For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

DEXBUTRIN

1. Generic Name

Dextromethorphan Hydrobromide & Bupropion Hydrochloride Extended Release Tablets (45 mg+ 105 mg)

2. Qualitative and quantitative Composition:

Each film coated bilayer tablet contains

Dextromethorphan Hydrobromide I.P…….45 mg

Bupropion Hydrochloride I.P……..105 mg

(As Extended Release)

Excipients……..q.s.

Colours: Ferric Oxide Red NF, Ferric Oxide Yellow NF, Titanium Dioxide IP

The Excipients used are Mannitol, Pregelatinized Starch, Ferric Oxide Yellow, Croscarmellose Sodium, Magnesium Stearate, hydroxyl Propyl Methyl Cellulose, Microcrystalline cellulose, L-Cysterine Hydrochloride, Povidone K-30, Isopropyl Alcohol, Colloidal Silicon Dioxide, Magnesium Stearate

3. Dosage form and strength

Dosage form: Film Coated bilayer tablet

Strength: Dextromethorphan Hydrobromide I.P 45 mg and Bupropion Hydrochloride I.P 105 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the Treatment of major depressive disorder (MDD) in adults.

4.2 Posology and method of administration

Posology

Important Recommendations Prior to Initiating and During Treatment with DEXBUTRIN.

Prior to initiating and during treatment with DEXBUTRIN

- assess blood pressure and monitor periodically during treatment
- screen patients for a personal or family history of bipolar disorder, mania, or hypomania
- screen patients to determine if they are receiving any other medications that contain bupropion or dextromethorphan

The recommended starting dosage of DEXBUTRIN (45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) is one tablet once daily in the morning.

After 3 days, increase to the maximum recommended dosage of one tablet twice daily, given at least 8 hours apart. Do not exceed two doses within the same day.

Dosage Recommendations in Patients with Renal Impairment

The recommended dosage of DEXBUTRIN for patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m2) is one tablet once daily in the morning.

Dosage Recommendations for Concomitant Use with Strong CYP2D6 Inhibitors

The recommended dosage of DEXBUTRIN when co-administered with strong CYP2D6 inhibitors is one tablet once daily in the morning.

Dosage Recommendations for Known CYP2D6 Poor Metabolizers

The recommended dosage for patients known to be poor CYP2D6 metabolizers is one tablet once daily in the morning.

Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with DEXBUTRIN. Conversely, at least 14 days must be allowed after stopping DEXBUTRIN before starting an MAOI antidepressant.

Method of administration

Administer DEXBUTRIN orally with or without food. Swallow tablets whole, do not crush,

divide, or chew.

4.3 Contraindications

DEXBUTRIN is contraindicated in patients

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate-release formulation of bupropion
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome
- with known hypersensitivity to bupropion, dextromethorphan, or other components of Dexbutrin. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion

4.4 Special warnings and precautions for use

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased

risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1 Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	**Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated**
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors. Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing DEXBUTRIN, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors

Seizure

Bupropion, a component of DEXBUTRIN, can cause seizure. The risk of seizure with bupropion is dose-related.

When a bupropion hydrochloride (HCl) sustained-release tablet was dosed up to 300 mg per day (approximately 1.5 times the maximum recommended daily dosage of DEXBUTRIN), the incidence of seizure was approximately 0.1% (1/1,000) and increased to approximately 0.4% (4/1,000) at the maximum recommended dosage for the sustained-release tablet of 400 mg per day (approximately 2 times the maximum recommended daily dosage of DEXBUTRIN).

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment

with DEXBUTRIN. DEXBUTRIN is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating DEXBUTRIN. If concomitant use of DEXBUTRIN with other bupropion containing products is clinically warranted, inform patients of the risk. Discontinue DEXBUTRIN and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension

DEXBUTRIN contains bupropion, which can cause elevated blood pressure and hypertension. The risk of hypertension is increased if DEXBUTRIN is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity.

Data from a comparative trial of a sustained-release tablet formulation of bupropion HCl, 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 hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this trial, 6.1% of subjects treated with the combination of sustained-release bupropion and NTS had hypertension compared with 2.5%, 1.6%, and 3.1% of subjects treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with sustained-release bupropion or placebo. Monitor blood pressure in patients who receive the combination of bupropion and nicotine replacement.

In a clinical trial of an immediate-release bupropion tablet formulation in MDD subjects with stable congestive heart failure (N=36), bupropion was associated with an exacerbation of pre-existing hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no controlled trials assessing the safety of bupropion in patients with a recent history of myocardial infarction or unstable cardiac disease.

Assess blood pressure prior to initiating treatment, and periodically monitor blood pressure during treatment with DEXBUTRIN

Activation of Mania or Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic manic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating DEXBUTRIN, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar

disorder, suicide, or depression). DEXBUTRIN is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions

DEXBUTRIN contains bupropion. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

DEXBUTRIN contains dextromethorphan. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating DEXBUTRIN. If concomitant use of DEXBUTRIN with other bupropion or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion, a component of DEXBUTRIN, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including DEXBUTRIN, in patients with untreated anatomically narrow angles.

Dizziness

DEXBUTRIN may cause dizziness. In controlled studies of DEXBUTRIN, 14% of patients receiving DEXBUTRIN and 6% of patients on placebo experienced dizziness. Take precautions to reduce the risk of falls, particularly for patients with motor impairment affecting gait or those with a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that DEXBUTRIN therapy does not affect them adversely.

Serotonin Syndrome

DEXBUTRIN contains dextromethorphan. Concomitant use of DEXBUTRIN with SSRIs or tricyclic antidepressants may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor

The concomitant use of DEXBUTRIN with MAOIs is contraindicated. In addition, do not initiate DEXBUTRIN in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking DEXBUTRIN discontinue DEXBUTRIN before initiating treatment with the MAOI.

Prior to initiating DEXBUTRIN, screen patients for use of other dextromethorphan-containing products. If concomitant use of DEXBUTRIN with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue DEXBUTRIN and/or concomitant serotonergic drug immediately if the above symptoms occur, and initiate supportive symptomatic treatment.

Embryo-fetal Toxicity

Based on animal studies, DEXBUTRIN may cause fetal harm when administered during pregnancy. In developmental toxicity studies in rats and rabbits, when a combination of dextromethorphan/quinidine was given to pregnant animals, fetal malformations (rabbits) and embryolethality were demonstrated in offspring. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. The separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

4.5 Drugs interactions

Drugs Having Clinically Important Interactions with DEXBUTRIN.

Table:2 Clinically Important Drug Interactions with DEXBUTRIN

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	Concomitant use of DEXBUTRIN with MAOIs increases the risk of hypertensive crisis and serotonin syndrome.
Intervention	DEXBUTRIN is contraindicated in patients taking MAOIs (including MAOIs such as linezolid or intravenous methylene blue) or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping DEXBUTRIN before starting an MAOI
Serotonergic Drugs	
Clinical Impact	Concomitant use of DEXBUTRIN with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when DEXBUTRIN is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of DEXBUTRIN and/or concomitant serotonergic drug.
Drugs that Lower Seizure Threshold	
Clinical Impact	DEXBUTRIN contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.

Intervention	Use caution when administering DEXBUTRIN concomitantly with drugs that lower the seizure threshold. Discontinue DEXBUTRIN and do not restart treatment if the patient experiences a seizure.

Strong Inhibitors of CYP2D6	
Clinical Impact	Concomitant use of DEXBUTRIN with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.
Intervention	Dosage adjustment is necessary when DEXBUTRIN is co-administered with strong inhibitors of CYP2D6. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.
Strong Inducers of CYP2B6	
Clinical Impact	Concomitant use of DEXBUTRIN with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of DEXBUTRIN.
Intervention	Avoid co-administration of DEXBUTRIN with strong inducers of CYP2B6. Consider alternatives to strong CYP2B6 inducers if needed.
Drugs Metabolized by CYP2D6	
Clinical Impact	<u>CYP2D6 Substrates</u> Coadministration of DEXBUTRIN with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. <u>Drugs that Require Metabolic Activation by CYP2D6</u> Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with DEXBUTRIN.
Intervention	<u>CYP2D6 Substrates</u> When used concomitantly with DEXBUTRIN, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index. <u>Drugs that Require Metabolic Activation by CYP2D6</u> Patients treated concomitantly with DEXBUTRIN may require increased doses of drugs that require activation by CYP2D6 to be effective.
Digoxin	

Clinical Impact	Coadministration of DEXBUTRIN with digoxin may decrease plasma digoxin levels.
Intervention	Monitor plasma digoxin levels in patients treated concomitantly with DEXBUTRIN and digoxin.
Dopaminergic Drugs	
Clinical Impact	CNS toxicity was reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions include restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.
Intervention	Use caution when administering DEXBUTRIN concomitantly with dopaminergic drugs.
Alcohol	
Clinical Impact	DEXBUTRIN contains bupropion which can increase adverse neuropsychiatric events or reduce alcohol tolerance.
Intervention	Consumption of alcohol should be minimized or avoided during treatment with DEXBUTRIN.

Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Based on animal studies, DEXBUTRIN may cause fetal harm when administered during pregnancy. DEXBUTRIN is not recommended during pregnancy. If a female becomes pregnant while being treated with DEXBUTRIN, discontinue treatment and counsel the patient about the potential risk to a fetus. In oral studies conducted in rats and rabbits, a combination of dextromethorphan/quinidine demonstrated developmental toxicity, including fetal malformations (rabbits) and embryolethality, when given to pregnant animals. When bupropion alone was administered to pregnant rats during organogenesis, there was no evidence of fetal malformations at doses up to approximately 21 times the maximum recommended human dose (MRHD) of 210 mg/day. When bupropion alone was given to pregnant rabbits during organogenesis, non-dose–related increases in incidence of fetal malformations, and skeletal variations were observed at doses approximately 2 to 5 times the MRHD and greater. Decreased fetal weights were seen at bupropion doses approximately 5 times the MRHD and greater. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which

corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. Based on these findings, DEXBUTRIN may cause fetal harm when administered to pregnant women. The available clinical data on the use of DEXBUTRIN during pregnancy is insufficient to evaluate for a drug-associated risk of major birth malformations, miscarriage, or other adverse maternal or fetal outcomes. However, there are available data on one of the individual components of DEXBUTRIN, bupropion. Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester have not identified an increased risk of congenital malformations overall .There are risks to the mother associated with untreated depression in pregnancy .The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants during pregnancy at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Data

Human Data

Bupropion Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall. The Registry was not designed or powered to evaluate specific defects but suggested a possible increase in cardiac malformations.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international bupropion Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database, which had a limited number of exposed cases with cardiovascular malformations, and a case-control study (11,700 infants with cardiovascular malformations and 20,093 infants with non-cardiovascular malformations) of self-reported antidepressant use, including bupropion (n=728), from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) or ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked

sufficient power to evaluate the LVOTO association. NBDPS found slightly increased risk for LVOTO after partially accounting for underlying maternal conditions (n = 14; adjusted odds ratio [OR] = 1.18; 95% CI: 0.58, 2.43), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data

In studies conducted in pregnant mice, dextromethorphan-bupropion was administered orally during the period of organogenesis at doses of 0-0, 26-57, 34-75, and 68-150 mg/kg/day, respectively. Administration of dextromethorphanbupropion did not affect body weight, weight gain, food consumption, or pregnancy at any dose level and did not produce gross pathologic findings or placental or fetal findings at any dose level. The no-effect level for reproductive organ findings in mice was 68-150 mg/kg in both sexes, which is approximately 3.7/3.5 times the MRHD for DEXBUTRIN on a mg/m^2 basis.

When dextromethorphan/quinidine was administered orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to pregnant rats during the period of organogenesis, embryo-fetal deaths were observed at the highest dose tested and reduced skeletal ossification was observed at all doses. Oral administration to pregnant rabbits during organogenesis in two separate studies (0/0, 5/60, 15/60, and 30/60 mg/kg day; 0/0, 5/100, 15/100, and 50/100 mg/kg/day) resulted in an increased incidence of fetal malformations at all but the lowest dose tested.

When dextromethorphan/quinidine was orally administered to female rats during pregnancy and lactation in two separate studies (0/0, 5/100, 15/100, and 30/100 mg/kg/day; 0/0, 5/100, 15/100, and 50/100 mg/kg/day), pup survival and pup weight were decreased at all doses, and developmental delay was observed in offspring at the mid and high doses. A no effect dose for adverse developmental effects was not identified.

When dextromethorphan/quinidine was orally administered (0/0, 5/50, 15/50, 25/50 mg/kg) to male and female rats on postnatal day (PND) 7, the highest dose resulted in neuronal death in brain (thalamus and medulla oblongata). PND 7 in rat corresponds to the third trimester of gestation through the first several months of life but may extend to approximately three years of age in humans.

In studies conducted in pregnant rats and rabbits, bupropion alone was administered orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively (approximately 21 and 14 times the MRHD, respectively, on a mg/m^2 basis). There was no evidence of fetal malformations in rats. When given to pregnant rabbits during organogenesis, non-dose–related increases in incidence of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately 2 times the MRHD on a mg/m2 basis) and greater. Decreased fetal weights were observed at doses of 50 mg/kg/day (approximately 5 times the MRHD on a mg/m2 basis) and greater. No maternal toxicity was evident at doses of 50 mg/kg/day or less. In a pre- and postnatal development study, bupropion

administered orally to pregnant rats at doses of up to 150 mg/kg/day (approximately 7 times the MRHD on a mg/m2 basis) from embryonic implantation through lactation had no effect on pup growth or development.

Lactation

Risk Summary

Data from published literature report the presence of bupropion and its metabolites in human milk .There are no data on the effects of bupropion or its metabolites on milk production. Limited data from post marketing reports of bupropion use in lactating patients have not identified a clear association of adverse reactions in the breastfed infant.

Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. It is not known whether dextromethorphan is present in human milk. There are no data on the effects of dextromethorphan on the breastfed infant or the effects on milk production. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with DEXBUTRIN and for 5 days following final dose.

Data

In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Post marketing reports have described seizures in breastfed infants. The relationship of bupropion exposure and these seizures is unclear.

Females and Males of Reproductive Potential

Based on animal studies, DEXBUTRIN may cause fetal harm when administered during pregnancy. However, the separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear. Use alternative treatment for females who are planning to become pregnant.

Pediatric Use

The safety and effectiveness of DEXBUTRIN have not been established in pediatric patients.

DEXBUTRIN contains bupropion. Antidepressants, including bupropion, increase the risk of suicidal thoughts and behaviors in pediatric patients.

Geriatric Use

Clinical studies with DEXBUTRIN did not include patients 65 years of age and older to determine whether they respond differently than younger adult patients.

Renal Impairment

Dosage adjustment of DEXBUTRIN is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m2). The pharmacokinetics of DEXBUTRIN have not been evaluated in patients with severe renal impairment. DEXBUTRIN is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment

No dose adjustment of DEXBUTRIN is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of DEXBUTRIN have not been evaluated in patients with severe hepatic impairment (Child-Pugh C). DEXBUTRIN is not recommended in patients with severe hepatic impairment.

CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metabolizers.

4.7 Effects on ability to drive and use machines

Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Dexbutrin therapy does not affect them adversely.

4.8 Undesirable effects

The following adverse reactions are

- Suicidal Thoughts and Behaviors in Adolescents and Young Adults
- Seizure
- Increased Blood Pressure and Hypertension
- Activation of Mania or Hypomania
- Psychosis and Other Neuropsychiatric Reactions
- Angle-closure Glaucoma
- Dizziness
- Serotonin Syndrome
- Embryo-fetal Toxicity

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Dextromethorphan and Bupropion was evaluated for safety in a total of 1114 patients with MDD or another indication from four studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication).One 6-week study in MDD employed placebo as a control arm. Two 6-week studies, one in MDD and one in another indication, employed bupropion as a control arm. In the patients treated with Dextromethorphan and Bupropion in the long-term study (n=876),597 received at least 6 months of treatment, and 110 received at least 12 months of treatment.

The data below are based on the 6-week, placebo-controlled study in which either Dextromethorphan and Bupropion (n=162) or placebo (n=164) was administered twice daily to patients with MDD (Study 1). Demographics of the patients who participated in this study are summarized in Clinical Studies

Adverse Reactions Leading to Discontinuation

In the 6-week placebo-controlled study, 4% of patients treated with Dextromethorphan and Bupropion and 0% of placebo-treated patients discontinued participation due to adverse reactions. The adverse reaction that led to study discontinuation in ≥1% of patients treated with Dextromethorphan and Bupropion was anxiety (2%).

Most Common Adverse Reactions

In the 6-week placebo-controlled clinical study, the most common (incidence ≥5% for Dextromethorphan and Bupropion and more than twice as frequently as placebo) adverse reactions were dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Table 3 shows the incidence of adverse reactions that occurred in ≥2% of patients treated with Dextromethorphan and Bupropion and more frequently than in patients treated with placebo in Study 1.

Table 3 Adverse Reactions Occurring in ≥ 2% of Adult Patients with MDD Treated with Dextromethorphan and Bupropion and More Frequently than in Patients Treated with Placebo in a 6-Week Placebo-Controlled Study (Study 1)

Adverse Reaction	Dextromethorphan and Bupropion (N=162) %	Placebo (N=164) %
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction[a]	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2

Arthralgia	3	0
Fatigue[b]	3	2
Paraesthesia[c]	3	0
Vision blurred	3	0

[a]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia

[b]Fatigue includes fatigue, lethargy

[c]Paraesthesia includes paraesthesia, hypoaesthesia

Postmarketing Experience

The following adverse reactions have been identified with the use of the individual components of Dextromethorphan and Bupropion , dextromethorphan and bupropion, during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dextromethorphan

Drowsiness, dizziness, nervousness or restlessness, nausea, vomiting, and stomach pain.

Bupropion

Body (General): Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.

Cardiovascular: Complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe), phlebitis, pulmonary embolism, and Brugada pattern/syndrome.

Digestive: Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, pancreatitis, and stomach ulcer.

Endocrine: Hyperglycemia, hypoglycemia, hyponatremia, and syndrome of inappropriate antidiuretic hormone secretion. Hemic and Lymphatic: Anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Glycosuria.

Musculoskeletal: Muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Abnormal electroencephalogram (EEG), aggression, agitation, akinesia, aphasia, coma, completed suicide, delirium, delusions, depression, dysarthria, euphoria, extrapyramidal syndrome (dyskinesia, dystonia, hypokinesia, parkinsonism), hallucinations, homicidal ideation, hostility, increased libido, manic reaction, neuralgia, neuropathy, panic, paranoid ideation, psychosis, restlessness, suicide ideation, suicide attempt, and unmasking tardive dyskinesia.

Respiratory: Pneumonia.

Skin and subcutaneous tissue disorders: Alopecia, angioedema, exfoliative dermatitis, hirsutism, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Special Senses: Deafness, increased intraocular pressure, and mydriasis.

Urogenital: Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Human Experience

There is limited clinical study experience regarding human overdosage with DEXBUTRIN. Overdosage information is based on experience with the individual components, dextromethorphan and bupropion. Metabolism of the dextromethorphan component of DEXBUTRIN is inhibited by the bupropion component, such that overdose due to DEXBUTRIN might be more severe or more persistent compared to overdose of dextromethorphan alone.

Dextromethorphan

Symptoms of dextromethorphan overdose include nausea, vomiting, stupor, coma, respiratory depression, seizures, tachycardia, hyperexcitability, and toxic psychosis. Other adverse effects include ataxia, nystagmus, dystonia, blurred vision, and changes in muscle reflexes. Dextromethorphan may cause serotonin syndrome, and this risk is increased by overdose, particularly if taken with other serotonergic agents, SSRIs or tricyclic antidepressants.

Bupropion

Overdoses of up to 30 grams or more of bupropion (approximately 143 times the maximum recommended dose of DEXBUTRIN) have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, mental status changes, sinus tachycardia, ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias, clonus, myoclonus, and hyperreflexia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Overdosage Management

Treatment of dextromethorphan overdosage should be directed at symptomatic and supportive measures. There are no known an□dotes for bupropion. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended.

5 Pharmacological properties

5.1 Mechanism of Action

Dextromethorphan is an uncompetitive antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The mechanism of dextromethorphan in the treatment of MDD is unclear.

The mechanism of action of bupropion in the treatment of MDD is unclear; however, it may be related to noradrenergic and/or dopaminergic mechanisms. Bupropion increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the reuptake of serotonin.

5.2 Pharmacodynamic properties

Cardiac Electrophysiology

At the maximum recommended dose, DEXBUTRIN does not prolong the QT interval to any clinically relevant extent.

5.3 Pharmacokinetic properties

DEXBUTRIN is a combination of dextromethorphan and bupropion. Bupropion inhibits the metabolism of dextromethorphan via CYP2D6. Dextromethorphan when co-administered with bupropion displays nonlinear pharmacokinetics at steady Page 17 state, with greater than dose-proportional changes in AUC and Cmax for varying doses of dextromethorphan [60 to 120 mg (0.67-1.33 times the maximum recommended dose of DEXBUTRIN)] and less than dose-proportional changes for varying doses of bupropion [150 to 300 mg (0.71-1.43 times the maximum recommended dose of DEXBUTRIN)].

Steady state plasma concentrations of dextromethorphan and bupropion when given as DEXBUTRIN are achieved within 8 days. The accumulation ratios for dextromethorphan at steady state when given as DEXBUTRIN are 20 and 32, respectively based on C_{max} and AUC_{0-12}, compared to 1.3 and 1.4, respectively, for dextromethorphan given without bupropion. The accumulation ratios for bupropion at steady state are 1.1 and 1.5, respectively based on C_{max} and AUC_{0-12}.

Absorption

The median T_{max} of dextromethorphan and bupropion when given as DEXBUTRIN was 3 hours and 2 hours, respectively.

The C_{max} of the hydroxybupropion metabolite occurred approximately 3 hours post-dose and was approximately 14 times the peak level of bupropion and its AUC_{0-12} was about 19 times that of bupropion. The C_{max} of the erythrohydroxybupropion and threohydroxybupropion metabolites occurred approximately 4 hours post-dose and were approximately equal to and 5

times that of bupropion, respectively. The AUC_{0-12} values were 1.2 and 7 times that of bupropion, respectively.

Effect of Food

DEXBUTRIN can be taken with or without food. Dextromethorphan C_{max} and AUC_{0-12} were unchanged and decreased by 14%, respectively, and bupropion C_{max} and AUC_{0-12} were increased by 3% and 6%, respectively, when DEXBUTRIN was administered with food.

Distribution

The plasma protein binding of dextromethorphan is approximately 60-70% and bupropion is 84%. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas, the extent of protein binding of the threohydroxybupropion metabolite is about half that seen with bupropion.

Elimination

Following 8 days of administration of DEXBUTRIN in extensive metabolizers, the mean elimination half-life of dextromethorphan was increased approximately 3-fold to 22 hours, as compared to dextromethorphan given without bupropion.

The mean elimination half-life of dextromethorphan and bupropion was 22 hours and 15 hours, respectively. The apparent elimination half-life of hydroxybupropion, erythrohydroxybupropion and threohydroxybupropion metabolites were approximately 35, 44 and 33 hours, respectively.

Metabolism

Dextromethorphan is primarily metabolized by CYP2D6 to dextrorphan. Bupropion is extensively metabolized with three active metabolites: hydroxybupropion, which is formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers, threohydroxybupropion and erythrohydroxybupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of threohydroxybupropion. 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. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion, while threohydroxybupropion and erythrohydroxybupropion are 5-fold less potent than bupropion.

Excretion

In CYP2D6 extensive metabolizers, approximately 37-52% of the orally administered dose of dextromethorphan is recovered in the urine. Less than 2% of the administered dose is excreted as unchanged parent drug in the urine. In CYP2D6 Page 18 poor metabolizers, approximately 45-83% of the administered dose is recovered in the urine. Approximately 26% of the administered dose is excreted as unchanged parent drug in the urine. Following oral administration of 200 mg of 14C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose was excreted as unchanged bupropion.

<u>Specific Populations</u>

Geriatric Patients

The pharmacokinetics of DEXBUTRIN have not been studied in patients 65 years or older.

Pediatric Patients

The pharmacokinetics of DEXBUTRIN in pediatric patients have not been studied.

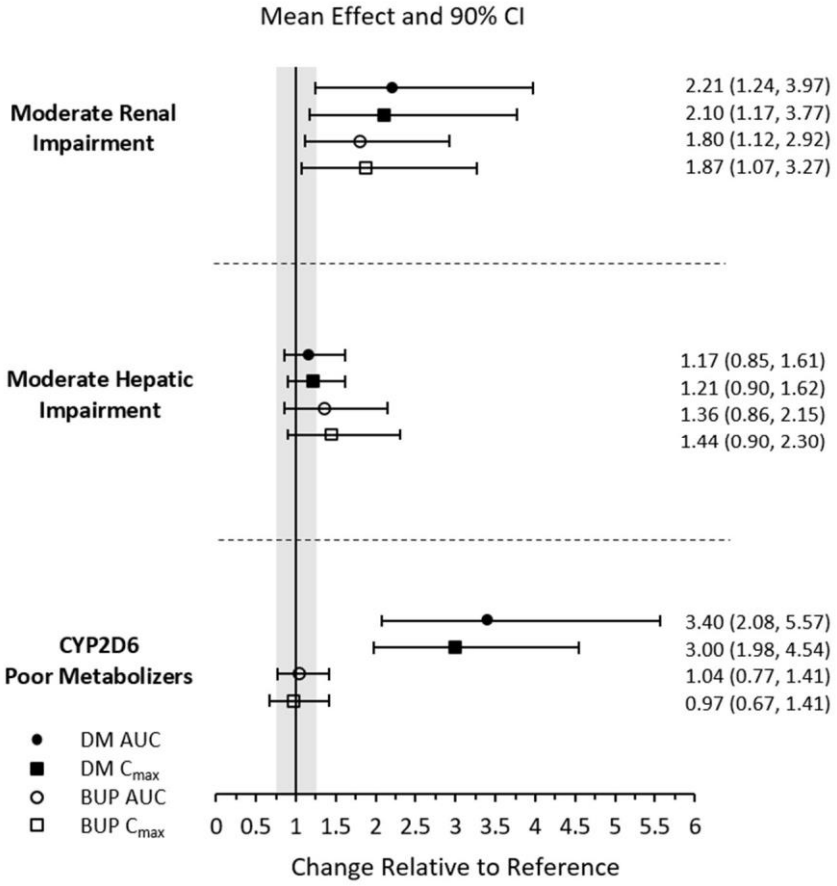
Male and Female/ Racial or Ethnic Groups

No significant pharmacokinetic differences based on sex and race have been observed for DEXBUTRIN.

Patients with Renal Impairment

Patients with Hepatic Impairment, and CYP2D6 Poor Metabolizers

Figure 1 : Effects of Renal Impairment, Hepatic Impairment, and CYP2D6 Poor Metabolizer Status on DEXBUTRIN PK



Results are based on plasma concentrations of DEXBUTRIN after 8 days of twice daily dosing. Data are GMRs and 90% CIs. Reference = matched healthy subjects for renal and hepatic impairment studies, and extensive or ultra-extensive CYP2D6 metabolizers. AUC = area under the plasma concentration time curve from zero to 12 hours; BUP = bupropion; CI = confidence interval; Cmax = maximum plasma concentration; DM = dextromethorphan; GMRs = geometric mean ratios; PK = pharmacokinetics

In Vitro Assessment of Drug Interactions

The potential for dextromethorphan and bupropion to inhibit or induce cytochrome P450 in vitro were evaluated in human liver microsomes.

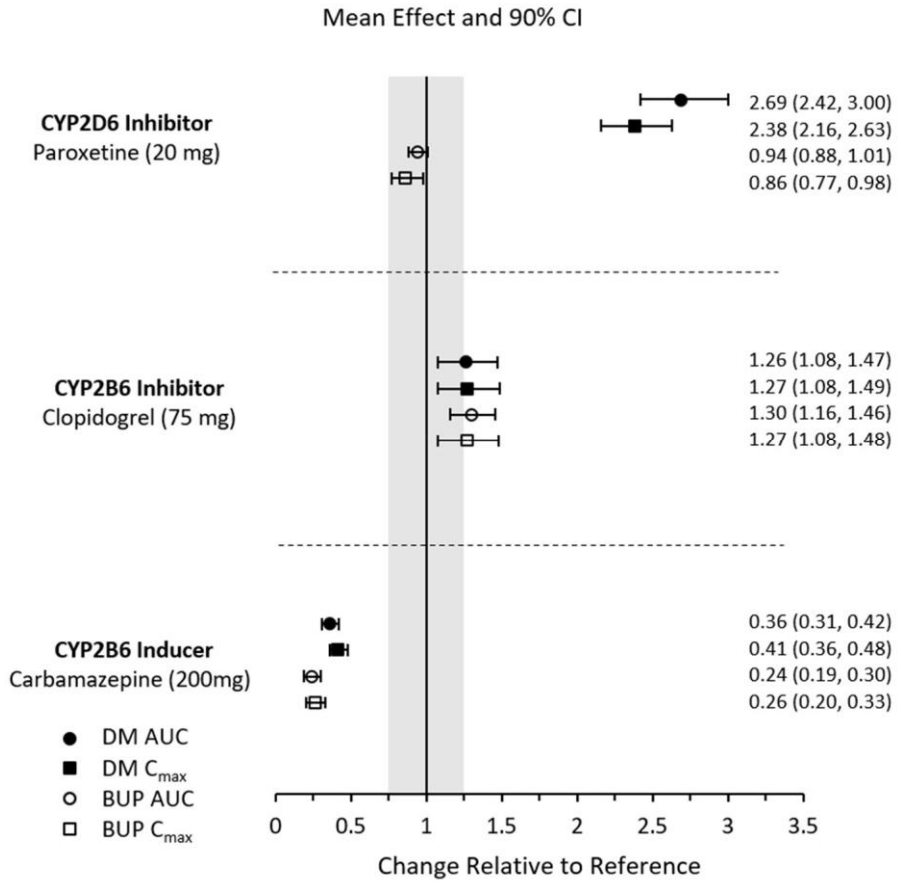
Bupropion and its metabolites (hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion) are inhibitors of CYP2D6. At therapeutically relevant concentrations dextromethorphan does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Dextromethorphan does not cause induction of CYP1A2, CYP3A4, or CYP2B6.

Dextromethorphan is a substrate of the human P-gp transporter. Dextromethorphan does not inhibit transporters at therapeutically relevant concentrations.

In Vivo Assessment of Drug Interactions

The effects of other drugs on the exposure to DEXBUTRIN are summarized in Figure 2

Figure 2 Effects of Co-administered Compounds on DEXBUTRIN PK



Results are based on steady state plasma concentrations of twice daily dosing of DEXBUTRIN. Data are GMRs and 90% CIs. AUC = area under the plasma concentration- me curve from zero to 12 hours; BUP = bupropion; CI = confidence interval; Cmax = maximum plasma concentration; DM=dextromethorphan; GMRs=geometric mean ratios; PK=pharmacokinetics

Digoxin

Literature data showed that digoxin exposure was decreased when a single oral dose of 0.5-mg digoxin was administered 24 hours after a single oral dose of extended-release 150 mg bupropion in healthy volunteers.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 26-week carcinogenicity study in the Tg.rasH2 transgenic mouse, dextromethorphan at oral doses up to 100 mg/kg/day did not show any evidence of carcinogenic potential.

In a two-year carcinogenicity study in rats, dextromethorphan was administered at an oral dose of 50 mg/kg/day. No biologically significant tumor findings were observed. This dose is approximately 5.4 times the maximum recommended human dose (MRHD) of 90 mg/day on a mg/m^2 basis.

Life time carcinogenicity studies were performed in rats and mice at bupropion doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 13.9 and 3.5 times the 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 (approximately 4.6 to 13.9 times the MRHD on a mg/m2 basis); lower doses were not tested. The ques on 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 tumors of the liver and other organs was seen in either study.

Mutagenesis

Dextromethorphan was negative in in vitro (bacterial reverse mutation, chromosomal aberration in human lymphocytes) and in vivo (mouse micronucleus) assays.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity assay. Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

Impairment of fertility

When dextromethorphan was co-administered with quinidine orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to male and female rats prior to and during ma ng, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested.

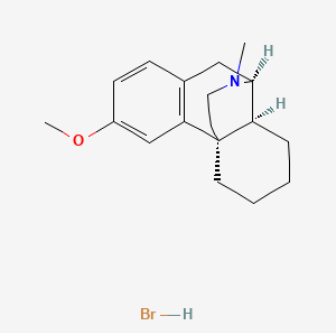
There were no effects on male and female fertility when rats were administered oral doses of bupropion up to 300 mg/kg/day (approximately 14 times the MRHD on a mg/m2 basis) in females prior to ma ng and either through Day 13 of gestation or through lactation, and in males for 60 days prior to and through ma ng. However, doses of 200 mg/kg/day (approximately 9 times the MRHD on a mg/m^2 basis) or greater, caused transient ataxia or behavioral changes in adult female rats. There were also no adverse effects on fertility, reproduction, or growth and development of male or female offspring.

The effects on fertility of administering dextromethorphan and bupropion in combination are not known at this time.

7 Description

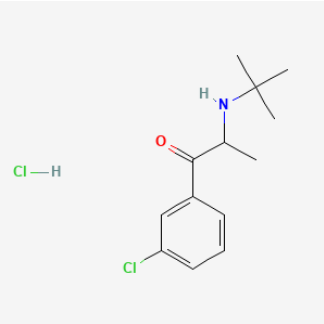
<u>Dextromethorphan Hydrobromide:</u>

Dextromethorphan Hydrobromide is ent-3-methoxy-9a-methylmorphian hydrobromide monohydrate. The empirical formula is $C_{18}H_{25}NO,HBr,H_2O$ and its molecular weight is 370.3 g/mol. The chemical structure of Dextromethorphan Hydrobromide is



Bupropion Hydrochloride:

Nortriptyline Hydrochloride is 1-propane, 1-(3-chlorophnyl)-2-[(1,1-dimethylethyl) amino)-, hydrochloride, (±)-;(±)-2-(teributyl amino)-3'-chloropropiophenone hydrochloride. The empirical formula is $C_{13}H_{18}CLNO,HCL$ and its molecular weight is 276.2 g/mol. The chemical structure of Bupropion Hydrochloride is



Dexbutrin:

Dextromethorphan Hydrobromide & Bupropion Hydrochloride Extended Release are Beige colored, round, biconvex, film coated tablets, plain on both sides. The Excipients used are Mannitol, Pregelatinized Starch, Ferric Oxide Yellow, Croscarmellose Sodium, Magnesium Stearate, hydroxyl Propyl Methyl Cellulose, Microcrystalline cellulose, L-Cysterine Hydrochloride, Povidone K-30, Isopropyl Alcohol, Colloidal Silicon Dioxide, Magnesium Stearate

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

DEXBUTRIN is available in pack of 10 Tablets.

8.4 Storage and handing instructions

Store below 30^0C

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10 Details of manufacturer

Exemed Pharmaceuticals.

Plot No.133/1, & 133/2, G.I.D.C.,

Selvas Road, Vapi-396195, Dist. Valsad,

Gujarat State India

11 Details of permission or licence number with date

Mfg Licence .No. G/25/2011 Issued on: 18.05.2024

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/DEXBUTRIN (45 mg + 105 mg)/May-2024/01/PI