

becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women, and for all women younger than 18 years of age.^{2,3} It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators,^{1,3} mifepristone, or a prostaglandin such as gemeprost or misoprostol.^{1,3} Various drugs, used alone and in combination, have been tried for *medical termination* of pregnancy. Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring about successful termination when used alone, but the high doses required can cause significant adverse effects.^{4,6} The most commonly used prostaglandins are gemeprost and misoprostol;^{3,4} others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects.³ The anti-progesterone mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.^{3,5,7} The antimetabolite methotrexate has also been used with misoprostol, but it has a delayed effect and the time from induction to abortion can be several days or weeks.^{4,5} Other methods that have been used for termination of pregnancy, particularly in the second trimester, include intra-amniotic use of dinoprost, hypertonic sodium chloride, or hyperosmolar urea augmented with oxytocin, carboprost, or dinoprost.¹

Uterine cramping and bleeding are associated with both surgical and medical termination processes. Surgical termination may be carried out under conscious sedation,^{1,2} local anaesthesia using paracervical block,^{1,3} or general anaesthesia.² Analgesia requirements in medical termination may be higher in younger women, nulliparous women, and those with longer gestations.^{3,4} Analgesics such as paracetamol, NSAIDs, and codeine are commonly used.⁶ Generally, bleeding lasts longer after medical termination than after vacuum aspiration.⁶ With medical termination using mifepristone plus a prostaglandin, bleeding is initially heavy but gradually diminishes over about 2 weeks, although minor bleeding can continue for longer.^{1,6}

Factors influencing the choice of method for termination include the stage of gestation, availability of surgical services and abortifacient drugs, and the woman's preference. The most common approaches are outlined below.

- In the early first trimester (up to 49 days) a medical method, using mifepristone followed by a prostaglandin, is preferred because the failure rate is higher with vacuum aspiration.^{2,6} Methotrexate followed by a prostaglandin is an alternative at this early stage,^{1,5} but expulsion can take several days or weeks.⁴ Either a surgical or medical method can be used between 49 and 63 days of gestation. However, oral misoprostol for medical termination becomes less effective as gestation progresses^{4,5} so a vaginal prostaglandin is preferred.^{2,5,6}
- In the late first trimester (up to 13 weeks) a surgical or medical method may be used. After 9 or 10 weeks of gestation, cervical preparation is used before surgical procedures and multiple doses of prostaglandin may be needed to achieve medical termination.²
- In mid-trimester termination (13 to 24 weeks) a surgical or medical method may be used. Cervical preparation is essential before surgical termination and multiple doses of prostaglandin will generally be required for medical termination.^{2,3}

Some of the methods used for termination of pregnancy are also used to hasten miscarriage after pregnancy failure or early fetal death. Surgical evacuation is effective but associated with a higher risk of infection than expectant management.⁸ Vaginal misoprostol can also hasten miscarriage, but oral use is less effective.⁹ For the management of intra-uterine fetal death in later pregnancy, see Labour Induction and Augmentation, above.

1. Stubblefield PG, *et al.* Methods for induced abortion. *Obstet Gynecol* 2004; **104**: 174–85.
2. 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)
3. Lalitkumar S, *et al.* Mid-trimester induced abortion: a review. *Hum Reprod Update* 2007; **13**: 37–52.
4. Hamoda H, Flett GMM. Medical termination of pregnancy in the early first trimester. *J Fam Plann Reprod Health Care* 2005; **31**: 10–14.

5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, issued October 2005). *Obstet Gynecol* 2005; **106**: 871–82.
6. WHO. Frequently asked clinical questions about medical abortion (2006). Available at: http://www.who.int/reproductive-health/publications/medical_abortion/faq.pdf (accessed 30/06/08)
7. Kulier R, *et al.* Medical methods for first trimester abortion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 30/06/08).
8. Nanda K, *et al.* Expectant care versus surgical treatment for miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
9. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).

Aglepristone (rINN)

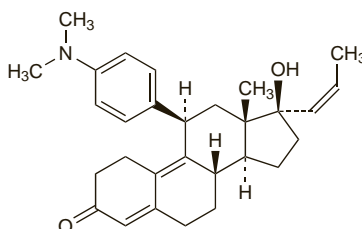
Aglepristone; Aglepristone; Aglepristonum; RU-46534. 1-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-[(Z)-propenyl]estra-4,9-dien-3-one.

Аглерпистон

C₂₉H₃₇NO₂ = 431.6.

CAS = 124478-60-0.

ATC Vet = QG03XB90.



Profile

Aglepristone has antiprogesterone activity and is used in veterinary medicine as an abortifacient in dogs.

Atosiban (BAN, USAN, rINN)

Atosibaani; Atosibanum; ORF-22164; RVV-22164. 1-(3-Mercaptopropionic acid)-2-[3-(p-ethoxyphenyl)-D-alanine]-4-L-threonine-8-L-ornithineoxytocin; [1-(3-Sulfinylpropyl)-2-(4-O-ethyltyrosine),4-L-threonine-8-L-ornithine]oxytocin.

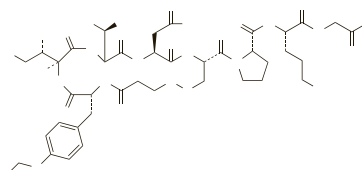
АТОЗИБАН

C₄₃H₆₇N₁₁O₁₂S₂ = 994.2.

CAS = 90779-69-4.

ATC = G02CX01.

ATC Vet = QG02CX01.



Adverse Effects and Precautions

Adverse effects reported in women receiving atosiban for premature labour include nausea and vomiting, headache, dizziness, flushes, tachycardia, hypotension, hyperglycaemia, and injection site reactions. Atosiban should not be used where continuation of pregnancy is hazardous to mother or fetus, including where gestational age is below 24 or over 33 weeks, in eclampsia or severe pre-eclampsia, intra-uterine growth retardation and abnormal fetal heart rate, suspected intra-uterine infection, placenta praevia, or abruptio placentae. Monitoring of uterine contractions and fetal heart rate is recommended during use, and blood loss should be monitored after delivery.

Although there has been some concern about fetal exposure, licensed product information states that no specific adverse effects on the newborn have been reported.

Pharmacokinetics

In women in premature labour, atosiban reaches steady-state plasma concentrations within one hour of the start of infusion, and has a terminal half-life of 1.7 hours after stopping infusion. Atosiban is 46 to 48% bound to plasma proteins, and crosses the

placenta. It is metabolised to an active metabolite, which is excreted in the urine; both atosiban and this metabolite are distributed into breast milk.

Uses and Administration

Atosiban is a peptide analogue of oxytocin (p.2015) but with oxytocin antagonist properties. It is used as a tocolytic in the management of premature labour (p.2003). Atosiban is given intravenously as the acetate, but doses are expressed in terms of the base. An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.

Premature labour. References.

1. Romero R, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000; **182**: 1173–83.
2. Valenzuela GJ, *et al.* Maintenance treatment of preterm labor with the oxytocin antagonist atosiban: the Atosiban PTL-098 Study Group. *Am J Obstet Gynecol* 2000; **182**: 1184–90.
3. Moutquin JM, *et al.* Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000; **182**: 1191–9.
4. The Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labor. *Br J Obstet Gynecol* 2001; **108**: 133–42.
5. The European Atosiban Study Group. The oxytocin antagonist atosiban versus the beta-agonist terbutaline in the treatment of preterm labor: a randomized, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001; **80**: 413–22.
6. French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001; **98**: 177–85.
7. Coomarasamy A, *et al.* Oxytocin antagonists for tocolysis in preterm labour—a systematic review. *Med Sci Monit* 2002; **8**: RA268–73.
8. Tsatsaris V, *et al.* Atosiban for preterm labour. *Drugs* 2004; **64**: 375–82.
9. Husslein P, *et al.* Atosiban versus usual care for the management of preterm labor. *J Perinat Med* 2007; **35**: 305–13.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Tractocile; **Austria**: Tractocile; **Belg.**: Tractocile; **Braz.**: Tractocile; **Cz.**: Tractocile; **Denm.**: Tractocile; **Fin.**: Tractocile; **Fr.**: Tractocile; **Ger.**: Tractocile; **Gr.**: Tractocile; **Hong Kong**: Tractocile; **Hung.**: Tractocile; **Irl.**: Tractocile; **Ital.**: Tractocile; **Malaysia**: Tractocile; **Mex.**: Tractocile; **Neth.**: Tractocile; **Norw.**: Tractocile; **NZ**: Tractocile; **Pol.**: Tractocile; **Port.**: Tractocile; **S.Afr.**: Tractocile; **Spain**: Tractocile; **Swed.**: Tractocile; **Switz.**: Tractocile; **UK**: Tractocile.

Carbetocin (BAN, rINN)

Carbetocina; Carbetocine; Carbetocinum; Karbetocin; Karbetosiini. 2,1-Desamino-4,1-dethio-*O*¹²-methyl[1-homocysteine]oxytocin; 1-Butyric acid-2-[3-(p-methoxyphenyl)-L-alanine]oxytocin.

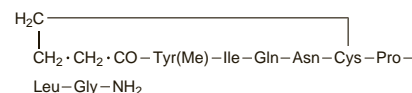
Карбетотин

C₄₅H₆₉N₁₁O₁₂S = 988.2.

CAS = 37025-55-1.

ATC = H01BB03.

ATC Vet = QH01BB03.



Adverse Effects and Precautions

Carbetocin has similar adverse effects and precautions to those associated with oxytocin when it is used after caesarean section (see p.2015). However, carbetocin should not be used at any stage of labour before delivery of the infant because its effects on the uterus last for several hours.

Breast feeding. In 5 women who were 7 to 14 weeks postpartum, carbetocin was measured in the breast milk within 90 minutes of a single 70-microgram intramuscular dose.¹ The ratio of milk to plasma concentrations was low, suggesting that very little carbetocin was distributed into breast milk. Licensed UK product information states that no significant effects on milk ejection were reported during clinical studies, and that any carbetocin ingested by a breast-fed infant would probably be degraded by enzymes in the gastrointestinal tract. The American Academy of Pediatrics considers that the use of carbetocin is usually compatible with breast feeding.²

1. Silcox J, *et al.* Transfer of carbetocin into human breast milk. *Obstet Gynecol* 1993; **82**: 456–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108%3f776> (accessed 30/06/08)

Interactions

Although reports are lacking, carbetocin may be involved in similar interactions to those that can occur with oxytocin (p.2016).

Pharmacokinetics

After intravenous injection of carbetocin, firm uterine contraction occurs within 2 minutes and lasts for several hours. Carbetocin undergoes a biphasic elimination, with a terminal elimination half-life of about 40 minutes. Less than 1% of a dose is excreted unchanged by the kidney. Carbetocin is distributed into breast milk.

Uses and Administration

Carbetocin is a synthetic analogue of oxytocin (p.2016) reported to have a longer duration of action. For the prevention of uterine atony and excessive bleeding after caesarean section under epidural or spinal anaesthesia, a single dose of 100 micrograms may be given by slow intravenous injection over 1 minute. Carbetocin must only be given after delivery of the infant, preferably before removal of the placenta.

♦ **References.**

- Hunter DJS, *et al.* Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. *Clin Pharmacol Ther* 1992; **52**: 60–7.
- Dansereau J, *et al.* Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after caesarean section. *Am J Obstet Gynecol* 1999; **180**: 670–6.
- Boucher M, *et al.* Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. *J Obstet Gynaecol Can* 2004; **26**: 481–8.
- Leung SW, *et al.* A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *BJOG* 2006; **113**: 1459–64.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Duratocin; **Austral.:** Duratocin; **Canad.:** Duratocin; **Fr.:** Pabal; **Hong Kong:** Duratocin; **Hung.:** Pabal; **Malaysia:** Duratocin; **Mex.:** Lonactene; **Port.:** Pabal; **Singapore:** Duratocin; **UK:** Pabal.

Multi-ingredient: **Cz.:** Duratocin.

Carboprost (BAN, USAN, rINN)

Carboprostum; 15-Me-PGF₂; Methyl dinoprost; (15S)-15-Methylprostaglandin F₂; U-32921. (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxy-15-methylprosta-5,13-dienoic acid; (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(E)-(3S)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl]hept-5-enoic acid.

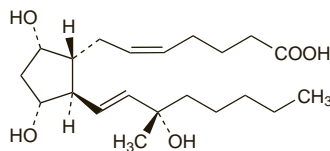
Карбопрост

C₂₁H₃₆O₅ = 368.5.

CAS — 35700-23-3.

ATC — G02AD04.

ATC Vet — QG02AD04.

**Carboprost Methyl** (BANM, USAN, rINNM)

Carboprost Méthyle; Carboprostum Methylis; Methyl Carboprost; Metil carboprost; U-36384. The methyl ester of carboprost.

Карбопрост Метил

C₂₂H₃₈O₅ = 382.5.

CAS — 35700-21-1.

ATC — G02AD04.

ATC Vet — QG02AD04.

Pharmacopoeias. In *Chin.*

Carboprost Trometamol (BANM, rINNM)

Carboprost trométamol; Carboprost Tromethamine (USAN); Carboprostum Trometamoli; Carboprostum trometamolum; Kaboprosttrometamol; Karboprost z trometamolem; Karboprostas trometamolis; Karboprosttrometamoli; Karboprost trometamol; U-32921E.

Карбопрост Трометамол

C₂₁H₃₆O₅·C₄H₁₁NO₃ = 489.6.

CAS — 58551-69-2.

ATC — G02AD04.

ATC Vet — QG02AD04.

Description. Carboprost trometamol is a compound of carboprost with trometamol in a ratio of 1:1.

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

Ph. Eur. 6.2 (Carboprost Trometamol). A white or almost white powder. Soluble in water. Store at a temperature below –15°.

USP 31 (Carboprost Tromethamine). A white to off-white powder. Soluble in water. Store at –25° to –10°.

Adverse Effects and Precautions

As for Dinoprostone, p.2007.

Carboprost may cause bronchospasm and, less frequently, dyspnoea and pulmonary oedema. Patients with cardiopulmonary disorders should be monitored for reductions in arterial-oxygen content.

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.

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

Effects on the neonate. For a report of inadvertent intramuscular administration of carboprost to a neonate, see under Dinoprostone, p.2007.

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

Uses and Administration

Carboprost is a synthetic 15-methyl analogue of dinoprost (prostaglandin F_{2α}; below). It is a uterine stimulant with a more prolonged action than dinoprost; the presence of the methyl group delays inactivation by enzymic dehydrogenation.

Carboprost is used for the termination of pregnancy (p.2004) and for the treatment of refractory postpartum haemorrhage due to uterine atony (p.2003) that is not controlled by oxytocin and ergot preparations. It is usually given intramuscularly as the trometamol salt but doses are expressed in terms of carboprost. Carboprost trometamol 1.3 micrograms is equivalent to about 1 microgram of carboprost.

For the **termination** of second trimester pregnancy (between 13 and 20 weeks of gestation) the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection and repeated every 1½ to 3½ hours depending on the uterine response. If necessary the dose may be increased to 500 micrograms, but the total dose given should not exceed 12 mg, and continuous use for more than 2 days is not recommended. If preferred, a test dose of 100 micrograms may be given initially. Carboprost trometamol has also been given intra-amniotically in a dose equivalent to 1 mg of carboprost over five minutes; this dose may be repeated after 24 hours if termination has not occurred and the membranes are intact. A total dose of 5 mg should not be exceeded.

Carboprost methyl given as vaginal pessaries has been tried for termination of pregnancy in the second trimester.

For the treatment of **postpartum haemorrhage** the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection as the trometamol salt at intervals of about 90 minutes; the interval may be reduced if necessary, but should not be less than 15 minutes. A total dose of 2 mg should not be exceeded.

Haemorrhagic cystitis. Carboprost trometamol instilled into the bladder successfully controlled cyclophosphamide-induced haemorrhagic cystitis (p.702) in 15 of 24 bone marrow transplant patients.¹ The dose consisted of 50 mL of solutions containing 2 to 10 micrograms/mL instilled four times daily for 7 days.

- Ippoliti C, *et al.* Intravesicular carboprost for the treatment of haemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46**: 811–15.

Preparations

USP 31: Carboprost Tromethamine Injection.

Proprietary Preparations (details are given in Part 3)

Belg.: Prostin/15M; **Canad.:** Hemabate; **Cz.:** Prostin 15M; **Denm.:** Prostinferem; **India:** Prostodin; **Neth.:** Prostin/15M; **NZ:** Prostin 15M; **Swed.:** Prostinferem; **UK:** Hemabate; **USA:** Hemabate.

Demoxycocin (rINN)

Deamino-oxytocin; Demoksitosiini; Demoxitocina; Démoxytocine; Demoxycocin; Desaminocitocina; Desamino-oxytocin; ODA-914. 1-(3-Mercaptopropionic acid)-oxytocin.

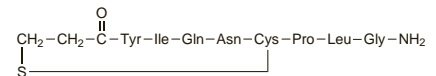
ДЕМОКСИТОЦИН

C₄₃H₆₅N₁₁O₁₂S₂ = 992.2.

CAS — 113-78-0.

ATC — H01BB01.

ATC Vet — QH01BB01.

**Profile**

Demoxycocin is a synthetic analogue of oxytocin (p.2015) and has similar properties. It has been given as buccal tablets for the induction and augmentation of labour. It has also been given before nursing to stimulate milk ejection, although it is generally recommended that oxytocics should not be used for this purpose (see p.2003).

Dinoprost (BAN, USAN, rINN)

Dinoprost; Dinoprostum; PGF₂; Prostaglandin F₂; U-14583. (5Z,13E)-(8R,9S,11R,12R,15S)-9,11,15-Trihydroxyprosta-5,13-dienoic acid; (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(E)-(3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid.

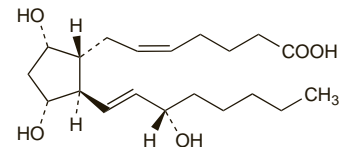
Динопрост

C₂₀H₃₄O₅ = 354.5.

CAS — 551-11-1.

ATC — G02AD01.

ATC Vet — QG02AD01.



NOTE. In *Martindale* the term dinoprost is used for the exogenous substance and prostaglandin F₂ for the endogenous substance.

Pharmacopoeias. In *Jpn.*

Dinoprost Trometamol (BANM, rINNM)

Dinoprost trométamol; Dinoprost Tromethamine (USAN); Dinoprostas trometamolis; Dinoprosttrometamoli; Dinoprost-trometamol; Dinoprost-trometamol; Dinoprostum Trometamoli; Dinoprostum trometamolum; Dinoprost-trometamol; PGF₂ THAM; Prostaglandin F₂ Trometamol; U-14583E.

Динопрост Трометамол

C₂₀H₃₄O₅·C₄H₁₁NO₃ = 475.6.

CAS — 38562-01-5.

ATC — G02AD01.

ATC Vet — QG02AD01.

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

Ph. Eur. 6.2 (Dinoprost Trometamol). A white or almost white powder. Very soluble in water; freely soluble in alcohol; practically insoluble in acetonitrile.

USP 31 (Dinoprost Tromethamine). A white to off-white crystalline powder. Very soluble in water; slightly soluble in chloroform; freely soluble in dimethylformamide; soluble in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Dinoprostone, p.2007.

Dinoprost can cause bronchoconstriction and bronchospasm with wheezing and dyspnoea has occurred, especially in asthmatic patients.

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.

Interactions

As for Dinoprostone, p.2008. Alcohol and beta agonists may reduce the efficacy of dinoprost.

♦ For a report of a severe reaction after the use of oxytocin, methyl-ergometrine, and dinoprost, see under Dinoprostone, p.2008.

Uses and Administration

Dinoprost is a prostaglandin of the F series (p.2374) with actions on smooth muscle; the endogenous substance is termed prostaglandin F₂ and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasoconstrictor on blood vessels and as a bronchoconstrictor on bronchial muscle.

Dinoprost is used principally for the termination of pregnancy (p.2004). It may also be used for missed abortion, hydatidiform