Profile
Meteneprost is a synthetic derivative of dinoprostone (prostaglandin E_2; p.2007). It is a uterine stimulant and has been studied for the termination of pregnancy.

◊ References.

1. Takkar D, *et al.* Early abortion by mifepristone (RU 486) followed by vaginal gel (meteneprost) versus oral (misoprostol) prostaglandin. *Adv Contracept* 1999; **15:** 163–73.
2. An ICMR Task Force Study. A multicentre randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE gel (meteneprost) or 600 μg oral PGE (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. *Contraception* 2000; **62:** 125–30.

Methylergometrine Maleate *(BANM, rINNM)*

Maleato de metilergometrina; Methylergobasine Maleate; Méthylergométrine, hydrogénomaléate de; Méthylergométrine, Maléate de; Methylergometrini hydrogenomaleas; Methylergometrini Maleas; Methylergonovine Maleate; Metilergobazin Maleat; Metilergometrin Maleat. *N*-[(*S*)-1-(Hydroxymethyl)propyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-1-(hydroxymethyl)propyl]-6-methylergoline-8β-carboxamide hydrogen maleate.

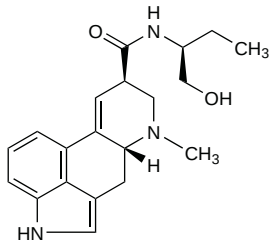
Метилэргометрина Малеат

$C_{20}H_{25}N_3O_2.C_4H_4O_4$ = 455.5.

CAS — 113-42-8 (methylergometrine); 57432-61-8 (methylergometrine maleate).

ATC — G02AB01.

ATC Vet — QG02AB01.



(methylergometrine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Methylergometrine Maleate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; slightly soluble in anhydrous alcohol. pH of a 0.5% solution is 4.4 to 5.2. Store in airtight containers. Protect from light.

USP 31 (Methylergonovine Maleate). A white to pinkish-tan, odourless, microcrystalline powder. Soluble 1 in 100 of water, 1 in 175 of alcohol, 1 in 1900 of chloroform, and 1 in 8400 of ether. pH of a 0.02% solution in water is between 4.4 and 5.2. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Stability. For mention of slight variations in the methylergometrine content of the injection after transport to a tropical climate, see under Ergometrine Maleate, p.2009.

Adverse Effects, Treatment, and Precautions
As for Ergometrine Maleate, p.2009.

Overdosage. References.

1. Aeby A, *et al.* Methylergometrine poisoning in children: review of 34 cases. *J Toxicol Clin Toxicol* 2003; **41:** 249–53.
2. Bangh SA, *et al.* Neonatal ergot poisoning: a persistent iatrogenic illness. *Am J Perinatol* 2005; **22:** 239–43.

Pharmacokinetics
Methylergometrine maleate is reported to be rapidly absorbed when given orally or intramuscularly, with onset of uterine contractions in about 5 to 15 minutes and 2 to 5 minutes, respectively. Oral bioavailability may show considerable interindividual variation. It undergoes extensive first-pass hepatic metabolism and only small amounts of unchanged drug are excreted in the urine. The elimination half-life is reported to be about 2 to 3 hours.

◊ The pharmacokinetics of methylergometrine maleate have been studied after oral doses in healthy subjects[1,2] and in postpartum women.[3] Small amounts of methylergometrine have been detected in breast milk.[4,5]

1. Mäntylä R, *et al.* Methylergometrine (methylergonovine) concentrations in the human plasma and urine. *Int J Clin Pharmacol Biopharm* 1978; **16:** 254–7.
2. de Groot ANJA, *et al.* Comparison of the bioavailability and pharmacokinetics of oral methylergometrine in men and women. *Int J Clin Pharmacol Ther* 1995; **33:** 328–32.
3. Allonen H, *et al.* Methylergometrine: comparison of plasma concentrations and clinical response of two brands. *Int J Clin Pharmacol Biopharm* 1978; **16:** 340–2.
4. Erkkola R, *et al.* Excretion of methylergometrine (methylergonovine) into the human breast milk. *Int J Clin Pharmacol Biopharm* 1978; **16:** 579–80.
5. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; **191:** 2168–73.

Uses and Administration
Methylergometrine maleate has an action on the uterus similar to that of ergometrine maleate (p.2009) and is used similarly in the active management of the third stage of labour, and in the prevention and treatment of postpartum or postabortal haemorrhage (p.2003). In the management of the third stage of labour, it may be given in a dose of 200 micrograms intramuscularly after delivery of the anterior shoulder or, at the latest, immediately after delivery of the infant. The same dose may be used for the prevention or treatment of postpartum or postabortal haemorrhage, and may be repeated every 2 to 4 hours as necessary up to a maximum of 5 doses. In emergencies it may be given in similar doses by slow intravenous injection over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. During the puerperium, methylergometrine maleate has been given in oral doses of 200 micrograms 3 or 4 times daily for up to a week or 125 to 250 micrograms up to 3 times daily.

Methylergometrine is a metabolite of methysergide (p.623).

Diagnosis and testing. For reference to the use of methylergometrine maleate in the diagnosis of variant angina, see Ergometrine Maleate, p.2010.

Preparations
USP 31: Methylergonovine Maleate Injection; Methylergonovine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Basofortina; ***Austria:*** Methergin; ***Belg.:*** Methergin; ***Braz.:*** Ergometrin; Methergin; ***Chile:*** Methergin†; ***Denm.:*** Methergin; ***Fin.:*** Methergin; ***Fr.:*** Methergin; ***Ger.:*** Methergin; Methylergobrevin; ***Gr.:*** Demergin; Methergin; ***Hong Kong:*** Methergin†; ***India:*** Ergogin; Ingagen-M; Methergin; Utergin; ***Indon.:*** Bledstop; Glomethyl; Methergin; Metherinal; Methovin; Metilat; Metvell; Myomergin; Myotonic; Pospargin; ***Israel:*** Methergin; ***Ital.:*** Methergin; ***Malaysia:*** Methergin; ***Mex.:*** Methergin; ***Neth.:*** Methergin; ***Philipp.:*** Medisyl; Mergot; Mergotrex; Methergin; Myometril; Usamema; ***Port.:*** Methergin; ***Spain:*** Methergin; ***Swed.:*** Methergin; ***Switz.:*** Methergin; ***Thai.:*** Ergotyl; Expogin; Metrine; Nathergen†; ***Turk.:*** Methergin; Metiler; Uterjin; ***USA:*** Methergine; ***Venez.:*** Methergin.

Multi-ingredient: ***Ger.:*** Syntometrin†.

Mifepristone *(BAN, USAN, rINN)*

C-1073; Mifepriston; Mifepristona; Mifépristone; Mifepristoni; Mifepristonum; RU-486; RU-38486. 11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-prop-1-ynylestra-4,9-dien-3-one.

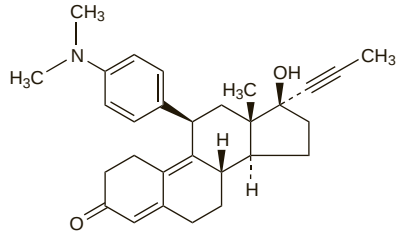
Мифепристон

$C_{29}H_{35}NO_2$ = 429.6.

CAS — 84371-65-3.

ATC — G03XB01.

ATC Vet — QG03XB01.



Pharmacopoeias. In *Chin.*

Adverse Effects
Uterine bleeding and cramps often occur after the use of mifepristone in procedures for the termination of pregnancy, and will occur in almost all patients after the addition of a prostaglandin. Bleeding typically continues for about 9 to 16 days, and may be severe enough to warrant curettage and transfusion in a small proportion of patients. However, prolonged heavy bleeding may also be a sign of incomplete abortion or other complications that require medical or surgical intervention. Other adverse effects of mifepristone include malaise, dizziness, chills, fever, headache, diarrhoea, nausea, vomiting, skin rashes, and urticaria; although some of these effects may be caused by the prostaglandin given after mifepristone.

Serious, sometimes fatal, infections have occurred in women undergoing abortion, although no causal relationship has been established between these events and the use of mifepristone.

Effects on the cardiovascular system. For a report of a woman who died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone, see p.2018.

Effects on the fetus. Studies in *rabbits*, but not *rats* or *mice*, suggest mifepristone causes fetal malformation. There have been reports of normal fetal development after the use of mifepristone alone in mothers who subsequently decided to continue their pregnancy.[1,2] However, in two reports, use of mifepristone was possibly related to malformations of the fetus including sirenomelia.[2,3] Cerebellar agenesis has been reported after a failed medical termination using mifepristone and gemeprost (see under Dinoprostone, p.2007).

1. Lim BH, *et al.* Normal development after exposure to mifepristone in early pregnancy. *Lancet* 1990; **336:** 257–8.
2. Pons J-C, *et al.* Development after exposure to mifepristone in early pregnancy. *Lancet* 1991; **338:** 763.
3. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; **352:** 323.

Toxic shock syndrome. Fatal toxic shock syndrome occurred in 5 women who underwent medical termination of pregnancy using mifepristone and misoprostol.[1,2] In 4 cases it was specified that mifepristone 200 mg had been given orally, followed by misoprostol 800 micrograms vaginally.[2] Within a week of termination, these patients presented with signs and symptoms that included abdominal pain, nausea and vomiting, tachycardia, hypotension, oedema, haemoconcentration, profound leucocytosis, and absence of fever. Postmortem examination found evidence of endometritis and toxic shock syndrome that was attributed to *Clostridium sordellii* infection. This is an infrequent human pathogen, but the authors of one report[2] noted that *C. sordellii* infection of the genital tract had also been reported in 8 women after delivery, suggesting that pregnancy, childbirth, or termination of pregnancy may predispose a small number of women to acquire this organism, and that associated dilatation of the cervix may allow for ascending infection. Although there has also been some speculation about the possible mechanisms, both pharmacological[3] and physical,[4] by which oral mifepristone or vaginal misoprostol might potentiate *C. sordellii* infection, a causal relationship between these drugs and the 5 reported deaths has not been established.[5]

1. Sinave C, *et al.* Toxic shock syndrome due to Clostridium sordellii: a dramatic postpartum and postabortion disease. *Clin Infect Dis* 2002; **35:** 1441–3.
2. Fischer M, *et al.* Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. *N Engl J Med* 2005; **353:** 2352–60.
3. Miech RP. Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; **39:** 1483–8.
4. Sicard D, Chauvelot-Moachon L. Comment: pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; **39:** 2142–3.
5. FDA. Questions and answers on Mifeprex (mifepristone) November 4, 2005. Available at: http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa20050719.htm (accessed 30/06/08)

Precautions
The use of mifepristone is contra-indicated in women with a confirmed or suspected ectopic pregnancy, because medical termination using mifepristone and a prostaglandin will not be effective (for use with methotrexate, see below). The expected symptoms of a medical termination may also be similar to those of a ruptured ectopic pregnancy. Mifepristone is also contra-indicated in patients with chronic adrenal failure or severe uncontrolled asthma. Use in those with renal or hepatic impairment is also not recommended. Mifepristone should be given with care to patients with less severe asthma or with chronic obstructive airways diseases, haemorrhagic or cardiovascular disease or associated risk factors, or anaemia. Therapy may need to be adjusted in patients receiving long-term corticosteroid treatment; a corticosteroid may need to be given if acute adrenal suppression is suspected. Care is also required in patients receiving anticoagulants because of the increased risk of severe bleeding. Patients with prosthetic heart valves or those with a history of infective endocarditis should be given chemoprophylaxis when undergoing pregnancy termination. As with other means of terminating pregnancy, rhesus-negative women who have not been rhesus immunised will require protection with anti-D immunoglobulin.

Porphyria. Mifepristone is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions
The metabolism of mifepristone is mediated by the cytochrome P450 isoenzyme CYP3A4. Theoretically, use with other drugs that inhibit or induce this isoen-