livery of the infant; contractions are reported to occur within 2 to 7 minutes. Delivery of the placenta is actively assisted while the uterus is firmly contracted.

In the prevention or treatment of **postpartum haemorrhage**, a similar dose of ergometrine maleate with oxytocin is given intramuscularly following delivery of the placenta or when bleeding occurs. A combined intravenous preparation of ergometrine maleate with oxytocin has been used but is no longer recommended. Ergometrine maleate alone is used for prevention or treatment of postpartum or postabortal haemorrhage in a usual intramuscular dose of 200 micrograms. The dose may be repeated in severe bleeding, but is rarely needed more often than once in 2 to 4 hours. In emergencies such as excessive uterine bleeding, ergometrine maleate has been given intravenously in a dose of 200 micrograms; single doses of 250 to 500 micrograms have also been used. Intravenous doses should be given over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. Parenteral treatment of haemorrhage may be followed by ergometrine maleate 200 to 400 micrograms orally 2 to 4 times daily until the danger of atony and haemorrhage has passed, which is usually 48 hours. Tablets have also been given sublingually.

In the treatment of mild secondary postpartum haemorrhage, ergometrine maleate has been given orally.

Ergometrine tartrate was formerly used.

Diagnosis and testing. Ergometrine maleate[1-8] or methylergometrine maleate[9,10] have been used in a provocation test for the diagnosis of Prinzmetal's angina (variant angina) (p.1157).

1. Waters DD, *et al*. Ergonovine testing in a coronary care unit. *Am J Cardiol* 1980; **46:** 922–30.
2. Health and Public Policy Committee, American College of Physicians. Performance of ergonovine provocative testing for coronary artery spasm. *Ann Intern Med* 1984; **100:** 151–2.
3. Song J-K, *et al*. Safety and clinical impact of ergonovine stress echocardiography for diagnosis of coronary vasospasm. *J Am Coll Cardiol* 2000; **35:** 1850–6.
4. Kashima K, *et al*. Long-term outcome of patients with ergonovine induced coronary constriction not associated with ischemic electrocardiographic changes. *J Cardiol* 2001; **37:** 301–8.
5. Palinkas A, *et al*. Safety of ergot stress echocardiography for non-invasive detection of coronary vasospasm. *Coron Artery Dis* 2001; **12:** 649–54.
6. Song JK, *et al*. Prognostic implication of ergonovine echocardiography in patients with near normal coronary angiogram or negative stress test for significant fixed stenosis. *J Am Soc Echocardiogr* 2002; **15:** 1346–52.
7. Sueda S, *et al*. Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations. *Coron Artery Dis* 2004; **15:** 491–7.
8. Coma-Canella I, *et al*. Ergonovine test in angina with normal coronary arteries: is it worth doing it? *Int J Cardiol* 2006; **107:** 200–6.
9. Bertrand ME, *et al*. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982; **65:** 1299–1306.
10. Lablanche JM, *et al*. Réflexions d'un comité d'experts de la Société française de cardiologie concernant l'usage du maléate de méthylergométrine (Methergin) dans la détection d'une vasomotricité coronaire anormale. *Arch Mal Coeur Vaiss* 1995; **88:** 247–53.

Preparations

BP 2008: Ergometrine and Oxytocin Injection; Ergometrine Injection; Ergometrine Tablets;
USP 31: Ergonovine Maleate Injection; Ergonovine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Evina; Metrergina; ***Braz.:*** Ergotrate†; ***Gr.:*** Mitrotan; ***Mex.:*** Ergotrate; ***Thai.:*** Gynaemine; ***USA:*** Ergotrate.

Multi-ingredient: ***Austral.:*** Syntometrine; ***Hong Kong:*** Syntometrine†; ***Irl.:*** Syntometrine; ***Malaysia:*** Syntometrine; ***NZ:*** Syntometrine; ***S.Afr.:*** Syntometrine; ***UK:*** Syntometrine.

Ergot

Cornezuelo del centeno; Secale Cornutum.

Спорынья

Description. Ergot consists of the sclerotium of the fungus *Claviceps purpurea* (Hypocreaceae) developed in the ovary of the rye, *Secale cereale* (Gramineae). It contains not less than 0.15% of total alkaloids, calculated as ergotoxine, and not less than 0.01% of water-soluble alkaloids, calculated as ergometrine. Some authorities have expressed alkaloidal content in terms of ergotamine and ergometrine.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p.620.

Epidemic ergot poisoning, arising from the ingestion of ergotised rye bread, is now seldom seen. Two forms of epidemic toxicity, which rarely occur together, have been described: a gangrenous form characterised by agonising pain of the extremities of the body followed by dry gangrene of the peripheral parts, and a rarer nervous type giving rise to paroxysmal epileptiform convulsions.

Poisoning. A report of an outbreak of ergotism, attributed to the ingestion of infected wild oats (*Avena abyssinica*), in Ethiopia.[1]

1. King B. Outbreak of ergotism in Wollo, Ethiopia. *Lancet* 1979; **ii:** 1411.

Uses and Administration

Ergot has the vasoconstricting and oxytocic actions of its constituent alkaloids, especially ergotamine (p.620) and ergometrine (above). A liquid extract or tablets of prepared ergot were formerly used as an oxytocic. Preparations containing ergot extracts have been promoted for use in dyspepsia and nervous disorders.

Preparations

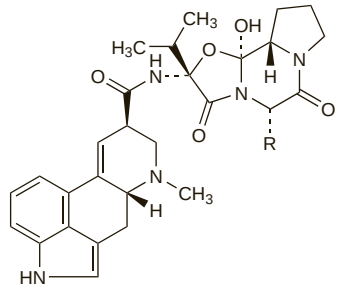
Proprietary Preparations (details are given in Part 3)
India: Ergotab.

Ergotoxine

Ecboline; Ergotoxina.

Эрготоксин

CAS — 8006-25-5 (ergotoxine); 8047-28-7 (ergotoxine esilate); 8047-29-8 (ergotoxine phosphate); 564-36-3 (ergocornine); 511-08-0 (ergocristine); 511-09-1 (α-ergocryptine); 20315-46-2 (β-ergocryptine).



Ergocornine	R = $CH(CH_3)_2$
Ergocristine	R = $CH_2C_6H_5$
α-Ergocryptine	R = $CH_2CH(CH_3)_2$
β-Ergocryptine	R = $CH(CH_3)CH_2CH_3$

Profile

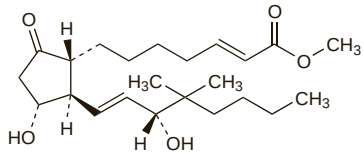
Ergotoxine is a mixture of naturally occurring ergot alkaloids. It contains equal proportions of ergocornine ($C_{31}H_{39}N_5O_5$ = 561.7), ergocristine ($C_{35}H_{39}N_5O_5$ = 609.7), and ergocryptine ($C_{32}H_{41}N_5O_5$ = 575.7) as the α- and β-isomers. The esilate was formerly used as an oxytocic and in the treatment of migraine. Ergotoxine phosphate has also been used.

Gemeprost *(BAN, USAN, rINN)*

16,16-Dimethyl-*trans*-Δ^2-prostaglandin E_1 methyl ester; Gémeprost; Gemeprosti; Gemeprostum; ONO-802; SC-37681. Methyl (2*E*,13*E*)-(8*R*,11*R*,12*R*,15*R*)-11,15-dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-dienoate; Methyl (*E*)-7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyloct-1-enyl]-5-oxocyclopentyl}hept-2-enoate.

Гемепрост

$C_{23}H_{38}O_5$ = 394.5.
CAS — 64318-79-2.
ATC — G02AD03.
ATC Vet — QG02AD03.



Adverse Effects and Precautions

As for Dinoprostone, p.2007. Vaginal bleeding and mild uterine pain may occur. Pulse and blood pressure should be monitored in patients given gemeprost.

The effects of gemeprost on the fetus are not known. 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.

Incidence of adverse effects. The incidence of vomiting (19 or 35%) and diarrhoea (12 or 19%) in 2 studies of patients treated with gemeprost pessaries was similar to that seen with other prostaglandins, but gemeprost was reported to cause less uterine pain.[1,2]

1. Cameron IT, Baird DT. The use of 16,16-dimethyl-trans-Δ prostaglandin E methyl ester (gemeprost) vaginal pessaries for the termination of pregnancy in the early second trimester: a comparison with extra-amniotic prostaglandin E . *Br J Obstet Gynaecol* 1984; **91:** 1136–40.
2. Andersen LF, *et al*. Termination of second trimester pregnancy with gemeprost vaginal pessaries and intra-amniotic PGF : a comparative study. *Eur J Obstet Gynecol Reprod Biol* 1989; **31:** 1–7.

Effects on the cardiovascular system. Periods of ventricular standstill of up to 6 seconds were seen in a patient during treatment with gemeprost vaginal pessaries.[1] The patient required temporary cardiac pacing, but no persistent cardiac rhythm disturbances were detected on follow-up. Severe cardiogenic shock due to vasospasm, and subsequent stroke, has been reported in a patient who had received gemeprost pessaries some hours earlier; myocardial infarction ensuing from coronary spasm was reported in a second patient.[2]

1. Kalra PA, *et al*. Cardiac standstill induced by prostaglandin pessaries. *Lancet* 1989; **i:** 1460–1.
2. Schulte-Sasse U. Life threatening myocardial ischaemia associated with the use of prostaglandin E to induce abortion. *Br J Obstet Gynaecol* 2000; **107:** 700–2.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including gemeprost (see under Dinoprostone, p.2007).

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including gemeprost, for termination of pregnancy or induction of labour, see under Dinoprostone, p.2007.

Interactions

As for Dinoprostone, p.2008.

Uses and Administration

Gemeprost is a synthetic analogue of alprostadil (prostaglandin E_1; p.2183). It is used to soften and dilate the cervix and as a uterine stimulant in the termination of pregnancy (p.2004). In the first trimester, a pessary containing gemeprost 1 mg is inserted into the vagina 3 hours before surgery to ripen the cervix. Gemeprost may also be used for termination of pregnancy in the second trimester when a 1-mg pessary is inserted every 3 hours to a maximum of 5 pessaries. If this is ineffective, one further course may be given starting 24 hours after the beginning of the first course. If termination is not well established after 10 pessaries, alternative treatment should be used to complete uterine evacuation. In the case of intra-uterine fetal death in the second trimester, only one course of up to 5 pessaries should be given. Vaginal gemeprost is also used after oral mifepristone (p.2012) in the termination of pregnancy.

Preparations

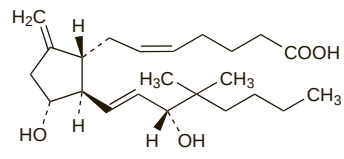
Proprietary Preparations (details are given in Part 3)
Austral.: Cervagem; ***Denm.:*** Cervagem; ***Fin.:*** Cervagem†; ***Fr.:*** Cervageme; ***Ger.:*** Cergem; ***Hong Kong:*** Cervagem†; ***Ital.:*** Cervidil; ***Jpn:*** Preglandin; ***Malaysia:*** Cervagem; ***Norw.:*** Cervagem†; ***NZ:*** Cervagem; ***Singapore:*** Cervagem; ***Swed.:*** Cervagem.

Meteneprost *(USAN, rINN)*

9-Deoxo-16,16-dimethyl-9-methylene-prostaglandin E_2; Méténéprost; Meteneprostum; U-46785. (5*Z*,13*E*)-(8*R*,11*R*,12*R*,15*R*)-11,15-Dihydroxy-16,16-dimethyl-9-methyleneprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyloct-1-enyl]-5-methylenecyclopentyl}hept-5-enoic acid.

Метенепрост

$C_{23}H_{38}O_4$ = 378.5.
CAS — 61263-35-2.



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.

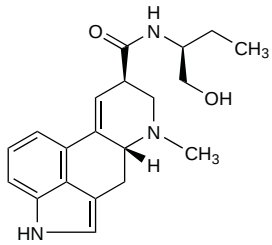
Метилэргометрина Малеат

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

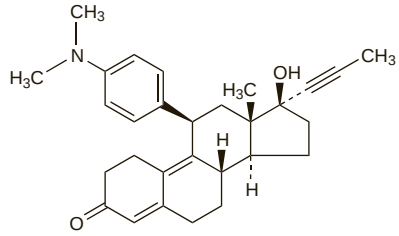
Мифепристон

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