senses
Common: visual disturbance, taste disorders. *Uncommon*: tinnitus.

Genitourinary
Rare: Urinary frequency and/or retention.

Hepatic
Rare: elevated liver enzymes, jaundice and hepatitis.

DOSAGE AND ADMINISTRATION:

Bupropion-RL tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse effects including seizures.

Use in Adults
It is recommended that treatment is started while the patient is still smoking and a "target stop date" set within the first two weeks of treatment with Bupropion-RL, preferably in the second week.

The initial dose is 150mg to be taken daily for three days, increasing to 150mg twice daily. There should be an interval of at least 8 hours between successive doses.

The maximum single dose must not exceed 150mg and the maximum total daily dose must not exceed 300mg.

Insomnia is a very common adverse event which is often transient. Insomnia may be reduced by avoiding bedtime doses (provided there is at least 8 hours between doses). If clinically indicated, dose reduction may be considered (see Clinical Trials).

Patients should be treated for at least 7 weeks.

Discontinuation should be considered if the patient has not made significant progress towards abstinence by the seventh week of therapy, since it is unlikely that they will stop smoking during that attempt.

Individualisation of Therapy
Patients are more likely to quit smoking and remain abstinent if they receive counselling. When prescribing Bupropion-RL, physicians should review the patients overall smoking cessation program. It is important to provide brief but effective counselling to patients at each clinic visit, including asking patients about their smoking status at each visit, advising patients to stop smoking, and arranging a follow-up visit.

Patients should be encouraged to identify and avoid smoking trigger factors, and advised to inform family, friends and co-workers of their decision to quit so that appropriate support can be provided.

Combination Treatment with Bupropion-RL and a Nicotine Transdermal System
The recommended posology does not require modification if Bupropion-RL is used in combination with Nicotine Transdermal Systems for nicotine dependence (See 'Precautions').
Use in Children and Adolescents
The safety and efficacy of Bupropion-RL tablets in patients under 18 years of age have not been established.

Use in patients with liver impairment
Bupropion-RL should be used with caution in patients with liver impairment.

Because of increased variability in the pharmacokinetics in patients with mild to moderate hepatic cirrhosis, a reduced frequency of dosing should be considered (see PHARMACOKINETICS and PRECAUTIONS).

Bupropion-RL should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg on alternate days in these patients (see PHARMACOKINETICS and PRECAUTIONS).

OVERDOSAGE:

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose have been reported. In addition to those events reported as Adverse Reactions, overdose has resulted in symptoms including drowsiness, hallucinations and loss of consciousness.

Seizures have been reported in approximately one third of all reported overdoses with bupropion (in patients treated for depression and smoking cessation). Although most patients recovered without sequelae, deaths associated with overdoses of bupropion have been reported rarely in patients ingesting massive doses of the drug. Where fatalities have occurred, there are no data on time to death following overdose.

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

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 also recommended. No specific antidote for bupropion is known.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION:

Biconvex, round, white, film-coated sustained release tablets, branded GX CH7, containing 150mg of bupropion hydrochloride, in blister packs of 30 and 90, tablets.

STORAGE CONDITIONS:

Store below 25°C.

NAME AND ADDRESS OF SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

POISON SCHEDULE OF THE MEDICINE:

S4

DATE OF TGA APPROVAL: 29 January 2009

[TM]Bupropion-RL is a trade mark of the GlaxoSmithKline group of companies.

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