

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Cafergot[®] Suppositories 2mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ergotamine tartrate PhEur 2mg and caffeine PhEur 100mg.

3. PHARMACEUTICAL FORM

2mg off-white suppositories, 3cm in length, 1cm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute attacks of migraine and migraine variants unresponsive to simple analgesics.

4.2 Posology and method of administration

Adults:

There is considerable inter-individual variation in the sensitivity of patients to ergotamine. Care should therefore be exercised in selecting the optimum therapeutic dose for an individual patient which will not give rise to unwanted effects, either acutely or chronically. The maximum recommended dosages should not be exceeded and ergotamine treatment should not be administered at intervals of less than 4 days.

For maximum efficacy, the optimal dose (in the preferred presentation) should be administered immediately prodromal symptoms are experienced.

One suppository should be administered at the first warning of an attack. This dose is normally sufficient, although some individuals may require higher dosages which should never exceed 2 suppositories (4mg ergotamine) in 24 hours. It is essential to use the minimum effective dose.

The maximum recommended weekly dosage of 4 suppositories (8mg ergotamine) should never be exceeded.

Children under 12 years: Not recommended.

Elderly: Whilst there is no evidence to suggest that the elderly require different dosages of Cafergot, the contraindications of this drug are common in the elderly, eg. coronary heart disease, renal impairment, hepatic impairment and severe hypertension. Caution should therefore be exercised when prescribing for this age group.

4.3 Contraindications

Known hypersensitivity to ergot alkaloids, caffeine, or any other components of the formulation.

Patients with impaired peripheral circulation, obliterative vascular disease, coronary heart disease, inadequately controlled hypertension, septic conditions or shock. Impaired hepatic or renal function, temporal arteritis and patients with hemiplegic or basilar migraine are also contraindicated.

Pregnancy or nursing mothers.

Concomitant treatment with macrolide antibiotics, HIV-protease or reverse-transcriptase inhibitors, azole antifungals (see 4.5 Interactions with other medicinal products and other forms of interaction).

Concomitant treatment with vasoconstrictive agents (including ergot alkaloids, sumatriptan and other 5HT₁-receptor agonists (see 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

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

Continued daily use of Cafergot or use in excess of the recommended doses must be avoided since this 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 over dosage: hypoaesthesia, paraesthesia (eg 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 are used excessively over years, they may induce fibrotic changes, in particular of the pleura and retroperitoneum. There have also been rare reports of fibrotic changes of the cardiac valves.

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

Rare cases of solitary rectal or anal ulcer have occurred from abuse of ergotamine containing suppositories, usually at higher than recommended doses or with continuous use at the recommended dose for many years.

4.5 Interaction with other medicinal products and other forms of interaction

Ergotism (increased peripheral vasoconstriction)

Several drugs increase the risk of ergotism (vasoconstriction, convulsions, other CNS and GI effects) and concomitant use of the following with Cafergot should be avoided (see section 4.3): -

Antibacterials

- Macrolides (eg erythromycin, azithromycin, clarithromycin, spiramycin) or telithromycin
- quinupristin/dalfopristin
- tetracycline

Antifungals

- Imidazoles (eg ketaconazole, miconazole)
- Triazoles (eg itraconazole, posaconazole, voriconazole)
- Antivirals (eg amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, atazanavir, efavirenz)

5HT₁ agonists

- Avoid Cafergot for 6 hours after almotriptan, rizatriptan, sumatriptan or zolmitriptan. Avoid almotriptan, rizatriptan, sumatriptan or zolmitriptan for 24 hours after Cafergot.
- Avoid Cafergot for 24 hours after eletriptan or frovatriptan. Avoid eletriptan or frovatriptan for 24 hours after Cafergot.

Cimetidine

Sympathomimetic agents

Beta-blockers

Other vasoconstrictors - excessive nicotine may enhance vasoconstriction

Other

Anaesthetics

- Halothane reduces the effect of ergometrine on the parturient uterus

Antidepressants

- Reboxetine - possible increase in hypertension in association with ergot

4.6 Pregnancy and lactation

Ergotamine-containing products are contraindicated in pregnancy due to 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 are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

Dizziness and feelings of anxiety (trembling, sweating etc) have been reported with Cafergot. If a patient is affected they should not drive, operate machinery or take part in activities where these reactions may put themselves or others at risk.

4.8 Undesirable effects

The caffeine component of Cafergot may give rise to unwanted stimulant effects.

Side effects of Cafergot are related in the main to the ergotamine component.

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 (greater than or equal to 1 in 10); common (less than or equal to 1 in 100, less than 1 in 10); uncommon (greater than or equal to 1 in 1,000, less than 1 in 100); rare (greater than or less than 1 in 10,000, less than 1 in 1,000) very rare (less than 1 in 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
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: Ergotism²

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 vascular ischemia of the extremities and other tissues (such as renal or cerebral vasospasm)

Rare cases of intestinal ischaemia have been associated with chronic use and overuse of ergotamine-containing preparations. Rarely, headache may be provoked either by chronic overdosage or by rapid withdrawal of the product.

Excessive use of ergotamine-containing products for prolonged periods may result in fibrotic changes, in particular of the pleura and retroperitoneum. Rare cases of fibrosis of cardiac valves have also been reported.

The occurrence of drug induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot (see 4.4 Special Warnings and Precautions).

Rectal and anal ulcers may occur after long term use or use at doses higher than recommended dose of ergotamine containing suppositories (see 4.4 Special Warnings and Precautions).

4.9 Overdose

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

Ergotism is defined as an intense arterial vasoconstriction, producing signs and symptoms of vascular ischemia of the extremities such as tingling, numbness 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 ischaemia of other tissues such as renal and cerebral vasospasm. Most cases of ergotism are associated with chronic intoxication and/or overdose.

Treatment: should be directed to the elimination of ingested material by aspiration and gastric lavage.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ergotamine is a highly vasoactive ergot alkaloid having characteristically complex pharmacological actions. It is a partial tryptaminic agonist in certain blood vessels and both a partial agonist and antagonist of α -adrenergic receptors of blood vessels.

Although its exact mode of action in migraine is not known, its therapeutic effects have been attributed to its ability to cause vasoconstriction, thereby eliminating the painful dilation/pulsation of branches of the external carotid artery.

5.2 Pharmacokinetic properties

There is great interindividual variation in the absorption of ergotamine in patients and volunteers. Bioavailability is of the order of 5% or less by oral or rectal administration. After im or iv administration, plasma concentrations decay in a bi-exponential fashion. The elimination half life is 2 to 2.5 hours and clearance is about 0.68L/h/kg. Metabolism occurs in the liver. The major enzyme involved in the metabolism of ergotamine is Cytochrome P450 (CYP) 3A4. The primary route of excretion is biliary.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid, lactose, Suppocire AM.

6.2 Incompatibilities

None

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Carton of 30 suppositories in an aluminium blister pack.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7. MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Ltd
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SN15 2BB

8. MARKETING AUTHORISATION NUMBER

PL16853/0003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 June 1998

10. DATE OF REVISION OF THE TEXT

30 March 2009