



Prescribing Summary



Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Anticholinergic - Antispasmodic - Sedative

INDICATIONS AND CLINICAL USE: Functional symptoms, such as hot flushes, perspiration, palpitations, dizzy spells, restlessness, apprehension, fatigue, insomnia, headache, for example, in patients with anxiety-tension states associated with menopause.

Menopausal women who are treated with ◇BELLERGA[®] Spacetabs[®] (belladonna-ergotamine-phenobarbital) exhibiting atrophic vaginitis and/or osteoporosis, require specific therapy for these conditions, if indicated.

CONTRAINDICATIONS: Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities, with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease or reverse transcriptase inhibitor therapy when ergotamine was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) (see **WARNINGS:** CYP 3A4 Inhibitors and also **PRECAUTIONS:** Drug Interactions).

Concomitant treatment with vasoconstrictor agents (including ergot alkaloids, sumatriptan and other 5HT₁ receptor agonists) is contraindicated (see **PRECAUTIONS:** Drug Interactions).

Narrow-angle glaucoma, septic conditions, shock, obliterative vascular disease, inadequately controlled hypertension, peripheral vascular disease, coronary heart disease, temporal arteritis, hemiplegic or basilar migraine, severe disorders of renal or hepatic function, porphyria, malnutrition, prostatic hypertrophy, known hypersensitivity to ergot alkaloids, caffeine, or any other components of the formulation.

BELLERGA Spacetabs are contraindicated during pregnancy because ergotamine has oxytocic and vasoconstrictor effects on the placenta and umbilical cord.

Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in infants. Thus, BELLERGA Spacetabs are contraindicated in nursing mothers.



Safety Information

WARNINGS: Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of ergotamine with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. 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. Hence, concomitant use of these medications is contraindicated. (See also **CONTRAINDICATIONS.**)

CYP 3A4 Inhibitors

Coadministration 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: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole and clotrimazole. These lists are not exhaustive and the prescriber should consider the effects on

CYP 3A4 of other agents being considered for concomitant use with ergotamine.

Fibrotic Complications

There have been a few reports of patients using ergotamine therapy over a long-term period or in an excessive way who developed 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.

PRECAUTIONS: Administer with caution to patients with pyloric obstruction or angina pectoris. Excessive dryness of the mouth and visual disturbances are signs of overdosage or sensitivity to belladonna alkaloids. Reduction of dosage may be necessary. If excessive or prolonged dosage is contemplated, the physician should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Symptoms such as tingling in the fingers or toes should be reported to the physician immediately and the drug should be discontinued at once. Due to presence of a barbiturate, BELLERGA may be habit-forming. Patients who are being treated with BELLERGA Spacetabs should be informed of the maximum doses allowed and of the first symptoms of overdosage: paresthesia (e.g., numbness, tingling) in the fingers and toes, non-migraine-related nausea and vomiting and symptoms of myocardial ischemia (e.g., precordial pain).

Patients with mild to moderate hepatic impairment, especially cholestatic patients, should be appropriately monitored.

Excessive use of ergotamine-containing drugs over the years 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**).

Like all drugs, BELLERGA Spacetabs should be kept out of the reach of children.

OCCUPATIONAL HAZARDS: Barbiturate-containing preparations may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery.

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

The prolonged ingestion of barbiturates gives rise to enzyme induction. This increases the rate of metabolism of certain drugs, including oral anticoagulants and oral contraceptives, thus reducing their effectiveness.

See also phenobarbital monograph.

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 BELLERGA 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.

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**).

ADVERSE EFFECTS: Visual disturbances, dry mouth, flushing and drowsiness may occur. In children, behavioural disturbances and cognitive impairment may occur due to the presence of phenobarbital.

Paresthesia (e.g., numbness, tingling), pain and weakness in the extremities, or peripheral vasoconstriction may occur. If ergotamine-containing drugs are used excessively over years, they 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.

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.

To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at 1-866-234-2345.



Administration

DOSAGE: One Spacetab in the morning and one in the evening. Weekly maximum: 16 tablets.

Availability and storage:

Each compressed tablet (speckled dark green, orange and light lemon yellow, and embossed with an "S" in a triangle on one side and double-scored on the other) contains: ergotamine tartrate USP 0.6 mg, levorotatory belladonna alkaloids 0.2 mg and phenobarbital USP 40.0 mg. Also contains: cornstarch, lactose and tartrazine. Bottles of 100.



Study References

1. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 5th ed. Baltimore, MD: Williams & Wilkins; 1998:389-93.
2. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet*. 2000;38(1):41-57.
3. Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. *Clin Pharmacokinet*. 2001;40(11):833-68.
4. Malaty LI, Kuper JJ. Drug interactions of HIV protease inhibitors. *Drug Saf*. 1999;20(2):147-69.
5. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet*. 2000;38(2):111-80.
6. Peyronneau MA, Delaforge M, Riviere R, Renaud JP, Mansuy D. High affinity of ergopeptides for cytochromes P450 3A. Importance of their peptide moiety for P450 recognition and hydroxylation of bromocriptine. *Eur J Biochem*. 1994;223(3):947-56.

Supplemental Product Information

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

Symptoms

Symptoms include: nausea, vomiting and abdominal discomfort, usually after an acute overdose of ergotamine (these symptoms may be masked by the action of the belladonna); numbness, tingling, pain and cyanosis of the extremities, with diminished or absent peripheral pulses; drowsiness, confusion, incoordination and coma (convulsions, while a feature of acute ergotamine and belladonna poisoning, may be masked by the depressant action of the barbiturate and hence may not be common in a theoretical BELLERGERAL intoxication); respiratory depression, which may be early in onset, pronounced and persistent; hypotension, followed by a typical shock-like state in more severe cases; respiratory complications and renal failure, which are not uncommon late sequelae of severe barbiturate intoxication, and; hypothermia or hyperthermia.

The danger of BELLERGERAL intoxication is increased when the drug is ingested in the presence of alcohol, phenothiazines, minor tranquilizers and/or narcotics.

Treatment

The drug can be eliminated by gastric lavage and administration of activated charcoal. Supportive symptomatic treatment is required with close monitoring of cardiovascular and respiratory systems. In the event of vasospasm, vasodilators such as nitroprusside sodium are indicated.

Special Features Due to Ergotamine Overdosage

Marked peripheral vasospasm with coldness, and poor or absent pulses in the hands and feet are commonly associated with acute ergotamine poisoning. Warmth, but not heat, and protection must be afforded to the ischemic limbs. Vasopressors should be avoided.

Vasodilators, such as sodium nitroprusside or tolazoline, may be used with benefit.

Product Monograph available on request.

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