Cafergot®

(Ergotamine Tartrate with Caffeine)

کیفرگاٹ®

(ایرگوٹامائن ٹارٹریٹ کیفین کے ساتھ)

Composition and pharmaceutical form
Cafergot® tablets contains: 1 mg ergotamine tartrate and 100 mg caffeine.
Active moieties
Ergotamine and Caffeine.
Indications
Treatment of acute attacks of migraine with or without aura.
Dosage and administration
Dosage
General target population
Cafergot® should be given at the first symptoms of an attack.
If supplementary antimigraine medication is required, the use of any ergotamine-containing preparations, dihydroergotamine or sumatriptan or other 5-hydroxtryptamine (5HT1)- receptor agonists must be avoided (see section Contraindications).
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 as mentioned below.
Maximum dose per attack or per day
6 mg ergotamine tartrate = 6 tablets.
Maximum weekly dose
10 mg ergotamine tartrate = 10 tablets.
Special populations
Renal impairment
Cafergot® is contraindicated in patients with severe renal impairment (see section Contraindications).
Hepatic impairment
Patients with mild to moderate hepatic impairment should be appropriately monitored (see section Warnings and Precautions).
Cafergot® is contraindicated in patients with severe hepatic impairment (see section Contraindications).
Paediatrics
Safety and efficacy has not been established in paediatric patients.
Geriatrics (65 years age and above)
No studies have been performed in elderly patients (65 years age and above).
Contraindications
• Known hypersensitivity to ergot alkaloids, caffeine, or any other components of the formulations (see section Description and Composition).
Pregnancy and breast-feeding (see section Women of child-bearing potential, pregnancy, breastfeeding and fertility).
Impaired peripheral circulation, obliterative vascular disease, coronary heart disease, inadequately controlled hypertension, septic conditions, shock.
• Severe renal impairment.
• Severe hepatic impairment.
• Temporal arteritis.
• Hemiplegic or basilar migraine.
• Concomitant treatment with macrolide antibiotics, HIV protease or reverse transcriptase inhibitors, azole antifungals (see section Interactions).
• Concomitant treatment with vasoconstrictor agents (including ergot alkaloids, sumatriptan and other 5HT1 receptor agonists) (see section Interactions).
Warnings and precautions
Administration
Cafergot® is only indicated for the treatment of acute migraine attacks and not for prevention.
Patients who are being treated with **Cafergot®** should be informed of the maximum doses allowed and of the first symptoms of overdosage: 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.
Prolonged or excessive usage
Continued daily use of **Cafergot®** or its use in excess of the recommended doses must be avoided since it may cause vasospasm. 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.

Cardiovascular
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.
Hepatic impairment
Patients with mild to moderate hepatic impairment, especially cholestatic patients should be appropriately monitored.
Drug-induced headaches
The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with **Cafergot®**
Visual disturbances
Cases with sudden and transient loss of vision have been reported in post-marketing use. This adverse event may be related to vasospasm and ischaemic episode. Patients should stop using **Cafergot®** immediately if they experience visual disturbances and seek medical help in a timely manner.
Driving and using machines
Patients should not drive a vehicle or operate machinery if they experience visual disturbances.
Adverse drug reactions
The following adverse drug reactions (Table 1) have been derived from clinical trials and post-marketing experience with **Cafergot®** via spontaneous case reports and literature cases. Because these post-marketing reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.
Table -1 Adverse drug reactions (derived from clinical trials and post-marketing experience)

Immune system disorders	
Rare:	Hypersensitivity[1]
Nervous system disorders	
Common:	Dizziness
Uncommon:	Paraesthesia (e.g. tingling), hypoaesthesia (e.g. numbness)
Not known:	Somnolence, Drug induced headaches**
Eye disorders	
Not known:	Visual Impairment
Ear and labyrinth disorders	
Rare:	Vertigo
Cardiac disorders	
Uncommon:	Cyanosis
Rare:	Bradycardia, tachycardia
Very rare:	Myocardial ischaemia, myocardial infarction
Not known:	Endocardial fibrosis*
Vascular disorders	
Uncommon:	Peripheral vasoconstriction
Rare:	Blood pressure increased
Very rare:	Gangrene
Respiratory, thoracic and mediastinal disorders	
Rare:	Dyspnoea
Not known:	Pleural fibrosis*
Gastrointestinal disorders	
Common:	Nausea and vomiting (not migraine related), abdominal pain
Uncommon:	Diarrhoea
Not known:	Retroperitoneal fibrosis*
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 vascular ischemia of the extremities and other tissues (such as renal or cerebral vasospasm).
*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 also section Warnings and Precautions).

The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with **Cafergot® (see section Warnings and Precautions).

Interactions

Anticipated interactions resulting in a contraindication

Strong CYP3A4 inhibitors

The concomitant use of cytochrome P450 3A4 (CYP3A4) inhibitors such as macrolide antibiotics (e.g. troleandornycin, erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine), or azole antifungals (e.g. ketoconazole, itraconazole, voriconazole) and **Cafergot**® (see section Contraindications), since this can result in an elevated exposure to ergotamine and ergot toxicity (vasospasm and ischemia of the extremities and other tissues).

Vasoconstrictors

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

Observed interactions resulting in a concomitant use not recommended

Any possible increase in plasma concentration of caffeine due to interaction with other drug(s) may translate to increase in absorption of ergotamine. Caffeine undergoes extensive metabolism by CYP1A2 and the drugs that enhance or reduce the enzyme activity can modulate the metabolic clearance of caffeine. Fluoroquinolones, mexiletine, fluvoxamine, and oral contraceptives can increase the plasma exposure of caffeine. Interactions of caffeine with sympathomimetics can lead to increased blood pressure.

Observed interactions to be considered

Beta-blockers

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

Anticipated interactions to be considered

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.

Serotonin reuptake inhibitors

Concurrent use of ergotamine with Serotonin reuptake inhibitors (e.g. amitriptyline) including selective agents (e.g. sertraline) can lead to serotonin syndrome and need to be used with caution.

CYP3A4 inducers

Drugs (e.g. nevirapine, rifampicin) inducing CYP3A4 can lead to decrease in pharmacological action of ergotamine.

Absence of interaction

No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

Women planning to become pregnant should not take **Cafergot**®. When pregnancy is confirmed in women taking **Cafergot**® the treatment should be discontinued immediately. (See following subsection Pregnancy, as well as section Contraindications and section Non-clinical safety data).

Pregnancy

Cafergot® is contraindicated during pregnancy because ergotamine has oxytocic and vasoconstrictor effects on the placenta and umbilical cord. In a reproductive performance study and a peri-/post-natal study in female rats, an increased number of still births and/or peri-/post-natal mortality were observed following administration of oral ergotamine/caffeine (1:100). At high oral doses, ergotamine induced fetal retardation in experimental animals. The observation has been attributed to reduced uteroplacental blood flow (see section Non-clinical safety data).

Breast-feeding

Cafergot® is contraindicated in nursing mothers. Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhoea, weak pulse and unstable blood pressure in infants. Caffeine is also excreted in breast milk.

Fertility

In male rats receiving the combination of oral ergotamine and caffeine (1:100), fertility was not impaired (see section Non-clinical safety data).

Overdosage

Symptoms: nausea, vomiting, somnolence, 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 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, 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 nitroglycerin should be initiated.

Clinical pharmacology

Pharmacotherapeutic group, ATC code

Antimigraine preparations, NO2C A52.

Pharmacodynamics /Mechanism of action (MOA)

Ergotamine aborts attacks of migraine with or without aura by its specific vasotonic action on distended extracranial arteries. Ergotamine can cause vasoconstriction by stimulating alpha adrenergic and 5-HT receptors. It displays moderate to high affinity for various serotonin receptor subtypes, however its beneficial effect in migraine are primarily linked to agonist at 5-HT18 and 5-HT 10. Caffeine accelerates and increases the enteral absorption of ergotamine. Also caffeine exerts its analgesic activity through blockade of peripheral pronociceptive actions of adenosine and the activation of central noradrenergic pathways that constitute an endogenous painsuppressing system.

Pharmacokinetics

Ergotamine

Absorption

Studies using tritium-labeled ergotamine indicate that 62% of an oral dose is absorbed from the gastrointestinal tract. Peak plasma levels are reached about 2 hours after ingestion. In terms of unchanged drug its absolute bioavailability is about 2% when given orally. It has been suggested that the therapeutic effects of the drug are partially due to active metabolites.

Distribution

Protein binding for ergotamine amounts to 98%.

Biotransformation/Metabolism

Ergotamine is extensively metabolized in the liver and is a substrate for CYP3A4 enzyme system.

Elimination

Parent drug and metabolites are mainly excreted in the bile. Their elimination from plasma is biphasic, with alpha and beta half-lives of 2.7 and 21 hours, respectively.

Caffeine

Absorption

After oral administration, caffeine is rapidly and almost completely absorbed from the GI tract and peak plasma concentrations are reached in 15-120 minutes.

Distribution

Plasma protein binding of caffeine is 35%. Caffeine is distributed relatively uniformly throughout all body tissues, including cerebrospinal fluid, breast milk, saliva and semen. The volume of distribution is about 0.7 L/kg. Caffeine crosses the placental barrier.

Biotransformation/Metabolism

Caffeine is metabolized to a large extent by CYP1A2 to paraxanthine. Paraxanthine is further metabolized to uracil and uric acid derivatives by demethylation and hydroxylation. Plasma elimination half-life is about 3.5 hours.

Elimination

The metabolites are excreted mainly in the urine. The clearance of caffeine is increased by smoking.

Clinical studies

Cafergot® is an established product.

Non-clinical safety data

Mutagenicity

No mutagenicity study was performed with ergotamine/caffeine combinations. In vivo models showed no evidence of mutagenic activity of ergotamine, and therefore are considered devoid of genotoxic potential. The overall evidence from numerous genetic toxicity studies indicates that caffeine has no genotoxic potential at exposures relevant to man.

Carcinogenicity

No study is available which evaluated the carcinogenic potential of ergotamine or ergotamine/caffeine combinations. Studies in rodents showed no carcinogenic activity of caffeine.

Reproductive toxicity

The combination of oral ergotamine and caffeine (1:100) revealed no teratogenic potential in pregnant rats and rabbits. At high oral ergotamine doses, developmental toxicity (e.g. decreased fetal body weight, delayed skeletal ossification or increased prenatal mortality) was observed in experimental animals. This observation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone induced by ergotamine. In animal studies, caffeine was found to be teratogenic at very high doses only.

Special precautions for storage

Protect from heat, light and moisture.

Cafergot® must be kept out of the reach and sight of children.

Nature and contents of container

Pack of 10 Tablets.

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔

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Manufactured by:
Indus Pharma (Pvt.) Ltd.,
Korangi Industrial Area, Karachi.