dose is limited to a maximum of 12 mg, although again some manufacturers recommend a lower weekly limit of 8 mg. It is also recommended that patients should receive no more than 2 courses per month. Similar doses may be given sublingually.

Ergotamine tartrate may also be given rectally as suppositories, especially if the oral route is not effective or not practicable. The rectal dose of ergotamine tartrate is 2 mg repeated, if necessary, one hour later. Usually, not more than 4 mg should be given in 24 hours and not more than 8 mg in one week with an interval of at least 4 days between successive 24-hour courses.

A more rapid onset of action may be achieved by oral inhalation. One dose containing 360 micrograms of ergotamine tartrate has been inhaled at the onset of the attack and repeated, if necessary, at 5-minute intervals. Not more than 6 inhalation doses should be taken in 24 hours and not more than 12 in one week, with an interval of at least 4 days between successive 24-hour courses.

Ergotamine is used in patients with cluster headache to treat individual attacks of headache but since such attacks are short-lived oral inhalation may be preferable to oral, sublingual, or rectal routes. Doses used are similar to those given to treat migraine. It has also been used to prevent headache attacks during cluster periods, when it is usually given daily in low doses for up to 2 weeks, either orally or rectally (see below).

Migraine and cluster headache. Ergotamine was formerly one of the main drugs used to treat acute attacks of migraine (p.616) unresponsive to non-opioid analgesics, but triptan serotonin (5-HT_1) agonists such as sumatriptan are now preferred. Since ergotamine may exacerbate the nausea and vomiting that commonly develops as a migraine attack progresses it is often necessary to give an antiemetic as well. Poor oral bioavailability may be reduced further during a migraine attack and ergotamine has sometimes been given sublingually, rectally, or by inhalation. Adverse effects limit the dose that can be used for an individual attack and prevent the long-term use that would be required for migraine prophylaxis.

Ergotamine may be used similarly in cluster headache (p.616) to treat individual headaches during a cluster period. Ergotamine is also used in low doses given by mouth or rectally for limited periods of up to 2 weeks in the prophylaxis of headache attacks during a cluster period. Regimens that have been tried for such prophylaxis include 1 to 2 mg of ergotamine tartrate given 1 to 2 hours before an expected attack or 1 to 2 hours before bedtime for nocturnal attacks. The total maximum dose of ergotamine tartrate that may be given weekly for the prevention of cluster headache is less well established than for the treatment of migraine. Ergotamine is often given for only 5 to 6 days in each week, which allows the patient to assess whether the cluster period has ended.

References.

1. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45:** 577–84.
2. Tfelt-Hansen P, *et al*. Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 2000; **123:** 9–18.

Orthostatic hypotension. Ergotamine and dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p.1530). Ergotamine is believed[1] to be less selective than dihydroergotamine (p.619) in its actions and affects both venous capacitance and peripheral resistance.[2,3] However, the oral bioavailability of ergotamine is greater[2] than that of dihydroergotamine and there have also been some reports of successful treatment with inhaled[3,4] or rectal[5] ergotamine.

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39:** 74–85.
3. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153:** 474–85.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51:** 648–60.
5. Toh V, *et al*. Ergotamine use in severe diabetic autonomic neuropathy. *Diabet Med* 2006; **23:** 574–6.

Preparations

BP 2008: Ergotamine Sublingual Tablets;
USP 31: Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Ergotamine Tartrate Inhalation Aerosol; Ergotamine Tartrate Injection; Ergotamine Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Ergodryl Mono†; ***Austria:*** Ergokapton; ***Chile:*** Jaquedryl; ***Ger.:*** ergo sanol spezial N; Ergo-Kranit Migrane; Migrexa†; ***Hung.:*** Ergam; ***Ital.:*** Ergotan; ***Philipp.:*** Avamigran; ***Thai.:*** Ergosia; Gynaemine; ***USA:*** Ergomar.

Multi-ingredient: ***Arg.:*** Cafergot; Cefalex; Ibu-Tetralgin; Ibumar Migra†; Ibupirac Migra; Integrobe Plus; Jaquedryl†; Migra Dioxadol; Migra Donixina; Migral; Migral Compositum; Migral II; Mikesan; Solacil; Tetralgin; Tetralgin Novo; Zilactin-E†; ***Austral.:*** Cafergot; Ergodryl†; ***Austria:*** Avamigran; Cafergot; Migril; Secokapton; Synkapton; ***Belg.:*** Cafergot; ***Braz.:*** Migrane; Neogrein; Ormigrein; ***Canad.:*** Bellergal; Cafergot; Cafergot-PB†; Ergodryl; Gravergol†; ***Chile:*** Bellergal Retardado†; Cafergot-PB†; Cefalmin; Cinabel; Clonalgin Compuesto; Ergobelan; Ergonef; Fredol; Migra-Nefersil; Migragesic; Migranol; Migratam; Ultrimin; ***Cz.:*** Bellaspon†; ***Denm.:*** Ergokoffin; Gynergen Comp; ***Fin.:*** Anervan; ***Fr.:*** Gynergene Cafeine; ***Ger.:*** Avamigran N†; Cafergot N†; Ergo-Kranit†; Ergoffin†; Migratan S†; RubieNex spezial†; ***Gr.:*** Cafergot; ***Hong Kong:*** Cafergot; Gravergol†; Migril†; ***Hung.:*** Kefalgin; ***India:*** Migranil; ***Indon.:*** Bellapheen; Cafergot; Ericaf; ***Irl.:*** Migranat; Migril†; ***Israel:*** Cafergot; Temigran; ***Ital.:*** Cafergot; Virdex; ***Malaysia:*** Cafergot; ***Mex.:*** Cafergot; Caftar; Ergocaf; Optium; Sydolil; Trinergot; ***Neth.:*** Cafergot; Ercycof†; ***Norw.:*** Anervan; ***NZ:*** Cafergot; ***Pol.:*** Bellergot; Coffecom; ***Port.:*** Avamigran†; Migretil; ***S.Afr.:*** Cafergot; Cafergot-PB†; Migril; ***Singapore:*** Cafergot; ***Spain:*** Cafergot; Cafergot-PB†; Hemicraneal; ***Swed.:*** Anervan; Cafergot; ***Switz.:*** Bellagotin†; Cafergot; Cafergot-PB; ***Thai.:*** Avamigran; Bellergal†; Benera; Cafergot; Degran; Neuramizone; Poligot-CF; Polygot; Tofago; ***Turk.:*** Avmigran; Bellergal; Cafergot; Ergafein; ***UK:*** Cafergot; Migril; ***USA:*** Bel-Phen-Ergot S; Bellamine; Bellergal-S; Cafatine; Cafatine-PB; Cafergot; Ercaf; Folergot-DF; Phenerbel-S; Wigraine†; ***Venez.:*** Cafergot†; Ervostal; Migradorixina; Traveget.

Feverfew

Camomille, grande; Matricaria; Mattram; Nat' kopretiny řimbaby; Őszi margitvirág; Reunuspäivänkakkara; Tanaceti parthenii herba; Vaistinių skaistenių žolė.

Pharmacopoeias. In *Eur.* (see p.vii) and in *US*. US also describes Powdered Feverfew.
Ph. Eur. 6.2 (Feverfew). The dried, whole or fragmented aerial parts of *Tanacetum parthenium*. It contains not less than 0.2% of parthenolide ($C_{15}H_{20}O_3$ = 248.3), calculated with reference to the dried drug. It has a camphoraceous odour. Protect from light.
USP 31 (Feverfew). It consists of the dried leaves of *Tanacetum parthenium* (Asteraceae), collected when the plant is in flower. Store in a dry place. Protect from light.

Adverse Effects and Precautions

Mouth ulceration and soreness have been reported following ingestion of feverfew, and may be due to sensitisation; if they occur feverfew should be withdrawn. Contact dermatitis has been reported. Feverfew is reputed to have abortifacient properties and it is suggested that preparations should not be used in pregnancy.

Effects on the blood. There have been suggestions that feverfew may increase the risk of bleeding during surgery or in patients taking anticoagulants. However, although inhibition of platelet aggregation has been reported *in vitro* or in *animals* a review[1] of clinical studies noted that feverfew did not appear to affect haematological safety parameters.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Interactions

It has been suggested that feverfew may enhance the effects of anticoagulants (but see Effects on the Blood, above).

Uses and Administration

Feverfew consists of the dried leaves of the plant *Tanacetum parthenium* (Asteraceae). It is a traditional herbal remedy used in the prophylaxis of migraine. Its effects have been attributed to the plant's content of sesquiterpene lactones, notably parthenolide. A preparation of the dried leaf powder, which has been standardised to provide a minimum of 0.2% parthenolide, is available in some countries. A suggested oral dose is 250 mg daily; a lower dose of 100 mg daily has also been given..

Migraine. Feverfew is a traditional herbal remedy used in the prophylaxis of migraine (p.616). Studies of standardised preparations of the freeze-dried powdered leaf have produced variable results in preventing or ameliorating migraine attacks, and systematic reviews[1,2] suggest that its effectiveness in preventing migraine remains to be established.

1. Vogler BK, *et al*. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998; **18:** 704–8.
2. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Rheumatoid arthritis. Feverfew has been used as a herbal medicine for the treatment of arthritis but although it has anti-inflammatory activity *in vitro*, a clinical trial[1] found it to be ineffective in rheumatoid arthritis.

1. Pattrick M, *et al*. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis* 1989; **48:** 547–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Herbal Headache Relief†; ***Braz.:*** Tanaceto; Tenliv; ***Canad.:*** Tanacet; ***UK:*** Migraherb; Tanacet.

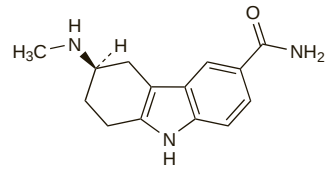
Multi-ingredient: ***Austral.:*** Albizia Complex; Extralife Arthri-Care; Extralife Migrai-Care; Guaiacum Complex†; ***Ital.:*** Neuralta Migren.

Frovatriptan *(BAN, rINN)*

Frovatriptaani; Frovatriptán; Frovatriptanum; SB-209509AX (frovatriptan or frovatriptan succinate); VML-251 (frovatriptan or frovatriptan succinate). (6*R*)-5,6,7,8-Tetrahydro-6-methylaminocarbazole-3-carboxamide.

Фроватриптан

$C_{14}H_{17}N_3O$ = 243.3.
CAS — 158747-02-5.
ATC — N02CC07.
ATC Vet — QN02CC07.



Frovatriptan Succinate *(BANM, USAN, rINNM)*

Frovatriptan, Succinate de; Frovatriptani Succinas; SB-209509AX (frovatriptan or frovatriptan succinate); Succinato de frovatriptán; VML-251 (frovatriptan or frovatriptan succinate).

Фроватриптана Суксинат

$C_{14}H_{17}N_3O,C_4H_6O_4,H_2O$ = 379.4.
CAS — 158930-17-7.
ATC — N02CC07.
ATC Vet — QN02CC07.

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Frovatriptan should not be used in patients with severe hepatic impairment. No dosage adjustment is needed in mild or moderate hepatic impairment.

Interactions

As for Sumatriptan, p.626.

Fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2 and has been shown to increase the blood levels of frovatriptan by 27 to 49%.

Pharmacokinetics

After oral doses, peak plasma-frovatriptan concentrations are attained in 2 to 4 hours, and bioavailability is about 20% in men and 30% in women. Food may delay the time to peak plasma concentrations by about 1 hour. Frovatriptan is 15% protein bound. It is primarily metabolised by the hepatic cytochrome P450 isoenzyme CYP1A2. About 32% of an oral dose is excreted in the urine and 62% in faeces. The plasma elimination half-life of frovatriptan is about 26 hours.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Buchan P, *et al*. Clinical pharmacokinetics of frovatriptan. *Headache* 2002; **42** (suppl 2): S54–S62.
2. Elkind AH, *et al*. Pharmacokinetics of frovatriptan in adolescent migraineurs. *J Clin Pharmacol* 2004; **44:** 1158–65.

Uses and Administration

Frovatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Frovatriptan is given orally as the succinate although doses are expressed in terms of the base; frovatriptan succinate 3.9 mg is equivalent to about 2.5 mg of frovatriptan.

The recommended dose is 2.5 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of at least 2 hours. The maximum dose of frovatriptan in 24 hours is 5 mg in the UK although, in the USA, a maximum daily dose of 7.5 mg is allowed.

◊ References.

1. Goldstein J. Frovatriptan: a review. *Expert Opin Pharmacother* 2003; **4:** 83–93.