SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CAFERGOT ® Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ergotamine tartrate ..... 1 mg

Anhydrous caffeine.....100 mg

For one tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Migraine attacks, migraine equivalents and related types of vascular headaches.

4.2 Posology and method of administration

Posology

Adults:
The usual recommended dose is 1 to 2 mg of ergotamine tartrate (i.e. 1 to 2 tablets), as soon as the migraine prodromes occur.

If symptoms reappear after administration of the medicinal product, a second dose may be given within 24 hours, allowing for an interval of at least 2 to 3 hours between the two doses.

The maximum daily dose must never exceed 4 mg of ergotamine tartrate (i.e. 4 tablets).
It is recommended that patients count the number of days in a month in which they took the medicinal product. Treatment must be reviewed if the patient requires more than 2 days of treatment per week for more than 3 months, to allow for the prescription of a maintenance treatment.

Special populations:

Paediatric population (younger than 12 years)
There are no data concerning the use of ergotamine in children. Therefore, the use of Cafergot in this age group is not recommended.

Elderly (older than 65 years)
The safety and efficacy of Cafergot have not been assessed in patients aged over 65 years. Therefore, use in this age group is not recommended.

Renal impairment
Cafergot is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment
Cafergot is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of administration
Oral use

4.3 Contraindications

- Known hypersensitivity to ergot alkaloids, caffeine or to any of the excipients mentioned in section 6.1.
- Disorders that predispose the patient to angiospastic reactions: coronary insufficiency (particularly unstable angina or coronary spastic angina), severe infectious states, shock, obliterative coronary artery disease, peripheral vascular diseases such as Raynaud's phenomenon, hyperthyroidism, history of transient ischaemic attack or cerebral disorders, or poorly controlled hypertension.
- Temporal arteritis.
- Hemiplegic or basilar migraine.
- Severe renal or hepatic impairment.
- Pregnancy and breast-feeding.
- In combination with triptans, macrolide antibiotics (except spiramycin), ritonavir-boosted protease inhibitors, efavirenz, azole antifungals, triclabendazole, the quinupristin/dalfopristin combination, stiripentol, diltiazem, boceprevir, telaprevir, cobicistat, and the ombistavir/parateprevir combination (see section 4.5).

Patients with mild to moderate hepatic dysfunction, particularly those with symptoms of cholestasis must be appropriately monitored.

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).

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 not recommended in patients aged under 12 years or over 65 years.

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

Cafergot should never be administered as a continuous, long-term maintenance treatment.
Repeated administration at brief intervals (see section 4.2) requires special monitoring: the onset of any clinical signs indicative of poor vascular tolerance must lead to the immediate discontinuation of treatment.
Treated patients must be informed of the maximum dose that should not be exceeded and of the initial symptoms of overdose:

- ischaemic and trophic episodes in the extremities: onset of paresthesia (numbness, tingling), pain or vasoconstriction, even at the usual doses, must be investigated,
- nausea and vomiting not related to the migraine,
- symptoms of myocardial ischaemia (precordialgia).

As soon as the symptoms of overdose appear, treatment should be discontinued and the patient should consult his or her doctor as soon as possible.

Long-term or excessive use is contraindicated as it may lead to:

- fibrosis (especially pleural or retroperitoneal). Rare cases of cardiac valve fibrosis have been reported.

Ergotism including severe symptoms of peripheral blood vessel vasoconstriction, which may be potentially fatal.

Patients suffering from mild to moderate liver failure, especially those with hepatic cholestasis, must receive suitable follow-up.

The excessive use of antimigraine treatment may lead to the onset of chronic daily headaches, requiring the temporary withdrawal of treatment.

Athletes' attention must be drawn to the fact that this medicinal product contains ergotamine, which is included in the list of doping substances.

Due to the presence of lactose, this medicinal product is contraindicated in cases of congenital galactosaemia, glucose-galactose malabsorption or lactase deficiency.

4.5 Interaction with other medicinal products and other forms of interaction

Expected interactions leading to a contraindication

Potent inhibitors of CYP3A4
The concomitant use of cytochrome P450 3A4 (CYP3A4) inhibitors, such as macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungal agents (e.g. ketoconazole, itraconazole, voriconazole) with Cafergot should be avoided (see section 4.3), since this may cause increased exposure to ergotamine and risks of ergotism (vasospasm and ischaemia of the extremities and other tissues).

Vasoconstrictors
The concomitant use of vasoconstrictors, including medicinal products containing ergot alkaloids, sumatriptan and other 5HT1 receptor agonists, or nicotine (e.g. heavy smoking), and sympathomimetics should be avoided since this may cause increased vasoconstriction (see section 4.3).

Interactions observed leading to non-recommendation of concomitant use
Any potential increase in plasma caffeine concentrations due to an interaction with one or more other medicinal products may lead to a rise in ergotamine absorption. Caffeine is significantly metabolised by CYP1A2 and medicinal products that increase or reduce enzyme activity may affect the metabolic clearance of caffeine. Fluoroquinolones, mexiletine, fluvoxamine and oral contraceptives may increase plasma exposure to caffeine. Interactions between sympathomimetics and caffeine can cause a rise in blood pressure.

Observed interactions to be taken into account

Beta-blockers
A few cases of vasospastic reactions have been reported in patients treated concomitantly with medicinal products containing ergotamine and propranolol.

Expected interactions to be taken into account

Moderate/weak CYP3A4 inhibitors
Moderate to weak CYP3A4 inhibitors such as cimetidine, clotrimazole, fluconazole, grapefruit juice, quinupristin/dalfopristin and zileuton may also increase exposure to ergotamine and caution is required if they are used concomitantly.
Serotonin reuptake inhibitors
The concurrent use of ergotamine and serotonin reuptake inhibitors (e.g. amitriptyline), including selective agents (e.g. sertraline), may cause serotonin syndrome and requires caution.

CYP3A4 inducers
CYP3A4-inducing medicinal products (e.g. nevirapine, rifampicin) can cause a reduction in the pharmacological activity of ergotamine.

Absence of interaction
No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INTERACTIONS RELATED TO ERGOTAMINE
Contraindicated combinations (see section 4.3)

- **Triptans (almotriptan, fovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, eletriptan)**: risk of hypertension, coronary artery vasoconstriction. An interval of 24 hours should be left between discontinuation of the triptan and administration of the alkaloid.
- **Macrolides (except spiramycin)**: ergotism, with the possibility of necrosis in the extremities (decrease in hepatic elimination of ergot alkaloids).
- **Protease inhibitors (e.g. amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir**): ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid).
- **Reverse transcriptase inhibitors (delavirdine, efavirenz)**: ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid).
- **Voriconazole**: ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid).
- **Quinupristin-dalfopristin (in combination):** ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid).
- **Stiripentol**: ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid).
- **Diltiazem**: ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid).
- **Phenylpropanolamine**: risk of vasoconstriction and/or episodes of hypertension.
- **Triclabendazole**: ergotism, with the possibility of necrosis in the extremities (inhibition of hepatic metabolism of the ergot alkaloid). An interval of 24 hours should be left between the discontinuation of treatment and ergotamine, and vice versa.

Inadvisable combinations (see section 4.4)

- **Dopaminergic ergot alkaloids (bromocriptine, cabergolin, pergolide, lisuride)**: risk of vasoconstriction and/or episodes of hypertension.
- **Alpha sympathomimetics (oral and/or nasal route) (etilephrine, midodrine, naphazoline, oxymetazoline, phenylephrine, synephrine, tetryzoline, tuaminoheptane, tymazoline)**: risk of vasoconstriction and/or episodes of hypertension.
- **Indirect sympathomimetics (except phenylpropanolamine) (ephedrine, phenylephrine, pseudoephedrine)**: risk of vasoconstriction and/or episodes of hypertension.

Combinations requiring precautions for use

- **Beta-blockers (propanolol, oxprenolol)**: ergotism; some cases of arterial spasm with ischaemia in the extremities have been observed (cumulative vascular effects). Increased clinical monitoring, especially during the first weeks of combination therapy.

INTERACTIONS RELATED TO CAFFEINE

Inadvisable combinations

- **Enoxacin**: increase in plasma caffeine concentrations, which may lead to excitation and hallucinations due to a decrease in hepatic metabolism.

Combinations to be taken into account

- **Ciprofloxacin, norfloxacin**: increase in plasma caffeine concentrations, which may lead to excitation and hallucinations due to a decrease in hepatic metabolism.
- **Mexiletine**: increase in plasma caffeine concentrations due to the inhibition of its hepatic metabolism by mexiletine.

4.6 Pregnancy and lactation

Pregnancy

In animal studies, testing revealed a teratogenic effect with ergotamine tartrate. These effects can be attributed to a reduction in the utero-placental blood flow (see section 5.3).
Data concerning the use of ergotamine tartrate during pregnancy are limited.
In addition, this product has vasoconstrictive and oxytocic properties. Consequently, Cafergot should not be used during pregnancy.

Breast-feeding

Ergot derivatives are excreted into breast milk, and therefore breast-feeding is contraindicated during treatment with this medicinal product.

Ergotamine and caffeine are excreted into breast milk. Ergotamine may lead to symptoms such as vomiting, diarrhoea, weak pulse and irregular blood pressure in neonates. Cafergot is therefore contraindicated in breast-feeding mothers.

Fertility

In male rats receiving oral ergotamine and caffeine as combination therapy (1:100), fertility is not affected (see section 5.3).

4.7 Effects on ability to drive and use machines

Feelings of dizziness have been reported as an adverse effect of treatment. Caution is recommended in patients who carry out tasks requiring a certain degree of skill, such as driving or using machines. Patients with a history of dizziness or other central nervous system disorders should not drive or use machines.

4.8 Undesirable effects

The following undesirable effects have been determined based on clinical trials and post-marketing experience with Cafergot.

The frequencies in the table below are given as an indication, based on the following categories; very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); frequency not known

(cannot be estimated based on available data). Adverse reactions to this medicinal product are listed according to MedDRA system organ class.

System organ class	Adverse reactions
Immune system disorders	Rare: hypersensitivity reactions (such as skin rash, facial oedema, pruritus, urticaria, dyspnoea)
Nervous system disorders	Common: dizziness Uncommon: paresthesia in the fingers and toes, hypoesthesia, headache
Ear and labyrinth disorders	Rare: dizziness
Cardiac disorders	Uncommon: cyanosis Rare: bradycardia, tachycardia Very rare: myocardial ischaemia, myocardial infarction Frequency not known: valve fibrosis[c]
Vascular disorders	Uncommon: peripheral vasoconstriction[a] Rare: increased blood pressure Very rare: gangrene
Respiratory, thoracic and mediastinal disorders	Frequency not known: pleural fibrosis[c]
Gastrointestinal disorders	Common: nausea and vomiting (unrelated to migraine), abdominal pain Uncommon: diarrhoea Frequency not known: retroperitoneal fibrosis[c]
Musculoskeletal and connective tissue disorders	Uncommon: pain in the extremities, weakness in the extremities Rare: myalgia
Investigations	Very rare: absence of pulse
Injury, poisoning and procedural complications	Rare: ergotism[b]

[a] If signs of vasospasm are observed, administration of GYNERGÈNE CAFÉINÉ should be discontinued (see sections 4.4 and 4.9).

[b] Depending on the dose of ergotamine, intense arterial vasoconstriction may occur (ergotism). This may lead to signs and symptoms of vascular ischaemia in the extremities or in other tissues (such as renal or cerebral vasospasm) (see sections 4.4 and 4.9).

[c] Long-term or excessive use may lead to fibrosis (especially pleural or retroperitoneal fibrosis). Rare cases of cardiac valve fibrosis have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
All health care providers are to report all drug related problems (suspected adverse drug reaction and side effect) using the ADR reporting form also known as the 'Yellow form'.
- Forms can also be downloaded from the NAFDAC website on www.nafdac.gov.ng
- Filled reports can be scanned and emailed to npcadr@nafdac.gov.ng
- You can also report ADRs through **PRASCOR** (a Pharmacovigilance Rapid Alert System for Consumer Reporting is a short code service for consumers to alert NAFDAC of safety and quality issues via SMS.)
- You can also report by calling any of these numbers 08086899571, 09 2905110 or 07098211221.

4.9 Overdose

Ergotism is defined as intense arterial vasoconstriction that produces signs and symptoms of ischaemia in the extremities or other tissues (such as renal or cerebral vasospasms). Gangrene is possible if it is not treated. Most cases of ergotism are related to chronic intoxication and/or overdose and/or an interaction.

Symptoms

Abdominal pain, confusion, light-headedness, nausea, vomiting, headache, tachycardia or bradycardia associated with hypotension, respiratory disorders, dizziness, paresthesia, ischaemia, gangrene, seizure, shock, coma, as well as symptoms of vascular ischaemia, such as numbness, tingling, pain in the extremities, cyanosis and absence of pulse. In rare cases, patients may present myocardial infarction.

Treatment

In the event of acute intoxication, gastric emptying by gastric lavage and symptomatic treatment must be provided in a hospital setting, with close cardiovascular monitoring.

The administration of activated charcoal may reduce the gastric passage of ergotamine tartrate.

If vascular ergotism is confirmed, emergency treatment must be provided in a hospital setting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antimigraine preparation (ergot alkaloids)

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-HT1B and 5-HTID.

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 with tritium-labelled ergotamine indicate that approximately 62% of an oral dose is absorbed from the gastrointestinal tract. Peak plasma levels are achieved about 2 hours after ingestion.

Distribution
Protein binding for ergotamine amounts to 98%. In terms of unchanged drug its absolute bioavailability is about 2% when given orally.

Biotransformation
Ergotamine is extensively metabolised 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 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 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, salvia, and semen. The volume of distribution is about 0.7 L/kg. Caffeine crosses the placental barrier.

Biotransformation

Caffeine is metabolised to a large extent by CYP1A2 to paraxanthine. Paraxanthine is further metabolised 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.

5.3 Preclinical safety data

Chronic and subchronic toxicity

In an oral administration safety study with a duration of 26 weeks in Beagle dogs, ergotamine induced vomiting, salivation and slowed cardiac rhythm. Superficial necrosis of the margin of the ear was also commonly noted in dogs with drooping ears, as a consequence of the marked vasoconstrictive action of the drug.

Reproductive toxicity

There is no evidence of embryo mortality or teratogenic effects of ergotamine in rabbits treated with 1, 3 and 10 mg/kg a day and in rats treated with up to 3 mg/kg a day. However, in rats receiving 10 mg/kg a day, weight gain was inhibited in the mothers, with delayed foetal ossification and an increase in prenatal mortality. High doses of ergotamine result in constriction of the uterine blood vessels, reduced blood supply and consequent hypoxia, which is known to cause teratogenic effects in the offspring. The combination of ergotamine and caffeine in the proportion 1:100 (= tablets), administered orally to rats and rabbits, did not show any teratogenic potential. In a study of reproductive performance in male rats, fertility was not impaired. In a study of reproductive performance and in a peri-/postnatal study in female rats, an increase in the number of stillbirths and/or in peri-/postnatal mortality was observed.

In animal studies, caffeine was found to be teratogenic at very high doses only.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid, talc, magnesium stearate, pregelatinised starch, microcrystalline cellulose, iron oxide yellow.

6.2 Incompatibilities

None

6.3 Shelf life

24 Months

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

Amber glass bottle containing 20 tablets

6.6 Special precautions for disposal

No special requirements

7. Registrant

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8. Date of revision of the text

October 2016