

Cafergot

Ergotamine tartrate 1 mg and Caffeine 100 mg Tablets

Presentation

Cafergot tablets are round, flat with bevelled edge, 9 mm diameter, speckled yellow/white, inscribed with a breakline and XL on one side and plain on the other side. Each tablet contains 1 mg ergotamine tartrate and 100 mg caffeine.

Uses

Actions

Ergotamine aborts attacks of migraine with or without aura by its specific vasotonic action on distended extracranial arteries.

Caffeine accelerates and increases the enteral absorption of ergotamine.

Pharmacokinetics

Studies using tritium-labelled ergotamine indicate that 62% of an oral dose is absorbed from the gastrointestinal tract. Peak plasma levels are reached about 2 hours after ingestion. Ergotamine is extensively metabolized in the liver. In terms of unchanged drug its absolute bioavailability is about 2% when given orally and about 5% when given by the rectal route. It has been suggested that the therapeutic effects of the drug are partially due to active metabolites. Protein binding amounts to 98%. Parent drug and metabolites are mainly excreted in the bile. Their elimination from plasma is biphasic, with half-lives of 2.7 and 21 hours, respectively.

Caffeine is rapidly and almost completely absorbed; it is metabolized to a large extent. The metabolites are excreted mainly in the urine. Plasma elimination half-life is about 3.5 hours, protein binding 35%.

Indications

Treatment of acute attacks of migraine with or without aura.

Dosage and Administration

Cafergot should be given at the first symptoms of an attack.

Adults

The first time Cafergot is taken, an initial dose of 2 Cafergot tablets orally, is recommended. If relief is not obtained within half an hour, a further tablet should be administered; this may be repeated at half-hourly intervals, but the maximum daily dose indicated below should not be exceeded.

For subsequent attacks the initial dose may be increased to 3 tablets, depending on the total dose required in previous attacks. If pain persists, additional doses of 1 tablet may be taken at half-hourly intervals up to the maximum dose (see below).

Children (6 to 12 years)

The initial dose is 1 Cafergot tablet; additional doses of 1 tablet may be given twice only, if required, in the course of an attack.

The following restriction must be observed:

If supplementary antimigraine medication is required, the use of any ergotamine-containing preparations, intranasal or parenteral dihydroergotamine or sumatriptan or other 5HT₁-receptor agonists must be avoided (see Contraindications).

Maximum dose per attack or per day

Adults: 6 mg ergotamine tartrate = 6 tablets.

Children: 3 mg ergotamine tartrate = 3 tablets.

Maximum weekly dose

Adults: 10 mg ergotamine tartrate = 10 tablets.

Children: 5 mg ergotamine tartrate = 5 tablets.

Contraindications

- Known hypersensitivity to ergot alkaloids, caffeine, or any other components of the formulation.
- Pregnancy and breast-feeding.
- Impaired peripheral circulation, obliterative vascular disease, coronary heart disease, inadequately controlled hypertension, septic conditions, shock.
- Severe renal or hepatic impairment.
- Temporal arteritis.
- Hemiplegic or basilar migraine.
- Concomitant treatment with macrolide antibiotics, HIV protease or reverse transcriptase inhibitors, azole antifungals
- Concomitant treatment with vasoconstrictor agents including ergot alkaloids, sumatriptan and other 5HT₁ receptor agonists

Warnings and Precautions

Cafergot is only indicated for the treatment of acute migraine attacks and not for prevention.

Continued daily use of Cafergot or its use in excess of the recommended doses must be avoided since they may cause vasospasm.

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

Patients who are being treated with Cafergot should be informed of the maximum doses allowed and of the first symptoms of overdose: hypoaesthesia, paresthesia, e.g. numbness, tingling in the fingers and toes, non-migraine-related nausea and vomiting, and symptoms of myocardial ischaemia e.g. precordial pain. If symptoms such as tingling in the fingers or toes occur, the drug should be discontinued at once and the physician consulted.

If, contrary to recommendations, ergotamine-containing drugs including Cafergot 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.

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

The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot.

Preclinical safety data

Acute toxicity

LD₅₀ values after single intravenous injection of Cafergot (ergotamine/caffeine 1:50) were found to be 40 mg/kg in rabbits, 124 mg/kg in rats, and 111 mg/kg in mice. After single oral administration in mice, LD₅₀ was 474 mg/kg.

Chronic and subchronic toxicity

In a 26-week oral safety study in beagle dogs, ergotamine induced vomiting, salivation and decreased heart rate. In addition, superficial necrosis at the ear margin was observed, which is a common finding in lop-eared dogs and is due to the marked vasoconstrictor effect of the drug.

Carcinogenicity

There are no data about the carcinogenic potential of ergotamine.

Reproductive toxicity

Ergotamine showed no evidence for embryonal mortality or teratogenic effects in rabbits at 1, 3 and 10 mg/kg per day, and in rats at up to 3 mg/kg per day. However, in rats given 10 mg/kg per day, maternal weight increase was inhibited, fetal ossification retarded and prenatal mortality increased. High ergotamine doses constricted the uterine vessels, reduced blood supply and thus induced hypoxia which is known to be responsible for teratogenic effects in the offspring. The combination of ergotamine and caffeine (1:100) revealed no teratogenic potential in rats and rabbits. In a reproductive performance study in male rats, fertility was not impaired. In a reproductive performance study and a peri-/post-natal study in female rats, an increased number of stillbirth and/or peri-/post-natal mortality was observed. In animal studies, caffeine was found to be teratogenic only at very high doses.

Use during Pregnancy and Lactation

Category C

Cafergot is 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, diarrhoea, weak pulse and unstable blood pressure in infants. Thus, Cafergot is contraindicated in nursing mothers.

Effects on ability to drive and use machines

Patients experiencing dizziness, or impaired reactions, should not drive or operate machinery.

Adverse Effects

The most common of all side-effects are nausea and vomiting. Depending on the dose of ergotamine, signs and symptoms of vasoconstriction may occur. Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$), including isolated reports.

Table 1

Immune system disorders
Rare: Hypersensitivity reactions ¹
Nervous system disorders

Common:	Dizziness
Uncommon:	Paraesthesia (e.g. tingling), hypoaesthesia (e.g. numbness)
Ear and labyrinth disorders	
Rare:	Vertigo
Cardiac disorders	
Uncommon:	Cyanosis
Rare:	Bradycardia, tachycardia
Very rare:	Myocardial ischaemia, myocardial infarction
Vascular disorders	
Uncommon:	Peripheral vasoconstriction
Rare:	Increase in blood pressure
Very rare:	Gangrene
Respiratory, thoracic and mediastinal disorders	
Rare:	Dyspnoea
Gastrointestinal disorders	
Common:	Nausea and vomiting (not migraine related), abdominal pain
Uncommon:	Diarrhoea
Skin and subcutaneous tissue disorders	
Rare:	Rash, face oedema, urticaria
Musculoskeletal and connective tissue disorders	
Uncommon:	Pain in extremities
Rare:	Myalgia
General disorders and administration site conditions	
Uncommon:	Weakness in extremities
Investigations	
Rare:	Absence of pulse
Injury, poisoning and procedural complications	
Rare:	Ergotism ²

¹ Hypersensitivity reactions such as skin rash, face oedema, urticaria and dyspnoea.

² Ergotism is defined as an intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia of the extremities and other tissues. 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 (see Special warnings and special precautions).

The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot

Interactions

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 Cafergot must be avoided, 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 both inhibitors and substrates of CYP3A. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Some antidepressants such as fluoxetine, fluvoxamine or nefazodone may increase the levels of the ergot derivatives.

A few cases of vasospastic reactions have been reported among patients treated concomitantly with ergotamine-containing preparations and propranolol. 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

Overdosage

Symptoms

Nausea, vomiting, drowsiness, confusion, tachycardia, dizziness, respiratory depression, hypotension, convulsion, shock, coma, symptoms and complications of ergotism.

Ergotism is defined as an intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia of the extremities such as numbness, tingling and pain in the extremities, cyanosis, absence of pulse and if the condition is allowed to progress untreated, gangrene may result. Furthermore ergotism can also involve signs and symptoms of vascular ischemia of other tissues such as renal or cerebral vasospasm. Most cases of ergotism are associated with chronic intoxication and/ or overdose.

Treatment

In the case of orally ingested drug, administration of activated charcoal is recommended. In the case of very recent oral intake gastric lavage may be considered.

Treatment should be symptomatic. In the event of severe vasospastic reactions, i.v. 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 are recommended. In the event of coronary constriction, appropriate treatment such as nitroglycerin should be initiated.

Pharmaceutical Precautions

Protect from light. Store at or below 25 °C.
Cafergot must be kept out of the reach and sight of children.

Medicines Classification

Prescription Medicine

Package Quantities

Bottles of 100 tablets

Further Information

Cafergot tablets also contain tartaric acid, magnesium stearate, talc, maize starch, cellulose, iron oxide yellow (E172).

Name and Address

AFT Pharmaceuticals Ltd
9 Anzac Street (Level 2)

Takapuna
Auckland
Email:customer.service@aftpharm.com

Date of Preparation

1 April 2010