Medicines Adverse Reactions Committee

Meeting date	**12 September 2019**	Agenda item	3.1.1
Title	**Consideration of Cafergot (ergotamine tartrate + caffeine) under section 36 of the Medicines Act 1981**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Ergotamine tartrate + Caffeine	**Product name** Cafergot 1 mg + 100 mg tablets	**Sponsors** AFT Pharmaceuticals Limited	
PHARMAC funding	Funded		
Previous MARC meetings	Cafergot (ergotamine tartrate + caffeine) has been discussed previously at the following meeting: – 177thMeeting — 14 March 2019 Ergotamine containing products and pancreatitis.		
Classification	Prescription medicine		
Usage data	See section 2.5		
Advice sought	**The Committee is asked to advise whether:** – The Committee agrees with the considered benefits from Cafergot treatment. – The Committee agrees with the considered risks from Cafergot treatment. – The balance of benefits and risk for the use of Cafergot for the treatment of migraine is favourable or unfavourable. – If any regulatory action is required.		

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1.0 PURPOSE

At the 14 March 2019 MARC meeting, the Committee discussed the potential risk of pancreatitis in association with Cafergot treatment (see Annex 1 for the MARC report). The Committee recommended that Medsafe conduct a benefit risk review of Cafergot under section 36 of the Medicines Act 1981.

Section 36 states that if the Director-General has reason to believe that any medicine, not being a new medicine, may be unsafe or ineffective for the therapeutic purpose for which it is sold, he may, by notice in writing to an importer or manufacturer in New Zealand, state the reasons for his belief and require the importer or manufacturer to satisfy him of the safety or efficacy of that medicine. Outcomes of such a review may include imposing conditions on the supply of the medicine or prohibiting the supply of the medicine.

The purpose of this paper is to review the available information on benefits and risks with Cafergot according to section 36 of The Act.

The Committee are reminded that the possible regulatory actions include:

- no change
- updates to the data sheet
- imposition of other conditions, could include studies or provision of additional information
- cancellation of consent to distribute (could include a recall)
- communication, could be from MARC, Medsafe or the sponsor

2.0 BACKGROUND

2.1 Ergots

Cafergot contains 1 mg ergotamine and 100 mg caffeine. Ergotamine is an alkaloid derived from ergot, also called ergot fungi. Ergot alkaloids are widely used for therapy of acute migraine headaches and include ergotamine and also dihydroergotamine which is a semisynthetic derivative of ergot (1).

Ergot (or ergot fungi) is the dried sclerotium of the fungus *Claviceps purpurea*, which can arise in the ovary of the rye *Secale cereale*. These sclerotia can replace one or more of the kernels in a mature grain head with a hard, dark coloured, horn-like mass. Although ergot most readily attacks rye it can also infect other wild and cultivated cereals (barley, wheat, oats, sorghum), and other grasses. These sclerotia contain fungal toxins and are harvested along with the rest of the grain so that the ergots contaminate the food chain.

Figure 1. Ergot on wild oat.

Ergots (the blackened claw-like objects) of *Claviceps purpurea* on wild oat, *Avena fatua*.

Alkaloids produced by ergot can cause a severe reaction called ergotism. During the Middle Ages, ergotism was common. Eating rye bread contaminated with *C. purpurea* resulted in gangrene of limbs, disruption in functions of the CNS and even death. The illness was called St. Anthony's fire or Holy Fire referred to the burning sensation in the limbs experienced by sufferers (2). It was often cured by visiting the shrine of St. Anthony, which happened to be in an ergot-free region of France.

Additionally, some historians believe that ergot played a role in the Salem witch hunt of 1692. They think that some of the women in Salem developed peculiar behaviors and accused other women of being witches as a result of eating ergot- contaminated food (3).

Ergotamine has a long history of medical use, first to precipitate childbirth and control post-partum haemorrhage, and since 1926 to treat acute migraine. For many years, ergotamine was the mainstay of migraine therapy.

There are several semisynthetic derivatives of ergot, the most well-known being dihydroergotamine. Dihydroergotamine is an alpha-adrenergic blocker that is a weaker arterial vasoconstrictor and more potent venoconstrictor than ergotamine tartrate. Dihydroergotamine has fewer side effects than ergotamine and does not cause development of physical dependence or rebound headaches. Dihydroergotamine is very badly absorbed. Even if the medicine exists as tablets, only intranasal and injectable formulations are approved for example in the US (4, 5).

No dihydroergotamine product is available in New Zealand. The only approved ergotamine product is Cafergot as tablets.

This report will focus on ergotamine as Cafergot contains ergotamine. However, dihydroergotamine may be mentioned under certain circumstances.

2.2 Cafergot

2.2.1 Content and indication

One tablet of Cafergot contains 1 mg ergotamine, as the salt ergotamine tartrate, and 100 mg caffeine. The therapeutic indication for Cafergot is treatment of acute attacks of migraine with or without aura in adults (6). Cafergot was approved in NZ on 31 December 1969.

2.2.2 Dosing

Cafergot is indicated for the treatment of acute migraine attacks and not for prevention of migraine attacks. Cafergot should be given at the first signs of a migraine attack.

For adults at 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. The maximum weekly dose is 10 tablets. Taking Cafergot repeatedly over extended periods must be avoided (6).

Cafergot is not recommended for children under 18 years or for patients over 65 years of age. Safety and efficacy have not been established in pediatric patients. No studies have been performed in elderly patients.

If supplementary antimigraine medication is required, the use of vasoconstrictor agents such as any ergotamine-containing preparations, intranasal or parenteral dihydroergotamine or sumatriptan or other 5HT1-receptor agonists must be avoided (6).

2.2.3 Pharmacodynamics

Ergotamine shares structural similarities with the adrenergic, dopaminergic, and serotonergic neurotransmitters. As a result, ergotamine interacts with a variety of receptors and has wide-ranging effects on the physiologic processes that it mediates. As a comparison, sumatriptan and the newer triptans are much more selective to 5HT-receptors (1).

The mechanism of action in treatment of migraine attacks with or without aura is by 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 is primarily linked to agonist properties at 5-HT1B and 5-HT1D (6).

Ergotamine is highly potent at the 5-HT_{1B} and 5-HT_{1D} antimigraine receptors and, as a consequence, the plasma concentration necessary to produce the appropriate therapeutic and physiologic effects is very low. Peripheral vasoconstriction from ergotamine administration can persist for as long as 24 h, and repeated doses lead to cumulative effects long outlasting a migraine attack (7). The broad spectrum of activity at other monoamine receptors is responsible for the side effect profile (dysphoria, nausea, emesis, unnecessary vascular effects).

Caffeine is given with ergotamine tartrate with the intention of improving the latter's absorption, although whether it does so is not clear (8). However, most placebo-controlled trials of oral ergotamine alone have failed to show efficacy in the relief of migraine (4).

Characteristics of Cafergot, such as contraindications, warnings, precautions, adverse effects and interactions are primarily directed by the characteristics of ergotamine.

2.2.4 Pharmacokinetics

Ergotamine: oral absorption of ergotamine is 60-70%. However, due to high first-pass metabolism, ergotamine has a very low bioavailability of about 1% after an oral dose. There is also a high subject variability regarding bioavailability. Plasma protein binding is about 93 to 98%. Ergotamine is metabolised extensively in the liver via the cytochrome P450 isoenzyme CYP3A4. It has been suggested that the therapeutic effects of the drug are partially due to active metabolites (6). 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. About 4% of a dose is excreted in the urine (6, 8).

Tight receptor binding produces a longer duration of action. In one study after intramuscular injection, the effect on peripheral arteries, measured as a decrease in toe-arm systolic gradients, developed slowly and was well sustained after 29 hours (9).

Caffeine is rapidly and almost completely absorbed and peak plasma concentrations are reached in 15-120 minutes. Plasma protein binding of caffeine is 35%. Caffeine is metabolized to a large extent by CYP1A2 to paraxanthine, which is further metabolised to uracil and uric acid derivatives by demethylation and hydroxylation. The metabolites are excreted mainly in the urine. Plasma elimination half-life is about 3.5 hours.

2.2.5 Contraindications

The following contraindications are listed in the data sheet for Cafergot (6):

- Patients with impaired peripheral circulation, obliterative vascular disease, coronary heart disease, inadequately controlled hypertension or glaucoma, temporalis arthritis, septic conditions, shock or severe renal or hepatic impairment.
- Pregnancy and breast-feeding
- 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.

2.2.6 Special warnings and precautions for use

The following warnings and precautions are listed in the data sheet for Cafergot (6):

- Continued daily use of Cafergot or its 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. If chest pain occurs treatment should be withdrawn.
- Long-term use of ergotamine can cause ergotism, including severe cases of symptoms of constriction of peripheral blood vessels, with possible fatal outcome.

- 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.
- Patients with mild to moderate hepatic impairment, especially cholestatic patients should be appropriately monitored.
- The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot.
- 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.

2.2.7 Adverse effects

Adverse effects of ergotamine may be attributed either to its effects on the central nervous system, or to vasoconstriction of blood vessels and possible thrombus formation.

After therapeutic doses, nausea and vomiting commonly occur as a result of the direct emetogenic effect of ergotamine and some patients may also experience abdominal pain. Ergotamine can worsen the nausea and vomiting associated with migraine.

Weakness and muscle pains in the extremities and numbness and tingling of the fingers and toes may occur. There may occasionally be localised oedema and itching in hypersensitive patients.

Treatment should be stopped if symptoms of vasoconstriction develop. Susceptible patients, especially those with sepsis, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine. (8).

Chronic poisoning

As with any medication used for treatment of migraine attacks, ergotamine can be misused by being taken daily or almost daily. In chronic poisoning or ergotism, resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, severe circulatory disturbances may develop.

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, and absence of pulse. If the condition is allowed to progress untreated, gangrene may result.

Furthermore, ergotism can involve signs and symptoms of vascular ischemia of other tissues such as renal or cerebral vasospasm. Anginal pain, tachycardia/bradycardia, and hypertension/hypotension have been reported. Myocardial infarction has occurred rarely (8). In contrast to triptans, the contractile effect of ergotamine in the human isolated coronary artery is long lasting and persists even after repeated washings (10). Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves.

Chronic headache may occur. The use of ergotamine on 10 or more days per month has been considered to confer an increased risk for the development of medication-overuse headache (MOH) (11). Rebound headache is a major withdrawal symptom following the development of ergotamine dependence. The duration of withdrawal headaches has been found to vary with different drugs, and was in one study shorter in migraine-patients overusing triptans than in those overusing ergotamine or analgesics (12).

Acute poisoning

Symptoms of ergotamine overdose are nausea, vomiting, drowsiness, confusion, tachycardia, dizziness, respiratory depression, hypotension, convulsion, shock, coma, symptoms and complications of ergotism and fatalities have been reported (6).

Table 1 shows frequency of adverse effects as listed in the NZ data sheet. Adverse reactions are listed by MedDRA system organ class and ranked under heading of frequency: 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), not known (frequency cannot be estimated from the available data).

Table 1. Frequency of adverse events for Cafergot listed in the NZ data sheet.

Immune system disorders
Rare: Hypersensitivity reactions[1]
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 poisoning[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 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.

2.2.8 Interactions

Several interactions can occur if ergotamine are used together with other medicines.

Concomitant treatment with cytochrome P450 3A4 (CYP3A4) inhibitors such as macrolide antibiotics (all except spiramycin), HIV protease or reverse transcriptase inhibitors and azole antifungals (for example ketoconazole) is contraindicated.
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.

Concomitant treatment with vasoconstrictor agents including ergot alkaloids, sumatriptan, other 5HT1 receptor agonists, nicotine (e.g. heavy smoking) and sympathomimetics are contraindicated since this may result in enhanced vasoconstriction. Allow 24 hours between the discontinuation of triptans and the use of the alkaloid.

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

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

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.

Concomitant treatment with fluoroquinolones, mexiletine, fluvoxamine, and oral contraceptives is contraindicated. These medicines can modulate the metabolic clearance of caffeine which consequently may translate to increase in absorption of ergotamine (6).

2.2.9 Pregnancy and breastfeeding

Cafergot is contraindicated during pregnancy and breastfeeding.

Comments: The difficulties in absorption of ergotamine as well as its interactions, safety profile and many contraindications and warnings and precautions limits the value of ergotamine in the treatment of migraine.

2.3 Migraine

2.3.1 Epidemiology, causes and triggers

The pain of a migraine headache can be described as an intense pulsing or throbbing pain in one area of the head. It is often accompanied by extreme sensitivity to light and sound, nausea, and vomiting and can severely affect patients' quality of life.

About one in 10 people get migraines, with more women being affected than men. Migraines usually first occur between 10 and 30 years of age, and may get better in middle age. (13).

For many years, it was believed that migraines were linked to the dilation and constriction of blood vessels in the head. Newer research suggest that migraine is caused by inherited abnormalities in genes controlling the activities of certain cell populations in the brain (14).

Migraine is characterised by recurrent attacks triggered by a number of different factors such as stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances, and aspartame. The attacks unfold through a cascade of events that occur over the course of several hours to days. A typical migraine attack progresses through four phases:

1. The prodrome: affective or vegetative symptoms that appear 24 to 48 hours prior to the onset of headache. Symptoms include increased yawning, euphoria, depression, irritability and constipation.
2. The aura: About 25 percent of people with migraines experience the migraine aura. Auras are most often visual (e.g. bright lines, zig zag lines, loss of vision), but can also be sensory (e.g. paresthesia), auditory (e.g. tinnitus) or motor disturbances.
3. The headache: often but not always unilateral and tends to have a throbbing or pulsatile quality. Accompanying features may include nausea, vomiting, photophobia (sensitive to light), or phonophobia (sensitive to sound) during attacks.
4. The postdrome: some patients experience a phase during which sudden head movement transiently causes pain in the location of the antecedent headache. The patients often feel drained or exhausted (15).

The frequency and severity of migraine attacks differs for everyone, but it is common to get two to four headaches per month. Some people may get chronic migraine, with at least 15 migraine days per month, while others get attacks once or twice a year. Most sufferers are unable to work or function normally during their migraine.

2.3.2 Types of migraine

There are several types of migraine (16). The most common ones are:

- Migraine without aura. This is the most common type and 70-90% of people with migraine experience this type. The headache happens without the specific warning signs. During this type of migraine the patient will be likely to feel sick, may vomit or have diarrhoea and may become sensitive to light and/or sound. Attacks of migraine without aura last between 4 and 72 hours when untreated or unsuccessfully treated and the attacks may occur anything from once a year to several times per week.
- Migraine with aura is characterised by specific warning signs just before the migraine begins, such as seeing flashing lights. Patients who experience migraine with aura will have many or all the symptoms of a migraine without aura plus additional neurological symptoms (eg numbness, tingling, dizziness, confusion) which develop over a 5 to 20 minute period and last less than an hour. These neurological symptoms usually happen before a headache, which could be mild, or no headache may follow. Frequency can vary anywhere from once a year to several times per year. This type is experienced by 10-30% of patients with migraine.

Comment: The indication for Cafergot is treatment of acute attacks of migraine with or without aura. It has been recommended that ergotamine should not be used in complicated migraine, migraine with prolonged aura or familiar hemiplegic migraine (a rare type of migraine involving temporary weakness on one side of the body) (10).

2.3.3 Treatment of migraine

The NZ webpage Health Navigator describes drug treatment of migraine. The page was last reviewed in November 2017 and last updated in 5 March 2019 (13):

Migraine cannot be cured but symptoms during an attack can be relieved and further attacks can be prevented. Some things are commonly known to trigger migraines in some people. Avoiding these triggers can reduce the frequency and severity of the migraine attacks. Migraines vary between people and so does the treatment.

Medications for the treatment of migraines fall into a few categories:

- Pain-relieving medicines (paracetamol, NSAID, triptans), which are taken during the migraine attack.
- Medicines against nausea or vomiting (metoclopramide, domperidone or prochlorperazine).
- Prevention medicines (propranolol, atenolol, nadolol, metoprolol, timolol, amitriptyline, nortriptyline, topiramate, sodium valproate, gabapentin).

A usual approach is:

- Step 1: pain relievers such as paracetamol and NSAIDs such as ibuprofen, diclofenac, naproxen
- Step 2: triptans
- Step 3: combination treatment with a triptan and an NSAID.

Anti-sickness medicines may be used at any step to relieve nausea associated with migraine and can help the absorption of pain-relieving medicines (if taken before or at the same time). Examples include metoclopramide, domperidone and prochlorperazine.

Medicines to prevent migraines are an option for patients who suffer at least 2 attacks a month, experience significant disability even with suitable treatment for migraine and cannot take suitable treatment for migraine attacks. Note that Cafergot is not indicated for preventive treatment.

Health Navigator refers to the NICE Clinical Guidelines for management of migraine with or without aura from 2014, see below.

2.4 Recommendations for use of Cafergot

2.4.1 New Zealand

Regarding Cafergot the Health Navigator states that ergotamine (13):

- is only for people who have recurring migraines that cannot be managed by other medications
- has many side effects including nausea, vomiting, abdominal pain and muscle cramps
- should not be used more than twice per month.

2.4.2 NICE (2014)

Do not offer ergots for the acute treatment of migraine (17).

2.4.3 Martindale

In Martindale, ergot derivatives are described as a group of medicines that is rarely needed nowadays in the treatment of migraine (8).

2.4.4 Guidelines by the German Migraine and Headache Society and the German Society of Neurology (2019)

Ergotamines are effective for migraine attack therapy. However, the efficacy in prospective studies is poorly documented and they have more side effects than triptans and other acute therapeutics. Ergots should therefore no longer be used as the therapy of first choice. Patients who benefit from the longer duration of efficacy can continue to use ergotamine (18).

2.4.5 Various

- In 2009 the European Federation of Neurological Societies, EFNS, published a guideline for treatment of migraine (19). It states that there is limited evidence of ergotamine efficacy from placebocontrolled- or comparative trials (except comparisons with triptans showing better efficacy of the triptan). The advantage is a lower recurrence rate in some patients. Therefore ergotamine should be restricted to patients with very long migraine attacks or regular recurrence. There is also a warning that ergotamine can cause drug overuse headache very fast and in very low doses. Therefore use must be limited to 10 days per month.

- A review of European treatment guidelines for migraine from 2010 contains the following information regarding ergotamine: Almost all guidelines consider ergotamine effective and favourable for the treatment of migraine due to its low relapse rate, but because of its poor tolerability and an increased risk of overuse headache, some guidelines recommended ergotamine as a second-line treatment (EFNS and Germany), while others do not recommend it at all (Scotland) (20).

- Ergotamine/caffeine is recommended for moderate to severe migraine attacks in year 2017 guidelines from Taiwan (21).

2.5 Usage

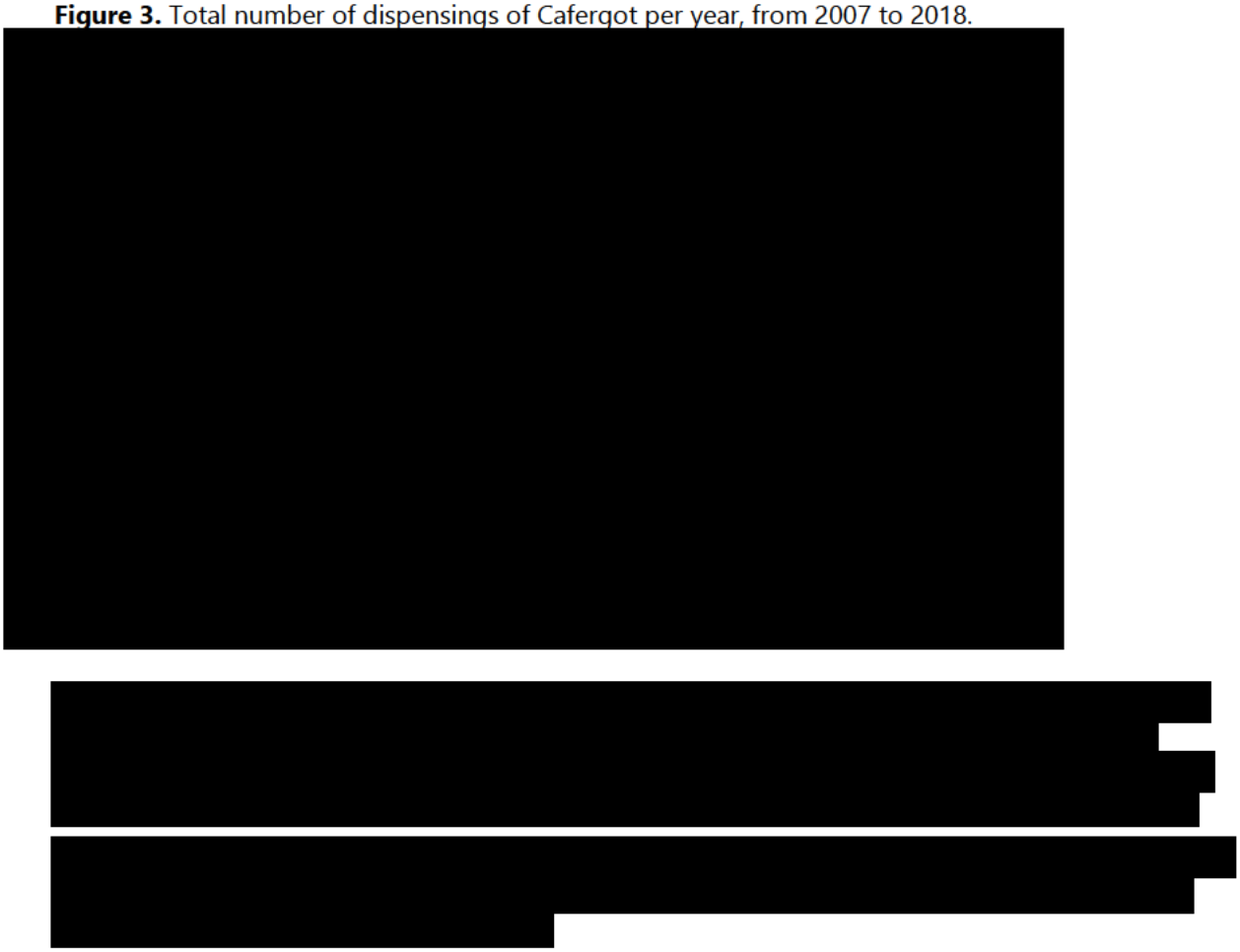
Usage data in New Zealand has been provided by BPAC and the source is the Pharmaceutical Collection.

Figure 2 shows the number of people receiving a dispensing of Cafergot at least once during a year (including those who only received a repeat).

Figure 2. Number of people receiving at least one dispensing of Cafergot per year.

Figure 3 shows the total number of dispensings of Cafergot per year, including repeats.

Figure 3. Total number of dispensings of Cafergot per year, from 2007 to 2018.



Use in different age groups

Figure 4 shows, as two examples, the amount of users per year who are 25-34 years old and 65-74 years old over the time period 2007 – 2018. Cafergot is not recommended for use in patients over 65 years of age.

Figure 4. Users of Cafergot per year in two different age groups, from2007 to 2018.

The number of users are decreasing in all age groups. However, if we look at the ratio of the number of Cafergot users in 2018 compared with the number of Cafergot users in 2007 expressed as the percentage, it shows that Cafergot users have become older on average year by year. See table 2.

Table 2. Number of Cafergot users per age group in 2018 divided by the number in 2007.

Age group	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
Ratio users 2018/users 2007	19.3%	33.7%	49.7%	30.3%	25.4%	39.7%	72.3%	82.7%	135.1%

Figure 5 shows the number of prescribers of Cafergot between 2007 and 2018.

Figure 5. Prescribers of Cafergot per year, from 2007 to 2018.

Comments: The number of Cafergot users and prescribers in New Zealand has decreased over the time period and the age of the Cafergot-users have increased. This may signal that there are not so many new patients starting Cafergot, but the ones that are already using Cafergot are continuing to do so.

Note that Cafergot is not recommended for use in patients over 65 years of age. The reason according to the data sheet is that no studies have been performed in elderly patients. Cafergot is no longer available in Canada. However, the product information from when it was available also contains a warning not to use in patients over 65 because of greater risk of adverse reactions in this patient population (22). The high use in the older age groups in NZ shown above is a concern.

2.6 CARM data

CARM has received 5 case reports for Cafergot up to 30 June 2019, see Annexe 2. One of the reports was the potential pancreatitis case that triggered the first MARC review of Cafergot in March 2019. The other reports were:

Comment: There are fewer CARM reports than predicted. As Cafergot is an old medicine it is a risk that side effects have stopped being reported over the years. Another reason may be that usage of Cafergot is relatively low.

2.7 Comments from Professional Organisations

As part of this risk benefit review, Medsafe sent letters to the Neurological Association of New Zealand, Royal Australasian College of Physicians, the Australian and New Zealand Association of Neurologists and the Neurological Foundation of New Zealand requesting from them any information and/or opinions they may have on the use, safety and efficacy of ergotamine (as in Cafergot).

We received the following comments from the Neurological Association of New Zealand:

- "I didn't even know it was still available. I never prescribe it but I guess we send it out to the general group as there may be some who use it still and have strong enough feelings to submit something. The only "risk" I see is that there may be patients who are on it as prescribed by their GP who have trouble coming off it."
- "My opinion is that Cafergot is obsolete for the treatment of migraine now that there is ready availability of more specific triptans for this purpose. I never prescribe Cafergot. In my opinion it is not an appropriate medication for new patients with migraine, but should be available on compassionate grounds for those already relying on it, at least until an effective alternative can be found.

  I would note that discontinuing Cafergot availability for patients using it regularly would need to be managed carefully and would likely necessitate specialist involvement, likely several visits per patient and even, possibly, inpatient management for IV DHE infusions in the withdrawal phase. Given the status of our clinic waiting list, as clinical director I would be very anxious about being able to fit such patients in and meeting this demand, hence my preference to ensure that the medication were made available to existing patients indefinitely, with the expectation that over a period of years the numbers using it would gradually diminish."
- "There are a small handful of Northland patients who still use this agent without adverse effects, and most for many years. I haven't prescribed it de novo for many years. It would be a shame to lose it altogether."
- "MARC wishes to discuss specifically about Cafergot but I am unclear if this would also have repercussions for all ergotamine preparations.

  Whilst I realise that perhaps many patients would still use this medication, I have never personally recommended this medication to my headache patients as there are better drugs that are available for acute migraine treatment. Cafergot being a combination analgesic medication, also potentially causes analgesic medication overuse headache. Patients can obtain this medication over the counter in some countries or buy this drug online; there is therefore always the potential for medication overuse. Cafergot has also been discontinued in some countries, thus prompting some ro buy this medication online.

  The situation for IV Dihydroergotamine (DHE) is different as this is administered under supervision in hospital.

  Therefore, my personal view is that IV DHE should still be available even if in reality, this is not often used due to various reasons.

  The MARC discussions should take into consideration the above, when discussing about ergotamine/ Cafergot."

- "Cafergot is rarely prescribed these days – but I suspect there are a few individuals who rely on it and would miss it (for better or worse – as an effective acute attack remedy; less so as a drug of misuse/analgesic related headache). Probably should go as one less drug prone to analgesic overuse.

  Ergotamine as an iv treatment, last resort for severe headache as per the protocol is presumably not affected by Cafergot's potential demise?"

We received the following comment through the Neurological Foundation:

- As a practising neurologist I can say that Cafergot is seldom used these days. However, it is very effective treatment for migraine in selected patients. I cannot remember prescribing Cafergot for many years, but there may be neurologists who use it more frequently. I do see occasional patients who still use Cafergot for their migraine. They have taken it for a long time and they have continued to use it because it is the only treatment that works for them.

Comment: This benefit risk analysis concerns Cafergot tablets only, which it is the only approved ergot alkaloid medicine on the NZ market.

3.0 SCIENTIFIC INFORMATION

3.1 Published studies and review articles

Ergotamine has been around for many years and never underwent a robust clinical trial programme such as those used nowadays for example for the triptans. A Pub Med search resulted in 7 clinical studies. Note, that the first four are short term studies of triptans in comparison to Cafergot and sponsored by triptan pharma companies. In the fifth study, medicines that cannot be recommended are used together with Cafergot. As all these studies are short term they are not reliable for safety assessment. Study number 6 and 7 focuses on safety. Below are summaries of the clinical studies and also some reasonably recent review articles.

3.1.1 Clinical trials, efficacy

3.1.1.1 The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine (23).

Aim:
To compare efficacy and safety of oral sumatriptan as a 100-mg dispersible tablet with 2 + 200 mg oral Cafergot.

Outcome measures:
Primary: Headache improvement to grade 0 or grade 1 after 2 h in patients whose initial headache severity was grade 2 or 3.
Other: Headache severity: 0, no pain; 1, mild pain; 2, moderate pain, and 3, severe pain.
The effect of migraine type (with or without aura) and duration of the attack prior to treatment on outcome.
Time to start of resolution of the migraine attack.
Incidence of nausea, vomiting, photophobia/phonophobia.
Use of other medication at 2 h.
Recurrence of migraine within 48 h of taking the test medication.
All outcomes recorded by the patients on a diary card.

Methods:
This was an international, multicentre, double-dummy, parallel-group trial involving 580 adult patients with a diagnosis of migraine (with or without aura) who had, for at least 1 year, experienced between one and six migraine attacks of moderate or severe intensity per month.

Patients were randomised to treatment with sumatriptan or Cafergot and were asked to treat a total of 3 attacks, or remain in the active phase of the trial for 12 weeks, whichever occurred first. Patients returned for follow-up clinic visits and tests 4-6, 8-10 and 12 weeks after issue of medication. Adverse effects were recorded.

Results:
A total of 490 patients were treated 3 times. The main results were:

- For 66% of patients treated with sumatriptan the intensity of the headache was reduced from severe/moderate to mild/none by 2 h, compared to 48% in the Cafergot group ($p<0.001$).
- The onset of headache resolution was more rapid in the sumatriptan group.
- Recurrence of migraine headache within 48 h was lower in the Cafergot group (30 %) compared to the sumatriptan group (41%) ($p=0.009$).
- Mean time to headache recurrence for patients in the Cafergot group was 24 h compared to 18 h in the sumatriptan group.
- Sumatriptan was significantly more effective at reducing the incidence of nausea/vomiting ($p<0.001$) and photophobia/phonophobia ($p < 0.001$) 2 h after treatment
- The incidence of adverse effect reporting was not significantly different between the groups. Nausea and/or vomiting, abdominal discomfort, and dizziness or vertigo were reported by a greater proportion of Cafergot-treated patients.

The authors discuss that recurrent headache was assessed by asking patients to record whether or not their headache returned within 48h. No account was taken to whether the patients had used other medication during the intervening period. Therefore the extent to which the patients who recorded recurrence can be attributed to any study medication in this trial is limited. They add that the difference may partly be explained by the short half-life of sumatriptan (approximately 2 h).

3.1.1.2 Christie S, Gobel H, Mateos V, et al, 2003. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine (24).

Outcome measures:
Headache relief and time to headache relief within 2 h, pain free and time to being pain free within 2 hours. Functional disability, medication preference, presence or absence of associated symptoms and headache recurrence within 24 h.

Methods:
A randomised study involving a total of 488 patients from 11 countries with a 6-month history of migraine with or without aura and 1 to 8 attacks per month treated either a first migraine attack with 1 rizatriptan 10 mg tablet and a second attack with 2 ergotamine 1 mg/caffeine 100 mg tablets or the reverse.

Headache severity over time was rated by the patients. They also rated their functional disability, medication preference, presence or absence of associated symptoms and headache recurrence within 24 h.

Results:
Of patients expressing a preference, more preferred rizatriptan to ergotamine/caffeine, mostly because of faster relief of headache (for both alternatives). Other results are shown in table 3:

Table 3.

Outcome measure	Rizatriptan	Cafergot	
Headache relief at 2 h	76%	47%	p ≤ 0.001
Pain free at 2 h	49%	24%	p ≤ 0.001
Without nausea after 2 h	83%	56%	p ≤ 0.001
Sustained Pain Freedom after 24 h	36%	20%	p ≤ 0.001
Need for additional medication after 2-24 h	28%	46%	p ≤ 0.001
Recurrence rates within 24 h	31%	15%	p ≤ 0.001

The authors comment that it is hard to interpret the recurrence rate numbers because recurrence is both conditional on initial headache relief at 2 h and confounded by the use of additional medication.

Both treatments were generally well tolerated. The overall incidence of any clinical adverse event was similar between the rizatriptan and ergotamine/caffeine groups (35.4 vs. 34.5%). The most common adverse events after ergotamine/caffeine, were nausea and dizziness.

3.1.1.3 Diener HC, Jansen JP, Reches A, et al. 2002. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison (25).

Outcome measures:
Patients recorded:
Primary measure: relief of headache 2 h after dosing.
Other: Pain free rates at 1 and 2 hours, functional impairment, if nausea, vomiting, photo-phonophobia. Recurrence headache within 24 h and use of rescue medicine. Adverse events were recorded.

Methods:
This was an international parallel group study involving 733 adult patients with a diagnosis of migraine (with or without aura) who had, for at least 1 year, experienced between at least 1 migraine attack every 6 weeks but not more than and six per month. Patients were randomly allocated to one treatment with eletriptan 40 or 80 mg, Cafergot 2 mg+200 mg or placebo.

Results:
Treatment with eletriptan was associated with a significantly greater proportion of patients achieving 2-h headache response (68% on 80 mg, 54% on 40 mg) ($P < 0.01$) compared with Cafergot (33%) and placebo (21%) ($P < 0.01$) and there was also a significant difference in amount pain free after 2h. Eletriptan was associated with a significantly lower rate of phono- photophobia, nausea or functional impairment after 2 h, while Cafergot had no advantage over placebo in this respect.

The recurrence rates were hard to calculate because of low numbers, but were higher in the eletriptan groups and the placebo group compared to the Cafergot group. However, the time to recurrence was longer in the eletriptan groups compared to the Cafergot group and the placebo group. More patients in the Cafergot group and the placebo groups used a second dose.

3.1.1.4 Lainez MJA, Galvàn J, Heras J et al, 2007. Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy (26).

Outcome measures:
Primary efficacy assessment: the proportion of patients pain free at 2 h.
Secondary efficacy assessments included for example: same at 15, 30, 60, and 90 min; proportion of patients with pain relief at 15, 30, 60, 90 and 120 min, the sustained pain-free rate (the proportion of

patients pain free at 2 h with no recurrence or use of rescue medication from up to 24 h post-dosing), the proportion of patients experiencing photophobia, nausea/vomiting or who needed rescue medication.

Methods:
This randomized clinical trial was conducted in Spain. Patients aged 18-65 years treated two migraine attacks of moderate-to-severe intensity: one with almotriptan tablets 12.5 mg (normal dose) and the other with ergotamine 2 mg plus caffeine 200 mg. The second study drug was not to be taken until 7 days after taking the first study drug. The patients had diagnosed migraine with or without aura with one to six attacks per month for >1 year and a diagnosis of migraine before age 50.

Results:
A total of 272 patients were randomised, but 43 were lost before receiving the study drug. Twenty-eight patient withdrew from the study, most because they did not have a migraine attack. Treatment with almotriptan was associated with a significantly greater proportion of patients achieving 2-h pain free (20.9% vs. 13.7%; P < 0.05) and 2-h pain relief (57.7% vs. 44.5%; P < 0.01) compared with ergotamine plus caffeine therapy; significant differences were not seen at 1 h.

Table 4 shows some additional secondary endpoints:

Table 4.

End-point	Almotriptan, % of patients	Ergotamine + caffeine, % of patients	*P*-value
Sustained pain free (SPF)*	20.3	11.5	<0.05
Sustained pain free plus no adverse events	18.1	9.9	<0.05
Rescue medication use	38.5	48.4	<0.05

*Defined as pain free at 2 h after treatment with no recurrence or use of rescue medication from 2 to 24 h post-treatment.

Almotriptan was associated with a significantly lower rate of photophobia at 90 min (P < 0.05), phonophobia at 60, 90, and 120 min (P < 0.05 to <0.01), and nausea and vomiting at 90 and 120 min (P < 0.01). Sixteen patients reported adverse events during almotriptan treatment and 27 patients reported adverse events during the ergotamine plus caffeine therapy. However, the study was not powered to detect the differences in safety between almotriptan and ergotamine plus caffeine.

Almotriptan is not available in NZ. Rizatriptan is available. Eletriptan is approved but not available. All studies showed inferior efficacy of Cafergot compared to the triptan, for example regarding reduced pain/patients being pain free. Recurrence rate is higher in the triptan groups. Time to recurrence is longer for eletriptan compared to Cafergot. However, the recurrence rate data seems uncertain as other factors, such as other medicines used, may interfere with the results.

3.1.1.5 Miljković S, Smajlović Dz, Tirić Campara M et al, 2018. The first comparative double-blind trial on efficacy and safety of ergotamine based five-component combination and sumatriptan in migraine without aura (27).

This randomized, double-blind, double-dummy, placebo-controlled, parallel arm, multi-center study aimed to compare efficacy and safety of a complex fixed drug combination against migraine to a triptan.

A total of 201 patients with migraine without aura were randomized to receive one dose of an ergotamine based five-component drug combination or oral sumatriptan. The ergotamine based drug combination included ergotamine, caffeine, propyphenazone (analgesic), camylofin (anticholinergic) and mecloxamine (anticholinergic).

The results from the study suggested that the combination was more effective than sumatriptan. Only one, not serious, adverse effect occurred.

Comment: The authors claim the long effect of ergotamine as being the reason for the result. Considering the high number of medicines in the combination pack, though, it is not possible to draw any conclusions from this study. This mix of medicines also has many disadvantages because of safety risks, from propyphenazone – a medicine which safety has been disputed, or from anticholinergics. Most safety risks would not have appeared after a single dose.

3.1.2 Clinical trials, safety

3.1.2.1 Limmroth V, Katsarava Z, Fritsche G et al, 2002. Features of medication overuse headache following overuse of different acute headache drugs (28).

Outcome measures:
Mean Critical Duration of Overuse (MCDO) before Medication-Overuse Headache (MOH) occurred, Mean Critical Monthly Intake Frequencies (MCMIF) and Mean Critical Monthly Dosages (MCMD).

Methods:
This was a prospective study including 96 patients with medication-overuse headache (MOH) who underwent standardised inpatient withdrawal from their medication. Patient diaries and structured interviews were used to calculate MCDO, MCMIF, MCMD for each substance group. Focus was on newly approved triptans.

Results:
Sixty-nine patients had migraine (71%) and the rest had tension-type headache or a combination of the two. Forty-six patients of the total group (48%) overused analgesics, 12 (13%) overused ergots and 38 (39%) overused triptans. In the migraine group of patients, the MCDO was shortest for the triptans (1.8 years), longer for ergots (2.6 years) and the longest for analgesics (4.6 years). The MCMIF was lowest for triptans (18 single doses/month), higher for ergots (36 single doses/month) and highest for analgesics (114 single doses/month). Most of the patients overusing ergots had developed a tension-type headache while most patients overusing triptans had developed more migraine attacks or a migraine like daily headache.

3.1.2.2 Katsarava Z, Fritsche G, Muessig M et al, 2001. Clinical features of withdrawal headache following overuse of triptans and other headache drugs (29).

Introduction:
Complete withdrawal from headache medication is the treatment of choice for medication-overuse headache. The discontinuation however, results in a withdrawal headache, often associated with

nausea, vomiting and sleep disturbances. This study investigates duration and severity of withdrawal headache after overuse of various headache drugs.

Outcome measures:
Daily assessment of intensity of withdrawal headache, self-assessment of overall health, intensity of associated symptoms like nausea and the number of requested rescue medications.

Methods:
This was a prospective study including 95 patients with medication-overuse headache (MOH) who underwent standardised inpatient withdrawal from their medication. The patients were closely observed for 14 days. Focus was on newly approved triptans.

Results:
Sixty-nine patients had migraine (73%) and the rest had tension-type headache or a combination of the two. Fifty of the total patient group (53%) overused analgesics, 16 (17%) overused ergots and 29 (30%) overused triptans. Mean duration of withdrawal headache was significantly shorter in the triptan group compared to the ergot group and the analgesic group. The patents in the triptan group had significantly less associated symptoms and requested significantly less rescue medication.

Comment: The studies show some features of MOH and withdrawal headache, where the triptans seem to cause MOH earlier than ergots, but also take shorter time to withdraw from. Note though that the studies include only a few patients on ergots (and in addition it is unknown if they have overused ergotamine or dihydroergotamine) and the outcome measures are all determined by the patients.

3.1.3 Review articles

3.1.3.1 Tfelt-Hansen P, Saxena PR, Dahlöf C et al, 2000. Ergotamine in the acute treatment of migraine. A review and European consensus (10).

This is a consensus article, also covering the pharmacology of ergotamine. A specific feature of ergotamine and dihydroergotamine that is highlighted is their contractile effects in isolated human coronary arteries, being resistant to repeated wash contrary to the triptans. This appears to be mainly due to slow diffusion from the receptor biophase, and therefore the effects of ergotamine and dihydroergotamine last far longer than can be expected from plasma concentrations.

The authors note that even if this medicine has been used for a long time, there is a limited number of studies with contemporary methodology available. They present a summary of 18 controlled double-blind trials of oral ergotamine, from 1961 to 1999. Ten of the studies were comparing with placebo and in the other 8 ergotamine was the comparator. The initial dose of ergotamine was 1 to 5 mg and in several trials repeated intake of test medicines were used. The reported parameters for efficacy were not all validated and varied considerably and there were also other methodological flaws in some of the trials.

Table 5 shows the double-blind randomised trials with pure oral ergotamine (Erg) or ergotamine with caffeine (ErgC) in the treatment of migraine attacks.

Table 5. Summary of trials included in the review.

Trial	Drug	Initial (maximum) dosage (mg)	Study design	No. of attacks treated[a]	No. of patients (no. evaluated)	Result of trial
Ostfeld, 1961	Erg Pl	5	CO	1	44	More than 50% headache relief: Erg (70%) > Pl (39%)
Waters, 1970	Erg Pl	2–3	CO	?[b]	88 (79)	Benefited based on clinical interview: Erg (51%)/Pl (58%)
	ErgC Ergs Pl	2 (6) 2 (6)	CO	1	48	Escape medication: ErgC (22/48) = Ergs (22/46) > Pl (33/46)
Ryan, 1970	ErgC IsomC	2 (6) 130 (130)	CO	2	54	Mean headache duration: ErgC > IsomC
Yuill *et al.*, 1972	ErgC IsomC[c]	2 (6) 130 (390)	CO	1	38	Headache intensity[d]: IsomC (2.8) > ErgC (3.3). Nausea[d]: IsomC (1.1) > ErgC (2.0)
Hakkarainen *et al.*, 1979	Erg Tfa ASA Pl	1 200 500	CO	2	20	Mean duration of attack in h: Erg (3.8) = Tfa (3.2) = ASA (4.2) > Pl (7.1) Preference: all drugs > Pl
Hakkarainen *et al.*, 1978	Erg DextC[e] ASA	1 (3) 100 (200) 500 (1500)	CO	7	25	Mean of attack prevented: Erg (3.6) = DextC (2.6) > Pl (1.1)
Hakkarainen *et al.*, 1980	Erg DextC[e] ASA	1 (2) 100 (200) 500 (1000)	CO	7	25	Attack not prevented: Erg (53%) = DextC (59%) > Pl (82%)
Pradalier *et al.*, 1985	ErgC[f] Napxs	2 (4) 825 (1375)	Pa	6	114 (95)	For test drug taken within 2 h: Napxs > ErgC for headache relief. Later intake of test drug, NS[g]
Sargent *et al.*, 1988	ErgC Napxs Pl	2 (3) 825 (1100)	Pa	6	169 (122)	Relief of headache at 1 h: Napxs > Pl, ErgC = Pl. Overall efficacy: ErgC > Pl, Napxs = Pl
Kinnunen *et al.*, 1988	ErgC[f] Pirp Pl	2 (5) 200 (500)	CO	1	67 (61)	Escape medication: ErgC (18/59) = Pirp (18/58) > Pl (32/60). Duration of attacks in h: ErgC (6.5) > Pl (10.5) but versus Pirp NS. For most parameters, ErgC vs Pirp NS
Friedman *et al.*, 1989	ErgC[f] Pl	2 (6)	Pa	2	? (104)	Mean improvement from baseline on a 5-point headache scale after 2 h: ErgC (1.0) > Pl (0)[h].
The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991	ErgC Sum	2 100	Pa	3	580 (577)	Headache relief[i]: Sum (66%) > ErgC (48%)
Treves *et al.*, 1992	Erg Napxs	2 (4) 750 (1750)	Pa	6	79 (71?)	Napxs > Erg for overall efficacy rating of treatments on a 6-point scale (none to excellent) .Improvement of headache: Napxs = Erg
Le Jeunne *et al.*, 1997	ErgC CASA+M	1 900 + 10	Pa	3	268	Headache relief[i]: CASA + M (54%) > ErgC (36%)
Cortelli *et al.*, 1996	ErgC Diclo Pl	2 (6) 50 (150)	CO	1	63	Diclo > Pl (–15 mm mean difference for changes on a VAS scale after 1 h). Diclo > ErgC (–11.9 mm mean difference) ErgC = Pl (–2.8 mm mean difference)
McNeely and Goa, 1999	ErgC Diclo Pl	2 (5) 50 (200)	Pa	1	423	Diclo > Pl (–9 mm mean difference for changes on VAS scale after 2 h). Diclo = ErgC (–3.6 mm mean difference). ErgC = Pl (–5.4 mm mean difference).
Reches and Eletriptan Steering Committee, 1999	ErgC Ele Ele Pl	2 (4) 40 (80) 80 (160)	Pa	1		Headache relief[i]: Ele 80 (68%) > Ele 40 (58%) > ErgC (33%) > Pl (21%)

The table is modified from Tfelt-Hansen and Johnson (1993). ASA = aspirin; CASA + M = calcium carbasalate (equivalent to 900 mg of ASA) plus metoclopramide; DextC = dextropropoxyphene compound; Diclo = diclofenac; Erg = ergotamine; ErgC = ergotamine compound with caffeine (1 mg of ergotamine + 100 mg of caffeine); Ergs = ergostine (+ caffeine); Ele = eletriptan; IsomC = isometheptene compound; Napxs = naproxen sodium; Pirp = pirprofen; Sum = sumatriptan; Tfa = tolfenamic acid; Pl = placebo; CO = crossover; Pa = parallel group; NS or = = no statistical significant difference; > = more effective than. [a]Maximum number of attacks treated; [b]approximately one-quarter of patients did not have migraine (74); [c]only dose of isometheptene given (for other components, see reference); [d]verbal scale : 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe; [e]only doses for dextropropoxyphene [65 mg of the chloride (9) or 100 mg of the napsylate (10)] are indicated (for other components, see references); [f]contains other components in addition to caffeine, see references; [g]study conclusions weakened by the lack of use of double dummy technique; [h]patients refractory to ergot therapy were excluded; [i]a decrease from severe or moderate headache to no or mild headache.

Ergotamine was superior to placebo for some parameters in 7 trials, and no better than placebo in 3. In 3 comparative studies, ergotamine was superior to aspirin, and in other studies sumatriptan and eletriptan were superior to ergotamine. The authors conclude that the trials suggest that oral ergotamine is effective in treatment of migraine, but they do not quantify the benefit effectively. Early use in the attack was used in some trials but the results from that strategy were not convincing.

Headache recurrence, defined as a return or worsening of the headache and associated migraine symptoms within 24-72 h is a major issue with all acute migraine treatments. According to trials, about 1/3 of sumatriptan users, especially those with long attacks of 2-3 days, will consistently experience

headache recurrence. The general perception is that ergotamine carries a lower risk of headache recurrence than the triptans.

The authors question if it is possible to draw that conclusion based on trials data. The initial response and use of analgesics for early treatment of recurrent headache must be taken into account. In addition the time at which recurrence occurs must be considered, since headache is usually only monitored up to 24 h, although in one study (section 3.1.1.1), a significant difference of recurrence 48 hours after dosing (41% for oral sumatriptan and 30% for oral Cafergot) was noted. It is important to bear in mind that headache recurrence is assessed in a non-randomised population (those who originally responded to treatment). The opinion in this article is that headache recurrence is probably less likely with ergotamine.

As ergotamine has a low degree of receptor selectivity, the risk of side effects is high. About 10% of patients using oral ergotamine experience nausea and vomiting, probably caused by a direct effect on CNS emetic centres. Ergotamine usually induces bradycardia even if the blood pressure is not increased. Ergotamine can produce coronary vasoconstriction with ischemic changes and angina pain in patients with coronary artery disease. Ergotamine doses that produce peripheral vasoconstriction can also damage the capillary endothelium. Ergotamine also increases the motor activity of the uterus. Other side effects mentioned are already described in section 2.2.7.

The authors conclude that ergotamine is not a drug of first choice for treatment of acute migraine because of issues with efficacy and side effects. It may be useful though for a limited number of patients with prolonged duration of attacks (e.g. more than 48 hours) and possibly if headache recurrence is frequent. If used, the preferred route is rectal because of improved absorption.

3.1.3.2 Silberstein SD, McCrory DC, 2003. Ergotamine and dihydroergotamine: History, Pharmacology, and Efficacy (1).

This American review article describes characteristics of ergotamine and dihydroergotamine and also summarises 21 publications (many the same as in the review above) with these medicines given by different routes of administration based on the number of patients obtaining headache relief according to an a priori definition of at least a 50% reduction in pain severity. Many of the studies were small or had methodological problems, and the results were unclear, although for ergotamine they showed better effect compared to placebo in most trials, better effect compared to aspirin but not ketoprofen and naproxen, and inferior effect compared to triptans.

The conclusion is that ergotamine may be considered in the treatment of selected patients with moderate-to-severe migraine, especially patients with very long attacks or frequent headache recurrences.

Comment: The early studies on ergotamine had many methodological problems such as measuring efficacy in different ways or using different inclusion criteria. The studies also have conflicting results. Therefore there is a high uncertainty in the data. The most modern trials are those comparing ergotamine with triptans, where ergotamine in most cases has an inferior effect, especially when used orally. When compared with NSAIDs, Cafergot has for example shown inferior efficacy to naproxen and diclofenac.

There does not seem to be a common view as to ergotamine's place in clinical practice. The authors see a niche for treatment of patients with very long attacks, possibly because of the specific feature with the persistent contractile response by ergots, or frequent headache recurrence. There is limited evidence from the short term studies comparing Cafergot with triptans, when there was a difference in recurrent headache, but no evidence showing benefits from ergotamine compared to other medicines when this niche of patients have been treated.

3.1.3.3 Marmura MJ, Silberstein SD, Schwedt TJ, 2015. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies (30).

This study aims to provide an updated assessment of the evidence for individual pharmacological therapies for acute migraine treatment. A standardized literature search was performed to identify articles related to acute migraine treatment that were published between 1998 and 2013. The American Academy of Neurology Guidelines Development procedures were followed.

The author panel comprised headache experts. Two authors reviewed each abstract resulting from the search and determined whether the full manuscript qualified for review. Two reviewers studied each qualifying full manuscript for its level of evidence. Based on the quality of studies, a level of evidence was assigned for each drug, as Level A (established as effective (or ineffective) for acute migraine, Level B: Probably effective (or ineffective) for acute migraine, Level C: Possibly effective (or ineffective) for acute migraine or Level U: Evidence is conflicting or inadequate.

At least currently, only dihydroergotamine is available in the US. No new published well-designed studies on dihydroergotamine were found since the most recent guidelines. No new review of previous studies was done, and the assigned levels of evidence for these agents were based on the 2000 AAN Guidelines. The assigned level for ergotamine is Level C. For dihydroergotamine it is Level B (except for nasal spray where it is Level A).

3.1.3.4 Antonaci F, Ghiotto N, Shizheng W et al. 2016. Recent advances in migraine therapy (31).

This recent review discusses the efficacy and safety of currently used acute migraine drugs and also emerging pharmacological strategies for acute and preventive migraine treatment.

For ergotamine the article states that it is used in the treatment of long-lasting attacks with tendency of headache recurrence, probably because it is inexpensive and has a long duration of action. The prolonged interaction with a variety of receptors is also the reason why ergotamine generates frequent and various adverse effects. A major problem with ergot derivatives is ergotamine induced headache and rebound headache associated with frequent use. The conclusion is that ergotamine no longer can be considered a drug of choice as it carries a high risk of overuse.

The article presents a level of recommendation for antimigraine medicines, based on the quality of available evidence. Ergotamine however, (as well as dihydroergotamine), has not got a recommendation level at all.

Comment: Many review- or overview articles state that ergotamine has rather unclear benefits, especially when used orally, but may still have a role for the specific group of patients described above. They refer to the same sources, being the sumatriptan-cafergot study and the European consensus article.

3.2 Regulatory action

3.2.1 EMA 2013 (32)

The European Medicines Agency (EMA) reviewed medicines containing five ergot derivatives (dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline and the combination of dihydroergocryptine with caffeine) in 2013. One of the included indications was prevention of migraine headache, while treatment of acute migraine was not included.

The conclusion was that these medicines no longer should be used to treat several conditions involving blood circulation problems or problems with memory and sensation, or to prevent migraine headaches, since the risks are greater than the benefits in these indications. This was based on the review of available safety and efficacy data on ergot derivatives, including clinical studies, post-marketing data in Europe and the published literature. Findings are listed below:

- Fibrosis was most frequently reported with dihydroergotamine, including retroperitoneal, cardiac, pulmonary and pleural fibrosis. There were fewer reports of fibrotic reactions with the other ergot derivatives. The CHMP noted the difficulty of diagnosing fibrosis (due to delayed onset of symptoms) and the probability of under-reporting of fibrotic reactions.
- Ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis, through serotonergic receptor activation, which is extensively described in the literature. The varying affinity for serotonergic receptors of the different ergot derivatives, and the therapeutic doses used, may explain the differences observed in reporting frequencies for the fibrotic reactions.
- Cases of ergotism or potentially related symptoms were most frequently reported with dihydroergotamine. Patients were young (mean age 41 years-old), with a short time to onset after starting dihydroergotamine (less than 2 months, mean: 2 days). The severity of such adverse effects and their possible fatal outcome was underlined. Several cases of ergotism or symptoms potentially related to ergotism (including severe cases of symptoms of constriction of peripheral blood vessels) were also identified with the other ergot derivatives.
- The available efficacy data for the described indications were considered to be very limited. In addition, a scientific advisory group held in December 2012 did not consider there was evidence of a therapeutic need for ergot derivatives in the indications covered by the review.

Comment: Cafergot was not included in this review, possibly because it is not available in many countries in Europe. Cafergot should not be used for prevention of migraine, and has not got that indication in NZ. The findings are still interesting as the medicines are all ergot derivatives.

3.2.2 Health Canada, 2003 (33)

A new contraindication was applied to prescription products containing ergotamine or dihydroergotamine to not be taken at the same time as drugs that strongly inhibit certain liver enzymes ("CYP 3A4" enzymes). The metabolism of ergotamine is slowed down by these drugs which can lead to toxic levels of ergotamine causing serious decreases in blood flow to the brain or to the limbs (vasospasm or ischemia). Cases of stroke and gangrene have been reported from ergot toxicity, with some cases resulting in death or amputation.

Examples of drugs that were listed as strong "CYP 3A4" liver enzyme inhibitors included: protease inhibitors used in the treatment of HIV such as ritonavir, nelfinavir, indinavir, saquinavir, macrolide antibiotics such as erythromycin, clarithromycin and antifungal agents such as ketoconazole, itraconazole, fluconazole, clotrimazole.

There were additional medications and products, such as several antidepressants, which were not contraindicated, but which may also pose a potential risk of ischemia when taken with ergotamine-containing products.

Cafergot is no longer available in Canada. The only ergotamine product available is dihydroergotamine injection and nasal spray.

3.2.3 FDA (34)

Cafergot tablets are available in the US and indicated both to abort and prevent migraine.

The product information has a boxed warning, which is the strongest warning that FDA requires. A boxed warning signifies that clinical studies indicates that the medicine carries a significant risk of serious or even life-threatening adverse effects. The warning highlights the contraindication regarding coadministration of Cafergot with potent CYP 3A4 inhibitors:

Warning
Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of ergotamine tartrate and caffeine tablets with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of ergotamine tartrate and caffeine tablets, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated (see also CONTRAINDICATIONS and WARNINGS sections).

3.3 Summary of safety issues

There are various safety issues with ergotamine. Some occur commonly after therapeutic doses, for example nausea and vomiting. Patients may also experience abdominal pain, weakness and muscle pains in the extremities or numbness/tingling of the fingers and toes.

Use of ergotamine over a longer time or with high doses may cause more serious adverse effects. Note however that susceptible patients may show signs of acute or chronic poisoning with normal doses of ergotamine.

Chronic poisoning (or ergotism) may lead to severe circulatory disturbances in extremities which can develop into gangrene, anginal pain, tachycardia or bradycardia, and hypertension or hypotension. Myocardial infarction has occurred rarely. Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Acute overdosage may be fatal.

Chronic medication overuse headache may occur and rebound headache is a major withdrawal symptom following the development of ergotamine dependence.

3.4 Section 36 notice

On 2 April 2019, Medsafe issued the company a notice under section 36 of the Medicines Act 1981. The section 36 notice requested that the company provide the following information:

1. A summary of the efficacy of Cafergot in the approved indication, including absolute numbers of the patients expected benefits where available and data on the efficacy of comparators.
2. A review of all spontaneous reports of suspected adverse reactions to Cafergot and a review of the literature on safety of Cafergot.
3. Data on how Cafergot is used in New Zealand, including number of patients.
4. The latest Periodic Safety Update Report, reporting period 01 Dec 2015 to 30 Nov 2018, previously referred to.
5. Any further analyses of clinical trial data which may have been performed.
6. Any other relevant information you may have.
7. Proposals for risk minimisation plans for New Zealand.

The company's response to the section 36 notice is presented in section 4.0 of this report.

Comments: The New Zealand sponsor for Cafergot (ergotamine tartrate+caffeine) is AFT Pharmaceuticals Ltd. The international product owner is Advanzpharma.

4.0 INFORMATION PROVIDED BY THE COMPANY

4.1 Response to the section 36 notice

The full response to the section 36 notice from the company is attached as Annexe 3. The latest Periodic Safety Report was emailed separately and is attached as Annexe 4.

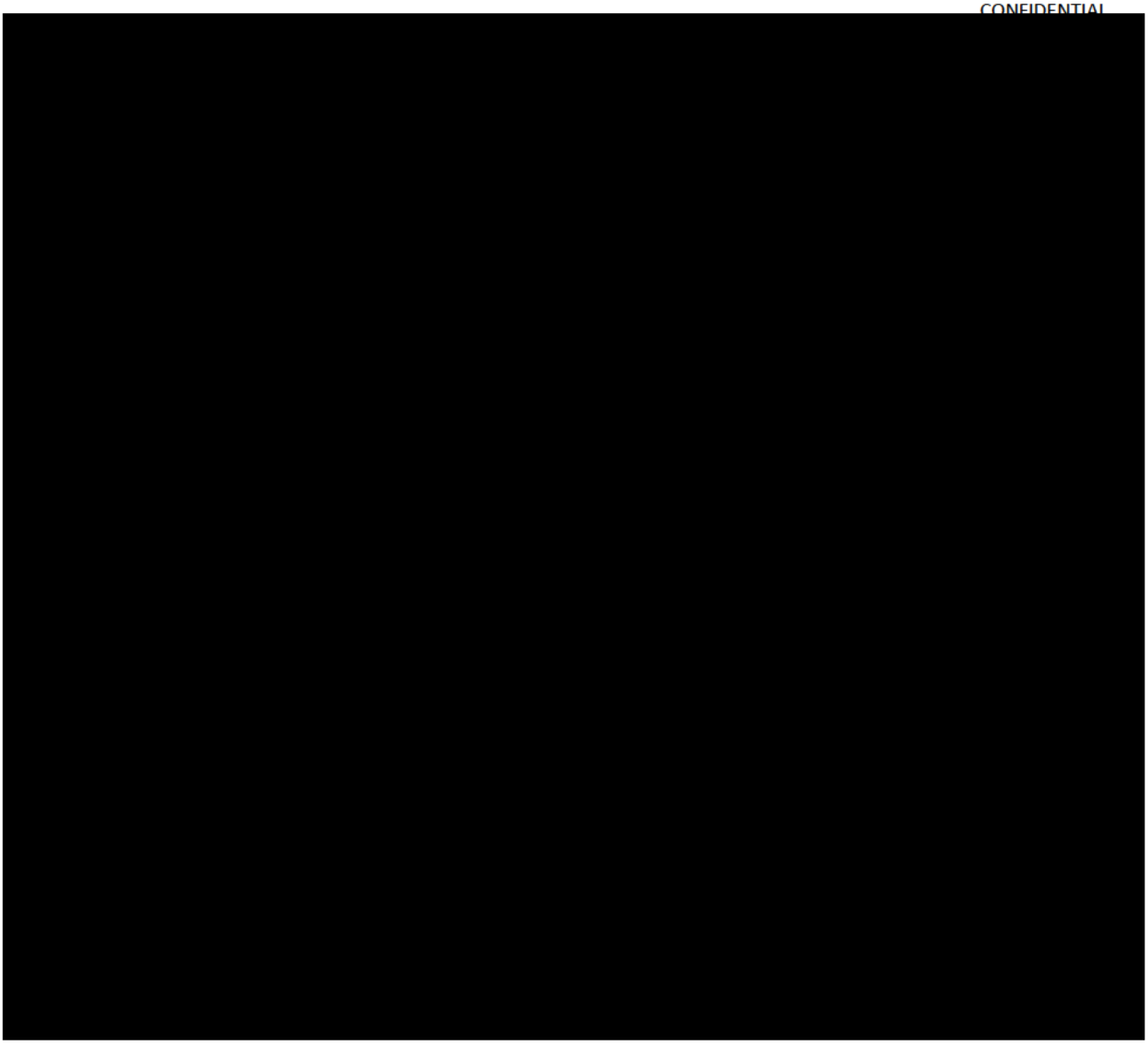
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

5.0 BENEFIT RISK REVIEW

5.1 Company benefit risk review

[redacted]

[redacted]

[redacted]

5.2 Medsafe benefit risk review

5.2.1 Medsafe's pre-market clinical evaluation

No pre-market clinical evaluation of Cafergot was performed when the medicine was approved in 1969. This product was grandfathered into the New Zealand market.

5.2.2 Benefits

For the purposes of this review, the benefits of Cafergot (ergotamine tartrate + caffeine) are considered to be:

Efficacy compared to placebo in some studies
There are studies where the efficacy of Cafergot has been compared to placebo. However, there is a high level of uncertainty in the data for several reasons, such as:

- The methodology of the studies did not follow modern GCP-standards. For example, the reported parameters for efficacy were not all validated.
- The results are conflicting although most studies show superiority compared to placebo.
- The dose of ergotamine differed between the studies.
- In some studies ergotamine was combined with caffeine and in some it was not.

Rectal administration of Cafergot showed better results than oral administration.
Combination with caffeine when Cafergot was used orally showed better results than giving ergotamine by itself.

Lower rate of headache recurrence in some studies
When triptans were developed, Cafergot was sometimes used as the comparator. These studies were of higher quality. The 4 studies referred to in this paper was industry sponsored and only included 1-3 treatment episodes.

The efficacy of Cafergot was generally inferior to the triptans in the studies and more patients on Cafergot experienced nausea/vomiting and photo- phonophobia. The benefit that has been raised as the reason for recommending Cafergot to some patients is the lower level of recurrence headache compared to the triptans. Three of the four studies measured recurrence headache within 24 h, but the sumatriptan study measured within 48 hours.

There was a higher number of recurrence headache in the triptan treatment groups (except in the almotriptan study where proportion of patients who were pain free after 2 h and had no recurrence or use of rescue medication within 24 h (SPS) were higher for almotriptan compared to Cafergot). Recurrence of migraine headache within 48 h was lower in the Cafergot group (30 %) compared to the sumatriptan group (41%) (p=0.009). In the eletriptan study, the time to recurrence was longer for eletriptan.

The authors of these studies discuss a number of factors that can interfere with recurrence rates, such as if the patients had used other medication during the intervening period or a second dose of study medication. Recurrence is also conditional on initial headache relief and depends on the observation

time. The extent to which the patients who recorded recurrence can be attributed to any study medication is therefore limited. However, there are also suggestions that differences may partly be explained by the short half-life of sumatriptan (approximately 2 h).

There are characteristics of ergotamine that may contribute to a lower recurrence rate. Peripheral vasoconstriction from ergotamine administration has been shown to persist for a long time and as long as 24 h, and repeated doses lead to cumulative effects long outlasting a migraine attack. In contrast to triptans, the contractile effect of ergotamine in the human isolated coronary artery is long lasting and persists even after repeated washings. However, this would not explain why the time to recurrence was longer for eletriptan as compared to Cafergot. According to the new research, migraine is not linked to the dilation and constriction of blood vessels in the head (see section 2.3.1), and therefore other explanations are probably important.

Ergotamine has been recommended for use to a limited number of patients with frequent headache recurrence or prolonged duration of attacks. There is no strong clinical evidence supporting this recommendation.

5.2.3 Risks

The risk drivers for Cafergot are:

1. Peripheral vasoconstriction.
2. Worsening of migraine symptoms.
3. Overuse leading to fibrosis and overuse headache.

The clinical studies referred to in this paper are short and do not capture safety risks associated with longer term use, and no studies over longer time periods have been found. There are several case reports in the literature regarding for example fibrosis, coronary problems or ischemia (35-37). The risks discussed below are known risks from Cafergot product information, other regulatory action, documentation from the company, review articles and guidelines.

Peripheral vasoconstriction.
The mechanism of action for Cafergot is vasoconstriction of blood vessels. As ergotamine shares structural similarities with the adrenergic, dopaminergic, and serotonergic neurotransmitters, the medicine interacts with a variety of receptors and have wide-ranging effects on the physiologic processes. Peripheral vasoconstriction from ergotamine administration has been shown to persist for a long time. Vasoconstrictive symptoms include for example ischemia, weakness, cold extremities and muscle pains and more serious symptoms may develop if ergotamine is overused or in treatment of susceptible patients.

Worsening of migraine symptoms.
Nausea and vomiting commonly occur as a result of the direct emetogenic effect of ergotamine and some patients may also have abdominal pain. Ergotamine can worsen the nausea and vomiting associated with migraine. About 10% of patients using oral ergotamine experience nausea and vomiting.

Overuse leading to fibrosis and overuse headache.
These effects occur most commonly with long-term therapy at relatively high doses. However, susceptible patients, especially those with sepsis, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine. Effects are:

Fibrosis

Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. An article on risk of fibrosis with medicines containing ergot derivatives was published in Prescriber Update in June 2014 (38).

Severe circular disturbances

Chronic poisoning (or ergotism) may lead to severe circulatory disturbances in extremities which can develop into gangrene, anginal pain, tachycardia or bradycardia, and hypertension or hypotension. Myocardial infarction has occurred rarely. Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Acute overdosage may be fatal.

Headache

Chronic headache may occur. The use of ergotamine on 10 or more days per month has been considered to confer an increased risk for the development of medication-overuse headache (MOH). Rebound headache is a major withdrawal symptom following the development of ergotamine dependence.

Additional risks associated with Cafergot use are the unreliable bioavailability, the high amount of interactions (some very serious), and the many contraindications and warnings.

6.0 DISCUSSION AND CONCLUSIONS

Migraine headaches vary in severity from moderate pain with no activity limitations to severe pain and prolonged incapacitation severely undermining quality of life. The headache is usually associated with nausea, vomiting, photophobia, or phonophobia. Most migraineurs are chronically affected by migraine and have recurrent episodic attacks with varying frequencies.

Migraine is treated acutely and preventatively. There are several medicines used for treatment of acute attacks and one of them is Cafergot. The usage of Cafergot has decreased a lot since more modern medicines, like the triptans, were developed. Cafergot has been withdrawn from some markets and many guidelines do not recommend Cafergot. A questionable effect due to limited data and low bioavailability together with a high risk of adverse events have been considered to be disadvantages of Cafergot. However, Cafergot is still used in countries which lack the economic resources to afford the more expensive triptans.

Cafergot is used in NZ, to a relatively low degree. Usage data shows that Cafergot is prescribed in higher age groups for whom it is not recommended to be used.

It has been difficult to find reliable data on efficacy and safety of Cafergot. The medicine has been approved in NZ for a long time and as it was grandfathered in, there is no clinical evaluation report. The clinical studies are either old and of uncertain quality or newer but with Cafergot used short term as a comparator.

Data on safety is also limited. As this is an old and not so often used medicine for example in NZ, there is a large risk that people simply have stopped reporting adverse effects. The safety profile of Cafergot seems to be quite well known. [redacted]
Review studies list the same adverse effects and usually refer to the same (not always reliable) clinical studies.

Some common side effects of Cafergot, like nausea and vomiting, unfortunately worsen the same symptoms of the migraine attack. Other side effects, like fibrosis, are unusual but very serious. Many of the more serious side effects occur after longer term use or if patients have risk factors for these effects. There are warnings and contraindications listed in the data sheet as well as maximal doses per day and week. However, Cafergot is considered to be a medicine that may be overused.

There may be a particular group of patients with high recurrence rates and long migraine attacks for which Cafergot may be effective, even if the evidence is uncertain. There were approximately 1,777 patients using Cafergot in NZ during 2018. The usage is decreasing and the users get older on average year by year. Cafergot is not generally used first-line for treatment of migraine so it is possible that many users are patients who have tried other treatment alternatives and Cafergot is the one that works for them.

Medsafe would like the Committee to consider 2 different patient groups with migraine when considering the benefits and risks for this medicine:

1. Patients with 1 migraine attack a month or less, no prophylactic treatment and a good response to NSAIDs. Other available alternatives are triptans, with better effect and less adverse effects compared to Cafergot. Is there a reason to keep Cafergot as a treatment alternative for these patients?

2. Patients with 3 or more migraine attacks a month even if they are on prophylactic treatment. These patients may have tried most alternatives without success and even consider Cafergot to be the medicine that works. Is there a reason to keep Cafergot as a treatment alternative for these patients, considering the risk of serious adverse effects, even if less common, associated with Cafergot use as well as the risk of overuse?

7.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The Committee agrees with the considered benefits from Cafergot treatment.
- The Committee agrees with the considered risks from Cafergot treatment.
- The balance of benefits and risk for the use of Cafergot for the treatment of migraine is favourable.
- If any regulatory action is required as outlined in the introduction to this paper.

8.0 ANNEXES

1. MARC report Ergotamine containing medicines and pancreatitis. March 14 meeting 2019.
2. CARM report Cafergot review.
3. Comments from Professional Organisations.
4. The full response to the section 36 notice from the company.
5. The latest Periodic Safety Report (Sent separately from Annex 4) from the company.

9.0 REFERENCES

1. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. Headache. 2003 Feb;43(2):144-66. PubMed PMID: 12558771. Epub 2003/02/01.

2. Madlom Z. The origin of drugs in current use: the ergot alkaloids story. 2002 [cited 2019 1 July 2019]. Available from: http://www.davidmoore.org.uk/sec04_03.htm.

3. WebMD. Ergot [accessed 1 August 2019]. Available from: http://www.webmd.com/vitamins/ai/ingredientmono-431/ergot.

4. UpToDate. Acute treatment of migraine in adults [updated 14 May 2018 accessed 20 February 2019]. Available from: https://www.uptodate.com/contents/acute-treatment-of-migraine-in-adults?search=ergotamine&source=search_result&selectedTitle=2~114&usage_type=default&display_rank=1.

5. Science Direct. Dihydroergotamine 2007 [accessed 16 August 2019]. Available from: https://www.sciencedirect.com/topics/neuroscience/dihydroergotamine.

6. AFT Pharmaceuticals LTD. Cafergot NZ data sheet 2018 [updated 13 February 2018 accessed 20 February 2019]. Available from: https://medsafe.govt.nz/profs/Datasheet/c/cafergottab.pdf.

7. Michael C. Lee MA. Ergotamine (Pain and analgesics). 2012. Science Direct.

8. Martindale Pp. Antimigraine Drugs 2014 [updated June 2014 accessed 20 February 2019]. Available from: http://www.pharmpress.com/files/docs/martindale38_samplechapter.pdf.

9. Tfelt-Hansen P, Paalzow L. Intramuscular ergotamine: plasma levels and dynamic activity. Clinical pharmacology and therapeutics. 1985 Jan;37(1):29-35. PubMed PMID: 3917386. Epub 1985/01/01.

10. Tfelt-Hansen P, Saxena PR, Dahlof C, Pascual J, Lainez M, Henry P, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. Brain : a journal of neurology. 2000 Jan;123 (Pt 1):9-18. PubMed PMID: 10611116. Epub 1999/12/28.

11. Ong JJY, De Felice M. Migraine Treatment: Current Acute Medications and Their Potential Mechanisms of Action. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2018 Apr;15(2):274-90. PubMed PMID: 29235068. Pubmed Central PMCID: PMC5935632. Epub 2017/12/14.

12. Kristoffersen ES, Lundqvist C. Medication-overuse headache: a review. Journal of pain research. 2014;7:367-78. PubMed PMID: 25061336. Pubmed Central PMCID: PMC4079825. Epub 2014/07/26.

13. Health Navigator. Migaine (severe headache) 2017 [updated 20 December 2018 accessed 20 February 2019]. Available from: https://www.healthnavigator.org.nz/health-a-z/m/migraine-severe-headache/.

14. Neurological Foundation of New Zealand. Migraine [accessed16 August 2019]. Available from: https://neurological.org.nz/disorders/migraine.

15. UpToDate. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults 2018 [accessed 16 August 2019]. Available from: https://www.uptodate.com/contents/pathophysiology-clinical-manifestations-and-diagnosis-of-migraine-in-adults?search=migraine-headaches-in-adults-beyond-the-basics&topicRef=3347&source=see_link.

16. The Migraine Trust. Types of Migraine 2019 [accessed 16 August 2019]. Available from: https://www.migrainetrust.org/about-migraine/types-of-migraine/.

17. National Institute for Health and Care Excellence (NICE). NICE Clinical Guidelines UK 2014 [updated 2014 accessed 20 February 2019]. Available from: https://pathways.nice.org.uk/pathways/headaches/management-of-migraine-with-or-without-aura.

18. Diener H, Holle-Lee D et al. Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology. Clinical and Translational Neuroscience. 2019:1-40.

19. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. European journal of neurology. 2009 Sep;16(9):968-81. PubMed PMID: 19708964. Epub 2009/08/28.

20. Antonaci F, Dumitrache C, De Cillis I, Allena M. A review of current European treatment guidelines for migraine. The journal of headache and pain. 2010 Feb;11(1):13-9. PubMed PMID: 20020170. Pubmed Central PMCID: PMC3452183. Epub 2009/12/19.

21. Hsu YC, Lin KC, Taiwan Headache Society T. Medical Treatment Guidelines for Acute Migraine Attacks. Acta neurologica Taiwanica. 2017 Jun 15;26(2):78-96. PubMed PMID: 29250761. Epub 2017/12/19.

22. Novartis Pharmaceuticals Canada Inc. Cafergot 2012 Product Information [accessed 27 August 2019]. Available from: https://pdf.hres.ca/dpd_pm/00018457.PDF.

23. Multinational Oral Sumatriptan and Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. The Multinational Oral Sumatriptan and Cafergot Comparative Study Group. European neurology. 1991;31(5):314-22. PubMed PMID: 1653139. Epub 1991/01/01.

24. Christie S, Gobel H, Mateos V, Allen C, Vrijens F, Shivaprakash M. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. European neurology. 2003;49(1):20-9. PubMed PMID: 12464714. Epub 2002/12/05.

25. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. European neurology. 2002;47(2):99-107. PubMed PMID: 11844898. Epub 2002/02/15.

26. Lainez MJ, Galvan J, Heras J, Vila C. Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy. European journal of neurology. 2007 Mar;14(3):269-75. PubMed PMID: 17355546. Epub 2007/03/16.

27. Miljkovic S, Smajlovic D, Tiric Campara M, Jurina R, Duranovic Vinkovic L, Jankovic SM, et al. The first comparative double-blind trial on efficacy and safety of ergotamine based five-component combination and sumatriptan in migraine without aura. Hippokratia. 2018 Jan-Mar;22(1):17-22. PubMed PMID: 31213753. Pubmed Central PMCID: PMC6528700. Epub 2018/01/01.

28. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. Neurology. 2002 Oct 8;59(7):1011-4. PubMed PMID: 12370454. Epub 2002/10/09.

29. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology. 2001 Nov 13;57(9):1694-8. PubMed PMID: 11706113. Epub 2001/11/14.

30. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. Headache. 2015 Jan;55(1):3-20. PubMed PMID: 25600718. Epub 2015/01/21.

31. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. SpringerPlus. 2016;5:637. PubMed PMID: 27330903. Pubmed Central PMCID: PMC4870579. Epub 2016/06/23.

32. European Medicines Agency (EMA). Ergot derivatives containing medicinal products 2013 [accessed 16 August 2019]. Available from:

https://www.ema.europa.eu/en/documents/referral/assessment-report-ergot-derivatives-containing-medicinal-products-dihydroergotamine_en.pdf.

33. Health Canada. New Contraindications for Medications Containing Ergotamine and Dihydroergotamine 2003 [cited 2019 16 August]. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2003/14025a-eng.php.

34. Daily Med (FDA). Drug Label Information Cafergot 2012 [accessed 16 August 2019]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b4a06de6-f837-43a8-ae7a-aadb38dd2a7d.

35. Murad MH, Miller FA, Glockner J. Multi-system fibrosis and long-term use of ergotamine. Annals of the Academy of Medicine, Singapore. 2011 Jul;40(7):327-8. PubMed PMID: 21870025. Epub 2011/08/27.

36. Baztarrica P CA, Real A et al. Acute coronary syndrome with elevation of ST associated with ergotamine abuse. Rom J Intern Med. 2019;57(1):69-71.

37. Demir S, Akin S, Tercan F, Aribogan A, Oguzkurt L. Ergotamine-induced lower extremity arterial vasospasm presenting as acute limb ischemia. Diagnostic and interventional radiology (Ankara, Turkey). 2010 Jun;16(2):165-7. PubMed PMID: 19821256. Epub 2009/10/13.

38. Medsafe Pharmacovigilance Team. Risk of fibrosis with medicines containing ergot derivatives 2014 [accessed 20 August 2019]. Available from: Risk of fibrosis with medicines containing ergot derivatives.