

New Zealand Data Sheet

1 CAFERGOT (ERGOTAMINE TARTRATE 1 MG AND CAFFEINE 100 MG TABLET)

CAFERGOT ergotamine tartrate 1 mg and caffeine 100 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ergotamine tartrate 1 mg and Caffeine 100 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute attacks of migraine with or without aura in adults.

4.2 Dose and method of administration

Cafergot should be given at the first signs of a migraine attack.

Dose

Adults

First attack:

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 of 6 tablets should not be exceeded.

Subsequent attacks:

If the pain persists, take 1 tablet every half an hour up to the maximum daily dose of 6 tablets. The maximum weekly dose is 10 tablets.

Children under 18 years

Not recommended.

Maximum dose per attack or per day

Adults: 6 mg ergotamine tartrate = 6 tablets.

Maximum weekly dose

Adults: 10 mg ergotamine tartrate = 10 tablets.

Special populations*Renal impairment*

Cafergot is contraindicated in patients with severe renal impairment (see Contraindications).

Hepatic impairment

Cafergot is contraindicated in patients with severe hepatic impairment (see Contraindications). Patients with mild to moderate hepatic impairment, especially patients with cholestasis, should be appropriately monitored (see Warnings and Precautions).

Pediatrics

Cafergot is not recommended in children and adolescents under the age of 18 years. Safety and efficacy have not been established in pediatric patients.

Geriatrics

Cafergot is not recommended for patients aged over 65 years. No studies have been performed in elderly patients (65 years age and above).

Method of administration**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).

Taking Cafergot repeatedly over extended periods must be avoided.

The concomitant use of an anti-emetic may enhance the action of the tablets.

4.3 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 impairment
- Severe hepatic impairment
- Temporal arteritis
- Hemiplegic or basilar migraine
- Concomitant treatment with cytochrome P450 3A4 (CYP3A4) inhibitors such as macrolide antibiotics (all except spiramycin), HIV protease or reverse transcriptase inhibitors and azole antifungals

- Concomitant treatment with vasoconstrictor agents including ergot alkaloids, sumatriptan, other 5HT₁ receptor agonists, nicotine (e.g. heavy smoking) and sympathomimetics
- Concomitant treatment with fluoroquinolones, mexiletine, fluvoxamine, and oral contraceptives as can modulate the metabolic clearance of caffeine and consequently may translate to increase in absorption of ergotamine
- Patients who developed fibrosis (retroperitoneal fibrosis, pleurisy, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion or similar condition) under previous treatment with an ergotamine derivative.

4.4 Special warnings and precautions for use

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

Cardiovascular effects

Continued daily use of Cafergot or its use in excess of the recommended doses must be avoided since this may cause vasospasm. If signs of vascular spasms are observed, Cafergot should be discontinued and treatment with a peripheral vasodilator initiated.

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. If chest pain occurs treatment should be withdrawn.

Ergotism

Long-term use of ergotamine can cause ergotism, including severe cases of symptoms of constriction of peripheral blood vessels, with possible fatal outcome.

To avoid the risk of ergotism 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.

Fibrotic complications

If, contrary to recommendations, ergotamine-containing drugs including Cafergot are used excessively over years, they may induce fibrotic changes, including pleural, retroperitoneal and pulmonary fibrosis. There have also been rare reports of fibrotic changes of the cardiac valves.

Hepatic impairment

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

Drug-induced headache

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 episodes. Patients should stop using Cafergot immediately if they experience visual disturbances and seek medical help.

4.5 **Interaction with other medicines and other forms of interaction**

Potent CYP3A4 inhibitors

The concomitant use of Cafergot with cytochrome P450 3A (CYP3A) inhibitors such as macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin; except spiramycin); HIV protease or reverse transcriptase inhibitors (e.g. amprenavir, atazanavir, fosamprenavir, ritonavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir, delavirdine, efavirenz); or azole antifungals (e.g. ketoconazole, itraconazole, voriconazole) must be avoided (see Contraindications). Concomitant use 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.

Moderate/weak CYP3A4 inhibitors

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

No pharmacokinetic interactions between ergotamine and cytochrome P450 isoenzymes are known.

Vasoconstrictors

Concurrent use of vasoconstrictor agents including preparations containing ergot alkaloids (bromocriptine, cabergoline, pergolide, lisuride), sumatriptan and other 5HT₁ receptor agonists (almotriptan, fovatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan), nicotine (e.g. heavy smoking) and sympathomimetics must be avoided since this may result in enhanced vasoconstriction, (see Contraindications). Allow 24 hours between the discontinuation of the triptans and the use of the alkaloid.

CYP3A4 inducers

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

Beta-blockers

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

Antidepressants

Some antidepressants such as fluoxetine, fluvoxamine or nefazodone may increase the levels of the ergot derivatives. Concurrent use of ergotamine with serotonin reuptake inhibitors (e.g. amitriptyline) including selective agents (e.g. sertraline) can lead to serotonin syndrome, caution is required for concurrent use.

CYP1A2

Caffeine undergoes extensive metabolism by CYP1A2. Concurrent use with substances like fluoroquinolones, mexiletine, fluvoxamine, oral contraceptives and sympathomimetics, that can reduce CYP1A2 activity may modulate the metabolic clearance of caffeine and consequently may translate to increase in absorption of ergotamine, see Contraindications.

4.6 **Fertility, pregnancy and lactation**

Pregnancy

Category C

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 stillbirths 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.

Women with the potential to become pregnant must use effective birth control throughout the treatment period.

Breastfeeding

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

Fertility

In male rats receiving the combination of oral ergotamine and caffeine (1:100), fertility was not impaired.

4.7 **Effects on ability to drive and use machines**

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

4.8 **Undesirable 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 are listed by MedDRA system organ class and 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 ($< 1/10,000$), not known (frequency cannot be estimated from the available data).

Immune system disorders

Rare: Hypersensitivity reactions¹

Nervous system disorders

Common: Dizziness

Uncommon: Paraesthesia (e.g. tingling) in fingers and toes, hypoaesthesia (e.g. numbness)

Rare: Drowsiness

Not known: Somnolence, drug-induced headache, an intensifying headache with autonomic disturbances occurs within 24-48 hours of ergotamine withdrawal and may

continue for 72 hours or longer. Headache is also a recognised symptom of caffeine withdrawal.

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: Hypertension

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 extremity, weakness in extremity

Rare: Myalgia, muscle spasms

Investigations

Rare: Pulse absent

Injury, poisoning and procedural complications

Rare: Ergot poisoning²

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions
<https://nzphvc.otago.ac.nz/reporting/>

4.9 **Overdose**

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Antimigraine preparations
ATC code: N02CA52

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 properties at 5-HT_{1B} and 5-HT_{1D}.

Regional changes to cerebral flows resulting from intracranial arterial vasodilatation accompany the migraine attack. The mechanism seems to be related to a reduction in systemic levels of serotonin which, in turn, leads to the vasomotor changes observed. Because of its direct vasoconstrictive effect on the smooth muscles of the dilated vessels, ergotamine aborts the migraine attack and vascular headaches. Ergotamine also acts on the vasomotor centres and leads to the blockage of peripheral alpha-adrenergic receptors.

Ergotamine exerts a tonic effect on the smooth vascular musculature and presents a particular affinity for arterial monoaminergic receptors (NA and HT), especially in the external carotid network.

Numerous studies performed in animals and humans have amply demonstrated that the vasoconstrictive action of ergotamine manifests itself selectively at the carotid and extracranial arteries and is due mainly to stimulation of serotonergic and alpha-adrenergic receptors.

As regards any changes in blood pressure, it has been demonstrated that these depend mainly on the pre-existing pressures: with Cafergot there is a slight and transient increase in pressure in normotensive subjects and hypotension in hypertensive subjects.

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 pain suppressing system.

5.2 **Pharmacokinetic properties**

Ergotamine

Absorption

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.

Distribution

Protein binding for ergotamine amounts to 98%.

Biotransformation

Ergotamine is extensively metabolized in the liver and is a substrate for the CYP3A4 enzyme system. It has been suggested that the therapeutic effects of the drug are partially due to active metabolites.

Elimination

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

Absorption

After oral administration, caffeine is rapidly and almost completely absorbed from the GI tract, and peak concentrations achieved after oral administration of 175 mg range between 5 - 10 µg/mL. 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

Caffeine is metabolized to a large extent by CYP1A2 to paraxanthine. Paraxanthine is further metabolised to uracil and uric acid derivatives by demethylation and hydroxylation.

Elimination

The metabolites are excreted mainly in the urine. Plasma elimination half-life is about 3.5 hours. The clearance of caffeine is increased by smoking.

5.3 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. Studies in rodents showed no carcinogenic activity of caffeine.

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 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 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.

Mutagenicity

No mutagenicity study was performed with ergotamine/caffeine combinations. In vivo models showed no evidence of mutagenic activity of ergotamine, and therefore is 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid,
Magnesium stearate
Talc
Maize starch
Cellulose
Iron oxide yellow (E172)

6.2 Incompatibilities

Not known

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Bottles of 100 tablets

6.6 Special precautions for disposal and other handling

No special requirements

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

AFT Pharmaceuticals Ltd
PO BOX 33203
Takapuna
Auckland
Contact number: 0800 423 823

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
31 December 1969

10 DATE OF REVISION OF TEXT

13 February 2018

Summary table of changes

Section changed	Summary of new information
All	Datasheet format updated
4.8	This section has been updated for addition of adverse effect as a result of signal detection, Analgesic-induced or rebound headaches after ergotamine withdrawal.
5	Pharmacotherapeutic group has been added