

PRESCRIBING INFORMATION

Bellergal[®] Spacetabs

(Ergotamine, Phenobarbital, Belladonna)

0.6mg Ergotamine tartrate, 40mg Phenobarbital, 0.2mg Belladonna Alkalloides

Anticholinergic - Antispasmodic - Sedative

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ERGOTAMINE, PHENOBARBITAL, and BELLADONNA TABLETS

PHARMACOLOGY

ERGOTAMINE

Limited information is available about the tissue distribution of ergotamine in humans. Following oral or intravenous administration in rats, ergotamine has been detected in high concentrations in the liver and lung and in lower concentrations in the kidney, heart, and brain. About 98% of the drug is protein bound. Studies based on an in vitro model system using porcine brain endothelial cells have shown that ergot alkaloids such as ergotamine are able to cross the blood-brain barrier reaching the central nervous system (CNS) in a high concentration. Ergotamine is extensively metabolized in the liver and cleared from the blood by first-pass hepatic metabolism resulting in low or undetectable systemic drug concentrations. Parent drug and metabolites are mainly excreted in the feces via biliary elimination, only a small amount is excreted in the urine.

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g. ritonavir) presumably due to inhibition of cytochrome P450 3A (CYP3A) metabolism of ergotamine (see **CONTRAINDICATIONS**). Ergotamine has also been shown to be an inhibitor of CYP3A catalysed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

PHENOBARBITAL

Phenobarbital, like many other barbiturates, is a nonselective central nervous system (CNS) depressant, capable of producing all degrees of depression from mild sedation and hypnosis to general anesthesia, deep coma and death. The extent of CNS depression varies with the route of administration, dose and pharmacokinetic characteristics of the particular barbiturates. Patient

specific factors such as age, physical or emotional state and the concomitant use of other drugs will also affect response.

The mechanism of action of phenobarbital is not completely known. Phenobarbital may act by enhancing and/or mimicking the synaptic action of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. The sedative-hypnotic action of phenobarbital may be due to an inhibition of conduction in the reticular formation resulting in a decrease in the number of impulses reaching the cerebral cortex.

Phenobarbital also lowers the serum bilirubin concentrations by inducing glucuronyl transferase, the enzyme which conjugates bilirubin.

Phenobarbital is rapidly absorbed from the gastrointestinal tract particularly if taken well diluted or on an empty stomach. Although it is rapidly distributed to all tissues and fluids with high concentrations in the liver, brain and kidney, it is the slowest of all the barbiturates because of its low lipid solubility which also delays the onset of action to over 60 minutes. It has the longest duration of action (10-12 hours) of the barbiturate because it is metabolised only to a small degree in the liver and up to 75% may be excreted unchanged renally. Phenobarbital is only about 20-45% bound to plasma proteins and has a half-life of 53 to 118 hours in adults.

BELLADONNA

Belladonna alkaloids, including atropine and scopolamine, competitively antagonize the effects of acetylcholine at peripheral and central muscarinic receptors, including exocrine glands, smooth and cardiac muscle, and intramural neurons. The physiological response to muscarinic receptor blockade varies among organs. Small doses of atropine depress salivary and bronchial secretion and sweating, while larger doses can lead to pupil dilation, increased heart rate (by inhibiting vagal effects on the heart), and the inhibition of gastric motility. Scopolamine exerts greater effects on the CNS, eye, and secretory glands than the other constituents, atropine and hyoscyamine. Hyoscyamine exerts similar actions to atropine but has more potent central and peripheral nervous system effects. The ratio of belladonna alkaloids following ingestion of BELLERGERAL Spacetabs also remains unclear.

INDICATIONS

Functional symptoms associated with menopause, such as hot flushes, perspiration, palpitations, dizzy spells, restlessness, apprehension, fatigue, insomnia, and headache.

BELLERGAL Spacetabs are not indicated for migraine, osteoporosis, atrophic vaginitis, or symptoms vulval or vaginal dryness.

CONTRAINDICATIONS

BELLERGAL Spacetabs should not be administered:

- to patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container
- with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) due to the risk of ergot toxicity (see **WARNINGS: CYP 3A4 Inhibitors** and **DRUG INTERACTIONS**)
- with delavirdine due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors
- to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). Patients with other significant underlying cardiovascular diseases (eg. atherosclerotic disease, congenital heart disease) should not receive BELLERGAL Spacetabs. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see **WARNINGS AND PRECAUTIONS**)
- with vasoconstrictor agents including ergot alkaloids, sumatriptan and other 5HT₁ receptor agonists (see **WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS**)
- to patients with porphyria, severe respiratory depression or pulmonary insufficiency, renal impairment, hepatic impairment, sleep apnea, suicidal potential, alcoholism, drug dependence or in the presence of uncontrolled pain (paradoxical excitement may be produced)
- to patients with septic conditions, shock, obliterative vascular disease, inadequately controlled hypertension, temporal arteritis, hemiplegic or basilar migraine, malnutrition, prostatic hypertrophy

- to patients with narrow-angle glaucoma
- during pregnancy because ergotamine has oxytocic and vasoconstrictor effects on the placenta and umbilical cord
- to nursing mothers
- because ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in infants

WARNINGS & PRECAUTIONS

Serious and/or life-threatening peripheral ischemia, including fatalities and cases of gangrene, has been associated with the co-administration of ergotamine with potent CYP 3A4 inhibitors. Examples include protease inhibitors macrolide antibiotics, and antifungal agents. Because CYP 3A4 inhibition elevates the serum levels of ergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased-(see CONTRAINDICATIONS).

CYP 3A4 Inhibitors

Co-administration of ergotamine with potent CYP 3A4 inhibitors such as HIV protease or reverse transcriptase inhibitors, azole antifungals, or macrolide antibiotics, has been associated with serious adverse events; for this reason, these drugs should not be given concomitantly with ergotamine (see **CONTRAINDICATIONS**). While these reactions have not been reported with less potent CYP 3A4 inhibitors, there is a potential risk for serious toxicity including vasospasm when these drugs are used with ergotamine. Examples of less potent CYP 3A4 inhibitors include, but not limited to: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole, and clotrimazole. The prescriber should consider the impact on CYP3A4 activity of other agents being considered for concomitant use with ergotamine.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events

The use of ergotamine has been associated with transient chest pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or

arrhythmia have occurred following the use of 5-HT₁ agonists. BELLERGAL Spacetabs should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see **CONTRAINDICATIONS**).

Oral administration of nitroglycerin markedly decreases the first-pass metabolism of dihydroergotamine and subsequently increases its oral bioavailability. Therefore, patients receiving sublingual nitroglycerin should avoid ergotamine and related drugs or be monitored for symptoms of ergotism if this is not possible.

Cardiac Events and Fatalities associated with 5-HT₁ Agonists

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. These reactions are manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia (e.g., muscle pains, numbness, coldness and pallor or cyanosis of the digits), angina or unusual syndromes, such as mesenteric ischemia. Consequently, BELLERGAL Spacetabs should be discontinued immediately if signs or symptoms of vasoconstriction develop.

Because BELLERGAL Spacetabs may cause coronary vasospasm and these effects may be additive, the use of BELLERGAL Spacetabs within 24 hours before or after treatment with other 5HT₁ receptor agonists, or ergotamine-containing drugs or their derivatives (eg. methysergide) is contraindicated (see **CONTRAINDICATIONS**).

Increased Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving other 5-HT₁ agonists with and without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. Isolated reports of chest pain, pulmonary edema, coronary vasospasm, transient cerebral ischemia, angina and subarachnoid hemorrhage have been received (see **CONTRAINDICATIONS**). In patients with controlled hypertension, BELLERGAL Spacetabs should be administered with caution. It is contraindicated in patients with uncontrolled or severe hypertension and should not be used with vasoconstrictors, including nicotine, because the combination may cause a further elevation of blood pressure.

Fibrotic Complications

There have been reports of patients using ergotamine therapy developing retroperitoneal and/or pleuropulmonary fibrosis. There have also been rare reports of fibrotic thickening of the aortic, mitral, tricuspid, and/or pulmonary valves with long-term continuous use of ergotamine-containing products. BELLERGAL Spacetabs should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

Psychologic and Physiologic Dependence

Prolonged use of phenobarbital and ergotamine may result in psychologic and physiologic dependence. Withdrawal symptoms may occur following abrupt termination causing nightmares or insomnia, sweating, irritability, tremor, weight loss, anorexia or after chronic use of large doses, resulting in delirium, seizures, or death. Withdrawal should be cautious and gradual.

Serious Dermatological Reactions

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis:

Serious and sometimes fatal dermatologic reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), have been reported with phenobarbital. Although serious reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of serious dermatological syndromes.

Musculoskeletal, Connective Tissue and Bone Disorders:

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with drugs containing phenobarbital, including BELLERGAL Spacetabs. The mechanism by which phenobarbital affects bone metabolism has not been identified. BELLERGAL Spacetabs should be administered with caution to patients at greater risk of developing osteoporosis. Prolonged use should be avoided.

Medication Overuse Headache

Overuse of treatments that include ergotamine has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

Occupational Hazards

Phenobarbital may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. The concomitant use of alcohol or other CNS depressants may have an additive effect. Patients should be warned accordingly. The incidence of fractures due to falls may be increased, particularly in the elderly.

Special Populations:

Pregnant women

BELLERGAL Spacetabs are contraindicated during pregnancy (see **CONTRAINDICATIONS**). Ergotamine has oxytocic and vasoconstrictor effects on the placenta and umbilical cord and is associated with increased motor activity of the uterus and may cause fetal distress and miscarriage.

Nursing women

BELLERGAL Spacetabs are contraindicated in nursing mothers (see **CONTRAINDICATIONS**). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in infants.

Pediatrics (< 18 years of age)

BELLERGAL Spacetabs are not recommended for use in children under 18 years of age.

DRUG INTERACTIONS

The concomitant use of alcohol or other CNS depressants may have an additive effect. Warn patients accordingly.

Strong CYP3A4 inhibitors

The concomitant use of cytochrome P450 3A (CYP3A) inhibitors such as macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g. ketoconazole, itraconazole, voriconazole) and BELLERGAL Spacetabs must be avoided (see **CONTRAINDICATIONS**), since this can result in an elevated exposure to ergotamine and ergot toxicity (vasospasm and ischemia of the extremities and other tissues). Ergot alkaloids have also been shown to be inhibitors of CYP3A. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Moderate/weak CYP3A4 inhibitors

Moderate to weak CYP3A4 inhibitors such as cimetidine, clotrimazole, fluconazole, grapefruit juice, quinupristin/dalfopristin and zileuton can also increase the exposure to ergotamine and caution is required for their concomitant use.

Vasoconstrictors

Concurrent use of vasoconstrictor agents including preparations containing ergot alkaloids, sumatriptan and other 5HT₁ receptor agonists, and nicotine (e.g. heavy smoking) must be avoided since this may result in enhanced vasoconstriction (see **CONTRAINDICATIONS**).

Estrogenic Hormones/Progestin

Drugs containing phenobarbital, including BELLERGAL Spacetabs, may increase the metabolism of estrogens and progestagens and reduce their effectiveness. Therapeutic monitoring is recommended should concomitant use be considered.

Amphetamines

Co-administration of amphetamines may delay the intestinal absorption of phenobarbital.

Cholestyramine resin

Cholestyramine resin may delay or reduce the absorption of phenobarbital.

ADVERSE EFFECTS

Visual disturbances, dry mouth, flushing, drowsiness may occur.

Paraesthesia (e.g. numbness, tingling), pain and weakness in the extremities or peripheral vasoconstriction may occur. Ergotamine containing drugs may induce fibrotic changes, in particular of the pleura and the retroperitoneum. There have also been rare reports of fibrotic changes of the cardiac valves (see **WARNINGS AND PRECAUTIONS**).

Owing to its vasoconstrictor properties ergotamine may cause precordial pain, myocardial ischemia or, in rare cases, infarction, even in patients with no known history of coronary heart disease.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with drugs containing phenobarbital, including BELLERGAL Spacetabs (see **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

Ergotamine poisoning results in nausea, vomiting, diarrhea, thirst, muscle pain, cold and pale skin, itching, a rapid and weak pulse, bradycardia or tachycardia, pain suggestive of angina, rise and/or fall of blood pressure (usually in that order), mental confusion, dizziness, headache, depression,

somnolence, hypotension, convulsion, shock, possible unconsciousness, coma, symptoms and complications of ergotism. Ergotism may present with an intense arterial vasoconstriction, producing signs and symptoms of vascular ischemia of the extremities such as numbness, tingling and pain in the extremities, cyanosis, and absence of pulse. If the condition is allowed to progress untreated, gangrene may result. Ergotism can also involve signs and symptoms of vascular ischemia of other tissues such as renal, cardiac, cerebral, or gastrointestinal vasospasm. Most cases of ergotism are associated with chronic intoxication and/or overdose. Neurological changes can rarely include convulsions and hemiplegia. Respiratory depression can occur.

Some symptoms (e.g. nausea, vomiting and abdominal discomfort) of ergotamine overdose may be masked by the action of belladonna.

Convulsions, while a feature of acute ergotamine and belladonna poisoning, may be masked by the depressant action of phenobarbital and may not be present in BELLERGAL Spacetabs intoxication.

Other signs of overdose include respiratory depression (may be early in onset, pronounced and persistent), and hypotension followed by a typical shock-like state in more severe cases.

Respiratory complications and renal failure may also be present (not uncommon late sequelae of severe barbiturate intoxication).

TREATMENT OF OVERDOSAGE

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

Elimination of the drug by gastric lavage and administration of activated charcoal is recommended.

Treatment should be symptomatic and supportive. In the event of severe vasospastic reactions, intravenous administration of a peripheral vasodilator such as nitroprusside, phentolamine or dihydralazine, local application of warmth to the affected area, and nursing care to prevent tissue damage is recommended. In the event of coronary constriction, appropriate treatment such as nitroglycerine should be initiated.

Special Features due to ergotamine overdose: marked peripheral vasospasm with coldness and poor or absent pulses in the hands and feet are commonly associated with acute ergotamine

poisoning. Warmth, heat and protection must be afforded the ischemic limbs. Vasopressors should be avoided.

DOSAGE AND ADMINISTRATION

Chronic daily use of ergotamine-containing products is not recommended due to the risk of ergotism and rare fibrotic complications.

Patients who are being treated with BELLERGAL Spacetabs should be informed of the maximum doses allowed and of the first symptoms of overdose: hypoesthesia, paresthesia (e.g. numbness, tingling) in the fingers and toes, nausea and vomiting, symptoms of myocardial ischemia (e.g. precordial pain) and symptoms of ergotism including cerebral ischemia (e.g. limb weakness, blurred vision and slurred speech).

Recommended Daily Dose:

One BELLERGAL Spacetab in the morning and 1 in the evening.

Maximum Weekly Dose: 16 tablets.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name: BELLERGAL Spacetabs

Common Name: Ergotamine, phenobarbital and belladonna

Each compressed tablet contains 0.6 mg ergotamine tartrate USP, 0.2 mg levorotatory belladonna alkaloids, 40 mg phenobarbital USP, cornstarch, lactose and tartrazine.

Storage Requirements:

BELLERGAL Spacetabs must be kept between 15°C to 30°C.

BELLERGAL Spacetabs must be kept out of the reach and sight of children.

AVAILABILITY OF DOSAGE FORMS

BELLERGAL Spacetabs

Speckled dark green, orange and light lemon yellow, embossed "T" on one side and double-scored on the other. Available in bottles of 100.