

## **CAFERGOT®**

### **COMPOSITION**

Cafergot® Tablets: Ergotamine tartrate 1 mg and Caffeine 100 mg.  
Cafergot® S Suppositories: Ergotamine tartrate 2 mg and Caffeine 100 mg.

### **DESCRIPTION**

Ergotamine tartrate ((5'S)-12'-hydroxy-2'-methyl-3',6',18-trioxo-5-benzylergotaman(+)-tartrate) is a slightly hygroscopic colourless, odourless crystal or white or yellowish-white crystalline powder. It is soluble in water, slightly soluble in ethanol and chloroform and practically insoluble in ether.

Caffeine (1,3,7,-trimethylpurine-2,6(3H,1H)-dione) is an odourless, silky white crystal, or white crystalline powder which sublimates readily. It is sparingly soluble in water and is slightly soluble in alcohol and ether.

Cafergot tablets are white, round sugar-coated, tablets with no markings. Cafergot S suppositories are whitish or with a tinge of grey/pink, approximately 30 mm in length and approximately 10 mm thick.

### **Action**

The mode of action of ergotamine in aborting attacks of migraine and other vascular headaches may be due to its direct vasoconstrictive action on the dilated extracranial arteries. Caffeine accelerates and increases the enteral absorption of ergotamine.

### **Pharmacokinetics**

There is limited information on the kinetics of ergotamine; it appears that there is great inter-individual variation in the absorption of ergotamine with the oral absorption being described as 62% in a study of elderly subjects. However, there appears to be extensive first pass metabolism. A study using rectal suppositories revealed low and variable plasma levels of ergotamine. Bioavailability is  $\leq 5\%$  from both oral and rectal formulations. It has been suggested that the therapeutic effects of the drug are partially due to active metabolites. There is very little information on distribution and protein binding. Metabolism occurs in the liver and the main mode of excretion is via the bile. Information on plasma half-life is based on a study of six elderly subjects which revealed that elimination of ergotamine was biphasic with half-lives of 2.7 and 21 hours in the alpha and beta phase respectively.

Caffeine is rapidly and totally absorbed and is completely bioavailable. The volume of distribution of caffeine is 0.5 to 0.8 L/kg with a tendency to have higher values in females than males. It is 35-40% protein bound, metabolised mainly in the liver and excreted predominantly in the urine. The half-life varies in individuals from 2.5 to 10 hours.

No formal pharmacokinetic data are available on the fixed combination of ergotamine tartrate and caffeine.

## **INDICATIONS**

Acute attacks of migraine, migraine variants and related types of vascular headaches.

## **CONTRAINDICATIONS**

- peripheral vascular disorders
- obliterative vascular disease
- coronary artery disease
- severe and/or inadequately controlled hypertension
- hepatic and renal insufficiency
- concomitant treatment with CYP3A4 inhibitors, including antifungals (ketoconazole, itraconazole), HIV-protease inhibitors or reverse transcriptase inhibitors (ritonavir, nelfinavir, indinavir, delavirdine) and macrolide antibiotics (erythromycin, clarithromycin) [see “PRECAUTIONS”]
- Concomitant treatment with vasoconstrictor agents (including ergot alkaloids, sumatriptan and other 5HT<sub>1</sub> receptor agonists) [see “PRECAUTIONS – Interactions with Other Drugs”]
- pregnancy and lactation
- septic conditions, shock
- temporal arteritis, hemiplegic or basilar migraine
- hypersensitivity to any component of the drug.

### **Use in Pregnancy (Category C)**

Ergotamine and ergot derivatives induce uterine contraction and may therefore cause premature parturition or hypertonic labour. Products containing ergotamine or ergot derivatives should therefore be avoided during pregnancy.

### **Use in Lactation**

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.

## **PRECAUTIONS**

### **CYP3A4 inhibitors**

There have been rare reports of serious adverse events in connection with the co-administration of ergot alkaloids and potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischaemia and/or ischaemia of the extremities. Examples of some of the more potent CYP3A4 inhibitors include the antifungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir and indinavir, and

the macrolide antibiotics erythromycin and clarithromycin. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine and clotrimazole. The use of CYP3A4 inhibitors with Cafergot should be avoided (see “CONTRAINDICATIONS”). These lists are not exhaustive and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with Cafergot.

### **Fibrotic complications**

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of ergot alkaloids. Rarely, prolonged use of ergot alkaloids has also been associated with cardiac valvular fibrosis (see “ADVERSE REACTIONS”).

Although signs and symptoms of vasospasm are rarely reported even after long term intermittent use of Cafergot, care should be taken to remain within the limits of the recommended dosage to avoid ergotism. Ergotism is manifested by symptoms and signs of peripheral vascular ischaemia due to vasoconstriction by direct action on the vascular smooth muscle. Headache, intermittent claudication, muscle pain, numbness, coldness and pallor of the digits may occur with chronic intoxication which, if allowed to progress, may result in gangrene.

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 of peripheral vascular disturbance appear, such as tingling in fingers or toes, weakness in legs, muscle pain etc., treatment should be discontinued at once and the physician consulted.

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

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, the treatment should be withdrawn.

Ergotamine has caused dependence when used on a regular basis for migraine prophylaxis. Caffeine dependence could also occur with withdrawal causing headache, tiredness, runny nose and muscle pain.

The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot. Withdrawal after long indiscriminate use has, in rare instances, led to patients developing withdrawal headaches.

Rare cases of a 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.

Like all drugs, Cafergot should be kept out of reach of children.

### **Interactions**

CYP3A4 inhibitors (e.g. macrolide antibiotics and protease inhibitors):

Pharmacokinetic interactions have been reported in patients treated orally with ergot alkaloids (e.g. increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of CYP3A4 metabolism of the alkaloids by troleandomycin. Ergot alkaloids have also been shown to be both inhibitors and substrates of CYP3A4 catalysed reactions and rare reports of ergotism have been obtained from patients treated with ergot alkaloids and macrolide antibiotics (e.g. troleandomycin, clarithromycin, erythromycin). Patients treated with ergot alkaloids and protease inhibitors (e.g. ritonavir), presumably due to inhibition of CYP3A4 metabolism of ergotamine (see “CONTRAINDICATIONS” and “PRECAUTIONS-CYP3A4 inhibitors”). No pharmacokinetic interactions involving other CYP450 isoenzymes are known.

### **Other vasoconstrictors:**

Ergotamine tartrate and caffeine should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker propranolol has been reported to potentiate the vasoconstrictive action of ergotamine tartrate and caffeine by blocking the vasodilating property of epinephrine. Nicotine (e.g. smoking) may provoke vasoconstriction in some patients, predisposing to a greater ischaemic response to ergot therapy. Concurrent use of ergotamine and caffeine with other ergot alkaloids, sumatriptan and other 5-HT<sub>1</sub> receptor agonists must also be avoided since this may result in enhanced vasoconstriction (see “CONTRAINDICATIONS”).

### **Effects on Ability to Drive or Operate Machinery:**

Patients experiencing dizziness or other central nervous system disturbances should not drive or operate machinery.

## **ADVERSE REACTIONS**

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**

<b>Immune system disorders</b>	
Rare:	Hypersensitivity reactions <sup>1</sup>
<b>Nervous system disorders</b>	
Common:	Dizziness
Uncommon:	Paraesthesia (e.g. tingling), hypoaesthesia (e.g. numbness)
Rare:	Drowsiness (Cafergot-PB only)
<b>Ear and labyrinth disorders</b>	

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

<sup>1</sup> Hypersensitivity reactions such as skin rash, face oedema, urticaria and dyspnoea.

<sup>2</sup> Ergotism is defined as an intense arterial vasoconstriction, producing signs and symptoms of peripheral 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 “Precautions”).

Dependence has been reported, with withdrawal headaches. The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot (see “Precautions”).

Rectal and anal ulcers may occur after long term use or use at doses higher than the recommended dose of ergotamine-containing suppositories.

## **DOSAGE**

Cafergot is specifically designed for the treatment of the acute migraine attack; it should be administered upon the first symptom of the attack.

### **Adults:**

An initial dose of two Cafergot tablets or one Cafergot S suppository is recommended. This dose is usually sufficient although some patients may require higher dosages, but the maximum daily dose indicated below should not be exceeded.

Maximum dose per attack or per day: 6 mg ergotamine tartrate - six tablets or three suppositories.

Maximum weekly dose: 10 mg ergotamine tartrate - ten tablets or five suppositories.

**Children:**

Cafergot S suppositories and Cafergot tablets are not recommended for use in children under 12 years.

The following restriction must be observed: If supplementary antimigraine medication is required, the use of any ergotamine-containing preparations, intranasal or parenteral dihydroergotamine, sumatriptan or other 5HT<sub>1</sub>-receptor agonist must be avoided [see “CONTRAINDICATIONS”].

**OVERDOSAGE**

Symptoms of acute poisoning include nausea, vomiting, diarrhoea, thirst, coldness of the skin, pain, numbness or tingling in the extremities, weak or absent pulses, tachycardia, hypertension or hypotension, drowsiness, dizziness, confusion, convulsions, respiratory distress coma, shock, 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 is symptomatic. Administration of activated charcoal is advised. Adequate pulmonary ventilation needs to be ensured, and hypotension corrected.

Arterial spasm could be treated with warmth and protection of the ischaemic limbs; vasodilators may be administered if required.

Nausea and vomiting may be relieved by metoclopramide. Anticoagulants and antibiotics may be given if necessary.

**PRESENTATION AND PACKING**

White, round sugar coated tablets with no markings containing 1 mg ergotamine tartrate and 100 mg caffeine. Bottles of 20.

Suppositories, whitish or with a tinge of grey/pink containing 2 mg ergotamine tartrate and 100 mg caffeine. Strips of 5.

Store below 25°C.

**POISON SCHEDULE**

Schedule S4 in all States.

**APPROVAL DATE**

Approved by the Therapeutic Goods Administration: 19 November 2002

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**SPONSOR**

Novartis Pharmaceuticals Australia Pty Ltd

(ABN 18 004 244 160)

54 Waterloo Road

NORTH RYDE NSW 2113

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