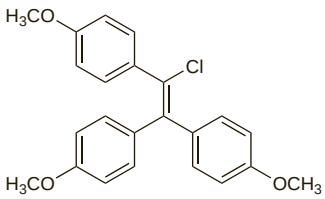
Chlorotrianisene *(BAN, rINN)*

Chlorotrianisène; Chlorotrianisenum; Clorotrianiseno; Klooritrianiseeni; Klortrianisen; NSC-10108; Tri-*p*-anisylchloroethylene. Chlorotris(4-methoxyphenyl)ethylene.

Хлоротрианизен

$C_{23}H_{21}ClO_3$ = 380.9.
CAS — 569-57-3.
ATC — G03CA06.
ATC Vet — QG03CA06.



Pharmacopoeias. In *Chin.*

Profile

Chlorotrianisene is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (p.2094). It has a prolonged action, and has been given orally for the treatment of menopausal symptoms, female hypogonadism, and prostatic carcinoma.

Chorionic Gonadotrophin *(BAN, rINN)* ⊗

CG; Choriogonadotrophin; Chorionic Gonadotropin; Chorioninis gonadotropinas; Gonadotrofina coriónica; Gonadotrophine Chorionique; Gonadotrophinum Chorionicum; Gonadotropin choriový; Gonadotropine chorionique; Gonadotropinum chorionicum; hCG; Human Chorionic Gonadotrophin; Koriongonadotropiini; Koriongonadotropin; Korion-gonadotropin; Koriyonik Gonadotrofin; Pregnancy-urine Hormone; PU.

Гонадотропин Хорионический
CAS — 9002-61-3.
ATC — G03GA01.
ATC Vet — QG03GA01.

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

Ph. Eur. 6.2 (Gonadotrophin, Chorionic). A dry preparation of placental glycoproteins extracted from the urine of pregnant women. The potency is not less than 2500 units/mg. A white to yellowish-white, amorphous powder. Soluble in water. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Chorionic Gonadotropin). A gonad-stimulating polypeptide hormone obtained from the urine of pregnant women. It has a potency of not less than 1500 USP units/mg. A white or practically white, amorphous powder. Freely soluble in water. Store in airtight containers at 2° to 8°.

Choriogonadotropin Alfa *(BAN, USAN, rINN)* ⊗

Choriogonadotropine Alfa; Choriogonadotropinum Alfa; Coriogonadotropina alfa.

Хориогонадотропин Альфа
CAS — 177073-44-8 (choriogonadotropin alfa); 56832-30-5 (α subunit); 56832-34-9 (β subunit).
ATC — G03GA08.
ATC Vet — QG03GA08.

Adverse Effects and Precautions

Adverse effects that have been reported with chorionic gonadotrophin include headache, tiredness, changes in mood, depression, restlessness, oedema (especially in males), and pain on injection. Treatment for cryptorchidism may produce premature epiphyseal closure or precocious puberty. Gynaecomastia has been reported. Ovarian hyperstimulation may occur, with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock, and thromboembolic disorders in severe cases.

Chorionic gonadotrophin should be given with care to patients in whom androgen-induced fluid retention might be a hazard as in asthma, epilepsy, migraine, or cardiovascular disorders, including hypertension, or renal disorders. Hypersensitivity reactions may occur and it is recommended that patients suspected to be susceptible should be given skin tests before treatment. It should not be given to patients with disorders that might be exacerbated by androgen release such as carcinoma of the prostate or precocious puberty. Use should also be avoided in the presence of breast, uterine, ovarian, and testicular tumours, as well as tumours of the hypothalamus, pituitary, thyroid, and adrenal glands.

Pharmacokinetics

Peak concentrations of chorionic gonadotrophin occur about 6 hours after an intramuscular dose and 16 to 20 hours after a subcutaneous injection. It is distributed primarily to the gonads. Blood concentrations decline in a biphasic manner, with half-lives of about 6 to 11 hours and 23 to 38 hours, respectively. Chorionic gonadotrophin is metabolised mainly in the kidneys. About 10 to 12% of an intramuscular dose is excreted in urine within 24 hours.

After subcutaneous doses, choriogonadotropin alfa has a bioavailability of about 40%. It is metabolised and excreted similarly to chorionic gonadotrophin.

Uses and Administration

Chorionic gonadotrophin is a hormone produced by the placenta and obtained from the urine of pregnant women. Its effects are mainly those of the gonadotrophin, luteinising hormone (p.2112), which is responsible for triggering ovulation and formation of the corpus luteum in women, and stimulates the production of testosterone by the testes in men. It is usually given by intramuscular injection although the subcutaneous route has also been used. Choriogonadotropin alfa is a recombinant form of chorionic gonadotrophin.

In *women* with **anovulatory infertility** due to absent or low concentrations of gonadotrophins, chorionic gonadotrophin is given to induce ovulation after follicular development has been stimulated with follicle-stimulating hormone or human menopausal gonadotrophins. A single dose of 5000 to 10 000 units of chorionic gonadotrophin is given by intramuscular injection to mimic the midcycle peak of luteinising hormone which normally stimulates ovulation. Up to 3 repeat injections of up to 5000 units each may be given within the next 9 days to prevent insufficiency of the corpus luteum. Chorionic gonadotrophin is also given with menotrophin as an adjunct to IVF procedures and other assisted conception techniques involving superovulation and oocyte collection.

Choriogonadotropin alfa is used similarly to induce ovulation in the treatment of anovulatory infertility, or as an adjunct to IVF procedures and other assisted conception techniques. A single dose of 250 micrograms is given, by subcutaneous injection, when optimal stimulation of follicular growth is achieved.

In *males*, chorionic gonadotrophin has been used in the treatment of prepubertal **cryptorchidism**. Regimens vary widely, but doses usually range from 500 to 4000 units three times weekly by intramuscular injection. Treatment should continue for 1 to 2 months after testicular descent.

Chorionic gonadotrophin is also given for male infertility associated with hypogonadotrophic **hypogonadism**. Again, there is considerable variation in the dosage regimen, and doses have varied from 500 to 4000 units two or three times weekly by intramuscular injection. A drug with follicle-stimulating activity such as menotrophin is often added to enable normal spermatogenesis.

In the treatment of **delayed puberty** associated with hypogonadism in males, an initial dose of chorionic gonadotrophin 500 to 1500 units is given twice weekly by intramuscular injection; the dose should be titrated against plasma-testosterone concentration.

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with chorionic gonadotrophin is widely used for cryptorchidism (p.2079). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, a predictor of future fertility.[3] Chorionic gonadotrophin may also be used as an adjuvant before surgery, to render the testes palpable,[4] but changes suggestive of inflammation in the testis have been reported following such treatment.[5]

1. Pyöräläinen S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (issued March 2008). Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Paediatric%20Urology.pdf (accessed 31/03/08)
4. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10-year experience. *J Urol (Baltimore)* 1996; **156:** 804–6.
5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19:** 293–8.

Delayed puberty. Use of chorionic gonadotrophin may be appropriate in boys with delayed puberty due to hypogonadotrophic hypogonadism (p.2079).

Infertility. In women with anovulatory infertility chorionic gonadotrophin and choriogonadotropin alfa can be used to provoke ovulation and provide luteal support once maturation of a suitable number of follicles has been stimulated by other means. They are used similarly in the various protocols for assisted reproduction. However, use is not recommended for assisted reproduction in patients at risk of ovarian hyperstimulation, such as those with polycystic ovary syndrome. In men with hypogonadotrophic hypogonadism chorionic gonadotrophin is used to stimulate and maintain spermatogenesis. The management of male and female infertility, including the role of chorionic gonadotrophin, is discussed on p.2080.

Malignant neoplasms. Control of Kaposi's sarcoma (p.675) has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but regrowth occurred when dosage was reduced or withdrawn.[1] Another study, using lower doses, was stopped due to toxicity and lack of benefit,[2] but others have confirmed benefit after intralesional injection.[3] There is some suggestion that preparations vary in their activity against the tumour and that it is not chorionic gonadotrophin itself, but some impurity (perhaps a ribonuclease[4] or the degradation product of the β-subunit[5]), that is the active principle.[3,6,7] Some contaminants may have a stimulant effect on the neoplasm, which might also contribute to the variable results.[5]

1. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. *Lancet* 1995; **346:** 118–19.
2. Bower M, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346:** 642.
3. Gill PS, *et al.* The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. *N Engl J Med* 1996; **335:** 1261–9. Correction. *ibid.* 1997; **336:** 1115.
4. Griffiths SJ, *et al.* Ribonuclease inhibits Kaposi's sarcoma. *Nature* 1997; **390:** 568.
5. Simonart T, *et al.* Treatment of Kaposi's sarcoma with human chorionic gonadotropin. *Dermatology* 2002; **204:** 330–3.
6. Gill PS, *et al.* Intralesional human chorionic gonadotropin for Kaposi's sarcoma. *N Engl J Med* 1997; **336:** 1188.
7. von Overbeck J, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346:** 642–3.

Obesity. A meta-analysis[1] involving 24 studies concluded that there was no evidence that chorionic gonadotrophin was effective in the treatment of obesity (p.2149).

1. Lijesen GKS, *et al.* The effect of human chorionic gonadotropin (HCG) in the treatment of obesity by means of the Simeons therapy: a criteria-based meta-analysis. *Br J Clin Pharmacol* 1995; **40:** 237–43.

Testicular function. Chorionic gonadotrophin is used in the assessment of testicular function in suspected primary hypogonadism and incomplete masculinisation. The *BNFC* states that for children 1 month to 18 years of age a dose of 1500 to 2000 units may be given once daily for 3 days (short stimulation test) or twice weekly for 3 weeks (prolonged test).

Preparations

BP 2008: Chorionic Gonadotrophin Injection;
USP 31: Chorionic Gonadotropin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Dinaron; Endocorion; Gonacor; Ovidrel; Pregnyl; Profasi†; ***Austral.:*** Ovidrel; Pregnyl; Profasi; ***Austria:*** Pregnyl; Profasi; ***Belg.:*** Choragon; Ovitrelle; Pregnyl; ***Braz.:*** Choragon†; Ovidrel; Pregnyl; Profasi HP; ***Canad.:*** Pregnyl†; Profasi HP; ***Chile:*** APL†; Gonacor; Ovidrel†; Pregnyl; Profasi†; ***Cz.:*** Ovitrelle; Praedyn†; Pregnyl; Profasi†; ***Denm.:*** Ovitrelle; Pregnyl; Profasi†; ***Fin.:*** Ovitrelle; Pregnyl; Profasi†; ***Fr.:*** Ovitrelle; ***Ger.:*** Choragon; Ovitrelle; Predalon; Pregnesin†; Primogonyl†; ***Gr.:*** Ovitrelle; Pregnyl; Profasi†; ***Hong Kong:*** Choragon; Choriomon; Ovidrel; Pregnyl; Profasi; ***Hung.:*** Choragon; Ovitrelle; Pregnyl; Profasi†; ***India:*** Corion; Profasi; Proligon†; Provigil; Pubergen; ***Indon.:*** Ovidrel; Pregnyl; ***Irl.:*** Ovitrelle; Pregnyl; Profasi; ***Israel:*** Chorigon†; Ovitrelle; Pregnyl; ***Ital.:*** Gonasi HP; Ovitrelle; Pregnyl; Profasi HP†; ***Malaysia:*** Choragon; Ovidrel; Pregnyl; Profasi†; ***Mex.:*** Choragon; Choriomon; Gonadotropyl C†; Ovidrel; Pregnyl; Profasi†; ***Neth.:*** Choragon; Ovitrelle; Pregnyl; Profasi†; ***Norw.:*** Ovitrelle; Pregnyl; Profasi†; ***NZ:*** Ovidrel; Profasi; ***Philipp.:*** Ovidrel; Pregnyl; ***Pol.:*** Choragon; Ovitrelle; Pregnyl; ***Port.:*** Ovitrelle; Pregnyl; Profasi HP†; ***Rus.:*** Choragon (Хорагон); Ovitrelle (Овитрель); Pregnyl (Прегнил); ***S.Afr.:*** APL; Pregnyl; Profasi; ***Singapore:*** Ovidrel; Pregnyl; Profasi†; ***Spain:*** Ovitrelle; Profasi HP†; ***Swed.:*** Ovitrelle; Pregnyl; Profasi†; ***Switz.:*** Choriomon; Ovitrelle; Pregnyl; Profasi†; ***Thai.:*** IVF-C; Ovidrel; Pregnyl; Profasi†; ***Turk.:*** Choragon; Ovitrelle; Pregnyl;

Profasi; **UK:** Choragon; Ovitrelle; Pregnyl; **USA:** Chorex†; Choron; Gonic; Novarel; Ovidrel; Pregnyl; Profasi; **Venez.:** Ovidrel; Pregnyl; Profasi†.

Multi-ingredient: **Ger.:** NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; **Mex.:** Gonakor.

Clomifene Citrate *(BANM, rINNM)* ⊗

Chloramiphene Citrate; Citrato de clomifeno; Clomifène, citrate de; Clomifeni citras; Clomiphene Citrate *(USAN)*; Klomifeenisitraatti; Klomifen Sitrat; Klomifencitrat; Klomifén-citrát; Klomifencitrát; Klomifeno citratas; MER-41; MRL-41; NSC-35770. A mixture of the *E* and *Z* isomers of 2-[4-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate.

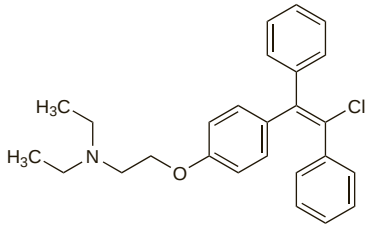
Кломифена Цитрат

$C_{26}H_{28}ClNO,C_6H_8O_7$ = 598.1.

CAS — 911-45-5 (clomifene); 15690-57-0 ((E)-clomifene); 15690-55-8 ((Z)-clomifene); 50-41-9 (clomifene citrate); 7599-79-3 ((E)-clomifene citrate); 7619-53-6 ((Z)-clomifene citrate).

ATC — G03GB02.

ATC Vet — QG03GB02.



(clomifene)

NOTE. Clomifene may be separated into its *Z*- and *E*-isomers, zuclomifene and enclomifene.

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

Ph. Eur. 6.2 (Clomifene Citrate). A white or pale yellow, crystalline powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Clomiphene Citrate). A white to pale yellow, essentially odourless powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water and in chloroform; sparingly soluble in alcohol; insoluble in ether; freely soluble in methyl alcohol.

Adverse Effects

The incidence and severity of adverse effects of clomifene citrate tend to be related to the dose used. The most commonly reported adverse effects are reversible ovarian enlargement and cyst formation, vasomotor flushes resembling menopausal symptoms, and abdominal or pelvic discomfort or pain, sometimes with nausea or vomiting. Ovarian hyperstimulation syndrome has occurred. Breast tenderness, abnormal uterine bleeding, weight gain, headache, and endometriosis have also been reported. Transient visual disturbances such as spots or flashes, after-images, and blurring of vision may occur, and there have been rare reports of cataracts and optic neuritis. Skin reactions such as allergic rashes and urticaria have occasionally been reported and reversible hair loss has been reported rarely. CNS disturbances have included convulsions, dizziness, lightheadedness, nervous tension, fatigue, vertigo, insomnia, and depression. Abnormalities in liver function tests and jaundice have sometimes been reported.

There is an increased risk of multiple births with clomifene therapy, but rarely more than twins. There is also an increased risk of ectopic pregnancy. Although there have been reports of congenital disorders such as neural tube defects or Down's syndrome in infants born to women treated with clomifene, the role of the drug in the causation of these defects has not been established and the incidence is reported to be similar to that for the general population.

Carcinogenicity. There have been a number of reports suggesting an association between drug therapy to treat infertility by stimulating ovulation and the subsequent development of ovarian cancer.[1-5] Concern has focused in particular on the use of clomifene citrate and gonadotrophins, and a study has reported an increased risk of ovarian cancer in women who had prolonged clomifene therapy (for one year or more) although not in those who received the drug for a shorter period.[6] No association between gonadotrophin therapy and ovarian cancer was noted in this study. The conclusions of this study were only tentative, since the numbers who developed ovarian cancer were small; it has been pointed out that a successfully achieved pregnancy may reduce the risk of some other cancers, and that the risks and benefits of the procedure are not easy to balance.[7] A review[8] of epidemiological and cohort studies concluded that clomifene was not associated with any increase in the risk of ovarian cancer when used for less than 12 cycles, but noted conflicting results, limitations of the data, and the need to control for infertility and nulliparity as risk factors for ovarian cancer. Further cohort[9,10] and case-control[11] studies, and pooled analyses,[12,13] have also found no association between use of clomifene and ovarian cancer.

As a matter of prudence the UK CSM has recommended that clomifene should not normally be used for more than 6 cycles.[14] However, the UK guidelines[15] on the treatment of infertility considered that the limit of 6 cycles related to one course of treatment only. In practice many women required more than one course and it was considered that benefit may be derived from use of up to 12 cycles.

1. Fishel S, Jackson P. Follicular stimulation for high tech pregnancies: are we playing it safe? *BMJ* 1989; **299:** 309–11.
2. Kulkarni R, McGarry JM. Follicular stimulation and ovarian cancer. *BMJ* 1989; **299:** 740.
3. Dietl J. Ovulation and ovarian cancer. *Lancet* 1991; **338:** 445.
4. Willemsen W, *et al.* Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993; **341:** 986–8.
5. Tewari K, *et al.* Fertility drugs and malignant germ-cell tumour of ovary in pregnancy. *Lancet* 1998; **351:** 957–8.
6. Rossing MA, *et al.* Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994; **331:** 77–6.
7. Whittemore AS. The risk of ovarian cancer after treatment for infertility. *N Engl J Med* 1994; **331:** 805–6.
8. Duckitt K, Templeton AA. Cancer in women with infertility. *Curr Opin Obstet Gynecol* 1998; **10:** 199–203.
9. Potashnik G, *et al.* Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertil Steril* 1999; **71:** 853–9.
10. Brinton LA, *et al.* Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 2004; **103:** 1194–1203.
11. Rossing MA, *et al.* A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; **160:** 1070–8.
12. Ness RB, *et al.* Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002; **155:** 217–24.
13. Kashyap S, *et al.* Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol* 2004; **103:** 785–94.
14. CSM/MCA. Clomiphene (Clomid, Serophene): possible association with ovarian cancer. *Current Problems* 1995; **21:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)
15. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence. Fertility: assessment and treatment for people with fertility problems (issued February 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/Fertility_full.pdf (accessed 30/06/08) or http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 30/06/08)

Effects on the CNS. An infertile woman had convulsions when given clomifene citrate;[1] only 5 other cases had been reported since 1963.

1. Rimmington MR, *et al.* Convulsions after clomiphene citrate. *BMJ* 1994; **309:** 512.

Effects on the eyes. As mentioned above, clomifene may cause visual disturbances, which resolve on stopping treatment. However, visual symptoms have persisted in a few cases.[1]

1. Purvin VA. Visual disturbance secondary to clomiphene citrate. *Arch Ophthalmol* 1995; **113:** 482–4.

Effects on the fetus. After reports of neural tube defects in fetuses conceived after ovulation induction, analyses of congenital defect registers and follow-up studies of clomifene use suggested that the drug might possibly be associated with an increase in risk.[1-5] However, subsequent studies reported no increased risk,[6-8] and a pooled analysis[9] of 10 epidemiological studies found no strong evidence to confirm an association. Further studies have also reported no increased risk of neural tube defects[10] or hypospadias in male offspring[11] after exposure to fertility treatment. However, another case-control study[12] did find a potential association between clomifene and neural tube defects, but noted that because of the low baseline prevalence of the malformation, the absolute risk difference would be small. It is not clear whether the underlying infertility itself affects the risk of congenital defects and whether it may confound the calculated risk associated with clomifene.[9]

1. Cornel MC, *et al.* Ovulation induction and neural tube defects. *Lancet* 1989; **i:** 1386.
2. Czeizel A. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 167.
3. Cuckle H, Wald N. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 1281.
4. Cornel MC, *et al.* Ovulation induction, in-vitro fertilisation, and neural tube defects. *Lancet* 1989; **ii:** 1530.
5. Vollset SE. Ovulation induction and neural tube defects. *Lancet* 1990; **337:** 178.
6. Mills JL, *et al.* Risk of neural tube defects in relation to maternal fertility and fertility drug use. *Lancet* 1990; **336:** 103–4.
7. Rosa F. Ovulation induction and neural tube defects. *Lancet* 1990; **336:** 1327.
8. Werler MM, *et al.* Ovulation induction and risk of neural tube defects. *Lancet* 1994; **344:** 445–6.
9. Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 1995; **64:** 936–41.
10. Whiteman D, *et al.* Reproductive factors, subfertility, and risk of neural tube defects: a case-control study based on the Oxford Record Linkage Study Register. *Am J Epidemiol* 2000; **152:** 823–8.
11. Sørensen HT, *et al.* Use of clomifene during early pregnancy and risk of hypospadias: population based case-control study. *BMJ* 2005; **330:** 126–7.
12. Wu YW, *et al.* Potential association between infertility and spinal neural tube defects in offspring. *Birth Defects Res A Clin Mol Teratol* 2006; **76:** 718–22.

Effects on mental function. Acute psychotic reactions with paranoid tendencies have occurred rarely during clomifene use.[1,2]

1. Siedentopf F, *et al.* Clomiphene citrate as a possible cause of a psychotic reaction during infertility treatment. *Hum Reprod* 1997; **12:** 706–7.
2. Oyffe I, *et al.* Clomiphene-induced psychosis. *Am J Psychiatry* 1997; **154:** 1169–70.

Precautions

Clomifene is contra-indicated in patients with liver disease or a history of liver dysfunction. It should not be used in pregnancy. Clomifene should not be used in women with uterine bleeding that is undiagnosed or caused by hormone-dependent tumours, or in patients with pre-existing mental depression or thrombophlebitis because of the risk of exacerbation. Patients should be warned of the possibility of multiple births.

Clomifene should not be given to women with ovarian cysts, except those with polycystic ovary syndrome, and the lowest doses possible should be used to minimise ovarian enlargement or cyst formation; some patients with polycystic ovary syndrome may have an exaggerated response to usual doses of clomifene. Patients should be instructed to report any abdominal or pelvic pain, distension, or weight gain, as this may indicate the presence or enlargement of ovarian cysts. They should also be evaluated for the presence of ovarian cysts before each cycle of treatment. If abnormal enlargement occurs, clomifene should not be given until the ovaries have returned to pre-treatment size, and subsequent doses should be reduced. Clomifene should be used with caution in patients with uterine fibroids, due to the potential for enlargement of the fibroids.

Treatment should be stopped if visual disturbances develop and the patient warned that this might affect their ability to drive or operate machinery. Long-term cyclic therapy is not recommended, because of the uncertainty regarding increased risk of ovarian cancer: a maximum of 6 cycles of treatment has generally been advised, but see also under Carcinogenicity, above.

Pharmacokinetics

Clomifene citrate is absorbed from the gastrointestinal tract. It is metabolised in the liver and slowly excreted via the bile. Unchanged drug and metabolites are excreted in the faeces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Enterohepatic recirculation takes place. The *E*-isomer is reported to be less well absorbed and more rapidly eliminated than the *Z*-isomer.

◊ References.

1. Szutu M, *et al.* Pharmacokinetics of intravenous clomiphene isomers. *Br J Clin Pharmacol* 1989; **27:** 639–40.

Uses and Administration

Clomifene is a nonsteroidal compound that has both oestrogenic and anti-oestrogenic properties, the latter residing principally in the *E*-isomer. Its action in stimulating ovulation is believed to be related to its anti-oestrogenic properties. It stimulates the secretion of pituitary gonadotrophic hormones, probably by blocking the negative feedback effect of oestrogens at receptor sites in the hypothalamus and pituitary.

Clomifene is the most widely used drug in the treatment of anovulatory infertility (p.2080). Therapy with clomifene will not be successful unless the woman, though anovulatory, is capable of ovulation and her partner is fertile. It is ineffective in primary pituitary or