ANNEX 1
CHEMICAL AND PHYSICAL DATA AND INFORMATION ON PRODUCTION AND USE FOR OESTROGENS AND PROGESTOGENS USED IN ORAL CONTRACEPTIVES, PROGESTOGEN-ONLY CONTRACEPTIVES AND POST-MENOPAUSAL HORMONAL THERAPY

Trade names for these compounds alone and in combination with other hormonal drugs are given in Annex 2.

1. Oestrogens

1.1 Conjugated oestrogens

The term 'conjugated oestrogens' refers to mixtures of at least eight compounds, including sodium oestrone sulfate and sodium equilin sulfate, derived wholly or in part from equine urine or synthetically from oestrone and equilin. Conjugated oestrogens contain as concomitant components the sodium sulfate conjugates of 17α-dihydroequilin, 17β-dihydroequilin and 17α-oestradiol (United States Pharmacopeial Convention, 1995).

1.1.1 *Nomenclature*

Sodium oestrone sulfate

Chem. Abstr. Serv. Reg. No.: 438-67-5

Chem. Abstr. Name: 3-(Sulfooxy)-estra-1,3,5(10)-trien-17-one, sodium salt

IUPAC Systematic Name: Estrone, hydrogen sulfate sodium salt

Synonyms: Estrone sodium sulfate; estrone sulfate sodium; estrone sulfate sodium salt; oestrone sodium sulfate; oestrone sulfate sodium; oestrone sulfate sodium salt; sodium estrone sulfate; sodium estrone-3-sulfate; sodium oestrone-3-sulfate

Sodium equilin sulfate

Chem. Abstr. Serv. Reg. No.: 16680-47-0

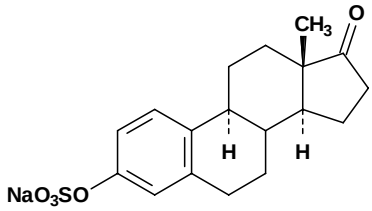
Chem. Abstr. Name: 3-(Sulfooxy)-estra-1,3,5(10),7-tetraen-17-one, sodium salt

IUPAC Systematic Name: 3-Hydroxy-estra-1,3,5(10),7-tetraen-17-one, hydrogen sulfate, sodium salt

Synonyms: Equilin, sulfate, sodium salt; equilin sodium sulfate; sodium equilin 3-monosulfate

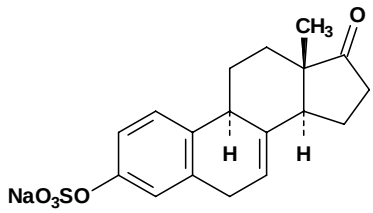
1.1.2 *Structural and molecular formulae and relative molecular mass*

Sodium oestrone sulfate



$C_{18}H_{21}O_5S.Na$ Relative molecular mass: 372.4

Sodium equilin sulfate



$C_{18}H_{19}O_5S.Na$ Relative molecular mass: 370.4

1.1.3 *Chemical and physical properties*

From Gennaro (1995)

(*a*) *Description*: Buff-coloured, odourless powder

(*b*) *Solubility*: Soluble in water

1.1.4 *Technical products and impurities*

Conjugated oestrogens contain not less than 52.5% and not more than 61.5% sodium oestrone sulfate and not less than 22.5% and not more than 30.5% sodium equilin sulfate, and the total of sodium oestrone sulfate and sodium equilin sulfate is not less than 79.5% and not more than 88.0% of the labelled content of conjugated oestrogens. Conjugated oestrogens contain as concomitant components (as sodium sulfate conjugates) not less than 13.5% and not more than 19.5% 17α-dihydroequilin, not less than 0.5% and not more than 4.0% 17β-dihydroequilin and not less than 2.5% and not more than 9.5% 17α-oestradiol, of the labelled content of conjugated oestrogens (United States Pharmacopeial Convention, 1995).

Conjugated oestrogens are available as tablets for oral administration, as an injection for parenteral administration and as a 0.0625% vaginal cream (American Hospital Formulary Service, 1997).

Conjugated oestrogens are also used in combination with several other pharmaceutical preparations, including medrogestone, medroxyprogesterone acetate and methyltestosterone (American Hospital Formulary Service, 1997; Reynolds, 1998).

Information available in 1995 indicated that conjugated oestrogens were manufactured or formulated in Argentina, Belgium, Brazil, Canada, France, India, Mexico, the Netherlands, Portugal, Switzerland and the United States (CIS Information Services, 1995).

1.1.5 *Analysis*

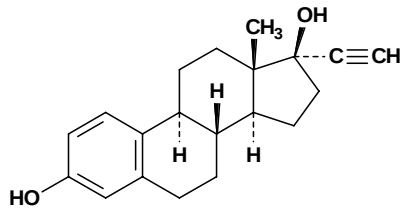
Gas chromatography with flame ionization detection is used for identification and for establishing the purity of conjugated oestrogens, their components and impurities (United States Pharmacopeial Convention, 1995).

1.2 Ethinyloestradiol

1.2.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 57-63-6
Deleted CAS Reg. No.: 77538-56-8
Chem. Abstr. Name: (17α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol
IUPAC Systematic Name: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
Synonyms: 17-Ethinyl-3,17-estradiol; 17-ethinylestradiol; 17α-ethinyl-17β-estradiol; 17α-ethynylestradiol; ethinylestradiol; 17-ethynylestradiol; ethynylestradiol; 17α-ethinylestradiol; ethynyloestradiol

1.2.2 *Structural and molecular formulae and relative molecular mass*



$C_{20}H_{24}O_2$ Relative molecular mass: 296.4

1.2.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998), unless otherwise specified

(*a*) *Description:* White to creamy- or slightly yellowish-white, odourless, crystalline powder
(*b*) *Melting-point:* 182–184°C
(*c*) *Solubility:* Practically insoluble in water; soluble in acetone (1 part in 5), ethanol (1 part in 6), chloroform (1 part in 20), dioxane (1 part in 4), diethyl ether (1 part in 4) and vegetable oils
(*d*) *Optical rotation*: $[\alpha]_D^{20}$, less than –27° to –30° (Council of Europe, 1997)

1.2.4 *Technical products and impurities*

Ethinyloestradiol is commercially available as tablets alone and in combination with progestogens, as described in the monograph on ‘Oral contraceptives, combined’.

1.2.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry and thin-layer chromatography as methods for identifying ethinyloestradiol; thin-layer chromatography, liquid chromatography, ultra-violet absorption spectrophotometry and potentiometric titration are used to assay the purity of ethinyloestradiol and to determine its content in pharmaceutical preparations (British Pharmacopoeial Commission, 1993; Secretaria de Salud, 1994, 1995; United States Pharmacopeial Convention, 1995; Schweizerischen Bundesrat, 1996; Council of Europe, 1997).

1.3 Mestranol

1.3.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 72-33-3

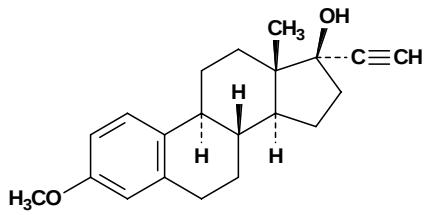
Deleted CAS Reg. No.: 43085-54-7; 53445-46-8

Chem. Abstr. Name: (17α)-3-Methoxy-19-norpregna-1,3,5(10)-trien-20-yn-17-ol

IUPAC Systematic Name: 3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol

Synonyms: Ethinylestradiol 3-methyl ether; 17α-ethinylestradiol 3-methyl ether; ethinyloestradiol 3-methyl ether; 17α-ethinyloestradiol 3-methyl ether; ethynylestradiol methyl ether; ethynylestradiol 3-methyl ether; 17-ethynylestradiol 3-methyl ether; 17α-ethynylestradiol 3-methyl ether; 17α-ethynylestradiol methyl ether; ethynyloestradiol methyl ether; ethynyloestradiol 3-methyl ether; 17-ethynyloestradiol 3-methyl ether; 17α-ethynyloestradiol 3-methyl ether; 17α-ethynyloestradiol methyl ether; 3-methoxy-17α-ethinylestradiol; 3-methoxy-17α-ethinyloestradiol; 3-methoxy-17α-ethynylestradiol; 3-methoxyethynylestradiol; 3-methoxy-17α-ethynyloestradiol; 3-methoxyethynyloestradiol; 3-methylethynylestradiol; 3-*O*-methylethynylestradiol; 3-methylethynyloestradiol; 3-*O*-methylethynyloestradiol; Δ-MVE

1.3.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{26}O_2$ Relative molecular mass: 310.4

1.3.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White to creamy-white, odourless, crystalline powder

(*b*) *Melting-point*: 150–151°C

(*c*) *Solubility*: Practically insoluble in water; sparingly soluble in ethanol; slightly soluble in methanol; soluble in acetone, dioxane and diethyl ether; freely soluble in chloroform

1.3.4 *Technical products and impurities*

Mestranol is commercially available as a component of combination tablets with norethisterone, chlormadinone acetate, norethisterone, ethynodiol diacetate, lynoestrenol or norethynodrel (Reynolds, 1998; see the monograph on 'Oral contraceptives, combined' and Annex 2).

1.3.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards as methods for identifying mestranol; ultra-violet absorption spectrophotometry and potentiometric titration with sodium hydroxide are used to assay its purity. Mestranol is identified in pharmaceutical preparations by thin-layer chromatography; liquid chromatography is used to assay for mestranol content (British Pharmacopoeial Commission, 1988; Secretaria de Salud, 1994; United States Pharmacopeial Convention, 1995; Schweizerischen Bundesrat, 1996; Society of Japanese Pharmacopoeia, 1996; Council of Europe, 1997).

1.4 Oestradiol

1.4.1 *Nomenclature*

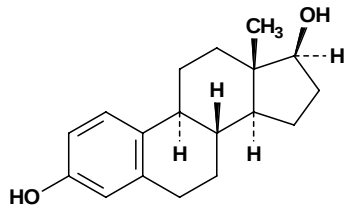
Chem. Abstr. Serv. Reg. No.: 50-28-2

Chem. Abstr. Name: (17β)-Estra-1,3,5(10)-triene-3,17-diol

IUPAC Systematic Name: Estra-1,3,5(10)-triene-3,17β-diol

Synonyms: Dihydrofollicular hormone; dihydrofolliculin; dihydromenformon; dihydrotheelin; dihydroxyestrin; 3,17β-dihydroxyestra-1,3,5(10)-triene; 3,17-epidihydroxyestratriene; β-estradiol; 17β-estradiol; 3,17β-estradiol; (d)-3,17β-estradiol; oestradiol-17β; 17β-oestradiol

1.4.2 *Structural and molecular formulae and relative molecular mass*



$C_{18}H_{24}O_2$ Relative molecular mass: 272.4

1.4.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White or creamy-white, odourless, crystalline powder

(*b*) *Melting-point*: 173–179°C

(*c*) *Solubility*: Practically insoluble in water; soluble in ethanol (1 part in 28), chloroform (1 part in 435), diethyl ether (1 part in 150), acetone and dioxane

(*d*) *Optical rotation*: $[\alpha]_D^{25}$, +76° to +83°

Oestradiol hemihydrate is a white crystalline powder: it is practically insoluble in water, soluble in ethanol and acetone and slightly soluble in dichloromethane and diethyl ether. Approximately 1.03 g of oestradiol hemihydrate are equivalent to 1 g of the anhydrous substance (Reynolds, 1998).

1.4.4 *Technical products and impurities*

Oestradiol is commercially available as micronized tablets, as topical transdermal patches, as a vaginal cream and as an extended-release vaginal insert (ring) (United States Food & Drug Administration, 1996; American Hospital Formulary Service, 1997).

1.5 Oestradiol benzoate

1.5.1 *Nomenclature*

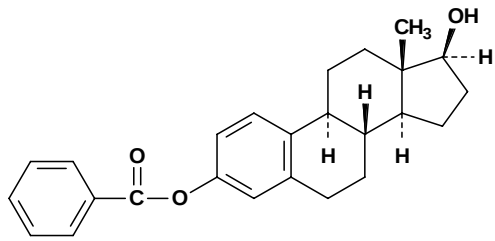
Chem. Abstr. Serv. Reg. No.: 50-50-0

Chem. Abstr. Name: (17β)-Estra-1,3,5(10)-triene-3,17-diol, 3-benzoate

IUPAC Systematic Name: Estradiol, 3-benzoate

Synonyms: Estradiol benzoate; β-estradiol benzoate; β-estradiol 3-benzoate; 17β-estradiol benzoate; 17β-estradiol 3-benzoate; estradiol monobenzoate; 1,3,5(10)-estratriene-3,17β-diol 3-benzoate; β-oestradiol benzoate; β-oestradiol 3 benzoate; 17β-oestradiol benzoate; 17β-oestradiol 3-benzoate; oestradiol monobenzoate; 1,3,5(10)-oestratriene-3,17β-diol 3-benzoate

1.5.2 *Structural and molecular formulae and relative molecular mass*



$C_{25}H_{28}O_3$ Relative molecular mass: 376.5

1.5.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1996)

(*a*) *Description*: White crystalline powder

(*b*) *Melting-point*: 191–196°C

(*c*) *Solubility*: Practically insoluble in water; slightly soluble in ethanol and diethyl ether; and sparingly soluble in acetone and vegetable oils

(*d*) *Optical rotation*: $[\alpha]_D^{25}$, +58° to +63°

1.5.4 *Technical products and impurities*

Oestradiol benzoate is commercially available as an injection (oily or aqueous suspension) and as implants (British Pharmacopoeial Commission, 1993; Society of Japanese Pharmacopoeia, 1996).

1.6 Oestradiol cypionate

1.6.1 *Nomenclature*

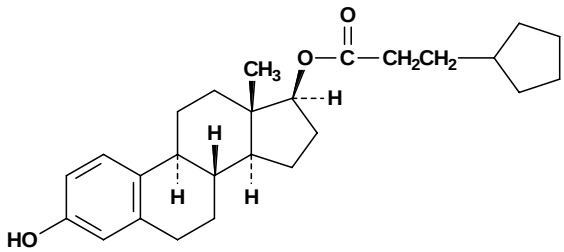
Chem. Abstr. Serv. Reg. No.: 313-06-4

Chem. Abstr. Name: (17β)-Estra-1,3,5(10)-triene-3,17-diol, 17-cyclopentanepropanoate

IUPAC Systematic Name: Oestradiol, 17-cyclopentanepropionate

Synonyms: Cyclopentanepropionic acid, 17-ester with oestradiol; cyclopentanepropionic acid, 3-hydroxyestra-1,3,5(10)-trien-17β-yl ester; depo-estradiol cyclopentylpropionate; depoestradiol cypionate; estradiol 17β-cyclopentanepropionate; estradiol cyclopentylpropionate; estradiol 17-cyclopentylpropionate; estradiol 17β-cyclopentylpropionate; 17β-estradiol 17-cyclopentylpropionate; estradiol cypionate; estradiol 17-cypionate; estradiol 17β-cypionate

1.6.2 *Structural and molecular formulae and relative molecular mass*



$C_{26}H_{36}O_3$ Relative molecular mass: 396.6

1.6.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1996)

(*a*) *Description*: White, odourless crystalline powder

(*b*) *Melting-point*: 151–152°C

(*c*) *Solubility*: Practically insoluble in water; soluble in ethanol (1 part in 40), chloroform (1 in 7), diethyl ether (1 in 2800), acetone and dioxane

(*d*) *Optical rotation*: $[\alpha]_D^{25}$, +45°

1.6.4 *Technical products and impurities*

Oestradiol cypionate is commercially available as injectable suspensions in oil for parenteral administration (United States Food & Drug Administration, 1996; American Hospital Formulary Service, 1997).

1.7 Oestradiol valerate

1.7.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 979-32-8

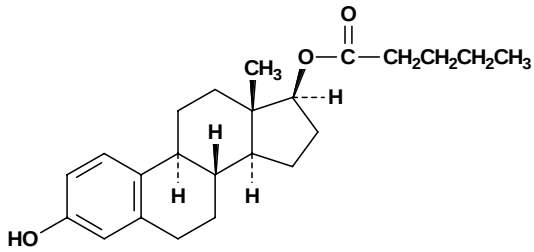
Deleted CAS Nos.: 907-12-0; 69557-95-5

Chem. Abstr. Name: (17β)-Estra-1,3,5(10)-triene-3,17-diol, 17-pentanoate

IUPAC Systematic Name: Estradiol 17-valerate

Synonyms: Oestradiol valerate; estradiol 17β-valerate; estradiol valerianate; estra-1,3,5(10)-triene-3,17β-diol 17-valerate; 3-hydroxy-17β-valeroyloxyestra-1,3,5(10)-triene

1.7.2 *Structural and molecular formulae and relative molecular mass*



$C_{23}H_{32}O_3$ Relative molecular mass: 356.5

1.7.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1996)

(*a*) *Description*: White, crystalline, odourless powder

(*b*) *Melting-point*: 144–145°C

(*c*) *Solubility*: Practically insoluble in water; soluble in benzyl benzoate, dioxane, methanol and castor oil; sparingly soluble in arachis oil and sesame oil

1.7.4 *Technical products and impurities*

Oestradiol valerate is commercially available as injectable suspensions in oil for parenteral administration; it is also commercially available as tablets alone or in combination with progestogens (Reynolds, 1996; United States Food & Drug Administration, 1996; American Hospital Formulary Service, 1997; Editions du Vidal, 1997).

Other esters of oestradiol that have been reported and that may have been used as pharmaceuticals include oestradiol 17β-acetate 3-benzoate, oestradiol 3,17β-dipropionate, oestradiol 3,17β-diundecylenate, oestradiol 17β-oenanthate, oestradiol 17β-hexahydrobenzoate, oestradiol 17β-phenylpropionate, oestradiol 17β-stearate, oestradiol 17β-undecylate and polyoestradiol phosphate.

1.7.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards and thin-layer chromatography as

methods for identifying oestradiol and its hemihydrate; ultra-violet absorption and liquid chromatography are used to assay its purity. Oestradiol in vaginal creams and tablets is identified by thin-layer chromatography; liquid chromatography is used to assay the oestradiol content of these preparations. Oestradiol in pellets and sterile suspensions is identified by infra-red spectroscopy with comparison to standards; ultra-violet absorption spectrophotometry is used to assay the oestradiol content. Methods for identifying oestradiol benzoate include infra-red absorption spectrophotometry with comparison to standards, fluorescence and thin-layer chromatography. Ultra-violet absorption spectrophotometry, thin-layer chromatography and liquid chromatography are used to assay its purity. Methods for identifying oestradiol cypionate include infra-red and ultra-violet absorption spectroscopy with comparison to standards; high-pressure liquid chromatography is used to assay its purity. Oestradiol valerate is identified in pharmaceutical preparations by infra-red absorption spectroscopy with comparison to standards, and liquid chromatography is used to assay the oestradiol valerate content (British Pharmacopoeial Commission, 1988, 1993; United States Pharmacopeial Convention, 1995; Society of the Japanese Pharmacopoeia, 1996; Council of Europe, 1997).

1.8 Oestriol

1.8.1 *Nomenclature*

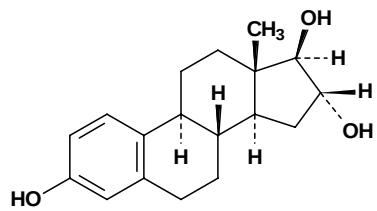
Chem. Abstr. Serv. Reg. No.: 50-27-1

Chem. Abstr. Name: (16α,17β)-Estra-1,3,5(10)-triene-3,16,17-triol

IUPAC Systematic Name: Estriol

Synonyms: Estra-1,3,5(10)-triene-3,16α,17β-triol; estratriol; 16α-estriol; 16α,17β-estriol; 3,16α,17β-estriol; follicular hormone hydrate; 16α-hydroxyestradiol; 3,16α,17β-trihydroxyestra-1,3,5(10)-triene; trihydroxyestrin

1.8.2 *Structural and molecular formulae and relative molecular mass*



$C_{18}H_{24}O_3$ Relative molecular mass: 288.4

1.8.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White, odourless, crystalline powder

(*b*) *Melting-point*: 282°C

(*c*) *Solubility*: Practically insoluble in water; sparingly soluble in ethanol; soluble in acetone, chloroform, dioxane, diethyl ether and vegetable oils

(*d*) *Specific rotation*: $[\alpha]_D^{25}$, +58°

1.8.4 *Technical products and impurities*

Oestriol is commercially available as tablets and as a cream. Sodium succinate and succinate salts of oestriol are also available (Morant & Ruppanner, 1991; Thomas, 1997).

1.8.5 *Analysis*

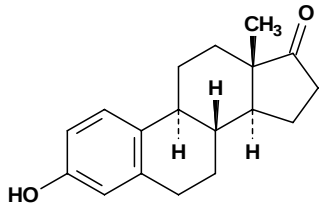
The Japanese and United States pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards as methods for identifying oestriol; ultra-violet absorption spectrophotometry, thin-layer chromatography and liquid chromatography are used to assay its purity (United States Pharmacopeial Convention, 1995; Society of Japanese Pharmacopoeia, 1996).

1.9 Oestrone

1.9.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 53-16-7
Deleted CAS Reg. No.: 37242-41-4
Chem. Abstr. Name: 3-Hydroxyestra-1,3,5(10)-trien-17-one
IUPAC Systematic Name: 3-Hydroxyestra-1,2,5(10)-triene-17-one
Synonyms: d-Estrone; d-oestrone

1.9.2 *Structural and molecular formulae and relative molecular mass*



$C_{18}H_{22}O_2$ Relative molecular mass: 270.4

1.9.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White to creamy-white, crystalline powder
(*b*) *Melting-point*: 254.5–256°C
(*c*) *Solubility*: Practically insoluble in water (0.003 g/100 mL at 25°C); soluble in ethanol (1 in 250), chloroform (1 in 110 at 15°C), acetone (1 in 50 at 50°C), dioxane and vegetable oils; slightly soluble in diethyl ether and solutions of alkali hydroxides
(*d*) *Specific rotation*: $[\alpha]_D^{22}$, +152°

1.9.4 *Technical products and impurities*

Oestrone is commercially available as pessaries and as a sterile suspension in water or 0.9% sodium chloride for injection. Oestrone benzoate and oestrone sodium sulfate are also available (Thomas, 1991; Gennaro, 1995; American Hospital Formulary Service, 1997).

1.9.5 *Analysis*

The United States Pharmacopeia specifies infra-red and ultra-violet absorption spectrophotometry with comparison to standards and thin-layer chromatography as methods for identifying oestrone; liquid chromatography is used to assay the purity of oestrone and to determine its content in pharmaceutical preparations (United States Pharmacopeial Convention, 1995).

1.10 Oestropipate

1.10.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 7280-37-7

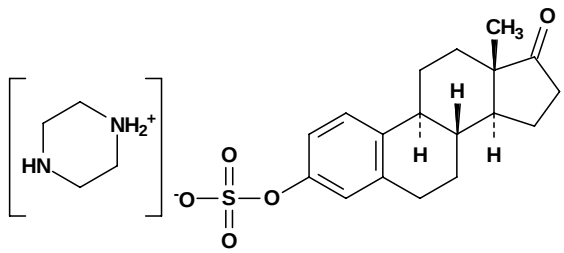
Deleted CAS No.: 29080-16-8

Chem. Abstr. Name: 3-(Sulfooxy)-estra-1,3,5(10)-trien-17-one, compd. with piperazine (1:1)

IUPAC Systematic Name: Estrone, hydrogen sulfate, compd. with piperazine (1:1)

Synonyms: Piperazine estrone sulfate; piperazine oestrone sulfate; 3-sulfatoxyestra-1,3,5(10)-trien-17-one piperazine salt; 3-sulfatoxyoestra-1,3,5(10)-trien-17-one piperazine salt

1.10.2 *Structural and molecular formulae and relative molecular mass*



$C_{22}H_{32}N_2O_5S$ Relative molecular mass: 436.6

1.10.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White to yellowish-white, odourless, fine crystalline powder

(*b*) *Melting-point*: 190°C; solidifies on further heating and decomposes at 245°C

(*c*) *Solubility*: Very slightly soluble in water, ethanol, chloroform and diethyl ether; soluble in warm water and warm ethanol (1 part in 500)

(*d*) *Optical rotation*: $[\alpha]_D^{25}$, +87.8°

1.10.4 *Technical products and impurities*

Oestropipate is available as tablets and as a vaginal cream (Gennaro, 1995; American Hospital Formulary Service, 1997). Information available in 1996 indicated that it was manufactured or formulated in the United Kingdom and the United States (Reynolds, 1996).

1.10.5 *Analysis*

Methods for the identification of oestropipate include infra-red absorption with comparison to standards and thin-layer chromatography; liquid chromatography and high-pressure liquid chromatography are used to assay its purity (United States Pharmacopeial Convention, 1995).

1.11 Production and use

1.11.1 *Production*

Oestrogens are either isolated from the urine of pregnant mares (conjugated and esterified oestrogens) or synthesized. The synthesis of ethinyloestradiol was first reported in 1938 by treatment of oestrone with potassium acetylide in liquid ammonia. It is believed to be produced commercially by the same method (Sittig, 1988). It was produced in the United States between 1945 and 1955 (United States Tariff Commission, 1947, 1956). Information available in 1995 indicated that ethinyloestradiol was manufactured or formulated in Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, India, Italy, Japan, Mexico, the Netherlands, Norway, Poland, Portugal, South Africa, Spain, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

The first synthesis of mestranol was reported in 1954 (Sittig, 1988). Commercial production in the United Kingdom was first reported in 1955. It was first marketed in Japan in 1960 (IARC, 1979). Mestranol is prepared by converting oestrone to its 3-methoxy analogue by reaction with methyl sulfate. The ethinyl group may then be introduced at position 17, either by reaction with sodium acetylide in liquid ammonia followed by hydrolysis or through a Grignard reaction with ethynyl bromide (Sittig, 1988; Gennaro, 1995). Information available in 1995 indicated that mestranol was manufactured or formulated in Argentina, Australia, Belgium, Brazil, Canada, Denmark, Germany, India, Japan, Mexico, New Zealand, South Africa, Spain, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

The countries in which oestrogens used in oestrogen replacement therapy are manufactured and/or formulated are listed in Table 1.

1.11.2 *Use*

Conjugated oestrogens, oestradiol and its semisynthetic esters, especially oestradiol valerate, are used mainly in the treatment of menopausal disorders and for the prevention and treatment of osteoporosis; they have been proposed for use in the prevention of cardiovascular diseases (Sullivan & Fowlkes, 1996) and of Alzheimer disease (Paganini-Hill & Henderson, 1994). Conjugated oestrogens are usually administered orally in a dose of

Table 1. Countries in which oestrogens used in oestrogen replacement therapy are manufactured or formulated

Country	Oestradiol	Oestradiol benzoate	Oestradiol valerate	Oestradiol oenanthate	Oestrone	Oestrone sulfate	Oestriol
Argentina	X	X	X	X			X
Australia	X	X	X		X	X	X
Austria	X		X				X
Belgium	X	X	X				X
Brazil	X	X	X	X		X	X
Canada	X	X	X	X	X		
Denmark	X	X	X				X
Finland	X		X			X	X
France	X	X	X		X		X
Germany	X	X	X		X	X	X
India		X					
Italy	X	X					
Japan	X	X	X				X
Mexico	X	X	X	X			X
Netherlands	X	X	X				X
New Zealand	X	X	X				
Poland		X					
Portugal	X	X		X			X
South Africa	X	X	X		X		X
Spain	X	X	X	X	X	X	X
Sweden	X	X					X
Switzerland	X	X	X		X		X
United Kingdom	X	X	X		X		X
United States	X	X	X				

From CIS Information Services (1995)

0.3–1.25 mg/day and have been used extensively in the United Kingdom and the United States for the treatment of climacteric symptoms. In Europe, micronized oestradiol and oestradiol valerate are the most popular preparations used in post-menopausal oestrogen therapy. Oestropipate at a dose of 0.75–3 mg per day has also been used (Ellerington *et al.*, 1992; American Hospital Formulary Service, 1997; British Medical Association, 1997).

Oestradiol is the main naturally occurring oestrogen. It is given in the form of oestradiol or one of its semisynthetic esters in cases of oestrogen deficiency, such as primary and secondary amenorrhoea, and in the menopause (Reynolds, 1996).

Oestradiol can be administered via a percutaneous patch in which the dose of hormone absorbed can be regulated by the surface area of the patch (Corson, 1993; Birkhäuser & Haenggi, 1994; Judd, 1994; Gordon, 1995). Patches are available that deliver oestradiol at a dose of 25, 37.7, 50, 75 or 100 μg daily. The patches should be changed once or twice weekly. Oestradiol can also be administered in the form of a gel applied directly to the skin (American Hospital Formulary Service, 1997; British Medical Association, 1997).

The metabolic products of oestradiol, oestrone and oestriol, are also used in clinical practice. Oestrone is a less potent oestrogen, but it is metabolized back to oestradiol (Williams & Stancel, 1996). It is administered orally, mainly as the sulfate. Oestriol is a weak oestrogen, with mainly local effects. It is used in vaginal creams and vaginal suppositories at a daily dose of 0.5–1 mg in the treatment of urogenital symptoms in women in whom systemic effects should be avoided (Reynolds, 1996; American Hospital Formulary Service, 1997; Editions du Vidal, 1997).

Ethinyloestradiol is used most extensively in oral contraceptives in combination with a progestogen. Other indications include peri-menopausal symptoms, hormonal therapy for hypogonadal women, treatment of post-partum breast engorgement and dysfunctional uterine bleeding and therapy for carcinoma of the breast and prostate. It is also used in conjunction with progestogens for the treatment of post-menopausal symptoms. Ethinyloestradiol is also used in conjunction with a progestogen as a post-coital contraceptive (Gennaro, 1995; Reynolds, 1996; Hatcher *et al.*, 1997).

Mestranol is an effective oestrogen for the typical uses of oestrogens, but it is marketed only in combination regimens typically containing 0.05 mg mestranol (Reynolds, 1996). Other indications for use of mestranol combined with a progestogen are in the treatment of dysmenorrhoea and menorrhagia, to produce cyclic withdrawal bleeding, in the treatment of pre-menstrual tension, amenorrhoea and idiopathic infertility, for emergency control of dysfunctional uterine bleeding, for endometriosis or to delay menstruation (Gennaro, 1995). Mestranol is also used with a progestogen to treat menopausal symptoms and for the prevention and treatment of osteoporosis (British Medical Association, 1997).

1.12 Regulations and guidelines

The only guidelines that could be found for use of oestrogens are those in national and international pharmacopoeias (Secretaria de Salud, 1994, 1995; United States Pharmacopeial Convention, 1995; Reynolds, 1996; Society of Japanese Pharmacopoeia, 1996; Council of Europe, 1997; Reynolds, 1998; Swiss Pharmaceutical Society, 1998).

2. Progestogens

2.1 Chlormadinone acetate

2.1.1 *Nomenclature*

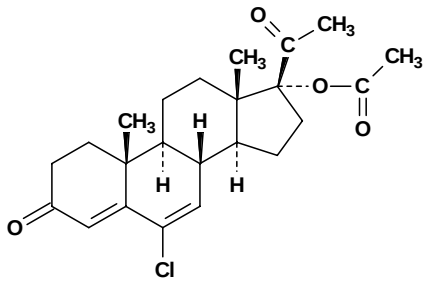
Chem. Abstr. Serv. Reg. No.: 302-22-7

Chem. Abstr. Name: 17-(Acetyloxy)-6-chloropregna-4,6-diene-3,20-dione

IUPAC Systematic Name: 6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione, acetate

Synonyms: 17α-Acetoxy-6-chloro-4,6-pregnadiene-3,20-dione; 6-chloro-Δ^6-17-acetoxyprogesterone; 6-chloro-Δ^6-[17α]acetoxyprogesterone

2.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{23}H_{29}ClO_4$ Relative molecular mass: 404.9

2.1.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Society of Japanese Pharmacopoeia (1996)

(*a*) *Description*: White to light-yellow, odourless crystals

(*b*) *Melting-point*: 212–214°C

(*c*) *Solubility*: Practically insoluble in water; very soluble in chloroform; soluble in acetonitrile; slightly soluble in ethanol and diethyl ether

(*d*) *Optical rotation*: $[\alpha]_D^{20}$, –10.0° to –14.0°

2.1.4 *Technical products and impurities*

Trade names for pharmaceutical preparations of chlormadinone acetate include Gestafortin and Luteran (Reynolds, 1996).

2.1.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards and liquid chromatography as methods for identifying chlormadinone acetate; liquid chromatography and ultra-violet absorption spectrophotometry are used to assay its purity (Secretaria de Salud, 1994, 1995; Society of Japanese Pharmacopoeia, 1996).

2.1.6 *Production and use*

Chlormadinone acetate does not occur naturally. Its synthesis was first reported in 1960, by the treatment of 17α-acetoxyprogesterone with ethyl orthoformate in the presence of an acid catalyst to produce the 3-enol ether of the corresponding 3,5-dione; conversion of this enol ether to 6-chloro-17α-acetoxyprogesterone with *N*-chlorosuccinimide is followed by dehydrogenation with chloranil (Brückner *et al*., 1961).

Information available in 1995 indicated that chlormadinone acetate was manufactured or formulated in Argentina, Austria, France, Germany, Japan, Mexico and Switzerland (CIS Information Services, 1995).

Chlormadinone acetate has not been used in the United States since 1970, when the only product (an oral contraceptive) was removed from the market. Its use in the United Kingdom was suspended in the same year. Before suspension, chlormadinone acetate was used in oral contraceptives either together with mestranol as a 'sequential' contraceptive or as a 'progestogen only' oral contraceptive (IARC, 1979). Chlormadinone acetate has been used (frequently in combination with mestranol) for treatment of threatened abortion (Notter & Durand, 1969) and dysmenorrhoea (Roland *et al.*, 1966).

2.2 Cyproterone acetate

2.2.1 *Nomenclature*

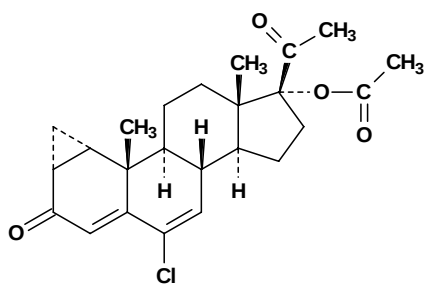
Chem. Abstr. Serv. Reg. No.: 427-51-0

Chem. Abstr. Name: (1β,2β)-17-(Acetyloxy)-6-chloro-1,2-dihydro-3′H-cyclopropa-[1,2]pregna-1,4,6-triene-3,20-dione

IUPAC Systematic Name: 6-Chloro-1β,2β-dihydro-17-hydroxy-3′H-cyclopropa[1,2]-pregna-1,4,6-triene-3,20-dione acetate

Synonyms: Cyproterone 17-*O*-acetate; cyproterone 17α-acetate; 1,2α-methylene-6-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione; 1,2α-methylene-6-chloro-$\Delta^{4,6}$-pregnadien-17α-ol-3,20-dione acetate; 1,2α-methylene-6-chloro-pregna-4,6-diene-3,20-dione 17α-acetate; methylene-6-chloro-17-hydroxy-1α,2α-pregna-4,6-diene-3,20-dione acetate

2.2.2 *Structural and molecular formulae and relative molecular mass*



$C_{24}H_{29}ClO_4$ Relative molecular mass: 416.9

2.2.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Council of Europe (1997)

(*a*) *Description:* White crystalline powder

(*b*) *Melting-point:* 200–201°C

(*c*) *Solubility*: Practically insoluble in water; very soluble in dichloromethane and acetone; soluble in methanol; sparingly soluble in ethanol

(*d*) *Specific rotation*: $[\alpha]_D^{20}$, +152° to +157°

2.2.4 *Technical products and impurities*

Cyproterone acetate is commercially available as tablets and as an injectable solution (Organizzazione Editoriale Medico Farmaceutica, 1995; British Medical Association, 1997).

2.2.5 *Analysis*

The European Pharmacopoeia specifies infra-red absorption spectrophotometry and thin-layer chromatography as methods for identifying cyproterone acetate; liquid chromatography and ultra-violet absorption spectrophotometry are used to assay its purity (Council of Europe, 1997).

2.2.6 *Production and use*

Cyproterone acetate does not occur naturally. No information was available on its synthesis. Information available in 1995 indicated that its was manufactured or formulated in Argentina, Australia, Austria, Belgium, Brazil, Canada, Finland, France, Germany, Japan, Mexico, New Zealand, South Africa, Spain, Switzerland and the United Kingdom (CIS Information Services, 1995).

Cyproterone acetate has a strong gonadotrophin-inhibiting effect and has clinical use as an anti-androgen for the treatment of hyperandrogenic disorders such as hirsutism, acne and seborrhoea in women. It is used as an oral contraceptive in combination with ethinyloestradiol. It is given in combination with oestradiol valerate to women over 35 up to the climacteric because its effects on the coagulation system are minimal (Hirvonen *et al*., 1988; Reynolds, 1996). Cyproterone acetate is also used in the treatment of prostate cancer and hypersexuality disorders (Cooper, 1986; Neumann & Topert, 1986; Namer, 1988) and is being investigated as a means of oral contraception in men (Moltz *et al*., 1980; Wang & Yeung, 1980; Meriggiola *et al*., 1996). In some European countries, cyproterone acetate is used in sequential preparations with oestradiol valerate in the treatment of climacteric complaints (Editions du Vidal, 1997).

2.3 Desogestrel

2.3.1 *Nomenclature*

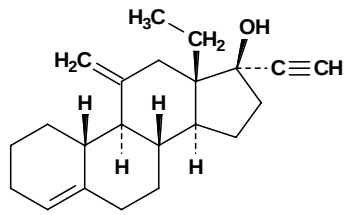
Chem. Abstr. Serv. Reg. No.: 54024-22-5

Chem. Abstr. Name: (17α)-13-Ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol

IUPAC Systematic Name: 13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol

Synonyms: 13-Ethyl-11-methylene-18,19-dinor-17α-4-pregnen-20-yn-17-ol; 17α-ethynyl-18-methyl-11-methylene-Δ^4-oestren-17β-ol

2.3.2 *Structural and molecular formulae and relative molecular mass*



$C_{22}H_{30}O$ Relative molecular mass: 310.5

2.3.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and British Pharmacopoeial Commission (1997)

(*a*) *Description*: White crystalline powder

(*b*) *Melting-point*: 109–110°C

(*c*) *Solubility*: Practically insoluble in water; slightly soluble in ethanol and ethyl acetate; sparingly soluble in *n*-hexane

(*d*) *Optical rotation*: $[\alpha]_D^{20}$, +53° to +57°

2.3.4 *Technical products and impurities*

Desogestrel is commercially available only in combination with ethinyloestradiol (Reynolds, 1996; American Hospital Formulary Service, 1997; British Medical Association, 1997; Editions du Vidal, 1997; LINFO Läkemedelsinformation AB, 1997; Reynolds, 1998).

2.3.5 *Analysis*

The British Pharmacopoeia specifies infra-red absorption spectrophotometry and thin-layer chromatography as methods for identifying desogestrel; liquid chromatography is used to assay its purity (British Pharmacopoeial Commission, 1997).

2.3.6 *Production and use*

Desogestrel does not occur naturally. It is produced by adding a solution of 11,11-methylene-18-methyl-Δ^4-oestren-17-one in tetrahydrofuran to potassium acetylide solution in tetrahydrofuran and acidified (Sittig, 1988).

Information available in 1995 indicated that desogestrel was manufactured or formulated in Argentina, Australia, Belgium, Brazil, Canada, France, Germany, India, Mexico, the Netherlands, South Africa, Spain, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

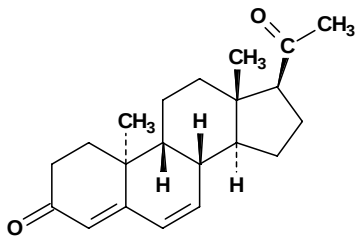
Desogestrel is a synthetic progestogen structurally related to levonorgestrel, with actions and uses similar to those of progestogens in general. It is reported to have potent progestogenic activity and little or no androgenic activity. It is used as the progestogenic component of combined mono- and multiphasic oral contraceptive preparations and as a subdermal implantable 'progestogen-only' contraceptive. A typical daily dose in combined oral contraceptives is 150 μg (Reynolds, 1997) with 30 μg ethinyloestradiol (Williams & Stancel, 1996; Editions du Vidal, 1997).

2.4 Dydrogesterone

2.4.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 152-62-5
Chem. Abstr. Name: (9β,10α)-Pregna-4,6-diene-3,20-dione
IUPAC Systematic Name: 10α-Pregna-4,6-diene-3,20-dione
Synonyms: 10α-Isopregnenone; dehydro-retroprogesterone; dehydroprogesterone

2.4.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{28}O_2$ Relative molecular mass: 312.5

2.4.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1996)

(*a*) *Description*: White to off-white, odourless, crystalline powder
(*b*) *Melting-point*: 169–170°C
(*c*) *Solubility*: Practically insoluble in water; soluble in acetone, chloroform (1 in 2), ethanol (1 in 40) and diethyl ether (1 in 200); slightly soluble in fixed oils; sparingly soluble in methanol
(*d*) *Specific rotation*: $[\alpha]_D^{25}$, –484.5° (in chloroform)

2.4.4 *Technical products and impurities*

Trade names for pharmaceutical preparations containing dydrogesterone are listed in Annex 2 (Table 5).

2.4.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards as methods for identifying dydroges-

terone; ultra-violet absorption spectrophotometry and liquid chromatography are used to assay its purity. Dydrogesterone is identified in pharmaceutical preparations by infra-red and ultra-violet absorption spectrophotometry; ultra-violet absorption spectrophotometry and liquid chromatography are used to assay for dydrogesterone content (British Pharmacopoeial Commission,1988; United States Pharmacopeial Convention, 1990).

2.4.6 *Production and use*

Dydrogesterone does not occur naturally. It is believed to be prepared commercially from lumisterol (9β,10α-ergosta-5,7,22-trien-3β-ol derived from ultra-violet-irradiated ergosterol) via a multistep synthesis involving oxidation, isomerization, lithium reduction, ozonolysis of the side-chain and a final zinc reduction (Budavari, 1996).

In hormonal therapy, dydrogesterone is used at doses of 10–20 mg per day for 10–14 days per cycle. Together with cyclic or continuous oestrogen, it gives effective cycle control and good protection of the endometrium. It does not inhibit secretion of follicle-stimulating hormone and does not increase basal body temperature (Reynolds, 1996; British Medical Association, 1997; Crook *et al.*, 1997).

2.5 Ethynodiol diacetate

2.5.1 *Nomenclature*

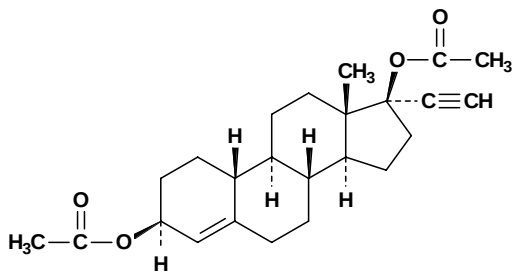
Chem. Abstr. Serv. Reg. No.: 297-76-7

Chem. Abstr. Name: (3β,17α)-19-Norpregn-4-en-20-yne-3,17-diol, diacetate

IUPAC Systematic Name: 19-Nor-17α-pregn-4-en-20-yne-3β,17β-diol, diacetate

Synonyms: Ethinodiol diacetate; ethynodiol acetate; β-ethynodiol diacetate

2.5.2 *Structural and molecular formulae and relative molecular mass*



$C_{24}H_{32}O_4$ Relative molecular mass: 384.5

2.5.3 *Chemical and physical properties of the pure substance*

(*a*) *Description:* White, odourless, crystalline powder (Reynolds, 1998)

(*b*) *Melting-point:* ~126–127°C (Budavari, 1996)

(*c*) *Solubility*: Very slightly soluble to practically insoluble in water; soluble in ethanol; freely to very soluble in chloroform; freely soluble in diethyl ether (Reynolds, 1998)

(*d*) *Optical rotation*: $[\alpha]_D^{20}$, –70° to –76° (British Pharmacopoeial Commission, 1993)

2.5.4 *Technical products and impurities*

Ethynodiol diacetate is commercially available alone or as a component of a combination tablet containing ethynodiol diacetate plus ethinyloestradiol or mestranol (Thomas, 1991; Kleinman, 1996; Medical Economics, 1996; US Food & Drug Administration, 1996; American Hospital Formulary Service, 1997; British Medical Association, 1997; Reynolds, 1998).

2.5.5 *Analysis*

The British and United States pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards as methods for identifying ethynodiol diacetate; potentiometric titration with sodium hydroxide and liquid chromatography are used to assay its purity. Thin-layer chromatography is specified to identify ethynodiol diacetate in combination formulations; liquid chromatography is used to assay the quantity of ethynodiol diacetate in combination tablets (British Pharmacopoeial Commission, 1993; United States Pharmacopeial Convention, 1995).

2.5.6 *Production and use*

Ethynodiol diacetate does not occur naturally. A method for its synthesis was first patented in the United States in 1965. Ethindrone is reduced to ethynodiol, which is acetylated with acetic anhydride in pyridine to produce ethynodiol diacetate. Ethynodiol diacetate can also be prepared from ethynodiol or from norethisterone by reducing the keto group to the carbinol and acetylating the 3- and 17-hydroxyls (Sittig, 1988; Gennaro, 1995). It is not known which process is used for commercial production.

Ethynodiol diacetate was introduced in France in 1965, in the United States in 1966, in Italy in 1971 and in the United Kingdom in 1973 (Sittig, 1988).

Information available in 1995 indicated that ethynodiol diacetate was manufactured or formulated in Argentina, Australia, Brazil, Canada, France, India, the Netherlands, New Zealand, South Africa, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

Ethynodiol diacetate is a progestogen with actions and uses similar to those of norethisterone; however, because it has a hydroxyl rather than a keto group at the 3-position of the A ring, it has stronger oestrogenic activity and is essentially devoid of androgenic activity. For use as an oral contraceptive, it has been combined with an oestrogen at a typical dose of 1 mg ethynodiol diacetate and either 35 or 50 µg ethinyloestradiol or 0.1 mg mestranol (Gennaro, 1995). It is also used as a ‘progestogen-only’ contraceptive (British Medical Association, 1997).

2.6 Gestodene

2.6.1 *Nomenclature*

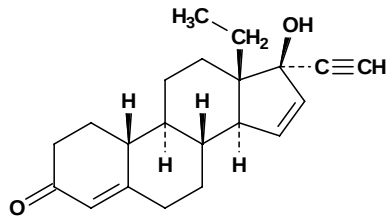
Chem. Abstr. Serv. Reg. No.: 60282-87-3

Deleted CAS Reg. No.: 110541-55-4

Chem. Abstr. Name: (17α)-13-Ethyl-17-hydroxy-18,19-dinorpregna-4,15-dien-20-yn-3-one

IUPAC Systematic Name: 13-Ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one

2.6.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{26}O_2$ Relative molecular mass: 310.4

2.6.3 *Chemical and physical properties of the pure substance*

From Budavari (1996)

(*a*) *Description*: Crystals

(*b*) *Melting-point*: 197.9°C

2.6.4 *Technical products and impurities*

Gestodene is commercially available as a component of combination tablets with ethinyloestradiol (Morant & Ruppanner, 1991; British Medical Association, 1997; Editions du Vidal, 1997; Thomas, 1997).

2.6.5 *Analysis*

No information was available to the Working Group.

2.6.6 *Production and use*

Gestodene does not occur naturally. It can be prepared from the 17-keto steroid [18-methyloestrone methyl ether] in a multistep synthesis involving palladium-catalysed conversion of its enol ether to an enone, reduction to the corresponding allylic alcohol, partial reduction of the aromatic ring, regeneration of the enone and ethinylation (Bohlman *et al*., 1989).

Information available in 1995 indicated that gestodene was manufactured or formulated in Argentina, Austria, Belgium, Brazil, Finland, France, Germany, Mexico, the Netherlands, New Zealand, Portugal, South Africa, Spain, Switzerland and the United Kingdom (CIS Information Services, 1995).

Gestodene is used only in combination with ethinyloestradiol as an oral contraceptive, at a dose of 0.075 mg gestodene and 20 or 30 μg ethinyloestradiol, and in a triphasic regimen at 0.05, 0.07 and 0.1 mg gestodene and 30, 40 and 30 μg ethinyloestradiol (Kleinman, 1996).

2.7 Levonorgestrel

2.7.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 797-63-7

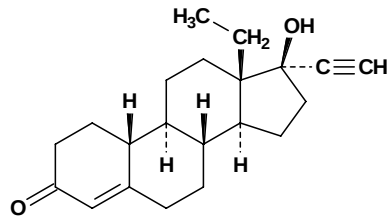
Deleted CAS Reg. No.: 797-62-6; 4222-79-1; 121714-72-5

Chem. Abstr. Name: (17α)-13-Ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one

IUPAC Systematic Name: 13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Synonyms: 13-Ethyl-17-ethynyl-17β-hydroxy-4-gonen-3-one; 13-ethyl-17α-ethynyl-17-hydroxygon-4-en-3-one; 13-ethyl-17α-ethynylgon-4-en-17β-ol-3-one; 13β-ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one; 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one; 17-ethynyl-18-methyl-19-nortestosterone; 18-methylnorethindrone; l-norgestrel; D-l-norgestrel; D-norgestrel

2.7.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{28}O_2$ Relative molecular mass: 312.5

2.7.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White, odourless, crystalline powder

(*b*) *Melting-point*: 235–237°C

(*c*) *Solubility:* Practically insoluble in water; slightly soluble in ethanol, acetone and diethyl ether; sparingly soluble in dichloromethane; soluble in chloroform

(*d*) *Specific rotation:* $[\alpha]_D^{20}$, –32.4°

2.7.4 *Technical products and impurities*

Levonorgestrel is commercially available as a single-ingredient tablet (Kleinman, 1996; Editions du Vidal, 1997); it is also available as an interuterine system and as a flexible, closed-capsule implant made of silicone rubber tubing (Medical Economics, 1996; LINFO Läkemedelsinformation AB, 1997). Levonorgestrel is also used in combi-

nation with ethinyloestradiol for contraception (Kleinman, 1996; Medical Economics, 1996; Editions du Vidal, 1997) and in combination with several other pharmaceutical preparations including oestradiol, oestradiol valerate, oestriol and ethinyloestradiol for hormonal replacement therapy (British Medical Association, 1997; Reynolds, 1998).

2.7.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet visible absorption spectrophotometry and optical rotation with comparison to standards as methods for identifying levonorgestrel; potentiometric titration and ultra-violet absorption spectrophotometry are used to assay its purity. Levonorgestrel is identified in pharmaceutical preparations by ultra-violet absorption visible spectrophotometry and thin-layer chromatography (British Pharmacopoeial Commission, 1993; United States Pharmacopeial Convention, 1995; Council of Europe, 1997).

2.7.6 *Production and use*

Levonorgestrel does not occur naturally. Several methods for the synthesis of norgestrel were reported in the early 1960s (Sittig, 1988; Budavari, 1996).

The activity of norgestrel is found in the levorotatory form D-l-norgestrel or levonorgestrel. Synthesis of the levorotatory form involves *meta*-cresol methyl ether, dimethyl malonate and *trans*-1,4-dibromo-2-butene as starting materials. The steroid skeleton was constructed by using an intramolecular Diels-Alder reaction of an *ortho*-quinodimethane derivative, preceded by photo-enolization of an appropriate methyl-substituted acetophenone derivative. Chirality was introduced at an early stage during a nucleophilic substitution reaction (Baier *et al*., 1985). It is not known if this synthesis is used commercially.

Information available in 1995 indicated that levonorgestrel was manufactured or formulated in Argentina, Australia, Austria, Belgium, Brazil, Canada, Finland, France, Germany, India, Mexico, the Netherlands, New Zealand, Portugal, South Africa, Spain, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

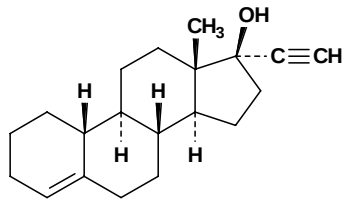
Levonorgestrel is used as a combined oral contraceptive with ethinyloestradiol in monophasic, biphasic and triphasic regimens. It is also used as a 'progestogen-only' contraceptive pill and subdermal implant (Kleinman, 1996).

2.8 Lynoestrenol

2.8.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 52-76-6
Deleted CAS Reg. No.: 60416-16-2
Chem. Abstr. Name: (17α)-19-Norpregn-4-en-20-yn-17-ol
IUPAC Systematic Name: 19-Nor-17α-pregn-4-en-20-yn-17-ol
Synonyms: 3-Desoxynorlutin; Δ^4-17α-ethinylestren-17β-ol; Δ^4-17α-ethinyloestren-17β-ol; ethynylestrenol; ethynyloestrenol; 17α-ethynylestrenol; 17α-ethynyloestrenol; 17α-ethynyl-17β-hydroxy-Δ^4-estrene; 17α-ethynyl-17β-hydroxy-Δ^4-oestrene

2.8.2 *Structural and molecular formulae and relative molecular mass*



$C_{20}H_{28}O$ Relative molecular mass: 284.4

2.8.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White crystalline powder

(*b*) *Melting-point*: 158–160°C

(*c*) *Solubility*: Practically insoluble in water; freely soluble in chloroform; soluble in ethanol, acetone and diethyl ether

(*d*) *Specific rotation*: $[\alpha]_D^{25}$, –13° (chloroform)

2.8.4 *Technical products and impurities*

Lynoestrenol is commercially available as a single-ingredient tablet and as a component of combination tablets containing ethinyloestradiol or mestranol (Kleinman, 1996; Editions du Vidal, 1997; Reynolds, 1998).

2.8.5 *Analysis*

Several international pharmacopoeias specify infra-red absorption spectrophotometry with comparison to standards as the method for identifying lynoestrenol; potentiometric titration with sodium hydroxide is used to assay its purity (British Pharmacopoeial Commission, 1993; Schweizerischen Bundesrat, 1996; Council of Europe, 1997).

2.8.6 *Production and use*

Lynoestrenol does not occur naturally. Synthesis of lynoestrenol was first reported in 1959 (de Winter *et al.*, 1959), by treatment of 19-nortestosterone with ethane-1,2-dithiol and boron trifluoride to give the 3-thioketal; treatment with sodium in liquid ammonia gives 17β-hydroxyoestr-4-ene, which by oxidation with chromic acid gives oestr-4-en-17-one. This can be converted to lynoestrenol by treatment with lithium acetylide or Grignard reagent. Whether this is the method used for commercial production is not known.

Information available in 1995 indicated that lynestrenol was manufactured or formulated in Argentina, Austria, Belgium, Brazil, France, Germany, Mexico, the Netherlands, South Africa, Spain and Switzerland (CIS Information Services, 1995).

Lynoestrenol is used primarily as a component of contraceptive tablets at a dose of 0.75–2.5 mg in conjunction with ethinyloestradiol. It is also used as a ‘progestogen-only’

contraceptive. It can be used in the treatment of dysfunctional uterine bleeding and endometriosis (Kleinman, 1996; Reynolds, 1996).

2.9 Medroxyprogesterone acetate

2.9.1 *Nomenclature*

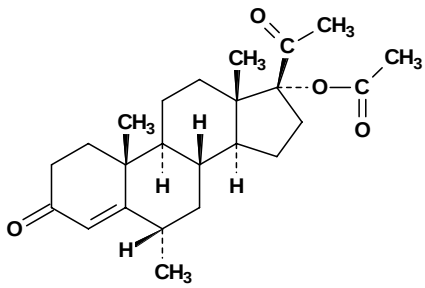
Chem. Abstr. Serv. Reg. No.: 71-58-9

Chem. Abstr. Name: (6α)-17-(Acetyloxy)-6-methylpregn-4-ene-3,20-dione

IUPAC Systematic Name: 17-Hydroxy-6α-methylpregn-4-ene-3,20-dione, acetate

Synonyms: 17α-Acetoxy-6α-methylprogesterone; depomedroxyprogesterone acetate; depo-progestin; depot-medroxyprogesterone acetate; DMPA; 17-hydroxy-6α-methylprogesterone, acetate; 17α-hydroxy-6α-methylprogesterone acetate; MAP; medroxyprogesterone 17-acetate; 6α-methyl-17-acetoxyprogesterone; 6α-methyl-17α-hydroxyprogesterone acetate

2.9.2 *Structural and molecular formulae and relative molecular mass*



$C_{24}H_{34}O_4$ Relative molecular mass: 386.5

2.9.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White to off-white, odourless, crystalline powder

(*b*) *Melting-point*: 207–209.5°C

(*c*) *Solubility*: Practically insoluble in water; slightly soluble in diethyl ether; sparingly soluble in ethanol and methanol; soluble in acetone and dioxane; freely soluble in chloroform

(*d*) *Specific rotation*: $[\alpha]_D^{25}$, +61° (in chloroform)

2.9.4 *Technical products and impurities*

Medroxyprogesterone acetate is commercially available as a single-ingredient tablet and as combination tablets with conjugated oestrogens, oestradiol or oestradiol valerate, and as sterile suspensions (Gennaro, 1995; Medical Economics, 1996; American Hospital Formulary Service, 1997; British Medical Association, 1997; Editions du Vidal, 1997).

2.9.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards and thin-layer chromatography as methods for identifying medroxyprogesterone acetate; ultra-violet absorption spectrophotometry and liquid chromatography are used to assay its purity. Medroxyprogesterone acetate is identified in pharmaceutical preparations by infra-red absorption spectrophotometry and liquid chromatography; ultra-violet absorption spectrophotometry and liquid chromatography are used to assay for its content in these preparations (British Pharmacopoeial Commission, 1993; Secretaria de Salud, 1994; United States Pharmacopeial Convention, 1995; Council of Europe, 1997).

2.9.6 *Production and use*

Medroxyprogesterone acetate does not occur naturally. Its synthesis was first reported in 1958. The bisethylene acetal of 17α-hydroxyprogesterone was treated with peracetic acid to give a mixture of 5α,6α-epoxy-17α-hydroxypregnane-3,20-dione bisethylene acetal and the corresponding 5β,6β-epoxide. The 5α,6α-epoxide was refluxed with methylmagnesium bromide in tetrahydrofuran to afford the bisethylene acetal of 5α,17α-dihydroxy-6β-methylpregnane-3,20-dione. Dehydration by dilute sodium hydroxide in pyridine produced 6β-methyl-17α-hydroxyprogesterone which was epimerized in chloroform saturated with gaseous hydrogen chloride to 6α-methyl-17α-hydroxyprogesterone. Alternatively, dehydration and epimerization of 5α,17β-dihydroxy-6β-methylpregnane-3,20-dione bisethylene acetal could be effected directly with chloroform or hydrogen chloride. Acylation with acetic anhydride, acetic acid and *para*-toluenesulfonic acid produced medroxyprogesterone acetate (Babcock *et al*., 1958)

Information available in 1995 indicated that medroxyprogesterone acetate is manufactured or formulated in Argentina, Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Japan, Italy, Mexico, the Netherlands, New Zealand, Portugal, South Africa, Spain, Sweden, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

For contraception, medroxyprogesterone acetate is given intramuscularly at a dose of 150 mg once every three months (depot medroxyprogesterone acetate). It is usually given within the first five days of the menstrual cycle (Reynolds, 1996).

Medroxyprogesterone acetate is used for post-menopausal hormonal therapy, for the treatment of dysfunctional uterine bleeding, secondary amenorrhoea and mild to moderate endometriosis. It is also used in the palliative treatment of some hormone-dependent malignant neoplasms, including breast, endometrial, renal and prostatic carcinoma (Reynolds, 1996).

Medroxyprogesterone acetate is also being explored as a means of oral contraception in men, given in combination with testosterone (Melo & Coutinho, 1977; Soufir *et al*., 1983).

2.10 Megestrol acetate

2.10.1 *Nomenclature*

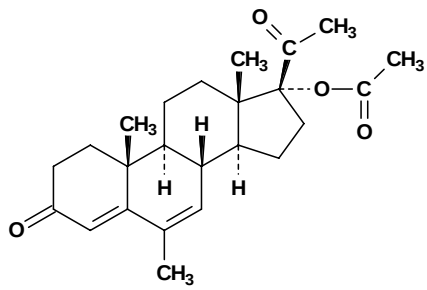
Chem. Abstr. Serv. Reg. No.: 595-33-5

Chem. Abstr. Name: 17-(Acetyloxy)-6-methylpregna-4,6-diene-3,20-dione

IUPAC Systematic Name: 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione, acetate

Synonyms: DMAP; megestryl acetate; MGA

2.10.2 *Structural and molecular formulae and relative molecular mass*



$C_{24}H_{32}O_4$ Relative molecular mass: 384.5

2.10.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White to creamy-white, odourless, crystalline powder

(*b*) *Melting-point*: 214–216°C

(*c*) *Solubility*: Practically insoluble in water (2 µg/mL at 37°C); very soluble in chloroform; soluble in acetone; slightly soluble in diethyl ether and fixed oils; sparingly soluble in ethanol

(*d*) *Specific rotation*: $[\alpha]_D^{24}$, +5° (in chloroform)

2.10.4 *Technical products and impurities*

Megestrol acetate is commercially available as tablets and as an oral suspension (Medical Economics, 1996; Editions du Vidal, 1997; LINFO Läkemedelsinformation AB, 1997).

2.10.5 *Analysis*

The British and United States pharmacopoeias specify ultra-violet and infra-red absorption spectrophotometry with comparison to standards as methods for identifying megestrol acetate alone and in pharmaceutical preparations; ultra-violet absorption spectrophotometry and liquid chromatography are used to assay its purity (British Pharmacopoeial Commission, 1993; United States Pharmacopeial Convention, 1995).

2.10.6 *Production and use*

Megestrol acetate does not occur naturally. It was first synthesized in 1959 and is now prepared by oxidation of 17α-acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one with aluminium *tert*-butoxide and *para*-quinone in dry benzene (Sittig, 1988).

Commercial production of megestrol acetate in the United States was first reported in 1976 (United States International Trade Commission, 1977). Information available in 1995 indicated that megestrol acetate was manufactured or formulated in Argentina, Australia, Belgium, Canada, Finland, France, Germany, Italy, the Netherlands, New Zealand, South Africa, Spain, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

Megestrol acetate is used in a few countries as an oral contraceptive, usually in combination with ethinyloestradiol. It is not used as an oral contraceptive in the United States, and such usage was discontinued in the United Kingdom in 1975 (IARC, 1979). It is used for palliative treatment of carcinoma of the breast or endometrium, in the treatment of acne, hirsutism and sexual infantilism in females and in the treatment of anorexia and cachexia in patients with AIDS or cancer (IARC, 1979; Gennaro, 1995; Reynolds, 1996).

2.11 Norethisterone

2.11.1 *Nomenclature*

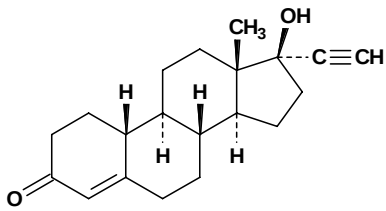
Chem. Abstr. Serv. Reg. No.: 68-22-4

Chem. Abstr. Name: (17α)-17-Hydroxy-19-norpregn-4-en-20-yn-3-one

IUPAC Systematic Name: 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one

Synonyms: Ethinylnortestosterone; 17α-ethinyl-19-nortestosterone; ethynylnortestosterone; 17-ethynyl-19-nortestosterone; 17α-ethynyl-19-nortestosterone; norethindrone; norethisteron; norethynodrone; 19-nor-17α-ethynyltestosterone; norpregneninolone

2.11.2 *Structural and molecular formulae and relative molecular mass*



$C_{20}H_{26}O_2$ Relative molecular mass: 298.4

2.11.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White or yellowish-white, odourless, crystalline powder

(*b*) *Melting-point*: 203–204°C

(*c*) *Solubility*: Practically insoluble in water; slightly to sparingly soluble in ethanol; slightly soluble in diethyl ether; soluble in chloroform and dioxane

(*d*) *Specific rotation*: $[\alpha]_D^{20}$, –31.7°

2.11.4 *Technical products and impurities*

Norethisterone is commercially available as single-ingredient tablets or as a component of combination tablets with ethinyloestradiol or mestranol (Morant & Ruppanner, 1991; Kleinman, 1996; Medical Economics, 1996; British Medical Association, 1997; Editions du Vidal, 1997).

2.11.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards and thin-layer chromatography as methods for identifying norethisterone; potentiometric titration, ultra-violet absorption spectrophotometry and thin-layer chromatography are used to assay its purity. Norethisterone is identified in pharmaceutical preparations by infra-red absorption spectrophotometry, thin-layer and liquid chromatography; potentiometric titration, ultra-violet absorption spectrophotometry and liquid chromatography are used to assay for norethisterone content (British Pharmacopoeial Commission, 1993; Secretaria de Salud, 1994, 1995; United States Pharmacopeial Convention, 1995; Schweizerischen Bundesrat, 1996; Society of the Japanese Pharmacopoeia, 1996; Council of Europe, 1997).

2.11.6 *Production and use*

Norethisterone does not occur naturally. A method for synthesizing norethisterone was first reported in 1954 (Djerassi *et al.*, 1954). It is prepared by reacting the methyl ester of oestrone with lithium metal in liquid ammonia to reduce ring A to the 4-ene state; the reduced product is oxidized with chromic acid in aqueous acetic acid to form oestr-4-ene-3,17-dione. In order to prevent the 3-keto group from participating in the ensuing ethynylation reaction, oestr-4-ene-3,17-dione is reacted with ethyl orthoformate in the presence of pyridine hydrochloride to form the 3-ethoxy-3,5-diene compound. Acetylene is passed into a solution of this compound in toluene, previously admixed with a solution of sodium in *tert*-amyl alcohol, to form the 17-ethynyl-17-hydroxy compound. Hydrolysis at the 3-ethoxy linkage by heating with dilute hydrochloric acid is accompanied by rearrangement of the 3-hydroxy-3,5-diene compound to the 3-oxo-4-ene compound.

Information available in 1995 indicated that norethisterone was manufactured or formulated in Australia, Brazil, Canada, France, Germany, India, Italy, Japan, Mexico, New Zealand, South Africa, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

Norethisterone is used as an oral contraceptive alone or combined with mestranol or ethinyloestradiol in monophasic, biphasic and triphasic regimens (Kleinman, 1996).

It is also used to delay menstruation and in the treatment of amenorrhoea, dysfunctional uterine bleeding, premenstrual tension, dysmenorrhoea and endometriosis (Gennaro, 1995; Taitel & Kafrisse, 1995; Reynolds, 1996).

2.12 Norethisterone acetate

2.12.1 *Nomenclature*

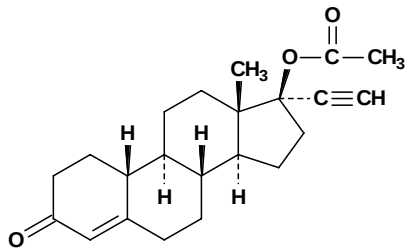
Chem. Abstr. Serv. Reg. No.: 51-98-9

Chem. Abstr. Name: (17α)-17-(Acetyloxy)-19-norpregn-4-en-20-yn-3-one

IUPAC Systematic Name: 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one, acetate

Synonyms: 17α-Ethinyl-19-nortestosterone 17β-acetate; 17α-ethinyl-19-nortestosterone acetate; 17α-ethynyl-19-nortestosterone acetate; norethindrone acetate; norethindrone 17-acetate; norethisteron acetate; norethisterone 17-acetate; 19-norethisterone acetate; norethynyltestosterone acetate; 19-norethynyltestosterone acetate; norethysterone acetate

2.12.2 *Structural and molecular formulae and relative molecular mass*



$C_{22}H_{28}O_3$ Relative molecular mass: 340.5

2.12.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White or creamy-white, odourless, crystalline powder (Reynolds, 1998)

(*b*) *Melting-point*: 161–162°C (Budavari, 1996)

(*c*) *Solubility*: Practically insoluble in water (1 g in > 10 L); soluble in ethanol (1 g in 10 mL), chloroform (1 g in < 1 mL), dioxane (1 g in 2 mL) and diethyl ether (1 g in 18 mL) (Gennaro, 1995; Reynolds, 1998)

(*d*) *Specific rotation*: $[\alpha]_D^{25}$, –32° to –38° (United States Pharmacopeial Convention, 1995)

2.12.4 *Technical products and impurities*

Norethisterone acetate is commercially available as single-ingredient tablets or as a component of combination tablets with ethinyloestradiol. For post-menopausal hormonal therapy, norethisterone acetate is used in combination with oestradiol, oestradiol hemihydrate or oestriol. It is also available as a percutaneous patch with oestradiol (Morant &

Ruppanner, 1991; Kleinman, 1996; Medical Economics, 1996; British Medical Association, 1997; Editions du Vidal, 1997).

2.12.5 *Analysis*

Several international pharmacopoeias specify infra-red absorption spectrophotometry with comparison to standards and thin-layer chromatography as methods for identifying norethisterone acetate; potentiometric titration and ultra-violet absorption spectrophotometry are used to assay its purity. Norethisterone acetate is identified in pharmaceutical preparations by infra-red absorption spectrophotometry and thin-layer chromatography; ultra-violet absorption spectrophotometry is used to assay for norethisterone acetate content (British Pharmacopoeial Commission, 1993; United States Pharmacopeial Convention, 1995; Council of Europe, 1997).

2.12.6 *Production and use*

Norethisterone acetate does not occur naturally. In a method for synthesizing norethisterone acetate, first patented in 1957, it is acetylated with acetic anhydride in pyridine (IARC, 1979).

Information available in 1995 indicated that norethisterone acetate was manufactured or formulated in Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, India, Mexico, New Zealand, Poland, Portugal, South Africa, Spain, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

Norethisterone acetate is used in combination with ethinyloestradiol for oral contraception at doses of 0.5–2.5 mg norethisterone acetate and 20–50 μg ethinyloestradiol (Gennaro, 1995; Kleinman, 1996; Editions du Vidal, 1997). It is also used as a 'progestogen-only' contraceptive (Kleinman, 1996; Editions du Vidal, 1997) and in post-menopausal hormonal therapy, both as tablets and percutaneously by a patch (British Medical Association, 1997).

Norethisterone acetate is used in the treatment of primary and secondary amenorrhoea, dysfunctional uterine bleeding, endometriosis and inoperable malignant neoplasms of the breast (Reynolds, 1996; British Medical Association, 1997).

2.13 Norethisterone oenanthate

2.13.1 *Nomenclature*

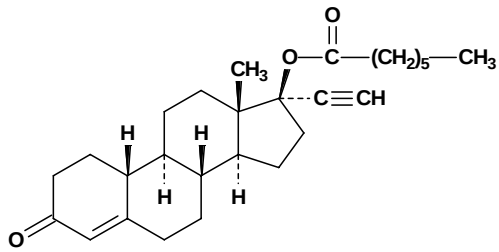
Chem. Abstr. Serv. Reg. No.: 3836-23-5

Chem. Abstr. Name: (17α)-17-(Heptanoyl)-19-norpregn-4-en-20-yn-3-one

IUPAC Systematic Name: 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one, heptanoate

Synonyms: Norethindrone enanthate; norethindrone oenanthate; norethisterone enanthate; norethisterone heptanoate; 17β-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate

2.13.2 *Structural and molecular formulae and relative molecular mass*



$C_{27}H_{38}O_3$ Relative molecular mass: 410.6

2.13.3 *Chemical and physical properties of the pure substance*

No information was available to the Working Group.

2.13.4 *Technical products and impurities*

Norethisterone oenanthate is available commercially in an oily solution for depot injection (Kleinman, 1996; Editions du Vidal, 1997).

2.13.5 *Analysis*

Norethisterone oenanthate is identified by thin-layer and liquid chromatography; liquid chromatography is used to assay its content (Secretaria de Salud, 1994).

2.13.6 *Production and use*

Norethisterone oenanthate does not occur naturally. It is probably synthesized by esterification with heptanoic acid.

Norethisterone oenanthate is used as a 'progestogen-only' contraceptive, mainly given intramuscularly at a dose of 200 mg once every two months, usually within the first five days of the menstrual cycle (Reynolds, 1996).

2.14 Norethynodrel

2.14.1 *Nomenclature*

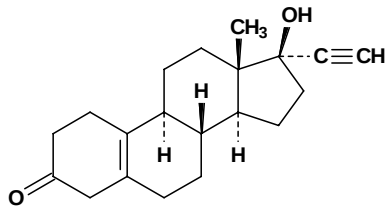
Chem. Abstr. Serv. Reg. No.: 68-23-5

Chem. Abstr. Name: (17α)-17-Hydroxy-19-norpregn-5(10)-en-20-yn-3-one

IUPAC Systematic Name: 17-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one

Synonyms: Enidrel; noretynodrel

2.14.2 *Structural and molecular formulae and relative molecular mass*



$C_{20}H_{26}O_2$ Relative molecular mass: 298.4

2.14.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998)

(*a*) *Description*: White, odourless, crystalline powder

(*b*) *Melting-point*: 169–170°C

(*c*) *Solubility*: Very slightly soluble in water; freely soluble in chloroform; soluble in acetone; sparingly soluble in ethanol

(*d*) *Optical rotation*: $[\alpha]_D^{25}$, +108° (in 1% chloroform)

2.14.4 *Technical products and impurities*

Norethynodrel was commercially available as a component of a combination tablet with mestranol (United States Food & Drug Administration, 1996).

2.14.5 *Analysis*

Several international pharmacopoeias specify infra-red absorption spectrophotometry with comparison to standards as the method for identifying norethynodrel; ultra-violet absorption spectrophotometry and potentiometric titration are used to assay its purity (British Pharmacopoeial Commission, 1980; United States Pharmacopeial Convention, 1995).

2.14.6 *Production and use*

Norethynodrel does not occur naturally. Synthesis of norethynodrel was first reported in 1954, in which oestradiol 3-methyl ether was reduced with lithium in liquid ammonia and the intermediate oxidized; ethynolation produced the 3-methyl ether of norethynodrel; treatment of this ether with acetic acid in methanol gave norethynodrel (Colton, 1954, 1955). Norethynodrel is now prepared by simultaneously saponifying and oxidizing dehydroepiandrosterone acetate by a series of reactions to 19-hydroxyandrost-6(6)-ene-3,17-dione. The hydroxymethyl group at the 10-position is then oxidized to carboxyl. The resulting acid is decarboxylated with simultaneous shifting of the double bond to give oestr-5(10)-ene-3,17-dione. Selective addition of acetylene at the expense of the 17-keto group yields norethynodrel (Gennaro, 1995).

Commercial production of norethynodrel was first begun in the United Kingdom in 1957 and in Japan and the United States in 1962. In 1960, the United States Food and Drug Administration licensed the first combined oral contraceptive pill, Enovid (norethynodrel

and mestranol), which contained much higher doses of hormones than are now routinely used (Drill, 1966; McLaughlin, 1982). It was introduced in the United Kingdom two years later (Thorogood & Villard-Mackintosh, 1993). Enovid was voluntarily withdrawn from the United States market in July 1992.

Norethynodrel is also used in the treatment of dysfunctional bleeding and endometriosis (Reynolds, 1996).

2.15 Norgestimate

2.15.1 *Nomenclature*

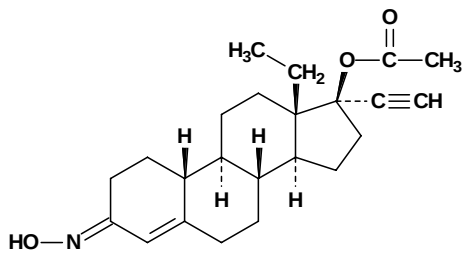
Chem. Abstr. Serv. Reg. No.: 35189-28-7

Chem. Abstr. Name: (17α)-17-(Acetyloxy)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one, 3-oxime

IUPAC Systematic Name: 13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester)

Synonyms: 17α-Acetoxy-13-ethyl-17-ethynylgon-4-en-3-one oxime; dexnorgestrel acetime

2.15.2 *Structural and molecular formulae and relative molecular mass*



$C_{23}H_{31}NO_3$ Relative molecular mass: 369.5

2.15.3 *Chemical and physical properties of the pure substance*

From Budavari (1996)

(*a*) *Description*: Crystals

(*b*) *Melting-point*: 214–218°C

(*c*) *Specific rotation*: $[\alpha]_D^{25}$, +110°

2.15.4 *Technical products and impurities*

Norgestimate is commercially available as a component of a combination tablet with ethinyloestradiol (Morant & Ruppanner, 1991; Kleinman, 1996; Medical Economics, 1996; British Medical Association, 1997; Editions du Vidal, 1997).

2.15.5 *Analysis*

Norgestimate can be separated and quantified in pharmaceutical preparations by high-performance liquid chromatography (Lane *et al.*, 1987).

2.15.6 *Production and use*

Norgestimate does not occur naturally. It can be prepared by pyrrolidine cyclocondensation of the appropriate secoestranedione followed by conversion to the 3-oxime with hydroxylamine (Roussel-UCLAF, 1979).

Information available in 1995 indicated that norgestimate was produced in Canada, Germany, Mexico, Switzerland, the United Kingdom and the United States (CIS Information Services, 1995).

Norgestimate is a synthetic progestogen structurally related to levonorgestrel, with actions and uses similar to those described for the progestogens in general. It is used as the progestogenic component of combined oral contraceptives in tablets containing 0.18, 0.215 and 0.25 mg norgestimate plus 35 μg ethinyloestradiol for a triphasic regimen (Kleinman, 1996; Reynolds, 1998).

2.16 Norgestrel

2.16.1 *Nomenclature*

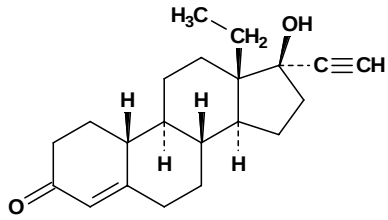
Chem. Abstr. Serv. Reg. No.: 6533-00-2

Chem. Abstr. Name: (17α)-dl-13-Ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one

IUPAC Systematic Name: dl-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Synonyms: (17α)-13-Ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one; methylnorethindrone; α-norgestrel; dl-norgestrel; DL-norgestrel

2.16.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{28}O_2$ Relative molecular mass: 312.5

2.16.3 *Chemical and physical properties of the pure substance*

From Budavari (1996) and Reynolds (1998), unless otherwise specified

(*a*) *Description*: White, practically odourless crystalline powder

(*b*) *Boiling-point*: 205–207°C

(*c*) *Solubility*: Practically insoluble in water; slightly to sparingly soluble in ethanol; sparingly soluble in dichloromethane; freely soluble in chloroform

(*d*) *Optical rotation*: $[\alpha]_D^{25}$, –0.1° to +0.1° (United States Pharmacopeial Convention, 1995)

2.16.4 *Technical products and impurities*

Norgestrel is commercially available as a single-ingredient tablet and as a component of combination tablets with ethinyloestradiol, oestradiol valerate or conjugated oestrogens (Morant & Ruppanner, 1991; Kleinman, 1996; Medical Economics, 1996; British Medical Association, 1997; Editions du Vidal, 1997).

2.16.5 *Analysis*

Several international pharmacopoeias specify infra-red and ultra-violet absorption spectrophotometry with comparison to standards as methods for identifying norgestrel; potentiometric titration and ultra-violet absorption spectrophotometry are used to assay its purity. Norgestrel is identified in pharmaceutical preparations by ultra-violet absorption spectrophotometry and thin-layer chromatography; potentiometric titration and liquid chromatography are used to assay for norgestrel content in these preparations (United States Pharmacopeial Convention, 1995; Society of Japanese Pharmacopoeia, 1996; Council of Europe, 1997).

2.16.6 *Production and use*

Norgestrel does not occur naturally. It was first synthesized in 1963 (Smith *et al*., 1963) and was first isolated as a racemic mixture of dl-13β-ethyl-17β-hydroxygon-4-en-3-one, which contains 50% of dextro- and levorotatory enantiomers (Edgren, 1963).

The activity of norgestrel is found in the levorotatory form of D-l-norgestrel or levonorgestrel. In a representative chemical synthesis, 6-methoxy-α-tetralone is reacted with vinylmagnesium bromide, and the resulting 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol is condensed with 2-ethyl-1,3-cyclopentanedione to form initially a tricyclic intermediate (secosteroid) containing all of the gonane skeleton carbon atoms. Cyclization of the secosteroid via dehydration yields a 13-ethylgona-1,3,5(10)-8,14-pentaene structure which is then successively reduced and ethynylated (Klimstra, 1969).

Information available in 1995 indicated that norgestrel was manufactured or formulated in Argentina, Austria, Belgium, Brazil, France, Germany, India, Japan, Mexico, the Netherlands, New Zealand, Portugal, South Africa, Spain, Swizerland, the United Kingdom and the United States (CIS Information Services, 1995).

Norgestrel is marketed as an oral contraceptive, both as a single entity and in combination with ethinyloestradiol. As a combination oral contraceptive, the dose is 0.25, 0.3 or 0.5 mg norgestrel plus 30 or 50 µg ethinyloestradiol per day (Kleinman, 1996). It is also marketed as a sequential preparation for post-menopausal hormonal therapy and has been used in combination with ethinyloestradiol to control menstrual disorders and endometriosis (Reynolds, 1996; British Medical Association, 1997).

2.17 Progesterone

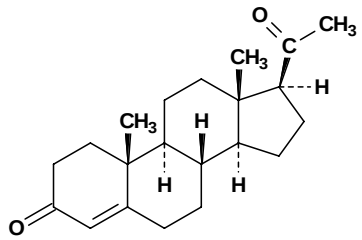
2.17.1 *Nomenclature*

Chem. Abst. Services Reg. No.: 57-83-0

Chem. Abstr. Name: Pregn-4-ene-3,20-dione

Synonyms: Corpus luteum hormone; luteal hormone; luteine; luteohormone; Δ^4-pregnene-3,20-dione

2.17.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{30}O_2$ Relative molecular mass: 314.5

2.17.3 *Chemical and physical properties*

From Weast (1977) and Windholz (1976), unless otherwise specified

(*a*) *Description*: Exists in two readily interconvertible crystalline forms: the α form, in white orthorhombic prisms, and the β form, in white orthorhombic needles

(*b*) *Melting-point*: α form, 128.5–131°C; β form, 121–122°C

(*c*) *Optical rotation*: $[\alpha]_D^{20}$, α form, +192°; β form, +172° to +182° (in 2% w/v dioxane)

(*d*) *Solubility*: Practically insoluble in water; soluble in ethanol (1 in 8), arachis oil (1 in 60), chloroform (1 in < 1), diethyl ether (1 in 16), ethyl oleate (1 in 60) and light petroleum (1 in 100) (Wade, 1977); soluble in acetone, dioxane and concentrated sulfuric acid; sparingly soluble in vegetable oils

2.17.4 *Technical products and impurities*

Progesterone is available in an oily solution for injection, as pessaries or suppositories and as an intrauterine device (Reynolds, 1996; British Medical Association, 1997; Editions du Vidal, 1997).

2.17.5 *Analysis*

Several international pharmacopoeias specify infra-red absorption spectrophotometry with comparison to standards and thin-layer chromatography as methods for identifying progesterone; thin-layer chromatography is used to assay its purity. Ultra-violet absorption spectrophotometry and high-pressure liquid chromatography are used to assay the progesterone content in pharmaceutical preparations (British Pharmacopoeial Commission, 1988; United States Pharmacopeial Convention, 1990; Society of Japanese Pharmacopeia, 1996).

2.17.6 *Production and use*

Progesterone is a naturally occurring steroidal hormone found in a wide variety of tissues and biological fluids, including cow's milk. It has also been found in certain plant species (IARC, 1979).

Progesterone was isolated in 1929 from the corpora lutea of sows by Corner and Allen and was first synthesized by Butenandt and Schmidt in 1934 by heating 4β-bromo-5β-pregnane-3,20-dione with pyridine (IARC, 1979). Progesterone is produced commercially by (1) the degradation of diosgenin (obtained from the Mexican yam, *Dioscorea mexicana*) to pregnenolone, which is converted to progesterone by Oppenauer oxidation; or (2) the oxidation of stigmasterol (obtained from soya bean oil) to stigmastadienone, which undergoes further modifications to progesterone. Progesterone can also be produced from cholesterol as a starting material (Dorfman, 1966; Harvey, 1975).

Commercial production of progesterone in the United States was first reported in 1939, and that in the United Kingdom was first reported in 1950. Progesterone was first marketed commercially in Japan in 1954–55 (IARC, 1979).

Progesterone is used in human medicine for the treatment of secondary amenorrhoea and dysfunctional uterine bleeding, although progestational agents which are active orally are generally preferred to progesterone. Dosage regimens for the administration of progesterone as an intramuscular injection vary, depending on whether it is administered as an aqueous suspension or as an oily solution. Micronized progesterone can be given orally in a dose of 100–300 mg per day; however, it causes progestogenic side-effects, of which drowsiness is the most common (Reynolds, 1996).

Progesterone-delivering intrauterine devices are used for contraception. Like those containing levonorgestrel, they are also suitable for post-menopausal hormone therapy, but the fact that they must be changed each year may diminish compliance (Treiman *et al*., 1995; Reynolds, 1996).

2.18 Regulations and guidelines

Concern about an enhanced risk for thrombosis related to use of desogestrel and gestodene in comparison with other oral contraceptives resulted in various responses from national authorities in Europe and New Zealand, although no action has been taken in some other countries (Griffin, 1996).

Chlormadinone acetate was removed from the market in the United Kingdom and the United States in 1970 (IARC, 1979). Ethynodiol diacetate is also no longer used in the United States (United States Food & Drug Administration, 1996). Megestrol has not been used as an oral contraceptive in the United Kingdom since 1975 and is not used in the United States (Wade, 1977). Norethynodrel as part of an oral contraceptive with mestranol (Enovid) was withdrawn from the United States market in July 1992.

The only guidelines that could be found for use of progestogens are those in national and international pharmacopoeias (Secretariat de Salud, 1994, 1995; United States Pharmacopeial Convention, 1995; Reynolds, 1996; Society of Japanese Pharmacopoeia, 1996; Council of Europe, 1997; Reynolds, 1998; Swiss Pharmaceutical Society, 1998).

3. References

American Hospital Formulary Service (1997) *AHFS Drug Information® 97*, Bethesda, MD, American Society of Health-System Pharmacists, pp. 2389, 2390, 2401–2408, 2472–2473

Babcock, J.C., Gutsell, E.S., Herr, M.E., Hogg, J.A., Stucki, J.C., Barnes, L.E. & Dulin, W.E. (1958) 6α-Methyl-17α-hydroxy-progesterone 17-acylates; a new class of potent progestins. *J. Am. chem. Soc*., **80**, 2904–2905

Baier, H., Durner, G. & Quinkert, G. (1985) [Total synthesis of (–)-norgestrel.] *Helvet. chim. Acta*, **68**, 1054–1068 (in German)

Birkhaüser, M.H. & Haenggi, W. (1994) Benefits of different routes of administration. *Int. J. Fertil*., **39** (Suppl. 1), 11–19

Bohlmann, R., Laurent, H., Hofmeister, H. & Weichert, R. (1989) *Preparation of Gestodene by a Novel Method*, German Patent issued to Schering AG, German Patent No. DE 3710728-1A

British Medical Association (1997) *British National Formulary*, No. 34, London, British Medical Association & The Pharmaceutical Press, pp. 313–353

British Pharmacopoeial Commission (1980) *British Pharmacopoeia 1980*, Vol. I, London, Her Majesty's Stationery Office, p. 310

British Pharmacopoeial Commission (1988) *British Pharmacopoeia 1988*, Vol. I, London, Her Majesty's Stationery Office, pp. 214, 361, 399–400, 468, 587

British Pharmacopoeial Commission (1993) *British Pharmacopoeia 1993*, Vol. I, London, Her Majesty's Stationery Office, pp. 263, 270, 382, 393, 406–408, 456–457, 1032–1033

British Pharmacopoeial Commission (1997) *British Pharmacopoeia 1993, Addendum 1997*, London, Her Majesty's Stationery Office, pp. 1971–1972

Brückner, K., Hampel, B. & Johnsen, U. (1961) [Synthesis and properties of monohalogenated 3-keto-$\Delta^{4,6}$-diene-steroids.] *Ber. Dtsch. chem. Ges*., **94**, 1225–1240 (in German)

Budavari, S., ed. (1996) *The Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., pp. 350–351, 469, 495, 587, 630–632, 637–638, 654, 749, 962, 988–990, 1010, 1149–1151

CIS Information Services (1995) *International Directory of Pharmaceutical Ingredients 1995/96 Edition*, Dallas, TX, pp. 204, 277, 283, 348–349, 376–378, 422, 546–547, 557, 605, 677–678, 746

Colton, F.B. (1954) Estradienes. *US Patent*, 2,691,028, 5 Oct. to G.D. Searle & Co. [*Chem. Abstr*., **49**, 11729i]

Colton, F.B. (1955) 13-Methyl-17-ethynyl-17-hydroxy-1,2,3,4,6,7,8,9,11,12,13,14,16,17-tetradecahydro-15*H*-cyclopentaphenanthren-3-one. *US Patent*, 2,725,389, 29 Nov. to G.D. Searle & Co. [*Chem. Abstr*., **50**, 9454f]

Cooper, A.J. (1986) Progestogens in the treatment of male sex offenders: A review. *Can. J. Psychiatr.*, **31**, 73–79

Corson, S.L. (1993) Clinical experiment with Systen, a new transdermal form of hormone replacement therapy. *Int. J. Fertil*., **38** (Suppl. 1), 36–44

Council of Europe (1997) *European Pharmacopoeia*, 3rd Ed., Strasbourg, pp. 700–701, 815–817, 821–822, 1094–1095, 1112–1113, 1153–1154, 1162–1163, 1245–1249

Crook, D., Godsland, I.F., Hull, J. & Stevenson, J.C. (1997) Hormone replacement therapy with dydrogesterone and 17β-oestradiol: Effects on serum lipoproteins and glucose tolerance during 24 month follow up. *Br. J. Obstet. Gynaecol*., **104**, 298–304

Djerassi, C., Miramontes, L., Rosenkranz, G. & Sondheimer, F. (1954) Steroids. LIV. Synthesis of 19-nor-17α-ethynyltestosterone and 19-nor-17α-methyltestosterone. *J. Am. chem. Soc*., **76**, 4092–4094

Dorfman, R.I. (1966) Hormones (sex). In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 2nd Ed., Vol. II, New York, Wiley & Sons, pp. 122–124

Drill, V.A. (1966). *Oral Contraceptives*, New York, McGraw-Hill, pp. 6–7

Edgren, R.A., Smith, H., Hughes, G.A., Smith, L.L. & Greenspan, G. (1963) Biological effects of racemic and resolved 13-ethyl-4-gonen-3-ones. *Steroids*, **2**, 731–737

Editions du Vidal (1997) *Vidal*, 73rd Ed., Paris, OVP, pp. 359–361, 412–413, 452–453, 474–475, 509, 561–562, 758–759, 903–904, 983, 1014, 1016–1017, 1023, 1036, 1042–1043, 1045–1046, 1051–1052, 1071–1072, 1125–1126, 1166, 1214, 1290–1291, 1335, 1346–1347, 1352–1353, 1356–1357, 1558, 1695–1696, 1699–1700, 1747–1748

Ellerington, M.C., Whitcroft, S.I. & Whitehead, M.I. (1992) HRT: Developments in therapy. *Br. med. Bull*., **48**, 401–425

Gennaro, A.R. (1995) *The Science and Practice of Pharmacy*, 19th Ed., Vol. II, Easton, PA, Mack Publishing Co., pp. 1089–1093, 1095–1097, 1099

Gordon, S.F. (1995) Clinical experience with a seven-day estradiol transdermal system for estrogen replacement therapy. *Am. J. Obstet. Gynecol*., **173**, 998–1004

Griffin, J.P. (1996) Editorial—Third generation oral contraceptives containing desogestrel and gestodene and the risk of thrombosis. *Adverse Drug React. Toxicol. Rev*., **15**, 5–7

Harvey, S.C. (1975) Hormones. In: Osol, A. et al., eds, *Remington's Pharmaceutical Sciences*, 15th Ed., Easton, PA, Mack, pp. 924–925

Hatcher, R.A., Rinckart, W., Blackburn, R. & Geller, J.S. (1997) *The Essentials of Contraceptive Technolology*, Baltimore, Population Information Program, Center for Communication Programs, The Johns Hopkins School of Public Health, pp. 5–23

Hirvonen, E., Stenman, U.H., Malkonen, M., Rasi, V., Vartiainen, E. & Ylostalo, P. (1988) New natural oestradiol/cyproterone acetate oral contraceptive for pre-menopausal women. *Maturitas*, **10**, 201–213

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 21, *Sex Hormones (II)*, Lyon, pp. 257–278, 365–375, 431–439, 441–460, 491–515

Judd, H.L. (1994) Transdermal estradiol—A potentially improved method of hormone replacement. *J. reprod. Med*., **39**, 343–352

Kleinman, R.L. (1996) *Directory of Hormonal Contraceptives*, London, IPPF Medical Publications

Klimstra, P.D. (1969) The role of progestin and estrogen in fertility control and maintenance. In: Chinn, L.J., Klimstra, P.D., Baran, J.S. & Pappo, R., eds, *The Chemistry and Biochemistry of Steroids*, Los Altos, CA, Geron-X, pp. 65–66

Lane, P.A., Mayberry, D.O. & Young, R.W. (1987) Determination of norgestimate and ethinyl estradiol in tablets by high-performance liquid chromatography. *J. pharm. Sci*., **76**, 44–47

LINFO Läkemedelsinformation AB (1997) *FASS 1997 Läkemedel I Sverige*, Stockholm, pp. 336–338, 672, 721, 723–725, 827

McLaughlin, L. (1982) *The Pill, John Rock and the Church*, Toronto, Little, Brown & Co., pp. 138–145

Medical Economics (1996) *PDR®: Physicians' Desk Reference*, 50th Ed., Montvale, NJ, Medical Economics Data Production Co., pp. 699–702, 974–976, 1858–1865, 1872–1880, 2087–2093, 2428, 2602–2607, 2636–2637, 2746–2764, 2770–2772, 2787–2807

Melo, J.F. & Coutinho, E.M. (1977) Inhibition of spermatogenesis in men with monthly injections of medroxyprogesterone acetate and testosterone enanthate. *Contraception*, **15**, 627–634

Meriggiola, M.C., Bremner, W.J., Paulsen, C.A., Valdiserri, A., Incorvaia, L., Motta, R., Pavani, A., Capelli, M. & Flamigni, C. (1996) A combined regimen of cyproterone acetate and testosterone enanthate as a potentially highly effective male contraceptive. *J. clin. Endocrinol. Metab.*, **81**, 3018–3023

Moltz, L., Römmler, A., Post, K., Schwartz, U. & Hammerstein, J. (1980) Medium dose cyproterone acetate (CPA): Effects on hormone secretion and on spermatogenesis in men. *Contraception*, **21**, 393–413

Morant, J. & Ruppanner, H., eds (1991) *Compendium Suisse des Medicaments* 1991, 12th Ed., Basel, Documed, pp. 38, 418–419, 521–523, 804, 985, 988–989, 1207–1208, 1439–1440, 1457–1458, 1711–1712, 1725–1726, 1901–1906, 2262–2263, 2452, 2462–2463

Namer, M. (1988) Clinical applications of antiandrogens. *J. Steroid Biochem.*, **31**, 719–729

Neumann, F. & Topert, M. (1986) Pharmacology of antiandrogens. *J. Steroid Biochem.*, **25**, 885–895

Notter, A. & Durand, P.M. (1969) Advantage of chlormadinone in threatened abortion. *Lyon méd.*, **221**, 659–666 (in French)

Organizzazione Editoriale Medico Farmaceutica (1995) *L'Informatore Farmaceutico* (Part I), 55th Ed., Milan, OEMF, p. 46

Paganini-Hill, A. & Henderson, V.W. (1994) Estrogen deficiency and risk of Alzheimer's disease in women. *Am. J. Epidemiol.*, **140**, 256–261

Reynolds, J.E.F., ed. (1996) *Martindale: The Extra Pharmacopoeia*, 31st Ed., London, The Pharmaceutical Press, pp. 1470–1510

Reynolds, J.E.F., ed. (1998) *Martindale, The Extra Pharmacopoeia* [Micromedex database CD-ROM]

Roland, M., Clyman, M., Decker, A. & Ober, W.B. (1966) Significance of dysmenorrhea in infertility. *Pac. med. Surg.*, **74**, 135–138

Roussel-UCLAF (1979) Steroid oximes. *Japanese Patent issued to Roussel-UCLAF, France*, Patent No. JP54048750

Schweizerischen Bundesrat (1996) *Pharmacopea Helvetica*, 7th Ed., Bern, Eidgenössicher Departement des Innern

Secretaria de Salud (1994) *Farmacopea de los Estados Unidos Mexicanos (Pharmacopoeia of the Mexican United States)*, 6th Ed., Mexico City, Comision Permanente de la Farmacopea de los Estados Unidos Mexicanos, pp. 538–540, 543–544, 634–635, 640–641, 1006–1007, 1308–1312

Secretaria de Salud (1995) *Farmacopea de los Estados Unidos Mexicanos (Pharmacopoeia of the Mexican United States)*, 6th Ed., Suppl. 1, Mexico City, Comision Permanente de la Farmacopea de los Estados Unidos Mexicanos, pp. 1774–1775, 1896–1900

Sittig, M. (1988) *Pharmaceutical Manufacturing Encyclopedia*, 2nd Ed., Vols 1 and 2, Park Ridge, NJ, Noyes Publications, pp. 445, 588–589, 598–599, 922, 954–955, 1100–1101

Smith, H., Hughes, G.A., Douglas, G.H., Hartley, D., McLoughlin, B.J., Siddall, J.B., Wendt, G.R., Buzby, G.C., Jr, Herbst, D.R., Ledig, K.W., McMenamin, J.R., Pattison, T.W., Suida, J., Tokolics, J., Edgren, R.A., Jansen, A.B.A., Gadsby, B., Watson, D.H.R. & Phillips, P.C. (1963) Totally synthetic (+)-13-alkyl-3-hydroxy and methoxy-gona-1,3,5(10)-trien-17-ones and related compounds. *Experientia*, **19**, 394–396

Society of Japanese Pharmacopoeia (1996) *JP XIII The Japanese Pharmacopoeia*, 13th Ed., Tokyo, pp. 281, 371–375, 500, 536—539, 593–594

Soufir, J.-C., Jouannet, P., Marson, J. & Soumah, A. (1983) Reversible inhibition of sperm production and gonadotrophin secretion in men following combined oral medroxyprogesterone acetate and percutaneous testosterone treatment. *Acta endocrinol.*, **102**, 625–632

Sullivan, J.M. & Fowlkes, L.P. (1996) The clinical aspects of estrogen and the cardiovascular system. *Obstet. Gynecol.*, **87**, 36S–43S

Swiss Pharmaceutical Society, ed. (1998) *Index Nominum, International Drug Directory*, 16th Ed., Stuttgart, Medpharm Scientific Publishers [MicroMedex CD-ROM]

Taitel, H.F. & Kafrissen, M.E. (1995) Norethindrone—A review of therapeutic applications. *Int. J. Fertil. menopausal Stud.*, **40**, 207–223

Thomas, J., ed. (1991) *Prescription Products Guide*, 20th Ed., Vol. 1, Victoria, Australian Pharmaceutical Publishing Co. Ltd, pp. 719, 968–969, 1249, 1285

Thomas, J., ed. (1997) *Australian Prescription Products Guide*, 26th Ed., Vol. 1, Victoria, Australian Pharmaceutical Publishing Co. Ltd, pp. 1177, 1890–1891

Thorogood, M. & Villard-Mackintosh, L. (1993) Combined oral contraceptives: Risks and benefits. *Br. med. Bull.*, **49**, 124–139

Treiman, K., Liskin, L., Kols, A. & Ward, R. (1995) IUDs—An update. *Popul. Rep.*, **23**, 1–35

United States Food & Drug Administration (1996) *Approved Drug Products with Therapeutic Equivalence Evaluations*, 16th Ed., Washington DC, United States Department of Health and Human Services, pp. 3-124–3-125, 3-127, 3-378, 3-424

United States International Trade Commission (1977) *Synthetic Organic Chemicals, US Production and Sales, 1976* (USITC Publication 833), Washington DC, United States Government Printing Office, p. 149

United States Pharmacopeial Convention (1990) *The United States Pharmacopeia*, 22nd rev./*The National Formulary*, 17th rev., Rockville, MD, pp. 486–487, 1154–1156

United States Pharmacopeial Convention (1995) *The 1995 US Pharmacopeia*, 23rd rev./*The National Formulary*, 18th rev., Rockville, MD, pp. 622–633, 638, 880–882, 941–945, 963, 1098–1103, 1105–1106

United States Tariff Commission (1947) *Synthetic Organic Chemicals, US Production and Sales, 1945* (TC Publication 157), Second Series, Washington DC, United States Government Printing Office, p. 141

United States Tariff Commission (1956) *Synthetic Organic Chemicals, US Production and Sales, 1955* (TC Publication 198), Second Series, Washington DC, United States Government Printing Office, p. 112

Wade, A., ed. (1977) *Martindale, The Extra Pharmacopoeia*, 27th Ed., London, Pharmaceutical Press, pp. 1422–1424

Wang, C. & Yeung, K.K. (1980) Use of low-dosage oral cyproterone acetate as a male contraceptive. *Contraception*, **21**, 245–272

Weast, R.C., ed. (1977) *CRC Handbook of Chemistry and Physics*, 58th Ed., Cleveland, OH, Chemical Rubber Co., p. C-444

Williams, C.L. & Stancel, G.M. (1996) Estrogens and progestins. In: Wonsiewicz, M.J. & McCurdy, P., eds, *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed., New York, McGraw-Hill, pp. 1411–1440

Windholz, M., ed. (1976) *The Merck Index*, 9th Ed., Rahway, NJ, Merck & Co., p. 1007

de Winter, M.S., Siegmann, C.M. & Szpilfogel, S.A. (1959) 17-Alkylated 3-deoxo-19-nortestosterones. *Chem. Ind*., **11 July**, 905