powder. It is odourless. Practically insoluble in water; soluble in alcohol, in acetone, in ether, in methyl alcohol, in propylene glycol, and in solutions of alkali hydroxides; slightly soluble in chloroform and in fatty oils.

Profile

Dienestrol is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (p.2094). It has been used as a 0.01% cream in the treatment of menopausal atrophic vaginitis. If used on a long-term basis in women with a uterus a progestogen is required.

Dienestrol diacetate has been used as an ingredient of topical preparations for skin disorders.

Porphyria. Dienestrol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

USP 31: Dienestrol Cream.

Proprietary Preparations (details are given in Part 3)
Denm.: Sexadien†; ***USA:*** Ortho-Dienestrol.

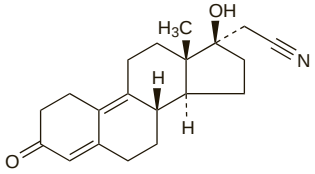
Dienogest *(BAN, USAN, rINN)*

Diénogest; Dienogesti; Dienogestum; STS-557. 17-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile.

Диеногест

$C_{20}H_{25}NO_2$ = 311.4.

CAS — 65928-58-7.



Profile

Dienogest is a nonethinylated progestogen (see Progesterone, p.2125) structurally related to nortestosterone. It is reported to have anti-androgenic properties. Dienogest is used as the progestogen component of some combined oral contraceptives (see p.2058); a typical daily dose is 2 mg. It is also used as the progestogen component in menopausal HRT (see p.2071) in a daily dose of 2 mg.

◊ Reviews.

1. Foster RH, Wilde MI. Dienogest. *Drugs* 1998; **56:** 825–33.
2. Wellington K, Perry CM. Estradiol valerate/dienogest. *Drugs* 2002; **62:** 491–504.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Jeanine.

Multi-ingredient: ***Austral.:*** Valette; ***Austria:*** Climodien; Jeanine; Lafamme; Valette; ***Belg.:*** Climodien; ***Cz.:*** Jeanine; Klimodien; ***Denm.:*** Climodien; ***Fr.:*** Climodiene; ***Ger.:*** Climodien; Lafamme; Valette; ***Gr.:*** Climodien†; ***Hung.:*** Klimodien†; ***Neth.:*** Climodien; Lafamme; ***Norw.:*** Climodien; ***Pol.:*** Jeanine; ***Port.:*** Climodien; Lafamme; Valette; ***Rus.:*** Climodien (Климодиен); Jeanine (Жанин); ***Spain:*** Climodien; Mevaren; ***Swed.:*** Climodien; ***Turk.:*** Climodien.

Diethylstilbestrol *(BAN, rINN)*

DES; Diéthylstilbestrol; Dietylstilbestrolum; Diethylstilboestrol; Dietilestilbestrol; Dietilstilbestrolis; Dietilstilbösztrol; Dietylstilbestrol; Dietyylistilbestroli; NSC-3070; Stilbestrol; Stilboestrol. (*E*)-αβ-Diethylstilbene-4-4′-diol.

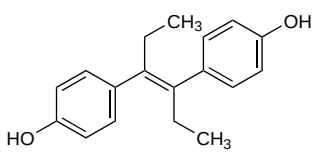
Диэтилстильбэстрол

$C_{18}H_{20}O_2$ = 268.4.

CAS — 56-53-1.

ATC — G03CB02; L02AA01.

ATC Vet — QG03CB02; QG03CC05; QL02AA01.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Diethylstilbestrol). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Diethylstilbestrol). A white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, in fatty oils, and in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Diethylstilbestrol Dipropionate *(BANM, rINNM)*

Diéthylstilbestrol, Dipropionate de; Diethylstilbestroli Dipropionas; Dipropionato de dietilestilbestrol; Stilboestrol Dipropionate. (*E*)-αβ-Diethylstilbene-4,4′-diol dipropionate.

Диэтилстильбэстрола Дипропионат

$C_{24}H_{28}O_4$ = 380.5.

CAS — 130-80-3.

ATC — G03CB02; L02AA01.

ATC Vet — QG03CB02; QL02AA01.

Adverse Effects and Precautions

Dose-related adverse effects of diethylstilbestrol include nausea, fluid retention, and arterial and venous thrombosis, and these effects are common at the doses used for palliation of cancer. Impotence and gynaecomastia occur in men, and withdrawal bleeding may occur in women, as may hypercalcaemia and bone pain in women treated for breast cancer. Diethylstilbestrol should be used with caution in those with cardiovascular disease or renal or hepatic impairment. Use of diethylstilbestrol is contra-indicated if pregnancy is suspected.

Adverse effects and precautions of oestrogens in general (steroidal compounds) are covered under Estradiol, on p.2097.

Historically, high doses of diethylstilbestrol and related substances were used for 'hormonal support' in pregnant women to try to prevent miscarriages and preterm births, most commonly in the USA. This practice was later shown to be ineffective. Adverse effects on the genito-urinary tract of offspring of these women have been noted. In particular, an increased incidence of changes in the cervix and vagina including adenosis and rarely clear-cell adenocarcinoma has been seen in postpubertal daughters of women who received diethylstilbestrol or related substances during pregnancy (see below). A possible increased incidence of abnormalities of the genital tract and of abnormal spermatozoa has been reported in male offspring similarly exposed (see below). The recipients themselves appear to be at a small increased risk of breast cancer (see below).

Carcinogenicity. ***BREAST.*** No statistically significant difference in the incidence of breast cancer was found among a group of 693 women given diethylstilbestrol during pregnancy 25 years earlier compared with a control group of 668 who were not.[1] This finding was, however, criticised[2] on the basis that the study lacked the statistical power to reject the null hypothesis. In another study[3] the incidence of breast cancer in 3033 women who had taken diethylstilbestrol in pregnancy during the period 1940 to 1960 was compared with the incidence in a comparable group of unexposed women. This study involved over 85 000 women-years of follow-up in each group and it was found that the incidence of breast cancer per 100 000 women-years was 134 in the exposed group and 93 in the unexposed group (a relative risk of 1.4). The authors concluded that in those women given diethylstilbestrol there was a moderately increased incidence of breast cancer but that some unrecognised concomitant of exposure could not be excluded as a possibility for the increase. Although this study suggested that the risk increased over time, subsequent follow-up,[4] while confirming a modest increase in risk overall, did not confirm a higher risk in these women as time went on. Further follow-up and analysis[5] of the combined data from these cohort studies[1,3,4] confirmed a modest increase in risk of breast cancer associated with diethylstilbestrol (relative risk 1.27, 95% confidence interval 1.07 to 1.52). Another large population cohort study[6] suggested that the risk of fatal breast cancer might also be increased in women who had been given diethylstilbestrol.

Two cases of breast cancer[7] in premenopausal women exposed to diethylstilbestrol *in utero* have raised the possibility that the risk of breast cancer may be increased in these women, in addition to the known genito-urinary risk (see below under Pregnancy, Effects on Female Offspring). However, a cohort study[8] involving 4536 women exposed *in utero* found no increased risk of other cancers overall, and did not show an increased risk of breast cancer (relative risk 1.18; 95% confidence intervals 0.56 to 2.49). A later study[9] of further follow-up of this cohort, plus additional data from another group, found that although the risk overall and for younger women was not increased, from the age of 40 years the risk increased to 1.91 (95% confidence interval 1.09 to 3.33). The risk appeared to increase further with greater age, but the relatively small number of cases in women aged 50 years and over made this harder to establish.

1. Bibbo M, *et al.* A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. *N Engl J Med* 1978; **298:** 763–7.
2. Clark LC, Portier KM. Diethylstilbestrol and the risk of cancer. *N Engl J Med* 1979; **300:** 263–4.
3. Greenberg ER, *et al.* Breast cancer in mothers given diethylstilbestrol in pregnancy. *N Engl J Med* 1984; **311:** 1393–8.
4. Colton T, *et al.* Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. *JAMA* 1993; **269:** 2096–2100.
5. Titus-Ernstoff L, *et al.* Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001; **84:** 126–33.
6. Calle EE, *et al.* Diethylstilbestrol and risk of fatal breast cancer in a prospective cohort of US women. *Am J Epidemiol* 1996; **144:** 645–52.
7. Huckell C, *et al.* Premenopausal breast cancer after in-utero exposure to stilboestrol. *Lancet* 1996; **348:** 331.
8. Hatch EE, *et al.* Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 1998; **280:** 630–4.
9. Palmer JR, *et al.* Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 1509–14.

GENITO-URINARY TRACT. See below under Pregnancy, Effects on Female Offspring.

KIDNEY. Renal carcinoma was associated with the long-term use of diethylstilbestrol for prostate cancer in 2 men.[1]

1. Nissenkorn I, *et al.* Oestrogen-induced renal carcinoma. *Br J Urol* 1979; **51:** 6–9.

LIVER. Hepatic angiosarcoma developed in a 76-year-old man who had received diethylstilbestrol 3 mg daily for 12 years.[1] Hepatoma developed in another elderly man who had received a similar dose for 4.5 years.[2]

1. Hoch-Ligeti C. Angiosarcoma of the liver associated with diethylstilbestrol. *JAMA* 1978; **240:** 1510–11.
2. Brooks JJ. Hepatoma associated with diethylstilbestrol therapy for prostate carcinoma. *J Urol (Baltimore)* 1982; **128:** 1044–5.

Effects on the blood. Adverse haematological effects reported with diethylstilbestrol have included severe bone-marrow changes in a 71-year-old man given diethylstilbestrol in a massive dose of 150 mg daily for 7 years[1] and fatal immune haemolytic anaemia in a 69-year-old man given weekly infusions of diethylstilbestrol 1 g for 9 weeks.[2] The latter reaction was due to an IgG antibody specific for diethylstilbestrol.

1. Anderson AL, Lynch EC. Myelodyspoietic syndrome associated with diethylstilbestrol therapy. *Arch Intern Med* 1980; **140:** 976–7.
2. Rosenfeld CS, *et al.* Diethylstilbestrol-associated hemolytic anemia with a positive direct antiglobulin test result. *Am J Med* 1989; **86:** 617–18.

Pregnancy. ***EFFECTS ON FEMALE OFFSPRING.*** The DESAD (Diethylstilbestrol and Adenosis) Project carried out by the National Cancer Institute in the USA led to several reports linking exposure to diethylstilbestrol *in utero* to adverse genital-tract effects.[1-3] It was reported that of nearly 300 young females with clear-cell adenocarcinoma of the genital tract, more than 80% had been exposed *in utero* to diethylstilbestrol-type hormones.[1] Patients had been aged 7 to 28 years at the time of diagnosis. Doses and duration of treatment varied widely; the association existed for both 1.5 mg of diethylstilbestrol daily throughout pregnancy and variable amounts for a week or more during the first trimester. Vaginal adenosis, rare in unexposed young women, was present in about a third of those exposed in the first 4 months of pregnancy, and cervical ectropion in more than two-thirds. Vaginal epithelial changes were most closely associated with early exposure to diethylstilbestrol, with the total dose, and with the duration of exposure; their incidence decreased with age. The risk of cancer in the first 25 years after exposure was small.[2] Fertility did not appear to be impaired in women who had been exposed *in utero* to diethylstilbestrol but the relative risk of an unfavourable outcome of pregnancy in such a group was 1.69. However, of the women who became pregnant, 81% of those exposed to diethylstilbestrol and 95% of control subjects had at least one full-term live birth.[3] In a review of vaginal adenosis and its association with maternal diethylstilbestrol ingestion during pregnancy[4] it was noted that the link between diethylstilbestrol and particularly the benign changes in the vagina and cervix (adenosis) seemed well established. The association between this drug and the development of genital malignancies was less clear, and the very low incidence in the prospective studies in the USA supported this concept. The problem was rare in the UK, but clinicians should be aware that it existed. Cases of vaginal adenosis in young women should be investigated and screened appropriately, and preferably referred to centres where colposcopic expertise was available. Treatment of simple vaginal adenosis should be avoided.

Later reviews[5,6] have highlighted the fact that adverse effects were still emerging in women who had been exposed to diethylstilbestrol *in utero* several decades before. The need for thorough medical screening of such women was emphasised; genital-tract examination was particularly important. It was pointed out[6] that many women exposed to diethylstilbestrol *in utero* were in the

reproductive stage of their lives and warranted special observation since a diethylstilbestrol-damaged genital tract posed a potential problem during pregnancy.[5,6] It has also been suggested, for example, that such women are at increased risk of developing pre-eclampsia.[7,8]

There has been concern about the possibility of transgenerational effects on the grandchildren of women given diethylstilbestrol during pregnancy. There has been very little reported on *female offspring of exposed women*, but there were no breast or gynaecological abnormalities found on examination of 28 daughters (over 15 years of age) of women who had been exposed *in utero* and had in many cases cervical and/or vaginal changes characteristic of diethylstilbestrol exposure.[9] Limited data from a Dutch cohort[10] of 16 284 mothers and 8934 sons suggested that the *male offspring of exposed women* may in turn be at greatly increased risk of hypospadias, although the absolute risk was small. A case-control study[11] also found an increased risk, but of a much smaller magnitude, and another cohort study[12] (including DESAD data) found no support for a greatly increased risk of hypospadias. The earlier cohort study that reported the greatly increased risk may have been affected by factors related to infertility, as the study was done in a cohort of subfertile women, about half of whom had undergone IVF.

Further information on the adverse effects of diethylstilbestrol in females exposed to the drug *in utero* can be obtained from the references listed below.[13-23] For mention of the possible increased risk of breast cancer in these women, see Carcinogenicity, above.

1. Professional and Public Relations Committee of the DESAD (Diethylstilbestrol and Adenosis) Project of the Division of Cancer Control and Rehabilitation. Exposure in utero to diethylstilbestrol and related synthetic hormones: association with vaginal and cervical cancers and other abnormalities. *JAMA* 1976; **236:** 1107–9.
2. O'Brien PC, *et al.* Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. *Obstet Gynecol* 1979; **53:** 300–8.
3. Barnes AB, *et al.* Fertility and outcome of pregnancy in women exposed in utero to diethylstilbestrol. *N Engl J Med* 1980; **302:** 609–13.
4. Emens M. Vaginal adenosis and diethylstilboestrol. *Br J Hosp Med* 1984; **31:** 42–8.
5. Anonymous. Diethylstilboestrol—effects of exposure in utero. *Drug Ther Bull* 1991; **29:** 49–50.
6. Wingfield M. The daughters of stilboestrol. *BMJ* 1991; **302:** 1414–15.
7. Mittendorf R, Williams MA. Stilboestrol exposure in utero and risk of pre-eclampsia. *Lancet* 1995; **345:** 265–6.
8. Troisi R, *et al.* Preeclampsia risk in women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2007; **110:** 113–20.
9. Kaufman RH, Adam E. Findings in female offspring of women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2002; **99:** 197–200.
10. Klip H, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. *Lancet* 2002; **359:** 1102–7.
11. Brouwers MM, *et al.* Hypospadias: a transgenerational effect of diethylstilbestrol? *Hum Reprod* 2006; **21:** 666–9.
12. Palmer JR, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology* 2005; **16:** 583–6.
13. Herbst AL, *et al.* Prenatal exposure to stilbestrol: a prospective comparison of exposed female offspring with unexposed controls. *N Engl J Med* 1975; **292:** 334–9.
14. Herbst AL, *et al.* Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. *Am J Obstet Gynecol* 1977; **128:** 43–50.
15. Kaufman RH, *et al.* Upper genital tract changes associated with in-utero exposure to diethylstilbestrol. *Am J Obstet Gynecol* 1977; **128:** 51–9.
16. Fowler WC, Edelman DA. In utero exposure to DES: evaluation and followup of 199 women. *Obstet Gynecol* 1978; **51:** 459–63.
17. Anderson B, *et al.* Development of DES-associated clear-cell carcinoma: the importance of regular screening. *Obstet Gynecol* 1979; **53:** 293–9.
18. Noller KL, *et al.* Maturation of vaginal and cervical epithelium in women exposed in utero to diethylstilbestrol (DESAD project). *Am J Obstet Gynecol* 1983; **146:** 279–85.
19. Robboy SJ, *et al.* Increased incidence of cervical and vaginal dysplasia in 3980 diethylstilbestrol-exposed young women: experience of the National Collaborative Diethylstilbestrol Adenosis Project. *JAMA* 1984; **252:** 2979–83.
20. Kaufman RH, *et al.* Upper genital tract changes and infertility in diethylstilbestrol-exposed women. *Am J Obstet Gynecol* 1986; **154:** 1312–18.
21. Melnick S, *et al.* Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix—an update. *N Engl J Med* 1987; **316:** 514–16.
22. Helmerhorst TJM, *et al.* Colposcopic findings and intraepithelial neoplasia in diethylstilbestrol-exposed offspring: the Dutch experience. *Am J Obstet Gynecol* 1989; **161:** 1191–4.
23. Giusti RM, *et al.* Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995; **122:** 778–88.

EFFECTS ON MALE OFFSPRING. The effects of exposure to diethylstilbestrol *in utero* have been studied in male offspring.[1-4] Problems in passing urine and abnormalities of the penile urethra were found to be more common in young males exposed to diethylstilbestrol *in utero* than in controls in one study.[1] In another,[2] genital tract abnormalities such as epididymal cysts, capsular induration, and defective testicles occurred in 41 of 163 diethylstilbestrol-exposed men compared with 11 of 168 controls; sperm counts and motility were also reduced in exposed males. In contrast, comparison of 828 men exposed to diethylstilbestrol *in utero* with 676 unexposed men suggested that, overall, diethylstilbestrol exposure did not result in an increased risk of genito-urinary abnormalities, infertility, or testicular cancer.[3] It was suggested that previously reported increased frequencies of such abnormalities may have resulted from a selection bias and/or from a difference in diethylstilbestrol usage. Another study[4] in 253 exposed men found that although there was an increased incidence of congenital malformations of the genitalia (18 cases compared with 5 of 241 controls), this was not associated with any decrease in fertility or impairment of sexual function. An analysis[5] of the combined data from 4 cohorts suggested that there was a small increase in the risk of infertility (relative risk 1.3, 95% confidence interval 1.0 to 1.6) in men who had been exposed to diethylstilbestrol, but that overall this was not associated with an increased likelihood of never fathering a pregnancy or live birth, and did not affect the number of pregnancies or live births. Data from these 4 cohorts was also analysed[6] for the development of cancer. The overall rates of cancer were similar to those in unexposed men and to national rates. The rate of testicular cancer was increased in men who had been exposed to diethylstilbestrol *in utero*, but this finding did not reach statistical significance and was limited to only one of the cohorts. Further follow-up will be needed as these men approach the age at which most cancers are diagnosed.

For reference to possible effects on the male *grandchildren* of women who took diethylstilbestrol (the offspring of women exposed *in utero*) see Effects on Female Offspring, above.

1. Henderson BE, *et al.* Urogenital tract abnormalities in sons of women treated with diethylstilbestrol. *Pediatrics* 1976; **58:** 505–7.
2. Anonymous. Offspring of women given DES remains under study. *JAMA* 1977; **238:** 932.
3. Leary FJ, *et al.* Males exposed in utero to diethylstilbestrol. *JAMA* 1984; **252:** 2984–9.
4. Wilcox AJ, *et al.* Fertility in men exposed prenatally to diethylstilbestrol. *N Engl J Med* 1995; **332:** 1411–16.
5. Perez KM, *et al.* National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril* 2005; **84:** 1649–56.
6. Strohsnitter WC, *et al.* Cancer risk in men exposed in utero to diethylstilbestrol. *J Natl Cancer Inst* 2001; **93:** 545–51.

Veterinary use. In the EU, the use of diethylstilbestrol or other stilbenes in veterinary medicine is banned unless prior steps are taken to ensure the treated animal and its products are not available for human or animal consumption.

Pharmacokinetics

Diethylstilbestrol is readily absorbed from the gastrointestinal tract. It is slowly metabolised in the liver and excreted in the urine and faeces, mainly as the glucuronide.

Uses and Administration

Diethylstilbestrol is a synthetic nonsteroidal oestrogen that has been used in the palliation of breast and prostate cancer.

Daily oral doses of 10 to 20 mg are occasionally used in the palliative treatment of malignant neoplasms of the breast in postmenopausal women (p.661). The usual oral dose in carcinoma of the prostate (p.671) is 1 to 3 mg daily; higher doses were formerly given. Diethylstilbestrol has also been used in the treatment of prostatic carcinoma in the form of its diphosphate salts (see Fosfestrol, p.2104).

Diethylstilbestrol has been used as pessaries in the short-term management of menopausal atrophic vaginitis.

Preparations

BP 2008: Diethylstilbestrol Pessaries; Diethylstilbestrol Tablets;
USP 31: Diethylstilbestrol Injection; Diethylstilbestrol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Novo Fosfostilben; ***Braz.:*** Destilbenol; ***Fr.:*** Distilbene; ***Irl.:*** Boestrol; ***Mex.:*** Dimeprost.

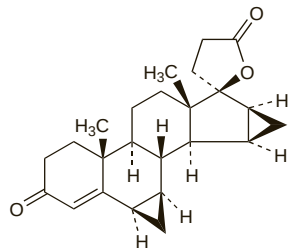
Drospirenone *(BAN, USAN, rINN)*

Dihydrospirenone; Drospirenon; Drospirenona; Drospirénone; Drospirenoni; Drospirenonum; SH-470; ZK-30595. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione.

Дроспиренон

$C_{24}H_{30}O_3$ = 366.5.

CAS — 67392-87-4.



Pharmacopoeias. In *US*.
USP 31 (Drospirenone). A white to off-white powder. Practically insoluble in water and in hexane; sparingly soluble in alcohol and in ethyl acetate; soluble in methyl alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. Drospirenone has antimineralocorticoid activity and therefore should not be used in patients at risk of hyperkalaemia, such as those with renal or hepatic impairment or adrenal insufficiency.

◊ Reviews.

1. Heinemann LAJ, Dinger J. Safety of a new oral contraceptive containing drospirenone. *Drug Safety* 2004; **27:** 1001–18.

Effects on the cardiovascular system. As with combined oral contraceptives containing other progestogens, there are reports[1-4] of thrombotic and ischaemic events in patients taking a preparation of ethinylestradiol and drospirenone. The extent of risk associated with hormonal contraceptives that contain drospirenone is mentioned under Venous Thromboembolism, p.2063.

1. Vayá A, *et al.* Transient ischaemic attack associated with the new contraceptive Yasmin. *Thromb Res* 2003; **112:** 121.
2. van Grootheest K, Vrieling T. Thromboembolism associated with the new contraceptive Yasmin. *BMJ* 2003; **326:** 257.
3. Ortí G, *et al.* Acute myocardial infarction associated with Yasmin oral contraceptive. *Clin Appl Thromb Hemost* 2007; **13:** 336–7.
4. Girolami A, *et al.* Retinal central artery occlusion in a young woman after ten days of a drospirenone-containing oral contraceptive (Yasmin). *Thromb Haemost* 2007; **98:** 473–4.

Renal impairment. US licensed product information for preparations containing drospirenone contra-indicates its use in renal impairment, and in the UK it is contra-indicated in severe impairment. A study[1] of women with renal impairment that was mild (creatinine clearance 50 to 80 mL/minute) or moderate (30 to 50 mL/min) found a trend toward increasing drospirenone exposure with decreasing creatinine clearance. Serum-potassium concentrations were not significantly altered by drospirenone, despite the concomitant use of other drugs that can also potentially increase potassium concentrations including beta blockers and ACE inhibitors.

1. Schürmann R, *et al.* Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. *J Clin Pharmacol* 2006; **46:** 867–75.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067, and Hormone Replacement Therapy, p.2076. Because drospirenone has antimineralocorticoid activity, it may potentially exacerbate the effects of drugs that can increase serum-potassium, such as ACE inhibitors, angiotensin II receptor antagonists, aldosterone antagonists, potassium-sparing diuretics, or NSAIDs. Drospirenone may also reduce blood pressure, such that antihypertensive treatment may require adjustment.

Diuretics. The pharmacokinetics of hydrochlorothiazide were not affected by the addition of drospirenone and estradiol in a placebo-controlled study of 36 hypertensive postmenopausal women.[1] However, those given the combination in this study developed lower blood pressure and higher serum-potassium concentrations, which was attributed to the antimineralocorticoid effect of drospirenone.[2] Nontheless, there were no cases of hyperkalaemia. It has been suggested that these potential antihy-