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.

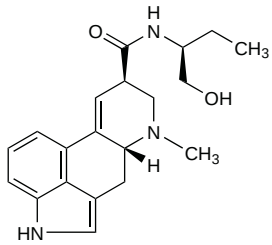
Метилэргометрина Малеат

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

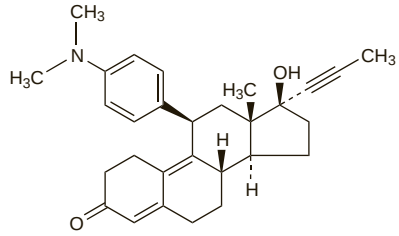
Мифепристон

$C_{29}H_{35}NO_2$ = 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-

zyme may result in changes in plasma concentration of mifepristone. *In-vitro* studies indicate that mifepristone itself inhibits CYP3A4; it should be used cautiously with CYP3A4 substrates that have a narrow therapeutic index.

NSAIDs. The effects of mifepristone on the uterus and cervix may be mediated by increased prostanoid synthesis resulting from its inhibitory effect on progesterone. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of mifepristone. However, a placebo-controlled study[1] in 28 women found that in the 13 given *naproxen* 500 mg orally 60, 48, 36, 24, and 12 hours before surgical termination of pregnancy the efficacy of mifepristone 100 mg given orally to soften the cervix was not reduced. Also, NSAIDs did not affect medical termination using mifepristone followed by misoprostol (see p.2013).

1. Rådestad A, Bygdeman M. Cervical softening with mifepristone (RU 486) after pretreatment with naproxen: a double-blind randomized study. *Contraception* 1992; **45:** 221–7.

Pharmacokinetics

After oral doses peak plasma concentrations of mifepristone occur after about 1 to 2 hours; bioavailability is about 70%. Mifepristone is about 98% bound to plasma proteins, mainly α_1-acid glycoprotein. Elimination is biphasic; a slow phase is followed by a more rapid terminal phase, with an elimination half-life of about 18 hours. Mifepristone undergoes hepatic oxidative metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and metabolites are excreted in the bile and eliminated in the faeces. Only a small fraction is detected in the urine.

◊ Reviews.

1. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. *Eur J Obstet Gynecol Reprod Biol* 2002; **101:** 113–20.

Uses and Administration

Mifepristone is a steroid derived from norethisterone that has potent antiprogestogenic activity. It is used in termination of pregnancy (see below), for either medical termination or for softening and dilatation of the cervix before surgical termination of pregnancy. Mifepristone is also used for labour induction after intra-uterine fetal death (see below).

In the UK the licensed regimen for the **termination** of pregnancies of up to 49 days is a single oral dose of 600 mg of mifepristone followed by a prostaglandin 36 to 48 hours later; prostaglandin treatment may be with either misoprostol 400 micrograms orally or gemeprost 1 mg vaginally. Alternatively, 200 mg of mifepristone may be given as a single dose followed, 36 to 48 hours later, by gemeprost 1 mg vaginally. Regimens containing vaginal gemeprost may also be used for the termination of pregnancies of up to 63 days. In the USA the licensed regimen for the termination of pregnancies up to 49 days of gestation is a single oral dose of 600 mg of mifepristone followed 2 days later by 400 micrograms of misoprostol orally, unless abortion has already been completed. As an adjunct to prostaglandin termination of pregnancy beyond the first trimester, the licensed dose in the UK is a single oral dose of mifepristone 600 mg; this is given 36 to 48 hours before scheduled prostaglandin administration, thus shortening the duration of the procedure and reducing the dose of prostaglandin required.

For **softening** and **dilatation of the cervix** before surgical termination of pregnancy during the first trimester, a single 200-mg dose of mifepristone is given 36 to 48 hours before the procedure.

For labour induction following intra-uterine **fetal death**, mifepristone 600 mg is given daily for 2 consecutive days; if labour has not started within 72 hours of the first dose, other methods of induction should be used.

Mifepristone has been tried for **other uses** such as postcoital contraception, endometriosis, uterine fibroids (leiomyomas), and for progestogen-dependent neoplasms such as meningiomas (see below). Mifepristone also has anti-glucocorticoid activity so it has been used in the treatment of Cushing's syndrome (below), and is under investigation in psychotic major depression (below).

◊ General references.

1. Heikinheimo O. Clinical pharmacokinetics of mifepristone. *Clin Pharmacokinet* 1997; **33:** 7–17.
2. Mahajan DK, London SN. Mifepristone (RU486): a review. *Fertil Steril* 1997; **68:** 967–76.
3. Koide SS. Mifepristone: auxiliary therapeutic use in cancer and related disorders. *J Reprod Med* 1998; **43:** 551–60.
4. DeHart RM, Morehead MS. Mifepristone. *Ann Pharmacother* 2001; **35:** 707–19.
5. Weingertner A-S, *et al.* Utilisations actuelles et potentielles de la mifépristone en gynécologie-obstétrique et dans les autres disciplines médicales. *J Gynecol Obstet Biol Reprod (Paris)* 2004; **33:** 692–702.
6. Tang OS, Ho PC. Clinical applications of mifepristone. *Gynecol Endocrinol* 2006; **22:** 655–9.

Contraception. Mifepristone has been established as an effective emergency contraceptive (p.2071). Initial studies found a dose of 600 mg given within 72 hours of coitus to be effective.[1,2] Subsequently lower doses, given up to 120 hours after coitus, have been shown to be well tolerated and as effective as standard emergency contraceptive regimens.[3-5] Studies[3,5,6] and meta-analyses[7,8] have confirmed the effectiveness of a dose of 10 mg. There was some evidence of a slight dose-response effect; it was calculated that there would be 1 extra pregnancy per 146 women treated if the dose were reduced from 25 to 10 mg, but the associated increase in availability of the drug might outweigh this.[8]

The development of a mifepristone-based standard contraceptive (p.2070) has been less successful. Regimens based on daily,[9] weekly,[10,11] or monthly[12,13] doses of mifepristone have been investigated.

1. Glasier A, *et al.* Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception. *N Engl J Med* 1992; **327:** 1041–4.
2. Webb AMC, *et al.* Comparison of Yuzpe regimen, danazol, and mifepristone (RU 486) in oral postcoital contraception. *BMJ* 1992; **305:** 927–31.
3. von Hertzen H, *et al.* Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; **360:** 1803–10.
4. Ashok PW, *et al.* Mifepristone versus the Yuzpe regimen (PC4) for emergency contraception. *Int J Gynecol Obstet* 2004; **87:** 188–93.
5. Hamoda H, *et al.* A randomized trial of mifepristone (10 mg) and levonorgestrel for emergency contraception. *Obstet Gynecol* 2004; **104:** 1307–13.
6. Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. *Lancet* 1999; **353:** 697–702.
7. Piaggio G, *et al.* Combined estimates of effectiveness of mifepristone 10 mg in emergency contraception. *Contraception* 2003; **68:** 439–46.
8. Piaggio G, *et al.* Meta-analyses of randomized trials comparing different doses of mifepristone in emergency contraception. *Contraception* 2003; **68:** 447–52.
9. Brown A, *et al.* Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J Clin Endocrinol Metab* 2002; **87:** 63–70.
10. Godfrey EM, *et al.* Low-dose mifepristone for contraception: a weekly versus planned postcoital randomized pilot study. *Contraception* 2004; **70:** 41–6.
11. Pei K, *et al.* Weekly contraception with mifepristone. *Contraception* 2007; **75:** 40–4.
12. Hapangama DK, *et al.* Feasibility of administering mifepristone as a once a month contraceptive pill. *Hum Reprod* 2001; **16:** 1145–50.
13. Narvekar N, *et al.* Toward developing a once-a-month pill: a double-blind, randomized, controlled trial of the effect of three single doses of mifepristone given at midcycle on the pattern of menstrual bleeding. *Fertil Steril* 2006; **86:** 819–24.

Cushing's syndrome. Mifepristone may be useful in Cushing's syndrome (p.2344) because of its glucocorticoid antagonist effects.

References.

1. Nieman LK, *et al.* Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab* 1985; **61:** 536–40.
2. van der Lely A-J, *et al.* Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med* 1991; **114:** 143–4.
3. Sartor O, Cutler GB. Mifepristone: treatment of Cushing's syndrome. *Clin Obstet Gynecol* 1996; **39:** 506–10.
4. Chu JW, *et al.* Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *J Clin Endocrinol Metab* 2001; **86:** 3568–73.

Depression. Mifepristone has been investigated in the management of depression (p.373) with psychotic features;[1-4] preliminary results suggest some benefit.

1. Belanoff JK, *et al.* An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* 2002; **52:** 386–92.
2. Simpson GM, *et al.* An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005; **66:** 598–602.
3. Flores BH, *et al.* Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 2006; **31:** 628–36.
4. DeBattista C, *et al.* Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol Psychiatry* 2006; **60:** 1343–9.

Ectopic pregnancy. Methotrexate with mifepristone may be more effective than methotrexate alone[1,2] for the medical treatment of ectopic pregnancy (p.749), although some have not found the combination to produce any benefit over methotrexate alone in the majority of women.[3]

1. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; **13:** 1987–90.
2. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; **179:** 640–3.
3. Rozenberg P, *et al.* Medical treatment of ectopic pregnancies: a randomized clinical trial comparing methotrexate-mifepristone and methotrexate-placebo. *Hum Reprod* 2003; **18:** 1802–8.

Endometriosis. Some results[1,2] have suggested that mifepristone, which is capable of suppressing ovarian function, may be of benefit in patients with endometriosis (p.2091).

1. Kettel LM, *et al.* Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis. *Fertil Steril* 1991; **56:** 402–7.
2. Kettel LM, *et al.* Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; **178:** 1151–6.

Fibroids. Mifepristone has been reported to produce significant decreases in uterine and leiomyoma volumes, and to reduce symptoms such as dysmenorrhoea and menorrhagia, when given to patients with fibroids (p.2107). However, data are from small uncontrolled studies using oral doses ranging from 5 to 50 mg daily, and endometrial hyperplasia has been noted.[1]

1. Steinauer J, *et al.* Systematic review of mifepristone for the treatment of uterine leiomyomata. *Obstet Gynecol* 2004; **103:** 1331–6.

Labour induction. A few studies[1-4] have reported that mifepristone was effective for cervical ripening and labour induction (p.2002) at term. A systematic review[5] considered that mifepristone was better than placebo but that there was still insufficient evidence to support its use. A later dose-finding study[6] found that single oral doses ranging from 50 to 600 mg were no more effective than placebo for inducing labour.

Mifepristone is used for cervical ripening and labour induction where intra-uterine fetal death has occurred,[7] usually in oral doses of 600 mg given daily for 2 days. The effective use of a lower single dose of 200 mg, followed by misoprostol given orally and/or vaginally, has also been described.[8,9]

1. Frydman R, *et al.* Labor induction in women at term with mifepristone (RU486): a double-blind, randomized, placebo-controlled study. *Obstet Gynecol* 1992; **80:** 972–5.
2. Giacalone PL, *et al.* Cervical ripening with mifepristone before labor induction: a randomized study. *Obstet Gynecol* 1998; **92:** 487–92.
3. Elliott CL, *et al.* The effects of mifepristone on cervical ripening and labor induction in primigravidae. *Obstet Gynecol* 1998; **92:** 804–9.
4. Stenlund PM, *et al.* Induction of labor with mifepristone—a randomized, double-blind study versus placebo. *Acta Obstet Gynecol Scand* 1999; **78:** 793–8.
5. Neilson JP. Mifepristone for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 30/06/08).
6. Berkane N, *et al.* Use of mifepristone to ripen the cervix and induce labor in term pregnancies. *Am J Obstet Gynecol* 2005; **192:** 114–20.
7. Cabrol D, *et al.* Induction of labor with mifepristone (RU 486) in intrauterine fetal death. *Am J Obstet Gynecol* 1990; **163:** 540–2.
8. Wagaarachchi PT, *et al.* Medical management of late intrauterine death using a combination of mifepristone and misoprostol. *BJOG* 2002; **109:** 443–7.
9. Väyrynen W, *et al.* Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. *Acta Obstet Gynecol Scand* 2007; **86:** 701–5.

Malignant neoplasms. Mifepristone has been used successfully in some patients with inoperable meningioma,[1-4] a brain tumour that may be progestogen-receptor positive. It has been given long term in oral doses of 200 mg daily, in some cases for more than 10 years. Adverse effects from long-term therapy have included fatigue, hot flushes, nausea, and depression; gynaecomastia has occurred in men and breast tenderness in women. Cessation of menstruation during mifepristone therapy occurs in premenopausal women, and there have been isolated cases of endometrial hyperplasia in pre- and postmenopausal women.

1. Grunberg SM, *et al.* Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *J Neurosurg* 1991; **74:** 861–6.
2. Lamberts SWJ, *et al.* Mifepristone (RU 486) treatment of meningiomas. *J Neurol Neurosurg Psychiatry* 1992; **55:** 486–90.
3. Spitz IM, *et al.* Management of patients receiving long-term treatment with mifepristone. *Fertil Steril* 2005; **84:** 1719–26.
4. Grunberg SM, *et al.* Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. *Cancer Invest* 2006; **24:** 727–33.

Termination of pregnancy. Mifepristone sensitises the myometrium to prostaglandins, increases uterine contractility, and softens and dilates the cervix.[1] It is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with prostaglandins for the termination of pregnancy (p.2004). Mifepristone has also been tried with methotrexate in the treatment of ectopic pregnancy (see above) and may be used to induce labour where intra-uterine fetal death has occurred (see above).

Mifepristone, followed 36 to 48 hours later by a prostaglandin, is an effective medical alternative to surgical methods for the termination of pregnancy in the *first trimester*.[1] Efficacy decreases with increasing gestational age, and the success rate may be affected by the choice of prostaglandin, its dose, and route of ad-

ministration. Termination success rates are highest for gestations of up to 49 days; after this the success rate for mifepristone with oral misoprostol tends to decrease compared with other regimens.[2] Vaginal gemeprost may be used with mifepristone for gestations of up to 63 days.[1] The usual dose of oral mifepristone is 600 mg, although lower doses of 200 and 400 mg have been studied in various regimens with prostaglandins and found to be as effective. However, a further reduction to 50 mg significantly reduced efficacy.[1,3]

Although surgical termination is commonly used for pregnancies of 9 to 13 weeks, there is increasing evidence to support the use of medical termination using mifepristone followed by misoprostol. A regimen using oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, has been described.[4,5] Two further vaginal doses of misoprostol 400 micrograms were given at intervals of 3 hours if the products of conception had not been passed (these doses could be given orally if vaginal bleeding was heavier than a normal period[5]). Surgical evacuation was then used if necessary. In a large case series of 1076 women,[6] medical abortion was successful in 95.8%. A regimen of oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally (or 600 micrograms sublingually), was used, with up to 5 further doses of misoprostol 400 micrograms (vaginally or sublingually) given at intervals of 3 hours if needed. The mean number of misoprostol doses used was 2.31.

Mifepristone is also used to ripen the cervix before vacuum aspiration for surgical termination in the first trimester. Oral doses of 600 mg have been used, but lower doses were also found to be more effective than placebo[7,8] and as effective as prostaglandins;[9-11] consequently, a dose of 200 mg is now often used.

Mifepristone followed by a prostaglandin may also be used for medical termination in the *second trimester* (mid-trimester termination; gestation of 13 to 24 weeks).[12,13] Similarly to early termination, a study found mifepristone 200 mg orally to be as effective as 600 mg when followed by misoprostol.[14] Further retrospective reviews have also reported mifepristone 200 mg followed by misoprostol[15] or gemeprost[16] to be effective.

In the UK the Royal College of Obstetricians and Gynaecologists' guidelines[17] for both early and mid-trimester terminations include the following regimens:

- for gestation up to 63 days (9 weeks), mifepristone 200 mg orally followed 24 to 72 hours later by misoprostol 800 micrograms vaginally; if abortion has not occurred 4 hours after administration of misoprostol in women at 49 to 63 days of gestation, a further dose of misoprostol 400 micrograms may be given orally or vaginally
- for gestation between 9 and 13 weeks, mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally; a maximum of 4 further doses of misoprostol 400 micrograms may be given every 3 hours, orally or vaginally, if necessary
- for mid-trimester termination (13 to 24 weeks), mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, then up to 4 further doses of misoprostol 400 micrograms given every 3 hours orally

Mifepristone followed by a prostaglandin has also been used as an effective alternative to surgical evacuation[18,19] in the management of first trimester *pregnancy failure*. As for termination, mifepristone doses of 200 and 600 mg orally, followed by misoprostol, appear to be equally effective,[20] although some studies[21,22] suggest that pretreatment with mifepristone does not improve the expulsion rate compared with vaginal or oral misoprostol alone.

1. Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with a prostaglandin analogue. *Contraception* 2006; **74:** 66–86.
2. Kahn JG, *et al.* The efficacy of medical abortion: a meta analysis. *Contraception* 2000; **61:** 29–40.
3. Marions L. Mifepristone dose in the regimen with misoprostol for medical abortion. *Contraception* 2006; **74:** 21–5.
4. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; **352:** 542–3.
5. Ashok PW, *et al.* A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. *Hum Reprod* 2002; **17:** 92–8.
6. Hamoda H, *et al.* Medical abortion at 9–13 weeks' gestation: a review of 1076 consecutive cases. *Contraception* 2005; **71:** 327–32.
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8. World Health Organization Task Force on Postovulatory Methods of Fertility Regulation. Cervical ripening with mifepristone (RU 486) in late first trimester abortion. *Contraception* 1994; **50:** 461–75.
9. Henshaw RC, Templeton AA. Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486). *Br J Obstet Gynaecol* 1991; **98:** 1025–30.
10. Ngai SW, *et al.* Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study. *Br J Obstet Gynaecol* 1996; **103:** 1120–3.
11. Ashok PW, *et al.* Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study. *Am J Obstet Gynecol* 2000; **183:** 998–1002.
12. Rodger M, Baird D. Pretreatment with mifepristone (RU486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. *Br J Obstet Gynaecol* 1990; **97:** 41–5.
13. Thong KJ, Baird DT. Induction of second trimester abortion with mifepristone and gemeprost. *Br J Obstet Gynaecol* 1993; **100:** 758–61.
14. Webster D, *et al.* A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. *Br J Obstet Gynaecol* 1996; **103:** 706–9.
15. Ashok PW, *et al.* Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. *Contraception* 2004; **69:** 51–8.
16. Tang OS, *et al.* Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. *Contraception* 2001; **64:** 29–32.
17. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/induced_abortionfull.pdf (accessed 30/06/08)
18. Chia KV, Ogbo VI. Medical termination of missed abortion. *J Obstet Gynaecol* 2002; **22:** 184–6.
19. Niinimäki M, *et al.* A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. *Fertil Steril* 2006; **86:** 367–72.
20. Coughlin LB, *et al.* Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? *J Obstet Gynaecol* 2004; **24:** 69–71.
21. Grønlund A, *et al.* Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation: a multi-center trial in Copenhagen county, Denmark. *Acta Obstet Gynecol Scand* 2002; **81:** 1060–5.
22. Stockheim D, *et al.* A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. *Fertil Steril* 2006; **86:** 956–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Mifegyne; ***Denm.:*** Mifegyne; ***Fin.:*** Mifegyne; ***Fr.:*** Mifegyne; ***Ger.:*** Mifegyne; ***Gr.:*** Mifegyne; ***India:*** Mifegest; MT Pill; ***Israel:*** Mifegyne; ***Neth.:*** Mifegyne; ***Norw.:*** Mifegyne; ***NZ:*** Mifegyne; ***Port.:*** Mifegyne; ***Rus.:*** Pencroftonum (Пенкрофтон); ***S.Afr.:*** Mifegyne; ***Spain:*** Mifegyne; ***Swed.:*** Mifegyne; ***Switz.:*** Mifegyne; ***UK:*** Mifegyne; ***USA:*** Mifeprex.

Misoprostol *(BAN, USAN, rINN)*

Misoprostoli; Misoprostolum; Mizoprostol; SC-29333. (±)-Methyl 7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl}heptanoate; (±)-Methyl (13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate.

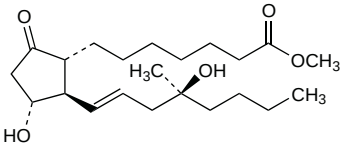
Мизопростол

$C_{22}H_{38}O_5$ = 382.5.

CAS — 59122-46-2.

ATC — A02BB01; G02AD06.

ATC Vet — QA02BB01; QG02AD06.



(11*R*, 16*S*)-Form

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Misoprostol). A clear, colourless or yellowish, hygroscopic, oily liquid. Practically insoluble in water; soluble in alcohol; sparingly soluble in acetonitrile. Store in airtight containers at –20°.

Adverse Effects

The commonest adverse effect of misoprostol is diarrhoea. Other gastrointestinal effects include abdominal pain, dyspepsia, flatulence, and nausea and vomiting. Increased uterine contractility and abnormal vaginal bleeding (including menorrhagia and intermenstrual bleeding) have been reported. Other adverse effects include skin rashes, headache, and dizziness. Hypotension is rarely seen at doses recommended for peptic ulcer disease.

Incidence of adverse effects. Data on misoprostol presented to the FDA have been summarised.[1] During controlled studies the most common adverse effect was diarrhoea (8.2% compared with 3.1% for placebo); it was dose-related but usually mild, only 8 of 2003 subjects receiving misoprostol having withdrawn because of incapacitating diarrhoea. Headaches and abdominal discomfort were also reported. The effects of misoprostol on the uterus and the potential risks of uterine bleeding or abortion in pregnant women were of more concern. In nonpregnant women taking part in the controlled studies there were menstrual complaints in 15 of 410 (3.7%) receiving misoprostol compared with 2 of 115 (1.7%) given placebo. In a study in pregnant women who had elected to undergo first trimester abortion, all 6 who had a spontaneous expulsion of the uterine contents had received 1 or 2 doses of misoprostol 400 micrograms the previous evening, while none of those given placebo aborted spontaneously; overall 25 of the 56 women given misoprostol had uterine bleeding compared with only 2 of 55 on placebo.

1. Lewis JH. Summary of the 29th meeting of the Gastrointestinal Drugs Advisory Committee, Food and Drug Administration—June 10, 1985. *Am J Gastroenterol* 1985; **80:** 743–5.

Effects on the fetus. Misoprostol on its own is only a weak abortifacient and is often ineffective when used alone for the termination of pregnancy (see below). However, it has been widely misused for this purpose in some countries, notably Brazil,[1,2] and anecdotal reports have associated congenital malformations with such misuse during the first trimester of pregnancy. A systematic review[3] of 4 case-control studies confirmed that misoprostol was associated with an increased risk of congenital abnormality, particularly Möbius syndrome and terminal transverse limb defects.

1. Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. *Lancet* 1993; **341:** 1258–61.
2. Coêlho HLL, *et al.* Misoprostol and illegal abortion in Fortaleza, Brazil. *Lancet* 1993; **341:** 1261–3. Correction. *ibid.*; 1486.
3. da Silva Dal Pizzol T, *et al.* Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. *Reprod Toxicol* 2006; **22:** 666–71.

Effects on the uterus. For reference to uterine rupture in women given misoprostol to induce labour or terminate pregnancy, see under Dinoprostone, p.2007.

Toxic shock syndrome. Fatal toxic shock syndrome has occurred in a few women who underwent medical termination of pregnancy using oral mifepristone and vaginal misoprostol, although a causal relationship between these drugs and the deaths has not been established (see under Mifepristone, p.2011).

Precautions

Misoprostol should not be used to treat peptic ulcer disease in patients who are pregnant or who may become pregnant because it can cause uterine contraction. It should be used with caution in patients in whom hypotension might cause severe complications. Patients with conditions such as inflammatory bowel disease, for whom profound diarrhoea could be dangerous, should be monitored carefully if misoprostol is given.

Like other prostaglandins used in the termination of pregnancy (see Dinoprostone, p.2008), misoprostol should not be used in women at increased risk of uterine rupture, such as those with multiple pregnancy or a uterus scarred by previous caesarean section. Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Breast feeding. Misoprostol acid was detected in the breast milk of 10 women given a single oral dose of misoprostol for postpartum uterine atony.[1] The concentration rose rapidly, peaked at about 1 hour, and had fallen towards the detection limit by about 5 hours after the dose. Product information for misoprostol licensed for use in gastric ulceration advises that it should not be given to breast-feeding women because misoprostol acid could potentially cause diarrhoea in the infant.

1. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; **191:** 2168–73.

Inflammatory bowel disease. Life-threatening diarrhoea was reported in a patient with unrecognised Crohn's disease after 6 doses of misoprostol.[1] Abdominal cramps, pain, and profuse watery diarrhoea also occurred after 3 doses of misoprostol in a woman with Crohn's disease.[2] In a cohort study of misoprostol taken with NSAIDs for arthritis there were 13 patients with a history of inflammatory bowel disease; 7 did not develop diarrhoea, 3 developed mild diarrhoea, 1 developed severe diarrhoea that stopped when misoprostol was withdrawn, and 2 developed bloody diarrhoea.[3]

1. Kornbluth A, *et al.* Life-threatening diarrhea after short-term misoprostol use in a patient with Crohn ileocolitis. *Ann Intern Med* 1990; **113:** 474–5.
2. Johnson JS, *et al.* Profuse diarrhea after misoprostol use in a patient with a history of Crohn's disease. *Ann Pharmacother* 1992; **26:** 1092–3.
3. Faich GA, *et al.* Diarrhea after misoprostol in Crohn disease. *Ann Intern Med* 1991; **114:** 342.

Interactions

NSAIDs. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of misoprostol used for termination of pregnancy by inhibiting uterine cramping. However, studies in women undergoing medical[1] or surgical[2] termination found that NSAIDs did not reduce the efficacy of misoprostol. In another study,[3] *diclofenac*