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.
7. WHO. The use of mifepristone (RU 486) for cervical preparation in first trimester pregnancy termination by vacuum aspiration. *Br J Obstet Gynaecol* 1990: **97:** 260–6.
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.

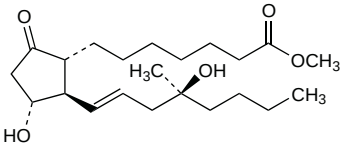
Мизопростол

$C_{22}H_{38}O_5$ = 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*

did not reduce the efficacy of medical termination using mifepristone followed by misoprostol.

1. Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. *Contraception* 1997; **56:** 165–8.
2. Li CFI, *et al.* A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. *Contraception* 2003; **67:** 101–5. Correction. *ibid.*; 339.
3. Fiala C, *et al.* The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation. *Hum Reprod* 2005; **20:** 3072–7.

Pharmacokinetics

Misoprostol is reported to be rapidly absorbed and metabolised to its active form (misoprostol acid; SC-30695) after oral doses; peak plasma concentrations of misoprostol acid occur after about 15 to 30 minutes. Food reduces the rate but not the extent of absorption. Misoprostol acid is further metabolised by oxidation in a number of body organs and is excreted mainly in the urine. The plasma elimination half-life is reported to be between 20 and 40 minutes. Misoprostol acid is distributed into breast milk.

◊ References.

1. Schoenhard G, *et al.* Metabolism and pharmacokinetic studies of misoprostol. *Dig Dis Sci* 1985; **30** (suppl): 126S–128S.
2. Karim A, *et al.* Effects of food and antacid on oral absorption of misoprostol, a synthetic prostaglandin E analog. *J Clin Pharmacol* 1989; **29:** 439–43.
3. Foote EF, *et al.* Disposition of misoprostol and its active metabolite in patients with normal and impaired renal function. *J Clin Pharmacol* 1995; **35:** 384–9.
4. Zieman M, *et al.* Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; **90:** 88–92.
5. Khan R-U, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. *Obstet Gynecol* 2003; **101:** 968–74.
6. Khan R-U, *et al.* Oral, rectal, and vaginal pharmacokinetics of misoprostol. *Obstet Gynecol* 2004; **103:** 866–70.
7. Schaff EA, *et al.* Comparison of misoprostol plasma concentrations following buccal and sublingual administration. *Contraception* 2005; **71:** 22–5.

Uses and Administration

Misoprostol is a synthetic analogue of alprostadil (prostaglandin E_1; p.2183).

It is used in the treatment of benign gastric and duodenal **ulceration** (below) including that associated with NSAIDs. The usual oral dose is 800 micrograms daily in two to four divided doses with food. Treatment is initially given for at least 4 weeks, even if symptoms are relieved sooner, and may continue for up to 8 weeks if necessary. Further courses may be used to treat relapse.

Misoprostol is also used prophylactically with NSAIDs to prevent NSAID-induced ulcers. The usual oral dose is 200 micrograms two to four times daily. A dose of 100 micrograms four times daily may be used in patients not tolerating the higher dose. Some preparations of NSAIDs contain misoprostol in an attempt to limit their adverse effects on the gastrointestinal mucosa.

Misoprostol may be used to ripen the cervix before surgical **termination of pregnancy** (below) in the first trimester. A single oral dose of misoprostol 400 micrograms is given 3 to 4 hours before surgery. It may also be used for medical termination of pregnancy at up to 49 days of amenorrhoea, in a single oral dose of 400 micrograms given 36 to 48 hours after mifepristone. Misoprostol has also been used for induction of labour and in the management of postpartum haemorrhage (see below).

◊ General reviews.

1. Goldberg AB, *et al.* Misoprostol and pregnancy. *N Engl J Med* 2000; **344:** 38–47.
2. Blanchard K, *et al.* Misoprostol for women's health: a review. *Obstet Gynecol* 2002; **99:** 316–32.
3. Lokugamage AU, *et al.* Misoprostol and pregnancy: ever-increasing indications of effective usage. *Curr Opin Obstet Gynecol* 2003; **15:** 513–18.
4. Chong YS, *et al.* Misoprostol: a quarter century of use, abuse, and creative misuse. *Obstet Gynecol Surv* 2004; **59:** 128–40.

Labour induction and augmentation. Prostaglandins are well established for the induction of labour (p.2002) and misoprostol has been widely investigated for this indication. A systematic review[1] of studies of misoprostol given *vaginally* found that it increased cervical ripening and induced labour. It was more effective than vaginal or intracervical dinoprostone, reducing the need for oxytocin augmentation and improving the rate of vaginal delivery achieved within 24 hours. It was also found to be more effective than intravenous oxytocin. Most studies used misoprostol tablets in a dose of 50 micrograms vaginally every 4 hours, but reported doses have varied from 25 micrograms every 2 to 3 hours, to 100 micrograms every 6 to 12 hours. Low doses of misoprostol resulted in more use of oxytocin, but caused less uterine hyperstimulation. Although unlicensed, misoprostol is reported to be used outside clinical studies particularly in the USA, and the American College of Obstetricians and Gynecologists has recommended a dose of 25 micrograms intravaginally every 3 to 6 hours.[2] Misoprostol has also been given *orally* but this route is less well established. A wide range of doses have been reported but most studies have used 50 micrograms every 4 hours. Some reviews have found oral to be less effective than vaginal misoprostol.[2,3] However, others[4] have concluded that oral use produces similar outcomes to vaginal misoprostol, with less hyperstimulation, but that comparison is complicated by the wide variation in doses. Overall, oral misoprostol appears to be at least as effective as vaginal dinoprostone, but because of limited data it should be used with caution.[4] The risk of uterine hyperstimulation may be increased with misoprostol by either route, particularly at higher doses,[1,4] and it should not be used in women with scarred uteri from previous caesarean delivery or uterine surgery[2] (see also Effects on the Uterus, under Adverse Effects of Dinoprostone, p.2007). There has also been some limited investigation of misoprostol given *sublingually*.[3,5,6]

Misoprostol has been tried for labour induction after intra-uterine fetal death, generally in higher doses than those used for labour at term. It has been used successfully in doses of 400 micrograms every 4 hours orally[7] and 400 micrograms every 12 hours vaginally.[8] A comparison of 200 micrograms given either orally or vaginally every 6 hours, to a maximum of 4 doses or until labour was established, found the time from induction to delivery to be shorter, and fewer women needed oxytocin augmentation, with vaginal use.[9]

Misoprostol may also be used for active management of the third stage of labour (see Postpartum Haemorrhage, below).

1. Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 30/06/08).
2. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. *Drug Safety* 2002; **25:** 665–76.
3. Bartusevicius A, *et al.* Oral, vaginal and sublingual misoprostol for induction of labor. *Int J Gynecol Obstet* 2005; **91:** 2–9.
4. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
5. Shetty A, *et al.* Sublingual misoprostol for the induction of labor at term. *Am J Obstet Gynecol* 2002; **186:** 72–6.
6. Shetty A, *et al.* Sublingual compared with oral misoprostol in term labour induction: a randomised controlled trial. *Br J Obstet Gynaecol* 2002; **109:** 645–50.
7. Pongsatha S, Tongsong T. Therapeutic termination of second trimester pregnancies with intrauterine fetal death with 400 micrograms of oral misoprostol. *J Obstet Gynaecol Res* 2004; **30:** 217–20.
8. Fawole AO, *et al.* Experience with intravaginal misoprostol in the management of intra-uterine fetal death. *Afr J Med Med Sci* 2004; **33:** 105–8.
9. Nyende L, *et al.* Comparison of vaginal and oral misoprostol, for the induction of labour in women with intra-uterine foetal death. *East Afr Med J* 2004; **81:** 179–82.

Organ and tissue transplantation. Misoprostol 200 micrograms orally four times daily improved renal function in ciclosporin-treated recipients of renal transplants.[1] The number of patients who had acute graft rejection was lower in the misoprostol group than in the placebo group. However, another study[2] did not indicate any difference in the incidence of rejection episodes or in renal function when misoprostol was added to immunosuppressant regimens for kidney transplantation, and misoprostol does not appear to have gained a role in the usual management of renal transplantation (p.1813).

1. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; **322:** 1183–8.
2. Pouteil-Noble C, *et al.* Misoprostol in renal transplant recipients: a prospective, randomized, controlled study on the prevention of acute rejection episodes and cyclosporin A nephrotoxicity. *Nephrol Dial Transplant* 1994; **9:** 552–5.

Peptic ulcer disease. Misoprostol is used in the prophylaxis and treatment of peptic ulceration (p.1702) in patients taking NSAIDs. There is good evidence that misoprostol can reduce the risk of gastric and duodenal ulcer formation in patients on long-term NSAID treatment,[1-4] and it appears more effective in this respect than histamine H_2-antagonists,[1] for which evidence of benefit against gastric injury is less persuasive. However, misoprostol's abdominal adverse effects, particularly diarrhoea and abdominal cramps, may limit its usefulness and patient acceptability. Omeprazole, which is equally effective in preventing NSAID-induced ulceration, is better tolerated.[3] Improved formulations, in which the active isomer of misoprostol is bound to a polymer, may reduce adverse effects.[5]

1. Koch M, *et al.* Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury: a meta-analysis of randomized controlled clinical trials. *Arch Intern Med* 1996; **156:** 2321–32.
2. Champion GD, *et al.* NSAID-induced gastrointestinal damage: epidemiology, risk and prevention, with an evaluation of the role of misoprostol: an Asia-Pacific perspective and consensus. *Drugs* 1997; **53:** 6–19.
3. Hawkey CJ, *et al.* Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1998; **338:** 727–34.
4. Rostom A, *et al.* Prevention of NSAID-induced gastroduodenal ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/06/08).
5. Chen D, *et al.* Stabilization and sustained-release effect of misoprostol with methacrylate copolymer. *Int J Pharmaceutics* 2000; **203:** 141–8.

Postpartum haemorrhage. Prostaglandins, usually given parenterally, have an accepted role in the management of established postpartum haemorrhage (p.2003) not controlled by oxytocin and ergot preparations. There have been reports[1-3] of the successful use of rectal misoprostol to control postpartum haemorrhage, using single doses of 800 or 1000 micrograms. A review[4] found that there was some evidence for reduced blood loss with lower doses of misoprostol, and suggested that oral, sublingual, rectal, or a combination of these, might be the most effective routes; possible regimens were 200 to 400 micrograms sublingually or rectally, or similar doses plus 200 micrograms orally. It also suggested that the oral dose of misoprostol should not exceed 600 micrograms because of the risk of hyperpyrexia. There have also been a few cases in which intra-uterine misoprostol 800 micrograms has controlled refractory secondary postpartum haemorrhage.[5,6]

Misoprostol has also been given immediately after delivery in the active management of third-stage labour. In a study[7] of more than 18 500 women treated in hospital, which compared oral misoprostol 600 micrograms with intramuscular or intravenous oxytocin, a higher proportion of women who received misoprostol had blood loss of at least 1000 mL and required additional oxytocics. Misoprostol was also associated with significantly more shivering and pyrexia. The results of this large study suggest that parenteral oxytocin is preferred for active management, but it has been argued that misoprostol may be particularly useful in preventing postpartum haemorrhage in developing countries where there is limited access to healthcare facilities and parenteral oxytocics.[8-10] Two placebo-controlled studies have addressed this argument, reporting that oral[11] or sublingual[12] misoprostol used in rural primary healthcare settings reduced postpartum haemorrhage, particularly severe haemorrhage (1000 mL or more). A systematic review[13] concluded that oral misoprostol was less effective than injectable oxytocics in reducing blood loss and the use of additional oxytocics, but that it may be used where no injectable uterotonic is available.

1. O'Brien P, *et al.* Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstet Gynecol* 1998; **92:** 212–4.
2. Lokugamage AU, *et al.* A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 2001; **80:** 835–9.
3. Shojai R, *et al.* Le misoprostol par voie rectale dans l'hémorragie de la délivrance: rectal misoprostol for postpartum hemorrhage. *Gynecol Obstet Fertil* 2004; **32:** 703–7.
4. Hofmeyr GJ, *et al.* Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; **112:** 547–53.
5. Adekanmi OA, *et al.* Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum haemorrhage. *BJOG* 2001; **108:** 541–2.
6. Oboro VO, *et al.* Intrauterine misoprostol for refractory postpartum hemorrhage. *Int J Gynecol Obstet* 2003; **80:** 67–8.
7. Gülmezoglu AM, *et al.* WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet* 2001; **358:** 689–95.
8. Darney PD. Misoprostol: a boon to safe motherhood...or not? *Lancet* 2001; **358:** 682–3.
9. Shannon C, Winikoff B. Use of misoprostol in third stage of labour. *Lancet* 2002; **359:** 709.
10. Langenbach C. Misoprostol in preventing postpartum hemorrhage: a meta-analysis. *Int J Gynecol Obstet* 2006; **92:** 10–18.
11. Derman RJ, *et al.* Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *Lancet* 2006; **368:** 1248–53.
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Termination of pregnancy. Prostaglandins are widely used for the termination of pregnancy (p.2004) and misoprostol has been studied both for cervical preparation and for inducing uterine contractions.

In the *first trimester*, misoprostol is used for cervical ripening before surgical termination; it has been reported to be effective when given orally, sublingually, or vaginally,[1-4] usually in a dose of 400 micrograms. Oral misoprostol (400 micrograms) given after mifepristone is effective in medical termination of early pregnancy of up to 63 days, and especially so at up to 49 days.[5,6] Misoprostol 800 micrograms has also been given vaginally after mifepristone,[7-10] and a regimen of 2 or 3 doses of sublingual misoprostol after oral mifepristone has been reported to be effective.[11] Successful use of vaginal misoprostol with intramuscular or oral methotrexate has also been described.[12-15]

Misoprostol on its own is only a weak abortifacient, particularly when given orally, and congenital malformations have been reported after failed abortion attempts using misoprostol alone (see Effects on the Fetus, above). However, there is interest in finding a regimen that is effective, particularly in countries where mifepristone is unavailable. A dose of 800 micrograms vaginally, repeated after 24 hours, has been suggested for pregnancy of up to 63 days.[16,17] A large study[18] has also reported that 800 micrograms given every 12 hours for 3 doses was less effective when given sublingually than vaginally; the routes were equally effective when misoprostol was given every 3 hours, but sublingual administration caused more adverse effects such as fever, chills, shivering, and diarrhoea.

Misoprostol has also been studied for termination of pregnancy during the *second trimester*. It has been used in various regimens to induce medical termination, given either alone[19,20] or after oral mifepristone,[21,22] and reported to be effective when given vaginally, sublingually, or orally. The time to complete abortion may depend on the dose, dosage interval, and route of administration. Compared with other prostaglandins, intravaginal misoprostol alone (generally as a single dose of 200 micrograms or repeated after 12 hours if necessary) has been reported to be as effective as dinoprostone for medical termination.[23] Another study[24] found 400 micrograms intravaginally every 3 hours, up to 5 doses, to be at least as effective as intra-amniotic carboprost. The use of buccal misoprostol to prepare the cervix before surgical termination has also been described.[25]

In the management of first trimester *pregnancy failure*, intravaginal misoprostol has been proposed as an alternative to surgery for evacuation of the uterus.[26] Doses have ranged from 400 to 800 micrograms, but the lower doses tend to be less effective.[27] Misoprostol has also been used with mifepristone for uterine evacuation after pregnancy failure (see Termination of Pregnancy, p.2012) and to induce labour where late *intra-uterine fetal death* has occurred (see Labour Induction, p.2012).

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Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cytotec; ***Austria:*** Cyprostol; ***Belg.:*** Cytotec; ***Braz.:*** Cytotec; ***Canad.:*** Cytotec†; ***Chile:*** Misotrol; ***Cz.:*** Cytotec†; ***Denm.:*** Cytotec; ***Fin.:*** Cytotec; ***Fr.:*** Cytotec; Gymiso; ***Ger.:*** Cytotec†; ***Gr.:*** Cytotec; ***Hong Kong:*** Cytotec; ***India:*** Cytolog; Misoprost; ***Indon.:*** Cytotec; Gastrul; Noprostol; ***Irl.:*** Cytotec; ***Israel:*** Cytotec; ***Ital.:*** Cytotec; Misodex; ***Malaysia:*** Cytotec; ***Mex.:*** Cytotec; ***Neth.:*** Cytotec; ***Norw.:*** Cytotec; ***NZ:*** Cytotec; ***Pol.:*** Cytotec; ***Port.:*** Cytotec; ***Rus.:*** Cytotec (Сайтотек)†; ***S.Afr.:*** Cytotec; ***Singapore:*** Cytotec; ***Spain:*** Cytotec; Glefos†; ***Swed.:*** Cytotec; ***Switz.:*** Cytotec; ***Thai.:*** Cytotec; ***Turk.:*** Cytotec; ***UK:*** Cytotec; ***USA:*** Cytotec; ***Venez.:*** Cytotec.

Used as an adjunct in: ***Arg.:*** Oxaprost; ***Austral.:*** Arthrotec; ***Austria:*** Arthrotec; ***Belg.:*** Arthrotec; ***Canad.:*** Arthrotec; ***Cz.:*** Arthrotec†; ***Denm.:*** Arthrotec; ***Fin.:*** Arthrotec; ***Fr.:*** Artotec; ***Ger.:*** Arthotec; ***Gr.:*** Arthrotec; ***Hong Kong:*** Arthrotec; ***Irl.:*** Arthrotec; ***Israel:*** Arthrotec; ***Ital.:*** Artrotec; Misofenac; ***Mex.:*** Artrenac Pro; Artrene; Artrotec; ***Neth.:*** Arthrotec; Artrotec; Misofenac; Normulen; ***Norw.:*** Arthrotec; ***Pol.:*** Arthrotec; ***Port.:*** Arthrotec; Diclotec; ***Rus.:*** Arthrotec (Артротек)†; ***S.Afr.:*** Arthrotec; ***Spain:*** Artrotec; Normulen; ***Swed.:*** Arthrotec; ***Switz.:*** Arthrotec; ***Thai.:*** Arthrotec†; ***UK:*** Arthrotec; Napratec; ***USA:*** Arthrotec; ***Venez.:*** Arthrotec.

Oxytocin *(BAN, rINN)*

Alpha-hypophamine; Hipofamina; Ocitocina; Oksitocinas; Oksitosiini; Oksitosin; Oxitocin; Oxitocina; Oxytocine; Oxytocinum. Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 cyclic (1→6) disulphide; [2-Leucine,7-isoleucine]vasopressin.

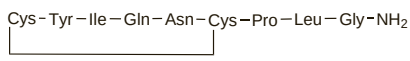
Окситоцин

$C_{43}H_{66}N_{12}O_{12}S_2$ = 1007.2.

CAS — 50-56-6.

ATC — H01BB02.

ATC Vet — QH01BB02.



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

Ph. Eur. 6.2 (Oxytocin). A cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary that stimulates contraction of the uterus and milk ejection in receptive mammals. It is obtained by chemical synthesis and is available in the freeze-dried form as an acetate. A white or almost white, hygroscopic powder. Very soluble in water and in dilute solutions of dehydrated alcohol and of acetic acid. A 2% solution in water has a pH of 3.0 to 6.0. Store at 2° to 8° in airtight containers. Protect from light.

Ph. Eur. 6.2 (Oxytocin Concentrated Solution). A solution of oxytocin with a concentration of not less than 250 micrograms of oxytocin per mL. It may contain a suitable antimicrobial preservative. A clear colourless liquid with a pH of 3.0 to 5.0. Store at 2° to 8°. Protect from light.

USP 31 (Oxytocin). A nonapeptide hormone having the property of causing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary glands. It is prepared by synthesis or obtained from the posterior lobe of the pituitary of healthy domestic animals used for food by man. Its oxytocic activity is not less than 400 units/mg. Store in airtight containers at 2° to 8°.

Units

12.5 units of oxytocin for bioassay are contained in about 21.4 micrograms of synthetic peptide (with human albumin 5 mg and citric acid) in one ampoule of the fourth International Standard (1978).

Adverse Effects

Oxytocin given in high doses, or to women who are hypersensitive to it, may cause uterine hyperstimulation with hypertonic or tetanic contractions, leading to uterine rupture and soft tissue damage. Effects in the fetus include bradycardia, arrhythmias, asphyxiation, and perhaps death.

Maternal deaths from severe hypertension and subarachnoid haemorrhage have occurred. Rapid intravenous injection of oxytocin has produced acute transient hypotension with flushing and reflex tachycardia. Postpartum haemorrhage, fatal afibrinogenaemia, and disseminated intravascular coagulation have been reported, but may be due to complications of labour induction rather than oxytocin itself.

High doses of oxytocin infused over prolonged periods can also cause water retention leading to hyponatraemia and intoxication, which may progress to convulsions, coma, and even death. Vasopressin-like activity (see p.2412) is more likely with oxytocin of natural origin but may occur even with the synthetic peptide.

Other adverse effects include headache, nausea and vomiting, skin rashes, cardiac arrhythmias, pelvic haematoma, and anaphylactic and other hypersensitivity reactions.

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

Adverse effects after intranasal use of oxytocin have included nasal irritation, rhinorrhoea, lachrymation, uterine bleeding, and violent uterine contractions.

Inappropriate use. In a 1988 comment on the misuse of oxytocin in labour,[1] it was noted that statements on the management of labour were often misinterpreted as meaning that all women who failed to make adequate progress in terms of cervical dilatation should be given oxytocin. This was only true if poor progress was due to poor uterine action, and would be dangerous where there was disproportion; the decision to use oxytocin required careful assessment by an experienced obstetrician. In the previous 2 years the authors had seen one case of fractured pelvis, 2 of ruptured uterus, and 7 of cerebral palsy from fetal hypoxia, all of which were thought to be due to the ill-advised use of oxytocin to augment labour. More than a decade later the injudicious use of oxytocin during labour, with adverse outcomes including neonatal brain damage and death, continues to be reported. A review[2] of obstetric malpractice claims in Sweden found that the incorrect use of oxytocin was obvious in 37 of 54 cases; often, the oxytocin infusion had been increased despite a non-reassuring fetal heart-rate pattern with or without overly frequent uterine contractions, or fetal monitoring was inadequate and hence fetal distress not recognised.

For reference to haemorrhage and to neonatal hyperbilirubinaemia occurring after an oxytocin challenge test, see under Uses and Administration, below.

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Neonatal jaundice. Analysis of neonatal jaundice in 12 461 single births confirmed a higher incidence of jaundice in offspring of mothers given oxytocin, independent of gestational age at birth, sex, race, epidural analgesia, method of delivery, and birth-weight, which were also associated with jaundice.[1] A later review[2] of 12 023 single births also found some of these factors to be associated with neonatal hyperbilirubinaemia, but not epidural analgesia or the use of oxytocin. Another smaller population study[3] also concluded that oxytocin was not significantly related to neonatal jaundice. In a total of 90 infants born to mothers after oxytocin-induced labour in 2 studies,[4,5] haematological disturbances were noted. These included erythrocyte fragility or reduction in erythrocyte deformability, hyponatraemia, hypoosmolality, and an increase in serum-bilirubin concentration. Glucose injection, used as a vehicle for oxytocin may have further aggravated these changes.[5] A comparison[6] of women who received oxytocin infusion in either glucose 5% or sodium chloride 0.9% found the use of glucose to be associated with more cases of hyponatraemia in cord plasma, and neonatal hyperbilirubinaemia. In contrast, another study[7] found no difference between these diluents, but did report that neonatal bilirubin concentrations were higher when oxytocin had been used for augmentation of labour, compared with labour induction.

See also under Oxytocin Challenge Test in Uses and Administration, below.

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