PRODUCT MONOGRAPH

[Pr] Dom-BUPROPION SR

Bupropion Hydrochloride Sustained Release Tablets, House Standard

100 mg and 150 mg

Antidepressant

DOMINION PHARMACAL
6111 Royalmount Ave, Suite 100
Montréal, Québec
H4P 2T4

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PART 1: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Summary Product Information

Route of Administration	Dosage Form/Strength	Nonmedicinal Ingredients
Oral	Tablets: 100 mg and 150 mg	**100 mg tablets :** carboxyvinyl polymer, colloidal silicon dioxide, FD&C Blue # 1, hypromellose, iron oxide black, glyceryl behenate, lactose anhydrous, magnesium stearate, polyethylene glycol, polyethylene oxide and titanium dioxide. **150 mg tablets** : carboxyvinyl polymer, colloidal silicon dioxide, glyceryl behenate, lactose anhydrous, magnesium stearate, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, talc and titanium dioxide. In addition, the 150 mg tablet contains also FD&C Red # 40 and FD&C Blue # 2.

INDICATIONS AND CLINICAL USE

Adults
Dom-BUPROPION SR (bupropion hydrochloride sustained-release tablets) is indicated for the symptomatic relief of major depressive illness. The effectiveness of bupropion hydrochloride sustained release in long-term use (greater than 8 weeks) has not been evaluated in controlled trials. Therefore, the physician who elects to use Dom-BUPROPION SR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Pediatrics (< 18 years of age)
Dom-BUPROPION SR (bupropion hydrochloride sustained-release tablets) is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

CONTRAINDICATIONS

To reduce the risk of seizures, Dom-BUPROPION SR (bupropion hydrochloride sustained-release tablets) is contraindicated in patients:

- Receiving bupropion extended release or any other medications that contain bupropion hydrochloride because the incidence of seizure is dose dependent (see WARNINGS and PRECAUTIONS)
- With a current seizure disorder or history of seizures (see WARNINGS and PRECAUTIONS).
- With a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures (see WARNINGS and PRECAUTIONS) noted in patients treated for bulimia with the immediate release formulation of bupropion.
- Undergoing abrupt withdrawal from alcohol or benzodiazepines or other sedatives.

To reduce risks due to drug interaction, the concomitant use of Dom-BUPROPION SR is contraindicated in patients currently taking:

- Monoamine oxidase (MAO) inhibitors.
- The antipsychotic thioridazine, since bupropion may inhibit thioridazine metabolism, thus causing an increase in thioridazine levels and a potential increased risk of thioridazine-related serious ventricular arrhythmias and sudden death.

At least 14 days should elapse between discontinuation of one drug and the start of another.

Dom-BUPROPION SR is contraindicated in patients with known hypersensitivity to bupropion or to any of the components of the formulation.

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**
- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional Data

- **There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages given an anti-depressant drug. This includes monitoring for agitation-type emotional and behavioural changes.

Seizures:

Patients should be made aware that Dom-BUPROPION SR (bupropion hydrochloride sustained release tablets) contains the same active ingredient (bupropion hydrochloride) as bupropion extended release. Dom-BUPROPION SR should NOT be administered to patients already receiving a product containing bupropion hydrochloride (see CONTRAINDICATIONS).

Data for bupropion hydrochloride sustained release tablets revealed a seizure incidence of approximately 0.1% (3 of 3,100 patients followed prospectively) in patients treated at the recommended dose range of 100 to 300 mg/day. The incidence of seizures increased to 0.4% (4/1000), above the recommended dose, at 400 mg/day. Data for the immediate release bupropion revealed a seizure incidence of approximately 0.4% (13 of 3,200 patients followed prospectively) in patients treated at doses of 300 to 450 mg/day. Additional data accumulated for the immediate release formulation of bupropion suggests that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, the disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

Predisposing Risk Factors for Seizures:

The risk of seizure occurring with bupropion use appears to be associated with the presence of predisposing risk factors. Therefore extreme caution should be used when treating patients with predisposing factors which increase the risk of seizures, including:

- Prior seizure (see CONTRAINDICATIONS).
- History of head trauma.
- Central nervous system (CNS) tumour.
- The presence of severe hepatic impairment.
- Excessive use of alcohol; addiction to opiates, cocaine, or stimulants.
- Use of concomitant medications that lower seizure threshold, including but not limited to: antipsychotics, antidepressants, lithium, amantadine, theophylline, systemic steroids, quinolone antibiotics, and anti-malarials.
- Use of over-the-counter stimulants or anorectics.
- Diabetes treated with oral hypoglycemics or insulin.

The above group of risk factors, including medications, should not be considered exhaustive; for each patient, all potential predisposing factors must be carefully considered.

In order to minimize the Risk of Seizure:

- The total daily dose of Dom-BUPROPION SR must not exceed 300 mg (the maximum recommended dose)
- No single dose of Dom-BUPROPION SR may exceed 150 mg, in order to avoid high peak concentrations of bupropion and/or its metabolites.

If a Seizure Occurs:
Patients should be warned that if they experience a seizure while taking Dom-BUPROPION SR, they should contact their doctor or be taken to a hospital emergency ward immediately, and should stop taking Dom-BUPROPION SR. Treatment should not be restarted if a patient has experienced a seizure while taking bupropion sustained release or bupropion extended release.

Hepatic Impairment:
The results of two single dose pharmacokinetic studies indicate that the clearance of bupropion is reduced in all subjects with Child-Pugh Grades C hepatic impairment, and in some subjects with milder forms of liver impairment. Given the risks associated with both peak bupropion levels and drug accumulation, Dom-BUPROPION SR is not recommended for use in patients with severe hepatic impairment. However, should clinical judgement deem it necessary, it should be used only with extreme caution at a reduced dose, to a maximum dose of 150 mg every other day.

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 (see DOSAGE AND ADMINISTRATION; ACTIONS AND CLINICAL PHARMACOLOGY; and WARNINGS AND PRECAUTIONS).

Potential for Hepatotoxicity:
In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

Clinical Worsening and Suicide:
The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dosage changes, either increases or decreases. Close supervision of high risk patients should accompany initial drug therapy, and consideration should be given to the need for

hospitalization. (See WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

It should be noted that a causal role for SSRIs and other newer anti-depressants in inducing self-harm or harm to others has not been established.

In order to reduce the risk of overdose, prescriptions for Dom-BUPROPION SR (bupropion hydrochloride) should be written for the smallest number of tablets consistent with good patient management.

Allergic Reactions:
Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion at a rate of 1-3 per thousand. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. In uncontrolled and controlled clinical trials, skin disorders, primarily rashes, pruritus, and urticaria, lead to discontinuation of 1.5% and 1.9 %, respectively of bupropion-treated subjects. A patient should stop taking Dom-BUPROPION SR and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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.

Bupropion should be discontinued immediately if any hypersensitivity reactions are experienced. Symptoms of hypersensitivity should be treated in accordance with established medical practice. Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion, and clinical management should be provided accordingly. In post-market experience, there have been reports of hypersensitivity reactions in patients who consumed alcohol while taking bupropion. As the contribution of alcohol to these reactions has been established, patients should avoid alcohol when they are taking bupropion (see Alcohol Interaction).

Agitation and Insomnia:
In placebo controlled trials patients receiving bupropion hydrochloride sustained release tablets experienced an increased incidence of insomnia and anxiety relative to those receiving placebo (see ADVERSE REACTIONS and WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM). These symptoms were sometimes of sufficient magnitude to require discontinuation of bupropion hydrochloride sustained release, or concurrent treatment with sedative/hypnotic drugs. Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in dose.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena:
Patients treated with bupropion hydrochloride sustained release have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations,

psychosis, concentration disturbance, paranoia and confusion. In some cases these abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania:
Antidepressants can precipitate manic episodes in bipolar patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Dom-BUPROPION SR is expected to pose similar risks.

Altered Appetite and Weight:
In clinical trials bupropion hydrochloride sustained release was associated with dose-related weight loss. In eight week controlled trials mean weight loss for trial completers was 0.1 kg for placebo, 0.8 kg for bupropion hydrochloride sustained release 100 mg/day, 1.4 kg at 150 mg/ day, and 2.3 kg at 300 mg/day. If weight loss is a major presenting sign of a patient's depressive illness, the potential anorectic and/or weight reducing effect of bupropion hydrochloride should be considered.

Cardiovascular Effects:
In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of pre-existing hypertension.

Data from a comparative study of the sustained-release formulation of bupropion , nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained- release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained- release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of pre-existing hypertension. Three patients (1.2%) treated with the combination of bupropion sustained release and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with bupropion sustained release or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. In a study of depressed inpatients with stable heart failure, bupropion was associated with a rise in supine blood pressure, resulting in discontinuation of two patients for exacerbation of baseline hypertension.

Hepatic Impairment:
Based on the variability reported for individual pharmacokinetic (PK) values of patients with mild hepatic impairment in a single dose pharmacokinetic study, patients with mild or moderate hepatic impairment should be initiated on the lowest recommended dose. Bupropion

is not recommended for patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS, and also DOSAGE AND ADMINISTRATION).

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see ACTIONS and CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment:
Bupropion is extensively metabolized in the liver to active metabolites, which are largely further metabolized before being excreted by the kidneys. Dom-BUPROPION SR treatment of patients with renal impairment should be initiated at a reduced dosage regimen, as 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.

Occupational Hazards:
Any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect their performance adversely.

Special Populations

Pregnancy, Labour and Delivery:

There are no adequate and well-controlled studies of bupropion hydrochloride sustained release in pregnant women. Dom-BUPROPION SR should thus not be used during pregnancy unless the potential benefit is judged to outweigh the potential risk.

First Trimester Exposure
Data from pregnancy registries have documented congenital malformations including cardiovascular (eg, ventricular and atrial septal defects) with maternal exposure to bupropion in the first trimester. Bupropion should be initiated during pregnancy or in women who intend to become pregnant only if benefits outweigh the potential risk to the fetus.

Third Trimester Exposure
Post-marketing reports indicate that some neonates exposed to SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants, such as bupropion hydrochloride sustained release, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. The frequency of symptoms may vary with each drug. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with Dom-BUPROPION SR during the third

trimester, the physician should carefully consider the potential risks and benefits of treatment. (See DOSAGE AND ADMINISTRATION).

Lactation:

Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Dom-BUPROPION SR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age):

Dom-BUPROPION SR is not indicated for use in patients below the age of 18 years (See WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self Harm. See also INDICATIONS, Pediatrics; DOSAGE AND ADMINISTRATION, Special Patient Populations-Children).

Geriatrics:

Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another single and multiple dose pharmacokinetic study, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Bupropion is extensively metabolized in the liver to active metabolites, of which some are eliminated by the kidney, while others are further metabolized before being excreted in urine. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see WARNINGS AND PRECAUTIONS, Hepatic or Renal Impairment).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The information included under ADVERSE REACTIONS is based on data from clinical trials with bupropion hydrochloride sustained release in the treatment of depression. Information on

additional adverse events associated with the sustained release formulation of bupropion as well as the immediate release formulation of bupropion, is included in a separate subsection (see Events Observed During Development and Post-Marketing Experience of Bupropion with other formulations or indications).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials
Adverse events commonly encountered during the clinical development of bupropion hydrochloride sustained release (incidence of 5% or greater; and higher incidence in bupropion hydrochloride sustained release - treated, than placebo-treated patients) were headache, constipation, dry mouth, nausea, dizziness, insomnia, tremor and tinnitus.

Adverse Events Associated with Discontinuation of Treatment
In placebo controlled studies of depression (987 patients treated with bupropion hydrochloride sustained release, and 385 treated with placebo), adverse events caused discontinuation in 7% of bupropion hydrochloride sustained release-treated patients and 3% of placebo-treated patients. The more common events leading to discontinuation of bupropion hydrochloride sustained release included nervous system disturbances (2.2%), primarily agitation, anxiety and insomnia; skin disorders (1.9%), primarily rashes, pruritus, and urticaria ; general body complaints (1.0%), primarily headaches, and digestive system disturbances (1.0%), primarily nausea. Two patients in bupropion hydrochloride sustained release treatment groups discontinued due to hallucinations (auditory or visual). The rates of premature discontinuation due to an adverse event were dose-related in these studies.

In an open label, uncontrolled (acute treatment and continuation) study of bupropion hydrochloride sustained release, 11% patients (361 out of 3100) discontinued treatment due to an adverse event. Adverse events leading to premature discontinuation in 1% or more of patients were: headache (1.1%), nausea (1.0%), and insomnia (1.0%). Adverse events leading to premature discontinuation in 0.5% to 1% of patients were: anxiety (0.8%), rash (0.8%), agitation (0.7%), irritability (0.5%), and dizziness (0.5%). In those patients (n =1577) who went into the continuation phase after 8 weeks of treatment, 6 (0.4%) discontinued due to alopecia. Because this study was uncontrolled, it is not possible to reliably assess the causal relationship of these events to treatment with bupropion hydrochloride sustained release.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 enumerates treatment-emergent adverse events that occurred at an incidence of 1% or more in placebo-controlled trials, and were more frequent in bupropion sustained-released group than the placebo group. Reported adverse events were classified using a COSTART-based Dictionary.

TABLE 2 - ADVERSE EVENTS (%) – Placebo-Controlled Studies

Treatment-Emergent Adverse Experiences Occurring in ≥1% of Patients in Any BUP SR Group for Studies 203, 205, and 212

Body System	Adverse Experience	% AEs BUP SR 100-150 (n=382)	% AEs BUP SR 200-300 (n=491)	% AEs PBO (n=385)
Body (General)	Asthenia	1.8	1.6	1.6
	Flu syndrome	6.2	2.4	3.1
	Headache	27.5	26.9	23.4
	Infection	4.7	7.5	6.5
	Accidental injury	1.8	1.8	1.8
	Pain	1.3	2.4	2.1
	Abdominal pain	3.9	3.5	1.6
	Back pain	1.8	4.5	3.1
	Chest pain	1	2.9	0.8
	Neck pain	1.3	2	1.3
Cardiovascular	Hot flashes	1.3	1	0.8
	Migraine	0.8	1.4	1
	Palpitations	2.9	2	1.6
	Tachycardia	1.6	0.6	0.5
Digestive	Anorexia	3.1	4.5	1.6
	Constipation	6.5	10.8	6.8
	Diarrhea	3.9	5.9	5.7
	Dry mouth	13.1	16.5	7
	Dyspepsia	4.2	4.7	4.4
	Flatulence	1.8	3.1	2.1
	Nausea	10.7	12.6	7.5
	Vomiting	1.8	3.9	1.6
Musculoskeletal	Arthralgia	2.6	0.8	0.5
	Leg cramps	1	0.2	0.5
	Myalgia	1.6	3.3	2.9
	Twitch	0.8	1	0.3
Nervous System	Agitation	1.6	3.5	1.8
	Anxiety	4.5	4.3	3.1
	CNS stimulation	0	1.2	0.5
	Dizziness	7.1	8.6	5.5
	Hypertonia	1	1.2	0.5
	Insomnia	7.9	11.4	6.5
	Irritability	2.4	3.9	1.6
	Decreased libido	1	0.6	0.5
	Nervousness	4.5	4.1	2.6
	Somnolence	2.6	2.0	2.1
	Tremor	3.1	6.1	0.8
Respiratory	Pharyngitis	1.3	2.9	1.8
	Rhinitis	9.9	6.7	9.6
	Sinusitis	1.6	2.4	2.1
Skin	Pruritus	2.4	2.2	1.6
	Rash	2.1	4.1	1.3
	Sweating	2.4	5.1	1.6
	Urticaria	0.8	1.4	0

Body System	Adverse Experience	% AEs BUP SR 100-150 (n=382)	% AEs BUP SR 200-300 (n=491)	% AEs PBO (n=385)
Special Senses	Amblyopia	2.9	2.4	1.8
	Taste perversion	1	1.4	0.3
	Tinnitus	3.9	5.1	1.8
Urogenital	Urinary Tract Infection	1	1.8	0.3
	Urinary frequency	1.3	2.4	1.6

Less Common Bupropion Hydrochloride sustained release Clinical Trial Adverse Drug Reactions (< 1%)

Events Observed During Development and Post-Marketing Experience of Bupropion with Other Formulations or Indications

In addition to the events noted above, the following adverse events have been reported in clinical trials and post-marketing experience with the sustained release formulation of bupropion in depressed patients and in non-depressed smokers, as well as in clinical trials and post-marketing experience with the immediate release formulation of bupropion.

The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with bupropion hydrochloride sustained release tablets (n = 3100). All treatment-emergent adverse events are included except those listed in Table 3, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than two patients.

Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labelling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained release bupropion are included. The extent to which these events may be associated with bupropion hydrochloride sustained release is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise.

Cardiovascular: Infrequent were postural hypotension, stroke and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS, Cardiovascular Effects), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Also observed were arthritis, muscle rigidity/fever/ rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm/dyspnea. Also observed was pneumonia and epistaxis.

Skin/Hypersensitivity: Rare was maculopapular rash. Also observed were alopecia, hirsutism, angioedema, exfoliative dermatitis, erythema multiforme, and Stevens-Johnson syndrome. 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.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

Seizures: Post-marketing reports suggest that the reintroduction of bupropion hydrochloride sustained release in patients who experienced a seizure is associated with a risk of seizure reoccurrence in some cases. Thus, patients should not restart Dom-BUPROPION SR therapy

if they have had a seizure on a bupropion formulation (bupropion sustained release or bupropion extended release). See WARNINGS and PRECAUTIONS.

Drug Abuse and Dependence

Dom-BUPROPION SR is likely to have a low abuse potential. There have been few reported cases of drug dependence and withdrawal symptoms associated with the immediate release formulation of bupropion. In human studies of abuse liability, individuals experienced with drugs of abuse reported that bupropion produced a feeling of euphoria and desirability. In these a single dose of 400 mg (1.33 times the recommended daily dose) of the immediate release formulation of bupropion produced mild amphetamine-like effects compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), which is indicative of euphorigenic properties and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. Higher doses could not be tested because of the risk of seizure.

DRUG INTERACTIONS

Overview

In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Therefore, the potential exists for a drug interaction between Dom-BUPROPION SR and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. Few systematic data have been collected on the metabolism of bupropion hydrochloride sustained release following concomitant administration with other drugs or alternatively, the effect of concomitant administration of bupropion hydrochloride sustained release on the metabolism of other drugs.

Following chronic administration of bupropion, 100 mg t.i.d. to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Drug-Drug Interactions

Drugs Metabolized By CYP2D6:

Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily, followed by a single dose of 50 mg desipramine, increased the $C_{max,}$ AUC, and $t_{1/2}$ of desipramine by an average of approximately two-, five- and two-fold,

respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Co-administration of Thioridazine Contraindicated
Administration of the antipsychotic thioridazine alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias such as torsades de pointes, and sudden death. As this effect appears to be dose-related, it is anticipated that risk increases with inhibition of thioridazine metabolism. An *in-vivo* study suggests that drugs which inhibit CYP2D6 will elevate plasma levels of thioridazine. Therefore concomitant use of thioridazine with Dom-BUPROPION SR is contraindicated (see CONTRAINDICATIONS).

Co-administration of other drugs metabolized by CYP2D6 isoenzyme
Co-administration of bupropion with other drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized 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.

MAO Inhibitors:
Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor, phenelzine (see CONTRAINDICATIONS).

Cimetidine:
The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were examined in a crossover study in 24 healthy young male volunteers, following oral administration of two 150 mg bupropion hydrochloride sustained release tablets with and without 800 mg of cimetidine. A single dose of cimetidine had no effect on single dose pharmacokinetic parameter estimates for bupropion, or hydroxybupropion, but caused a small statistically significant increase in the combined threohydro- and erythrobupropion AUC (16%) and C_{max} (32%).

Levodopa and Amantadine:
Limited clinical data suggest a higher incidence of neuropsychiatric adverse experiences, such as confusion, agitation and delirium, in patients receiving bupropion, concurrently with either levodopa or amantadine. Tremor, ataxia and dizziness were also reported. Administration of Dom-BUPROPION SR to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Clopidogrel and Ticlopidine:
Both clopidogrel and ticlopidine have been shown to significantly inhibit CYP2B6-catalysed bupropion hydroxylation. The mean area under the plasma concentration-time curve (AUC) of hydroxybupropion was reduced by 52% by clopidogrel and by 84% by ticlopidine. The AUC

of bupropion was increased by 60% with clopidogrel and by 85% with ticlopidine. Therefore, concomitant administration of bupropion and either clopidogrel or ticlopidine may result in increased plasma concentrations of bupropion and reduced concentrations of hydroxybupropion. This may affect the efficacy of bupropion and may also increase the risk of concentration-dependent adverse events of bupropion, such as seizures (see WARNINGS AND PRECAUTIONS, Seizures). Patients receiving drugs used to reduce blood clots (such as either clopidogrel and/or ticlopidine) are likely to require dose adjustments of bupropion.

Use of Bupropion Hydrochloride Sustained Release with Drugs that Predispose Patients to Seizures:
Concurrent administration of bupropion hydrochloride sustained release tablets with agents that lower seizure threshold (e.g., antipsychotics, other antidepressants, theophylline, lithium, systemic steroids etc) should be undertaken only with extreme caution (see WARNINGS AND PRECAUTIONS). Low initial dosing and gradual dose increases should be employed.

Other Drugs with CNS Activity:
The risk of using bupropion hydrochloride sustained release in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Dom-BUPROPION SR and such drugs is required.

Transdermal Nicotine Interaction:
(see WARNINGS AND PRECAUTIONS, Cardiovascular Effects)

Alcohol Interactions:
In post-marketing experience, there have been reports of adverse neuropsychiatric events, or reduced alcohol tolerance, in patients who were drinking alcohol during treatment with bupropion. Rarely, reports of fatal outcomes with this combination have been received; however, a causal relationship has not been established. The consumption of alcohol during treatment with bupropion should be avoided (also see WARNINGS AND PRECAUTIONS, Predisposing Risk Factor for Seizures).

DOSAGE AND ADMINISTRATION

Dom-BUPROPION SR (bupropion hydrochloride) is not indicated for use in children under 18 years of age (See WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

Recommended Dose and Dosage Adjustment:
The usual recommended dose of Dom-BUPROPION SR (bupropion hydrochloride sustained release tablets) is 100 mg to 150 mg/day given once daily. As with all antidepressants, the full antidepressant effect of Dom-BUPROPION SR may not be evident until several weeks of treatment. In patients who are not responding to a dose of 150 mg/day, the dose may be increased up to a maximum of 300 mg/day. Dose increases should occur at intervals of at least one week. **In order to minimize the risk of seizures (see WARNINGS), single doses of Dom-BUPROPION SR must not exceed 150 mg**. Doses of Dom-BUPROPION SR greater

than 150 mg/day should be administered b.i.d. preferably with at least 8 hours between successive doses.

Missed Dose:
Dom-BUPROPION SR should be taken at the same time each day and no more than the recommended dose should be taken each day. If the normal administration time has been missed, the dose should be skipped and administration resumed at the normal administration time of the following day.

Administration:
Patients should be advised to swallow Dom-BUPROPION SR Tablets whole with fluids, and NOT to chew, divide, crush or otherwise tamper with the tablets in any way that might affect the release rate of bupropion.

Treatment of Pregnant Women During the Third Trimester:
Post-marketing reports indicate that some neonates exposed to bupropion hydrochloride sustained release, SSRIs, or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with Dom-BUPROPION SR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Dom-BUPROPION SR in the third trimester.

Geriatrics or Debilitated Patients:
No pharmacokinetic or therapeutic trials have been conducted to systematically investigate dose requirements in patients who are elderly or debilitated (see WARNINGS and PRECAUTIONS). As such patients may have reduced clearance of bupropion and its metabolites, and/or increased sensitivity to the side-effects of CNS active drugs, treatment with Dom-BUPROPION SR should be initiated at the lowest recommended dose (100 mg/day).

Hepatic Impairment:
Mild and Moderate Hepatic Impairment: Given the variable pharmacokinetics of bupropion in patients with either mild or moderate hepatic impairment (Child-Pugh Grade A or B), treatment with Dom-BUPROPION SR should be initiated at the lowest recommended dose. Maintenance dose may be adjusted according to clinical response and tolerance. Caution should be exercised as there is no clinical experience with bupropion hydrochloride sustained release in hepatically impaired patients (see also WARNINGS AND PRECAUTIONS).

Severe Impairment: Given the risks associated with both peak bupropion levels and drug accumulation, Dom-BUPROPION SR is not recommended for use in patients with severe hepatic impairment. However, should clinical judgement deem it necessary, the drug should be used only with extreme caution (see also WARNINGS AND PRECAUTIONS). The dose should not exceed 150 mg every day or every other day in these patients. Any theoretical dose reduction for this patient population based on the findings of the pharmacokinetic studies may result in toxic drug levels in these patients (see ACTIONS AND CLINICAL PHARMACOLOGY; WARNINGS AND PRECAUTIONS).

Renal Impairment:
Dom-BUPROPION SR should be used with caution in patients with renal impairment due to the potential for drug accumulation, and a reduced frequency and/or dose should be considered (see ACTIONS, and CLINICAL PHARMACOLOGY, and WARNINGS and PRECAUTIONS).

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

Pediatrics:
Dom-BUPROPION SR is not indicated for use in children under 18 years of age (see INDICATION and WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

OVERDOSAGE

Human Overdose Experience:
In addition to those events reported under *Adverse Reactions*, overdose has resulted in symptoms including drowsiness, loss of consciousness, status epilepticus, and ECG changes such as conduction disturbances (including QRS prolongation) or arrythmias; cases of fatal outcome have been reported. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate. Three overdoses with bupropion sustained release (bupropion hydrochloride) occurred during clinical trials. One patient ingested 3000 mg of bupropion sustained release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of bupropion sustained release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3,600 mg of bupropion sustained release tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess". None of the patients experienced further sequelae.

The information included in the remainder of this section is based on the clinical experience with overdosage of the immediate release formulation of bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of immediate-release bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate release formulation of bupropion have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of the immediate release formulation alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when immediate release bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of immediate-release bupropion alone have been reported rarely in patients ingesting massive doses of immediate-release bupropion tablets. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Management of Overdose:

In the event of overdose, hospitalization is advised. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm (ECG) and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.

Due to the dose-related risk of seizures with bupropion hydrochloride sustained release, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Compendium of Pharmaceuticals and Specialties* (CPS).

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Dom-BUPROPION SR (bupropion hydrochloride) is an antidepressant of the aminoketone class. It is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitors or other known antidepressant agents. Its structure closely resembles that of diethylpropion. It is related to the phenylethylamines.

Mechanism of Action

The mechanism of bupropion's antidepressant activity is unknown but appears to be mediated by noradrenergic (and possibly dopaminergic), rather than serotonergic mechanisms. Preclinical studies have shown that bupropion blocks norepinephrine (NE) reuptake and dopamine (DA) reuptake. Its major metabolite (hydroxybupropion), which in man is present at blood levels 10-20-fold higher than bupropion, blocks only NE reuptake.

The non-serotonergic mechanism of action of bupropion likely contributes to a distinct side effect profile that includes low rates of sexual dysfunction and somnolence.

Pharmacodynamics

In vitro, bupropion and its major metabolites had essentially no affinity for β-adrenergic, dopaminergic, GABA, benzodiazepine, 5HT1A, glycine and adenosine receptors, and only weakly inhibited α-adrenergic receptors in rat brain, α2-adrenergic, 5HT2, and muscarinic cholinergic receptors. High concentrations of bupropion and its major metabolites did not inhibit MAO-A or MAO-B activity. Bupropion and its major metabolites had no significant affinity for the 5HT transport system.

Pharmacokinetics

Absorption:

Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of bupropion hydrochloride sustained release tablets in humans has not been determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%. Following oral administration of bupropion hydrochloride sustained release tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. In two single-dose (150 mg) studies the mean peak concentration (C_{max}) values were 91 and 143 ng/mL. At steady state, the mean C_{max} following a 150 mg dose every 12 hours was 136 ng/mL.

Three studies in healthy volunteers suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food. When taken following food, peak plasma concentration of bupropion (C_{max}) increased by 11%, 16% and 35% in three studies. The overall exposure to bupropion (AUC) increased by 17%, 17% and 19% in these three studies.

Distribution:

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200mcg/mL. The extent of protein binding of hydroxybupropion is similar to that of bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion. The volume of distribution (V_{ss}/F) estimated from a single 150 mg dose given to 17 subjects is 1,950 L (20% CV).

Metabolism:

Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the *tert*-butyl group of bupropion and/or reduction of the carbonyl group. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. In preclinical tests used to predict antidepressant activity, it has been observed that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one half to one tenth as potent. This may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion.

In vitro results indicate that biotransformation of bupropion to hydroxybupropion is catalyzed primarily by CYP2B6, and to a much lesser extent by CYP1A2, 2A6, 2C9, 2E1 and 3A4 isozymes. Detectable levels of hydroxybupropion are not observed with CYP1A1 and CYP2D6 isozymes. Cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Following a single 150 mg dose of bupropion in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The AUC of hydroxybupropion at steady state is about 17 fold higher than that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of hydroxybupropion, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the CYP2B6 isoenzyme. Although bupropion is not metabolized by CYP2D6, there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see WARNINGS AND PRECAUTIONS: Drug Interactions).

Excretion:
In two single-dose (150 mg) studies the mean (±% CV) apparent clearance (Cl/F) of bupropion was 135 (±20%) and 209 L/hr (±21%). Following chronic dosing of 150 mg of bupropion hydrochloride sustained release tablets every 12 hours for 14 days (n = 34), the mean Cl/F at steady state was 160 L/hr (±23%). The mean elimination half-life of bupropion (estimated from a series of studies) is approximately 21 hours. Estimates of the half-lives of the metabolites determined from a multiple-dose study were 20 hours (25%) for hydroxybupropion, 37 hours (35%) for threohydrobupropion, and 33 hours (30%) for erythrohydrobupropion. Steady-state plasma concentrations of bupropion and metabolites are reached within 5 and 8 days, respectively. 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 feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg/day.

Special Populations and Conditions
Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Pediatrics:
The pharmacokinetics of bupropion hydrochloride sustained release in individuals under 18 years old has not been evaluated.

Geriatrics:
The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times a day schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration: however, another single and multiple dose pharmacokinetic study, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see WARNINGS AND PRECAUTIONS, see DOSAGE AND ADMINISTRATION).

Race:
The influence of race (Asian, Black and Caucasian) on the pharmacokinetics of bupropion (bupropion hydrochloride immediate release tablets) was evaluated based on dose normalized data pooled from five healthy volunteer studies. A comparison of pharmacokinetic parameter values did not detect any important differences in race with respect to AUC (p=0.5564) and C_{max} (p=0.8184).

Hepatic Insufficiency:
The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in two single-dose studies, one in subjects with alcoholic liver disease and one in subjects with mild to severe liver cirrhosis.

The first study involved 8 subjects with alcoholic liver disease, and 8 healthy matched controls. While mean AUC values were not significantly different, individual AUC values for both the parent drug bupropion and the primary metabolite hydroxybupropion were more variable in subjects with alcoholic liver disease, and increased by approximately 50% over those of healthy volunteers. The mean half-life of the primary metabolite hydroxybupropion was significantly longer by approximately 40% in subjects with alcoholic liver disease than in healthy volunteers (32±14 hours versus 21±5 hours, respectively). For all other pharmacokinetic values, for both parent drug and metabolites, there were minimal differences between the two groups.

The second study involved 17 subjects with hepatic impairment (n = 9 mild/Grade A child-Pugh rating; n = 8 severe/Grade C Child-Pugh rating) and 8 healthy matched controls. In the severe group, the mean value for bupropion AUC was increased threefold over control values, with mean clearance decreased proportionately. Mean C_{max} and plasma half-life were increased by approximately 70% and 40% respectively. For the primary metabolites, mean AUC was increased by approximately 30% - 50%, with mean clearance decreased proportionately. Mean C_{max} was lower by approximately 30% to 70%, and mean plasma half life increased threefold.

In the mild group, while mean values were not statistically increased from those of controls, the variability in the pharmacokinetic values was higher in the subjects with impairment; a sub-group of 1 to 3 subjects (dependent on pharmacokinetic parameter examined) showed

individual values which were in the range of the severely impaired subjects. For the primary metabolites, the differences between groups in pharmacokinetic parameters were minimal.

In patients with hepatic impairment, treatment should be initiated at reduced dosage (see WARNINGS AND PRECAUTIONS, see DOSAGE AND ADMINISTRATION).

Effect of Smoking:
In a single dose study, there were no significant differences in the pharmacokinetics of bupropion or its major metabolites in smokers compared with non-smokers.

STORAGE AND STABILITY

Store between 15°C and 30 °C in a dry place, away from direct sunlight. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dom-BUPROPION SR (bupropion hydrochloride sustained release tablets) sustained release tablets:

100 mg: Each blue, round, biconvex, film-coated tablet, debossed with “BP" over “100" on one side and nothing on the other side contains the labelled amount of bupropion hydrochloride and the following inactive ingredients: carboxyvinyl polymer, colloidal silicon dioxide, FD&C Blue # 1, hypromellose, iron oxide black, glyceryl behenate, lactose anhydrous, magnesium stearate, polyethylene glycol, polyethylene oxide and titanium dioxide. Supplied in bottles of 60 tablets.

150 mg: Each purple, round, biconvex, film-coated, debossed tablets with “BP” over “150” on one side and nothing on the other side contains the labelled amount of bupropion hydrochloride and the following inactive ingredients: carboxyvinyl polymer, colloidal silicon dioxide, glyceryl behenate, lactose anhydrous, magnesium stearate, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, talc and titanium dioxide. In addition, the 150 mg tablet contains also FD&C Red # 40 and FD&C Blue # 2. Supplied bottles of 60 and 100 tablets.

PART II: SCIENTIFIC INFORMATION

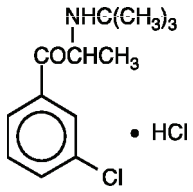
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Bupropion hydrochloride

Chemical Name: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride

Structural Formula:



Molecular Formula: $C_{13}H_{18}ClNO \cdot HCl$

Molecular Weight: 276.24 g/mol

Description: Bupropion hydrochloride is a white powder with slight characteristic odour and has a maximum solubility in water of 312 mg/mL @ 25ºC.

CLINICAL TRIALS

Bioavailability:

A single-dose, crossover comparative bioavailability study was performed under fasting conditions, on two bupropion sustained release tablet formulations using Dom-BUPROPION SR 150 mg SR tablets, by Dominion Pharmacal and WELLBUTRIN® 150 mg SR tablets, by GlaxoSmithKline Inc., in twenty-three (23) healthy male volunteers.

The results presented herein show that the criteria used to estimate bioequivalence between the two formulations were fulfilled. The relative geometric mean of the test to the reference formulation for C_{max} was within 80% and 125% for both the measured and the potency-corrected data. Furthermore, the 60% confidence interval of the relative geometric mean of the test to the reference formulation for the AUC_T was within the acceptance range of 80%-125% for both the measured and potency corrected data. The test formulation is judged to be equivalent under fasting conditions to the reference formulation on the basis of C_{max} and AUC_T parameters.

Bupropion (1 x 150 mg SR tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval 90%
AUC_T (ng·h/mL)	715.55 743.71 (31.0)	716.58 742.63 (27.9)	99.86	95.01 – 104.95
AUC_I (ng·h/mL)	768.32 797.84 (30.8)	773.14 801.72 (28.1)	99.38	94.79 – 104.19
C_{max} (ng/mL)	82.27 84.40 (22.9)	86.48 89.79 (30.0)	95.13	87.70 – 103.19
T_{max} § (h)	4.50 (2.00 – 6.00)	3.00 (2.50 – 5.00)		
$T_{½}$ € (h)	13.51 (37.9)	14.50 (33.2)		

*Dom-BUPROPION SR, 150 mg sustained release tablets, Dominion Pharmacal
†Wellbutrin® SR, 150 mg, sustained release tablets manufactured by GlaxoSmithKline Inc. and purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

A single dose crossover comparative bioavailability study was performed under fed conditions, on two bupropion sustained release tablet formulations using Dom-BUPROPION

SR 150 mg SR tablets, by Dominion Pharmacal and WELLBUTRIN® 150 mg SR tablets, by GlaxoSmithKline Inc., in twenty-three (23) healthy male volunteers.

The results presented herein show that the criteria used to estimate bioequivalence between the two formulations were all fulfilled. The relative geometric mean of the test to the reference formulation for C_{max} was within 80% and 125% for both the measured and the potency corrected data. Furthermore, the 90% confidence interval of the relative geometric mean of the test to the reference formulation for the AUC_T was within the acceptance range of 80% - 125% for both the measured and the potency-corrected data.

Therefore the test formulation is judged to be equivalent to the reference formulation on the basis of C_{max} and AUC_T parameters.

Bupropion (mg1 x 150 mg SR tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval 90%
AUC_T (ng·h/mL)	1057.57 1102.56 (27.8)	1037.04 1088.44 (29.4)	101.98	94.92 – 109.56
AUC_I (ng·h/mL)	1145.23 1197.3 (28.8)	1114.94 1169.59 (29)	102.72	95.71 – 110.24
C_{max} (ng/mL)	175.21 183.66 (28.3)	146.06 153.39 (30.9)	119.96	109.37 – 131.57
T_{max}§ (h)	3.50 (2.00 – 6.00)	3.50 (2.00 – 6.00)		
$T_{½}$€ (h)	15.68 (31.9)	14.34 (36.2)		

* Dom-BUPROPION SR, 150 mg sustained release tablets, Dominion Pharmacal
†Wellbutrin® SR, 150 mg, sustained release tablets manufactured by GlaxoSmithKline Inc. and purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Study Demographics and Trial Design

The effectiveness of bupropion hydrochloride sustained release in the treatment of moderate depression has been systematically evaluated at doses ranging from 50-400 mg/day in three multicentre, randomized, placebo-controlled, double-blind, parallel-group studies involving a total of 1420 patients of whom 1021 received active doses of the bupropion hydrochloride

sustained release and 399 received placebo. Each study included a one week placebo lead-in phase to identify and exclude placebo responders, followed by an 8 week treatment phase.

The response to treatment was evaluated at regular intervals using the Hamilton Rating Scale for Depression (HAMD), Clinical Global Impressions Scales of Severity (CGI-S) and Improvement (CGI-I) Scale. Both the observed and the last observation carried forward (LOCF) values were analyzed.

In one study comparing fixed daily doses of either 150 mg once daily (n=121) or 300 mg as 150 mg twice daily (n=120) bupropion hydrochloride sustained release to placebo (n=121), the HAMD, CGI-S (change form baseline) and CGI-I scores for both bupropion hydrochloride sustained release groups at endpoint were statistically significantly superior to placebo. Both active treatment groups showed a similar magnitude of improvement during the trial.

In a second study patients received fixed daily doses of either 100 mg, 200 mg, 300 mg or 400 mg/day (given on a twice daily schedule) bupropion hydrochloride sustained release or placebo. The magnitude of the mean change scores were consistently greater for all active groups than placebo by day 21. At endpoint, scores in the 100 mg group were statistically significantly superior to placebo on all rating scales, while the higher dose groups followed a similar pattern but did not achieve statistical significance.

A third study compared two flexible doses; 50-150 mg/day (given once daily), and 100-300 mg/day (twice daily schedule) to placebo (n = approximately 150 patients per group). Patients began at the lowest dose in the range and were titrated to the highest tolerated dose in the range over a period of 7 days. Investigators had the option to titrate down when a higher dose was not well tolerated. The mean daily dose calculated from day 8 onwards was 144 mg in the 50-150 mg arm and 276 mg in the 100-300 mg arm, indicating that the vast majority of patients remained on the highest allowable dose in their respective groups for the duration of the study. Efficacy measures at endpoint for the 50-150 mg/day group were statistically significantly superior to placebo. The higher dose group followed a similar pattern but did not achieve statistical significance at endpoint. A combined endpoint analysis of all patients treated with bupropion hydrochloride sustained release in the trial, demonstrated statistically significant superiority on all efficacy measures compared to placebo.

In summary, patients receiving bupropion hydrochloride sustained release at doses of 100 mg to 150 mg/day in single or divided doses experienced improvement relative to placebo on the major indices of depression. Clinical response did not improve with increasing dose, indicating a flat dose-response relationship in the range of doses studied.

DETAILED PHARMACOLOGY

Pharmacology

Bupropion is a novel, atypical antidepressant with mild CNS activating properties. Recent data suggest that a significant contribution to the pharmacology of bupropion is made by one of its two major metabolites, hydroxybupropion. Both bupropion and hydroxybupropion are

effective in animal models used to predict antidepressant activity in man. Their antidepressant activity appears to be noradrenergically mediated and based on their ability to block norepinephrine (NE) uptake.

As with other antidepressants, bupropion and hydroxybupropion reduce firing rates of NE neurons in the locus coeruleus. This effect is dependent on presynaptic stores of NE and can be blocked by α-adrenergic antagonists. The mild stimulating properties of bupropion appear to be due to its weak inhibition of dopamine (DA) uptake. This effect occurs at doses higher than those needed for antidepressant activity. The drug has no pharmacologically relevant effects on serotonin (5-HT).

Bupropion and its metabolites weakly but selectively inhibited DA uptake into synaptosomes obtained from rat and mouse striatum at concentrations much higher than are achieved in the plasma of patients receiving 450 mg of bupropion. Bupropion and hydroxybupropion had comparable potencies as inhibitors of [^{3}H]-l-NE uptake into synaptosomes obtained from either mouse or rat hypothalamus. The *threo*-aminoalcohol metabolite was 2- to 3-fold weaker (IC_{50} = 10-16 μM). The plasma level of hydroxybupropion achieved in patients is sufficiently high to solely account for the inhibition of NE uptake.

In vitro, bupropion and its metabolites had essentially no affinity for b-adrenergic, DA, GABA, benzodiazepine, 5-HT_{1A}, glycine and adenosine receptors and only weakly inhibited α -adrenergic receptors in rat brain, α_2-adrenergic, 5-HT_2, and muscarinic cholinergic receptors.

Pharmacodynamics:

Large i.v. doses of bupropion had no sustained adverse effects on the cardiovascular system of dogs (13-50 mg/kg cumulative) and cats (18.5 mg/kg). Transient (<10 min) significant, dose-dependent decreases in mean arterial pressure and cardiac output with variable effects on heart rate were observed following bolus IV injections; the effects were much greater following bolus administration than following equivalent infused doses. The effects were most likely related to the transient high plasma levels (approx 10 fold higher than both therapeutic plasma levels in man and plasma levels associated with the mouse antidepressant ED_{50}) and the local anesthetic-like activity. At all dose levels studied, effects on the ECG were entirely related to heart rate; there were no changes in the PR, QRS or QTC intervals. No arrhythmias were observed.

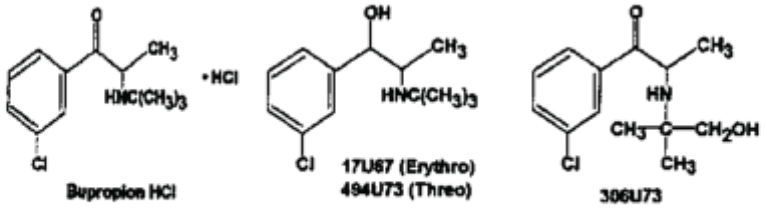
Oral administration of high doses did not produce deleterious cardiovascular effects in conscious dogs (25 mg/kg) and normotensive rats (25-50 mg/kg). Weak, transient dose-dependent effects on the pressor responses to exogenous NE and tyramine were seen in anaesthetized dogs; bupropion was approximately 10-fold weaker than imipramine in this regard. The compound essentially lacked sympathomimetic actions in dogs and cats.

Pharmacokinetics:

Preclinical metabolism and disposition studies involving bupropion were conducted in mice, rats, rabbits, and dog. More recent toxicokinetic studies comparing sustained release formulation materials to the immediate release ingredients were done in rats.

Qualitatively, animals (mouse, rat, rabbit, dog) produce the same metabolites present in man (see structures below), but quantitatively, there are distinct differences with the mouse being most similar to humans. In animal models, pharmacologic activity (relative to bupropion) of the basic metabolites were 57% for hydroxybupropion (306U73) and 21 % for the isomeric metabolites, erythrohydrobupropion (484U73) and threohydrobupropion (17U67). The acidic metabolites, *m*-chlorobenzoic and *m*-chlorohippuric acids possess no relevant pharmacologic activity. In man, at therapeutic doses, steady state levels of the major metabolite, hydroxybupropion, are 10 to 20-fold greater (AUC and C_{max}) than bupropion levels. Ratios of similar magnitude can occur in animals upon repeated dosing, but as a result of the induction of bupropion metabolism causing a great reduction in parent drug concentrations rather than increased metabolite levels. Such induction has not been observed in man. Bupropion and its metabolites have half-lives in man of 20-40 hr., while 1-2 hr. is typical of half-lives in animals. The isomeric metabolites erythrohydrobupropion and threohydrobupropion can be observed in these animal species, but attain plasma concentrations much lower than bupropion or hydroxybupropion. In man, the isomers are of intermediate presence, lower than hydroxybupropion, but similar to or higher than bupropion. It is apparent that no common laboratory animal species has reflected the disposition of bupropion in man.

Structures:



In vitro metabolism of bupropion was determined in human microsomal preparations and in cDNA-expressed human cytochrome P450 isozymes. The samples were assayed for parent drug and metabolites by HPLC and LC-MS. Bupropion was mainly metabolized to hydroxybupropion and the threo-amino alcohol metabolite in human microsomal preparations. Meta-chlorobenzoic acid was also formed but in relative minor amounts. The erythro-amino alcohol metabolite of bupropion was not detected.

In the studies using cDNA-expressed systems, hydroxybupropion was produced primarily by the CYP2B6 isozyme, although CYP1A2, 2A6, 2C9, 2E1, and 3A4 isozymes also metabolized bupropion at much slower rates. In human liver microsomes, the metabolism of bupropion to hydroxybupropion was significantly (72%) inhibited by orphenadrine, a CYP2B6 inhibitor. Much lower inhibition (23-39%) was observed with other selective inhibitors of CYP1A2, 2A6, 2C9, 2E1, and 3A4 isozymes. CYP1A1 and CYP2D6 (see PRECAUTIONS, Drugs Metabolized by CYP2D6) isozymes were not involved in the metabolism of bupropion.

The metabolism of bupropion to threohydrobupropion was not inhibited significantly by any cytochrome P450 inhibitors, but was strongly inhibited (> 85%) by the carbonyl reductase inhibitor, menadione. In summary, bupropion was metabolized to hydroxybupropion primarily by the CYP2B6 and appeared to be metabolized to threohydrobupropion by the carbonyl reductase. The pharmacokinetics of bupropion in humans is described further under ACTIONS AND CLINICAL PHARMACOLOGY.

Dom-BUPROPION SR (bupropion hydrochloride sustained release) is a sustained release tablet formulation of bupropion. In a study comparing chronic dosing with bupropion sustained release tablets 150 mg b.i.d. to the immediate release formulation of bupropion at 100 mg t.i.d., peak plasma concentrations of bupropion at steady state for bupropion sustained release tablets were approximately 85% of those achieved with the immediate release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all three of the detectable bupropion metabolites. Thus, at steady state, bupropion sustained release tablets and the immediate release formulation of bupropion are essentially bioequivalent for both bupropion and the three quantitatively important metabolites.

TOXICOLOGY

Three acute toxicity studies (LD_{50}) were carried out in mice and rats at doses ranging from 175 to 700 mg/kg. The LD_{50} ranged from 263 mg/kg in male Long-Evans rats to 636 mg/kg in female CD-1 mice. Clinical signs included convulsions, ataxia, loss of righting reflex, laboured breathing, prostration, salivation and ptosis.

Five repeated dose toxicity studies have been performed in the rat. In a 14-day oral toxicity study in rats, a reversible dose-related increase in absolute and relative liver weights (approximately 5-30%) was noted in males and females in all treated groups at termination of dosing. The doses used in this study were 0, 100, 200 and 300 mg/kg/day. These liver weight increases were related to microsomal enzyme production. No other treatment related changes were found. In a 90-day study, dose-related irritability and urinary incontinence was observed. A dose related increase in liver weight was noted. The dosage used was up to 450 mg/kg/day.

In a 55-week study in rats, a dose-related increase in the frequency of yellow staining of the fur around the anogenital region was observed. Other findings were dry brown material around the nose or mouth and moisture around the mouth, especially soon after dosing. No compound related effects on body weight, food consumption, haematology, biochemistry or urinalysis was observed. No compound related gross pathological findings were noted. Statistically significant increases in group mean liver and kidney weights across all treated groups and a slight increase in iron positive pigment in the spleens of males at 100 mg/kg/day were noted.

In repeat dose studies in dogs of up to fifty weeks, increased salivation, emesis and dry nose and/ or mouth were noted occasionally. Generally body trembling and weakness were also seen at 150 mg/kg/day. Dose related frequency of occurrence of slight to moderate decrease in

haemoglobin, haematocrit and total erythrocytes was noted at most intervals of analysis. Slight to moderate increase in SGPT and SGOT, alkaline phophatase and BSP retention was noted in some dogs.

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

Increase in liver weights with associated hypertrophy in rats and dogs are commonly observed in lifetime bioassays with high doses of drugs which are inducers of microsomal enzymes. Such enzyme induction has been noted in animals but not in humans receiving bupropion. Moreover, available human data do not indicate liver toxicity associated with bupropion immediate release or sustained release.

Carcinogenesis and Mutagenesis

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day bupropion, respectively. These doses are approximately ten and two times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. 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.

Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in two of five strains in Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenetic studies. The relevance of these results in estimating the risk to human exposure to therapeutic doses is unknown.

Reproduction and Teratology

A two generation reproductive and fertility study in Long Evans rats receiving 100, 200, 300 mg/kg bupropion daily by gavage revealed no treatment or compound related effects observed on mating or fertility performance. No compound related effects were observed in reproductive ability, fertility, gross anatomic abnormalities, foetal deaths or pup survival and growth during lactation. In F_1 generation females no compound related effects were observed on lactation, body weight at sacrifice, reproduction performance and post mortem findings. Similarly, no compound related findings were observed in the clinical condition, reproductive performance or necropsy of the F_1 males. In the F_2 generation, no compound related effects were observed on the male:female ratio of pups, survival or bodyweight. No compound related effects were observed on necropsy.

Teratology studies have been performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), and have revealed no evidence of harm to the fetus due to bupropion.

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PART III: CONSUMER INFORMATION

[Pr]Dom-BUPROPION SR
Bupropion Hydrochloride Sustained Release Tablets
100 mg and 150 mg

Dom-BUPROPION SR is a **Twice Daily** medication and should not be confused with other bupropion formulations.

This leaflet is PART III of a three-part "Product Monograph" published when Dom-BUPROPION SR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dom-BUPROPION SR. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medication, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
Dom-BUPROPION SR has been prescribed to you by your doctor to relieve your symptoms of:

- Depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)

What it does:
Dom-BUPROPION SR is one of a group of drugs called antidepressants. Dom-BUPROPION SR is thought to block reuptake of chemicals in the brain called *noradrenaline* and *dopamine*, which are linked with depression.

When it should not be used?
Do not take Dom-BUPROPION SR if you:

- know that you are allergic to bupropion, the medical ingredient, or any of the other ingredients in Dom-BUPROPION SR tablets.
- are taking any other medicines which contain bupropion, such as bupropion sustained release, bupropion extended release or bupropion immediate release.
- have been diagnosed with epilepsy or have a history of seizures.
- have or have had an eating disorder, for example binge eating (bulimia) or anorexia.
- are usually a heavy drinker who has just stopped or are about to stop drinking
- are taking monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide).
- are taking the antipsychotic thioridazine
- have liver or kidney problems
- are pregnant or trying to become pregnant, or if you think that you might be pregnant
- are breast feeding.

What the medicinal ingredient is:
Bupropion hydrochloride

What the non-medicinal ingredients are:
100 mg: carboxyvinyl polymer, colloidal silicon dioxide, FD&C Blue # 1, hypromellose, iron oxide black, glyceryl behenate, lactose anhydrous, magnesium stearate, polyethylene glycol, polyethylene oxide and titanium dioxide.

150 mg: carboxyvinyl polymer, colloidal silicon dioxide, glyceryl behenate, lactose anhydrous, polyethylene glycol, magnesium stearate, polyethylene oxide, polyvinyl alcohol, talc and titanium dioxide. In addition, the 150 mg tablet contains also FD&C Red # 40 and FD&C Blue # 2

What dosage forms it comes in:
Tablets: 100 mg and 150 mg

WARNINGS AND PRECAUTIONS

Dom-BUPROPION SR is a **Twice Daily** medication and should not be confused with other bupropion formulations.

During treatment with these types of medication it is important that you and your doctor have good ongoing communication about how you are feeling.

Dom-BUPROPION SR is not for use in Children under 18 years of age**.**

New or Worsened Emotional or Behavioural Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately.

Close observation by a doctor is necessary in this situation. Do not discontinue your medication on your own.

Important Warning about the Risk of Seizures:

- At the maximum recommended dose of 300 mg per day, approximately 1 in every 1000 people taking the maximum dose of Dom-BUPROPION SR is at risk of a fit (a seizure or convulsion).

BEFORE you use Dom-BUPROPION SR tell your doctor or pharmacist if you:

- have ever had any fits or seizures in the past.
- take other medications that may increase your chance of a seizure, including drugs for depression and some antibiotics.
- are taking any prescription or over-the-counter medications, or are planning on taking any prescription or over-the-counter medications during your therapy.
- have, or have had an eating disorder, for example binge eating (bulimia) or anorexia nervosa.
- have liver problems.
- have kidney problems.
- take more than the recommended amount of bupropion sustained release tablets. Dom-BUPROPION SR tablets should NOT be used if you are taking the smoking cessation aid ZYBAN or any other medications containing bupropion hydrochloride.
- have diabetes which is treated with insulin or other medications.
- have used over-the-counter diet aids
- have had a serious head injury
- drink alcohol. It is best not to drink alcohol at all or to drink very little while taking Dom-BUPROPION SR. If you drink a lot of alcohol and suddenly stop, you may increase your chance of having a seizure. Be sure to discuss your use of alcohol with your doctor before you begin taking Dom-BUPROPION SR.
- are pregnant, or thinking about becoming pregnant, or are breastfeeding.

Driving vehicles or using machinery:
Dom-BUPROPION SR may impair your ability to perform tasks requiring judgement or motor and cognitive skills.

Until you are reasonably certain that Dom-BUPROPION SR does not adversely affect your performance you should refrain from driving an automobile or operating hazardous machinery.

Effects on Pregnancy and Newborns
Post-marketing reports indicate that some newborns whose mother took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressant, such as bupropion sustained release, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying.

In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer anti-depressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting with your doctor.

INTERACTIONS WITH THIS MEDICATION

If you are taking or have recently been taking other medicines for depression called monoamine oxidase inhibitors (MAOIs) tell your doctor before taking Dom-BUPROPION SR.

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural herbal) especially:

- other antidepressants such as citalopram, paroxetine, venlafaxine
- the antipsychotic thioridazine
- other medications for mental illness such as haloperidol and risperidone.
- medicines for Parkinson's Disease such as levodopa, amantadine or orphenadrine.
- medicines used for epilepsy (such as carbamazepine, phenytoin, or phenobarbitone).
- cyclophosphamide or ifosfamide, drugs mainly used to treat cancer.
- drugs called beta blockers to treat heart conditions.
- medicines to regulate heart rhythm.
- medicines used to reduce blood clots (such as ticlopidine or clopidogrel).
- nicotine patches to help you stop smoking.
- In general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking Dom-BUPROPION SR.

PROPER USE OF THIS MEDICATION

Usual dose:
How to take Dom-BUPROPION SR

- The usual adult starting dose for sustained release bupropion is one 100 mg or 150 mg tablet once daily. Patients may have a dosage increase after one week to 300 mg daily. In order to minimize the risk of seizures (see WARNINGS) single doses of sustained release bupropion must not exceed 150 mg. Doses of sustained release bupropion greater than 150 mg/day should be administered b.i.d preferably with at least 8 hours between successive doses.
- Take your Dom-BUPROPION SR tablet at the same time each day. If you have any problems with your dosing routine, contact your doctor or pharmacist.
- Swallow your Dom-BUPROPION SR tablet whole, with fluids. Do not divide, chew or crush tablets.
- Take only the recommended dose prescribed by your doctor. Never increase the dose of Dom-BUPROPION SR you or those in your care are taking, unless your doctor tells you to.
- The effects of your medication may not be noticeable in the first few days of treatment, and significant improvement may take several weeks. If you are concerned that your medicine is not working, discuss this with your doctor.
- You should talk to your doctor before you stop taking your medication on your own.

Remember: This medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

Missed Dose:
Dom-BUPROPION SR should be taken at the same time each day and no more than the recommended dose should be taken each day. If your normal administration time has been missed, the dose should be skipped and administration resumed at the normal administration time of the following day**.**

Overdose
If you take too many tablets, you may increase the risk of a fit, or seizure(s), or other serious effects, including irregular heartbeat, which may be life threatening..

For management of a suspected drug overdose, contact your health care practitioner, hospital emergency department, or regional Poison Control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, Dom-BUPROPION SR can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

The most common side effects of Dom-BUPROPION SR are:
- headache
- dry mouth
- nausea
- constipation
- insomnia
- dizziness
- shakiness
- ringing in the ears

Uncommon side effects
These could affect less than one in every 100 people:
- Increased appetite
- Weight increase
- Bloating
- Migraine

New or Worsened Emotional or Behavioural Problems
A small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility or anxiety, or thoughts about suicide. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. See also the WARNINGS AND PRECAUTIONS section.

Effects on Newborns
Some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer antidepressant during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

Serious Side Effects

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN, AND WHAT TO DO ABOUT THEM				
Symptom/ effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Seizures [loss of consciousness with uncontrollable shaking ("fit"/ "convulsion")]			✓*
Very Rare	Severe allergic reactions [red and lumpy or blistering skin rash, swelling of the face or throat, trouble breathing, collapse, blackout, severe muscle or joint pains]			✓*
	Liver disorders, including hepatitis and jaundice [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		✓*	
	Poor blood glucose control	✓		
	Inability to urinate		✓	
	Hallucinations, delusions, paranoid ideation [sensing or believing things that are not there]		✓	
	Aggression		✓*	
See Warnings and Precautions	New or worsened emotional or behavioural problems		✓*	
	Rises in blood pressure	✓		

* If you think you have these side effects, it is important that you seek medical advice from your doctor straight away.

Approximately 1 in every 1000 people taking the maximum dose of Dom-BUPROPRION SR is at risk of a fit (a seizure or convulsion). The chance of a seizure happening is higher if you take too much, if you take certain medicines at the same time, if you drink alcohol, or if you are at higher than usual risk of seizures.

This is not a complete list of side effects. For any unexpected effects while taking Dom-BUPROPION SR contact your doctor or pharmacist.

HOW TO STORE IT

- Keep all medication out of the reach of children.
- Store between 15°C and 30 °C in a dry place away from direct sunlight. Protect from moisture.
- Keep container tightly closed.
- If your doctor tells you to stop talking Dom-BUPROPION SR please return any left over medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Dominion Pharmacal, at 1-888-550-6060.

This leaflet was prepared by
Dominion Pharmacal
Montreal Quebec
H4P 2T4

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