ANNEX 1
CHEMICAL AND PHYSICAL DATA ON COMPOUNDS USED IN COMBINED ESTROGEN–PROGESTOGEN CONTRACEPTIVES AND HORMONAL MENOPAUSAL THERAPY

Annex 1 describes the chemical and physical data, technical products, trends in production by region and uses of estrogens and progestogens in combined estrogen–progestogen contraceptives and hormonal menopausal therapy. Estrogens and progestogens are listed separately in alphabetical order. Trade names for these compounds alone and in combination are given in Annexes 2–4.

Sales are listed according to the regions designated by WHO. These are:

Africa: Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia and Zimbabwe

America (North): Canada, Central America (Antigua and Barbuda, Bahamas, Barbados, Belize, Costa Rica, Cuba, Dominica, El Salvador, Grenada, Guatemala, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago), United States of America

America (South): Argentina, Bolivia, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Guyana, Paraguay, Peru, Uruguay, Venezuela

Eastern Mediterranean: Afghanistan, Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen

Europe: Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino,

Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom of Great Britain and Northern Ireland, Uzbekistan

South-East Asia: Bangladesh, Bhutan, Democratic People's Republic of Korea, Democratic Republic of Timor-Leste, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand

Western Pacific: Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Viet Nam

1. Estrogens

1.1 Conjugated estrogens

The term 'conjugated estrogens' refers to mixtures of at least eight compounds, including sodium estrone sulfate and sodium equilin sulfate, that are derived wholly or in part from equine urine, are plant-based or are manufactured synthetically from estrone and equilin. Conjugated estrogens contain as concomitant components the sodium sulfate conjugates of 17α-dihydroequilin, 17β-dihydroequilin and 17α-estradiol (Pharmacopeial Convention, 2004).

1.1.1 *Nomenclature*

Sodium estrone sulfate

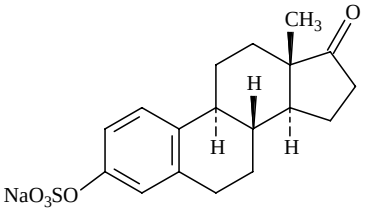
Chem. Abstr. Serv. Reg. No.: 438-67-5
Chem. Abstr. Name: 3-(Sulfooxy)-estra-1,3,5(10)-trien-17-one, sodium salt
IUPAC Systematic Name: Estrone, hydrogen sulfate sodium salt
Synonyms: Estrone sodium sulfate; estrone sulfate sodium; estrone sulfate sodium salt; oestrone sodium sulfate; oestrone sulfate sodium; oestrone sulfate sodium salt; sodium estrone sulfate; sodium estrone-3-sulfate; sodium oestrone sulfate; sodium oestrone-3-sulfate; 3-sulfatoxyestra-1,3,5(10)-trien-17-one, sodium salt

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-Hydroxyestra-1,3,5(10),7-tetraen-17-one, hydrogen sulfate, sodium salt
Synonyms: Equilin, sulfate, sodium salt; equilin sodium sulfate; sodium equilin 3-monosulfate; sodium equilin sulfate

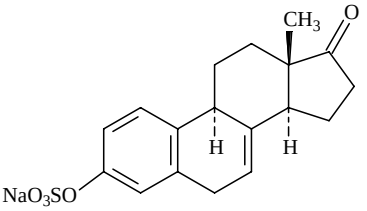
1.1.2 *Structural and molecular formulae and relative molecular mass*

Sodium estrone 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 (2000) and American Hospital Formulary Service (2005)

(*a*) *Description*: Buff-coloured, odourless or with a slight characteristic odour, amorphous powder (from natural sources); white to light buff, odourless or with a slight odour, crystalline or amorphous powder (synthetic)

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

1.1.4 *Technical products and impurities*

Conjugated estrogens contain 52.5% min. and 61.5% max. sodium estrone sulfate and 22.5% min. and 30.5% max. sodium equilin sulfate; the total of sodium estrone sulfate and sodium equilin sulfate is 79.5% min. and 88.0% max. of the labelled content of conjugated estrogens. Conjugated estrogens contain as concomitant components (as sodium sulfate conjugates) 13.5% min. and 19.5% max. 17α-dihydroequilin, 0.5% min. and 4.0% max. 17β-dihydroequilin and 2.5% min. and 9.5% max. 17α-estradiol of the labelled content of conjugated estrogens (Pharmacopeial Convention, 2004).

Conjugated estrogens are available as tablets for oral administration, as a liquid for parenteral injection and as a 0.0625% vaginal cream (American Hospital Formulary Service, 2005).

Conjugated estrogens (natural) are a mixture that contains the sodium salts of the water-soluble sulfate esters of estrone and equilin derived wholly or in part from equine urine or prepared synthetically from estrone and equilin. Conjugated estrogens (natural) also contain conjugated estrogenic substances of types that are excreted by pregnant mares and include δ8,9-dehydroestrone, 17α-dihydroequilenin, 17β-dihydroequilenin, 17α-dihydroequilin, 17β-dihydroequilin, equilenin, 17α-estradiol and 17β-estradiol (American Hospital Formulary Service, 2005).

Conjugated estrogens (synthetic) are a mixture of conjugated estrogens that are prepared synthetically from plant sources (i.e. soya and yams). Conjugated estrogens (synthetic) are commercially available as preparations that contain a mixture of nine of the 10 known conjugated estrogenic substances that are present in currently available commercial preparations of conjugated estrogens (natural). However, in contrast to currently available preparations of conjugated estrogens (natural), the conjugated estrogenic substances present in conjugated estrogens (synthetic) are prepared entirely synthetically (American Hospital Formulary Service, 2005).

1.1.5 *Use*

Conjugated estrogens are used mainly in the treatment of menopausal disorders (e.g. vasomotor symptoms, vulvar and vaginal atrophy) and for the prevention and treatment of osteoporosis. Conjugated estrogens are usually administered orally at a dose of 0.3–1.25 mg/day (American Hospital Formulary Service, 2005).

Table 1 presents comparative global data on sales of conjugated estrogens in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 1. Conjugated estrogens used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Africa	7 980	10 814	9 780
Eastern Mediterranean	51	3 102	1 683
Europe	448 555	508 776	192 332
North America	9 250	1 039 067	217 181
South America	15 330	103 701	32 713
South-East Asia	1 162	1 992	9 555
Western Pacific	17 521	70 675	27 576
Total	499 848	1 738 126	490 820

From IMS Health (2005)

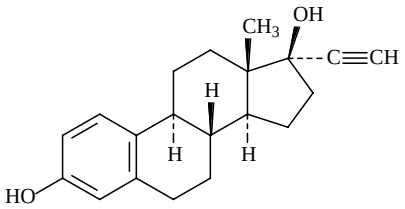
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

1.2 Ethinylestradiol

1.2.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 57-63-6
Deleted CAS Reg. No.: 77538-56-8; 406932-93-2
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: Ethinylestradiol; 17-ethinylestradiol; 17-ethinyl-3,17-estradiol; 17α-ethinyl-3,17-dihydroxy-Δ1,3,5-estratriene; 17α-ethinylestradiol; 17α-ethinyl-17β-estradiol; 17α-ethinylestra-1,3,5(10)-triene-3,17β-diol; 17α-ethinyl-1,3,5(10)-estratriene-3,17-diol; ethinyloestradiol; 17-ethynyl-3,17-dihydroxy-1,3,5-oestratrione; ethynylestradiol; 17-ethynylestradiol; 17α-ethynylestradiol; 17-ethynylestra-1,3,5(10)-triene-3,17β-diol; ethynyloestradiol; 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol

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 O'Neil (2001) and Sweetman (2005), 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° (Pharmacopeial Convention, 2004; Council of Europe, 2005)

1.2.4 *Technical products and impurities*

Ethinylestradiol is commercially available as tablets either alone or in combination with progestogens, as described in the monograph on Combined estrogen–progestogen contraceptives.

Reported impurities include: estradiol, 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone), 19-nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol and 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol (17β-ethinylestradiol) (British Pharmacopoeial Commission, 2004).

1.2.5 *Use*

Ethinylestradiol is a synthetic estrogen that acts similarly to estradiol. It is frequently used as the estrogenic component of combined oral contraceptive preparations; a typical daily dose is 20–50 μg. Ethinylestradiol is also used as an emergency contraceptive combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne and hirsutism, particularly when contraception is also required. Ethinylestradiol has also been used for hormonal menopausal therapy; doses of 10–20 μg daily were given (in conjunction with a progestogen in women with a uterus). For the treatment of female hypogonadism, 50 μg has been given up to three times daily for 14 consecutive days in every 4 weeks, followed by a progestogen for the next 14 days (Sweetman, 2005).

Table 2 presents comparative global data on sales of ethinylestradiol in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 2. Ethinylestradiol used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined estrogen–progestogen contraceptives			
Monophasic preparations (< 50 μg estrogen)			
Africa	2 564	2 955	3 881
Eastern Mediterranean	6 353	8 728	7 494
Europe	159 180	197 014	266 090
North America	55 356	67 909	101 390
South America	52 552	69 183	83 406
South-East Asia	11 807	29 288	58 282
Western Pacific	10 414	14 467	25 673
Subtotal	298 225	389 543	546 215
Monophasic preparations (≥ 50 μg estrogen)			
Africa	2 060	1 611	1 364
Eastern Mediterranean	1 942	827	126
Europe	15 319	9 577	4 932
North America	4 343	2 371	1 788
South America	23 611	19 761	14 395
South-East Asia	3 463	12 619	7 794
Western Pacific	2 125	2 000	1 371
Subtotal	52 863	48 765	31 770

Table 2 (contd)

Regions	1994	1999	2004
Biphasic preparations			
Africa	439	429	473
Eastern Mediterranean	70	59	217
Europe	25 126	22 918	18 833
North America	455	1 979	5 634
South America	41	732	1 297
South-East Asia	0	1	2
Western Pacific	312	211	95
Subtotal	26 442	26 330	26 551
Triphasic preparations			
Africa	4 447	5 360	4 477
Eastern Mediterranean	1 586	965	1 860
Europe	62 951	69 133	55 880
North America	39 551	48 081	51 048
South America	13 612	12 400	10 871
South-East Asia	352	2 232	3 389
Western Pacific	8 613	7 829	7 251
Subtotal	131 111	146 000	134 776
Total	508 641	610 638	739 312
Hormonal menopausal therapy			
Africa	226	0	0
Eastern Mediterranean	267	0	0
Europe	34 581	13 016	5 783
North America	1 187	333	81 863
South America	20 039	15 072	19 291
South-East Asia	5 714	5 041	5 297
Western Pacific	52 461	45 300	30 246
Total	114 475	78 761	142 480

From IMS Health (2005)
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

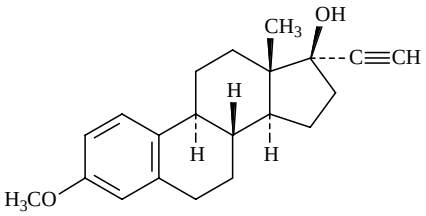
1.3 Mestranol

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 O'Neil (2001) and Sweetman (2005)

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

(*b*) *Melting-point*: 150–154 °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

(*d*) *Optical rotation*: $[\alpha]_D^{20}$, –20° to –24° (British Pharmacopoeial Commission, 2004; Council of Europe, 2005); +2° to +8° (Society of Japanese Pharmacopoeia, 2001; Pharmacopeial Convention, 2004)

1.3.4 *Technical products and impurities*

Mestranol is commercially available as a component of combination tablets with chlormadinone acetate, ethynodiol diacetate, levonorgestrel, lynoestrenol or norethisterone and formerly with norethynodrel (IPPF, 2002; Sweetman, 2005; see the monograph on Combined estrogen–progestogen contraceptives and Annex 2).

1.3.5 *Use*

Mestranol is a synthetic estrogen pro-drug that is rapidly metabolized to ethinylestradiol; it therefore acts similarly to estradiol. It is used as the estrogen component of combined oral contraceptive preparations at a usual daily dose of 50 µg. The progestogen component is frequently norethisterone. Mestranol has also been used as the estrogen component of some preparations for hormonal menopausal therapy. Administration has usually been in a sequential regimen with doses ranging from 12.5 to 50 µg daily, in combination with a cyclical progestogen (Sweetman, 2005).

Table 3 presents comparative global data on sales of mestranol in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 3. Mestranol used in combined estrogen–progestogen contraceptives and combined estrogen-progestogen menopausal therapy (thousands of standard units)

Region	1994	1999	2000
Combined hormonal contraceptives			
Monophasic preparations (≥ 50 µg estrogen)			
Africa	11	35	42
Europe	1 436	589	45
North America	2 983	1 587	928
South America	1 144	1 253	588
South-East Asia	1 381	882	645
Western Pacific	188	164	181
Subtotal	7 142	4 510	2 430
Biphasic preparations			
Europe	48	0	0
North America	624	479	220
South America	175	78	0
Subtotal	848	557	220
Total	7 990	5 067	2 650
Combined hormonal menopausal therapy			
Europe	2 794	939	0
North America	12 006	10 476	7 930
South-East Asia	299	17	0
Western Pacific	18 287	13 811	9 312
Total	33 386	25 243	17 242

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

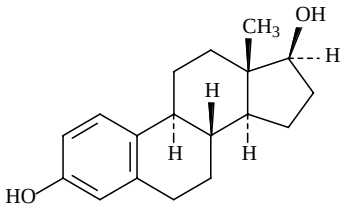
1.4 Estradiols

1.4.1 *Estradiol*

(*a*) *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

(*b*) *Structural and molecular formulae and relative molecular mass*



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

(*c*) *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(i) *Description*: White or creamy white, odourless, crystalline powder
(ii) *Melting-point*: 173–179 °C
(iii) *Solubility*: Practically insoluble in water; soluble in ethanol (1 part in 28), chloroform (1 part in 435), diethyl ether (1 part in 150), acetone, dioxane, and other organic solvents
(iv) *Optical rotation*: $[\alpha]_D^{25}$, +76° to +83° (in dioxane)

Estradiol hemihydrate is a white, or almost white, crystalline powder or colourless crystal; it is practically insoluble in water, sparingly soluble in ethanol, slightly soluble in dichloromethane and diethyl ether and soluble in acetone. Approximately 1.03 g estradiol hemihydrate are equivalent to 1 g of the anhydrous substance (Reynolds, 1996).

(*d*) *Technical products and impurities*

Estradiol is available commercially as oral and vaginal tablets, as a metered topical gel, as topical transdermal patches, as a vaginal cream and as an extended-release vaginal insert (ring) (American Hospital Formulary Service, 2005; Food and Drug Administration, 2005).

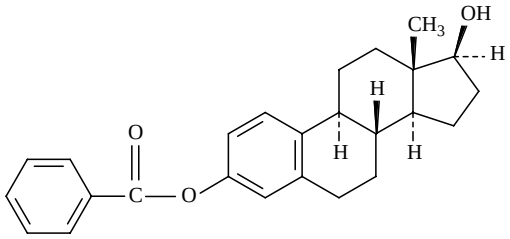
Reported impurities (for estradiol hemihydrate) include: estra-1,3,5(10),9(11)-tetraene-3,17β-diol, estra-1,3,5(10)-triene-3,17α-diol (17α-estradiol), 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone) and 4-methylestra-1,3,5(10)-triene-3,17β-diol (British Pharmacopoeial Commission, 2004).

1.4.2 *Estradiol benzoate*

(*a*) *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

(*b*) *Structural and molecular formulae and relative molecular mass*



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

(*c*) *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(i) *Description*: Almost white crystalline powder or colourless crystals that exhibit polymorphism
(ii) *Melting-point*: 191–196 °C
(iii) *Solubility*: Practically insoluble in water; slightly soluble in ethanol and diethyl ether; sparingly soluble in acetone and vegetable oils; and soluble in dioxane and dichloromethane
(iv) *Optical rotation*: $[\alpha]_D^{25}$, +58° to +63° (in dioxane)

(*d*) *Technical products and impurities*

Estradiol benzoate is commercially available for injection (oily or aqueous suspension) and implant (Society of Japanese Pharmacopoeia, 2001; British Pharmacopoeial Commission, 2004).

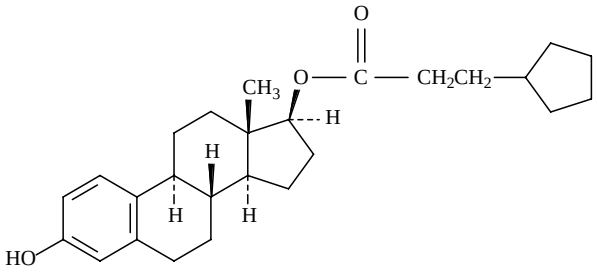
Reported impurities include: estradiol, estra-1,3,5(10)-triene-3,17β-diyl dibenzoate, 17β-hydroxyestra-1,3,5(10),9(11)-tetraen-3-yl benzoate, 3-hydroxyestra-1,3,5(10)-trien-17β-yl benzoate, 17α-hydroxyestra-1,3,5(10)-trien-3-yl benzoate and 17β-hydroxy-4-methylestra-1,3,5(10)-trien-3-yl benzoate (British Pharmacopoeial Commission, 2004).

1.4.3 *Estradiol cypionate*

(*a*) *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

(*b*) *Structural and molecular formulae and relative molecular mass*



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

(*c*) *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(i) *Description*: White, odourless crystalline powder
(ii) *Melting-point*: 151–152 °C
(iii) *Solubility*: Practically insoluble in water; soluble in ethanol (1 part in 40), chloroform (1 in 7), diethyl ether (1 in 2800), acetone and dioxane
(iv) *Optical rotation*: $[\alpha]_D^{25}$, +45° (in chloroform)

(*d*) *Technical products and impurities*

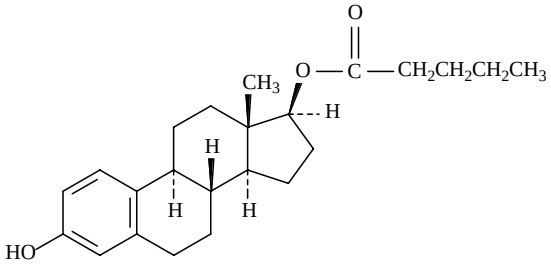
Estradiol cypionate is available commercially as injectable suspensions in oil for parenteral administration (American Hospital Formulary Service, 2005; Food and Drug Administration, 2005).

1.4.4 *Estradiol valerate*

(*a*) *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: 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; oestradiol valerate

(*b*) *Structural and molecular formulae and relative molecular mass*



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

(*c*) *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(i) *Description*: White, odourless, crystalline powder
(ii) *Melting-point*: 144–145 °C
(iii) *Solubility*: Practically insoluble in water; soluble in benzyl benzoate, dioxane, methanol and castor oil; sparingly soluble in arachis oil and sesame oil

(*d*) *Technical products and impurities*

Estradiol valerate is available commercially as injectable suspensions in oil for parenteral administration; it is also available commercially as tablets alone or in combination with progestogens (IPPF, 2002; American Hospital Formulary Service, 2005; Editions du Vidal, 2005; Sweetman, 2005).

Reported impurities include: estradiol, estra-1,3,5(10)-trien-3,17β-diyl dipentanoate, 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17β-yl pentanoate, 3-hydroxyestra-1,3,5(10)-trien-

17β-yl butanoate (estradiol butyrate), 17β-hydroxyestra-1,3,5(10)-trien-3-yl pentanoate and 3-hydroxy-4-methylestra-1,3,5(10)-trien-17β-yl pentanoate (British Pharmacopoeial Commission, 2004).

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

1.4.5 *Use of estradiols*

Estradiol is the most active of the naturally occurring estrogens. Estradiol and its semisynthetic esters and other natural estrogens are primarily used in hormonal menopausal therapy, whereas synthetic derivatives such as ethinylestradiol and mestranol have a major role as components of combined oral contraceptives. Estradiol may also be used in hormonal therapy for female hypogonadism or primary ovarian failure (Sweetman, 2005).

For hormonal menopausal therapy, oral preparations of estradiol are commonly used, as are transdermal patches. Transdermal gels, subcutaneous implants and a nasal spray are also available. Intramuscular injections were used formerly. In women with a uterus, a progestogen is also required, given cyclically or continuously, and is usually taken orally, although some transdermal preparations are available. Vaginal estradiol preparations are used specifically for the treatment of menopausal atrophic vaginitis; these are generally recommended for short-term use only, if given without a progestogen in women with a uterus, although specific recommendations vary between products (Sweetman, 2005).

For oral use, estradiol or estradiol valerate are normally given; doses are 1–2 mg daily cyclically or, more usually, continuously (Sweetman, 2005).

Estradiol may be used topically as transdermal skin patches to provide a systemic effect; a variety of patches are available that release between 25 and 100 μg estradiol every 24 h. Depending on the preparation, patches are replaced once or twice weekly. Topical gel preparations are also applied for systemic effect: the usual dose is 0.5–1.5 mg estradiol daily. A nasal spray is available that delivers 150 μg estradiol hemihydrate per spray. The usual initial dose is 300 μg daily; maintenance doses are 150–600 μg daily (Sweetman, 2005).

In order to prolong the duration of action, subcutaneous implants of estradiol may be used. The dose of estradiol is generally 25–100 mg and a new implant is given after about 4–8 months according to the concentrations of estrogen (Sweetman, 2005).

Estradiol may be used locally as vaginal tablets, as a 0.01% vaginal cream or as a 3-month vaginal ring (Sweetman, 2005).

Intramuscular injections of estradiol benzoate or valerate esters have been used as oily depot solutions, usually given once every 3–4 weeks. The cypionate, dipropionate, enanthate, hexahydrobenzoate, phenylpropionate and undecylate esters of estradiol have been used similarly. The enanthate and cypionate esters are used as the estrogen component of combined injectable contraceptives (Sweetman, 2005).

Tables 4 and 5 present comparative global data on sales of estradiol and methylestradiol, respectively, in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 4. Estradiol used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 µg estrogen)			
Eastern Mediterranean	0	0	3 075
South America	0	192	298
Subtotal	0	192	3 372
Biphasic preparations			
Europe	114	222	245
North America	0	0	2
Subtotal	114	222	248
Total	114	414	3 620
Combined hormonal menopausal therapy			
Africa	12 079	18 307	17 130
Eastern Mediterranean	7 849	15 895	23 611
Europe	698 456	1 254 408	854 592
North America	17 233	39 571	114 851
South America	62 451	163 521	136 594
South-East Asia	7 954	21 790	44 194
Western Pacific	12 558	84 200	38 764
Total	818 581	1 597 690	1 229 735

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

Table 5. Methylestradiol used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Eastern Mediterranean	10	0	0
South America	2023	2019	1767
South-East Asia	1694	2857	1839
Total	3727	4876	3606

From IMS Health (2005)

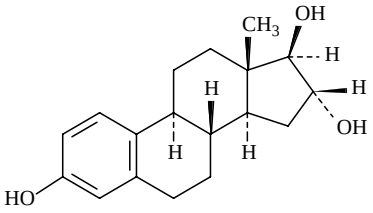
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

1.5 Estriol

1.5.1 *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

1.5.2 *Structural and molecular formulae and relative molecular mass*



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

1.5.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*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; freely soluble in pyridine
(*d*) *Specific rotation*: $[\alpha]_D^{25}$, +58° (in dioxane)

1.5.4 *Technical products and impurities*

Estriol is commercially available as tablets, pessaries and a cream. Sodium succinate and succinate salts of estriol are also available (Sweetman, 2005).

Reported impurities include: estradiol, estra-1,3,5(10),9(11)-tetraene-3,16α,17β-triol (9,11-didehydroestriol), estra-1,3,5(10)-triene-3,16α,17α-triol (17-epi-estriol), estra-1,3,5(10)-triene-3,16β,17β-triol (16-epi-estriol), estra-1,3,5(10)-triene-3,16β,17α-triol (16,17-epi-estriol), 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone); 3,16α-dihydroxy-estra-1,3,5(10)-trien-17-one, 3-hydroxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-17a-one and 3-methoxyestra-1,3,5(10)-triene-16α,17β-diol (estriol 3-methyl ether) (British Pharmacopoeial Commission, 2004).

1.5.5 *Use*

Estriol is a naturally occurring estrogen that has actions and uses similar to those described for estradiol. It is used for hormonal menopausal therapy. For short-term treatment, oral doses of estriol have been 0.5–3 mg daily given for 1 month, followed by 0.5–1 mg daily. Estriol has also been given in combination with other natural estrogens, such as estradiol and estrone; usual doses of estriol have ranged from about 250 µg to 2 mg daily. It is also administered intravaginally for the short-term treatment of menopausal atrophic vaginitis as a 0.01% or 0.1% cream or as pessaries containing 500 µg (Sweetman, 2005).

Table 6 presents comparative global data on sales of estriol in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 6. Estriol used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Europe	85 372	83 465	28 058
South-East Asia	3 151	5 249	6 577
Western Pacific	0	10	71
Total	88 523	88 724	34 706

From IMS Health (2005)

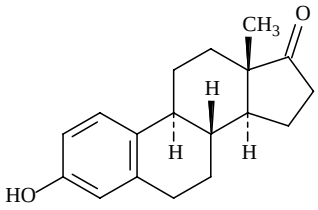
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

1.6 Estrone

1.6.1 *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

1.6.2 *Structural and molecular formulae and relative molecular mass*



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

1.6.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*a*) *Description*: White to creamy white, odourless, crystalline powder (exists in three crystalline phases: one monoclinic, the other two orthorhombic)

(*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° (in chloroform)

1.6.4 *Technical products and impurities*

Estrone is available commercially as pessaries and as a sterile suspension in water or 0.9% sodium chloride for injection. It is also available as a multicomponent tablet, cream and injectable solution (American Hospital Formulary Service, 2005; APPCo, 2005; Editions du Vidal, 2005).

1.6.5 *Use*

Estrone is a naturally occurring estrogen that has actions and uses similar to those described for estradiol. For hormonal menopausal therapy, estrone has been given orally at a dose of 1.4–2.8 mg daily, in a cyclical or continuous regimen, as a combination product with estradiol and estriol. Estrone has also been administered by intramuscular injection in oily solutions and aqueous suspensions. When used specifically for menopausal atrophic vaginitis, estrone has been administered vaginally (Sweetman, 2005).

Table 7 presents comparative global data on sales of estrone in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 7. Estrone used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Africa	765	754	812
Europe	499	69	48
North America	6	1	0
South America	34	6	0
Total	1305	829	860

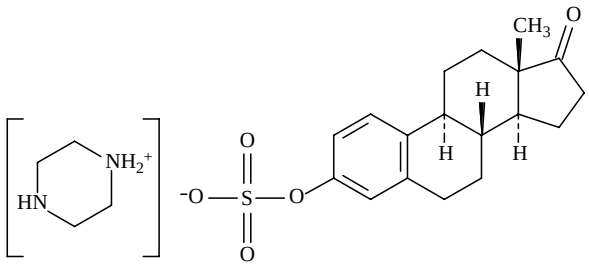
From IMS Health (2005)
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

1.7 Estropipate

1.7.1 *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

1.7.2 *Structural and molecular formulae and relative molecular mass*



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

1.7.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)
(*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° (in sodium hydroxide)

1.7.4 *Technical products and impurities*

Estropipate is available as tablets and as a vaginal cream (American Hospital Formulary Service, 2005).

Reported impurities include: estrone (British Pharmacopoeial Commission, 2004).

1.7.5 *Use*

Estropipate is a semi-synthetic conjugate of estrone with piperazine that is used for hormonal menopausal therapy. Its action is due to estrone to which it is hydrolysed in the body. Estropipate is given orally for the short-term treatment of menopausal symptoms; suggested doses have ranged from 0.75 to 6 mg daily, given cyclically or continuously. When used for longer periods for the prevention of postmenopausal osteoporosis, a daily dose of 0.75 or 1.5 mg is given cyclically or continuously. In women with a uterus, estropipate should be used in conjunction with a progestogen. Estropipate has also been used in the short-term treatment of menopausal atrophic vaginitis as a vaginal cream that contains 0.15%; 2–4 g of cream is applied daily (Sweetman, 2005).

Table 8 presents comparative global data on sales of estropipate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 8. Estropipate used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Europe	0	121	0
Total	0	121	0

From IMS Health (2005)
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

1.8 Regulations and guidelines

Guidelines for the use of estrogens are found in national and international pharmacopoeias (Secretaría de Salud, 1994, 1995; Society of Japanese Pharmacopoeia, 2001; Pharmacopeial Convention, 2004; Swiss Pharmaceutical Society, 2004; Council of Europe, 2005; Sweetman, 2005).

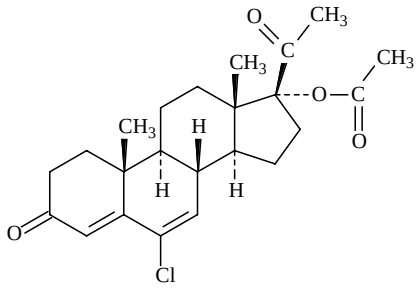
2. Progestogens

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 O'Neil (2001) and Society of Japanese Pharmacopoeia (2001)

(*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° (in acetonitrile) (Society of Japanese Pharmacopoeia, 2001); $[\alpha]_D$, +6° (in chloroform) (O'Neil, 2001)

2.1.4 *Technical products and impurities*

Chlormadinone acetate is available commercially as tablets, either alone or in combination with ethinylestradiol or mestranol (IPPF, 2002).

2.1.5 *Use*

Chlormadinone acetate is a progestogen that is structurally related to progesterone and that may have some anti-androgenic activity. It is given orally either alone or in combination with an estrogen in the treatment of menstrual disorders such as menorrhagia and endometriosis at doses of 2–10 mg daily either cyclically or continuously. It may also be used as the progestogen component of combined oral contraceptives at a dose of 1–2 mg daily, particularly in women with androgen-dependent conditions such as acne and hirsutism (Sweetman, 2005).

Table 9 presents comparative global data on sales of chlormadinone acetate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 9. Chlormadinone acetate used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 µg estrogen)			
Eastern Mediterranean	0	0	40
Europe	0	1 768	5 937
North America	0	0	72
South America	0	0	238
Subtotal	0	1 768	6 288
Monophasic preparations (≥ 50 µg estrogen)			
Europe	858	547	0
Subtotal	858	547	0
Biphasic preparations			
Europe	2 312	2 769	1 797
North America	506	329	167
Subtotal	2 818	3 098	1 964
Total	3 676	5 413	8 252
Combined hormonal menopausal therapy			
Africa	226	0	0
Eastern Mediterranean	267	0	0
Europe	860	0	0
North America	12 006	10 476	7 930
Western Pacific	509	365	299
Total	13 868	10 841	8 230

From IMS Health (2005)

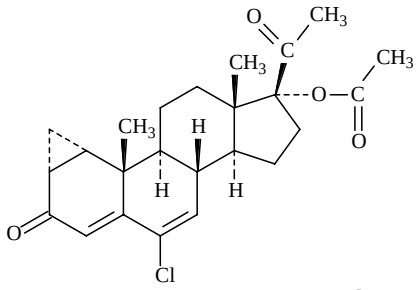
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

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 O'Neil (2001) and Council of Europe (2005)

(*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 an injectable solution (IPPF, 2002; British Medical Association/Royal Pharmaceutical Society of Great Britain, 2004; APPCo, 2005).

Reported impurities include: 3,20-dioxo-1β,2β-dihydro-3′*H*-cyclopropa[1,2]pregna-1,4,6-trien-17-yl acetate and 6-methoxy-3,20-dioxo-1β,2β-dihydro-3′*H*-cyclopropa[1,2]-pregna-1,4,6-trien-17-yl acetate (British Pharmacopoeial Commission, 2004).

2.2.5 *Use*

Cyproterone acetate is a progestogen that has anti-androgenic properties. It is typically used in conjunction with ethinylestradiol for the control of acne and hirsutism in women, and also provides contraception in these women. The usual oral doses are 2 mg cyproterone acetate with 35 μg ethinylestradiol given daily for 21 days of each menstrual cycle (Sweetman, 2005).

Table 10 presents comparative global data on sales of cyproterone acetate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 10. Cyproterone acetate used in combined estrogen–progestogen contraceptives, combined estrogen–progestogen menopausal therapy and other uses (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Biphasic preparations			
Europe	114	222	245
Total	114	222	245
Combined hormonal menopausal therapy			
Africa	0	2 064	1 503
Eastern Mediterranean	0	139	1 125
Europe	15 170	84 098	42 379
North America	0	6 322	5 324
South America	323	42 043	25 999
South-East Asia	0	3 461	10 455
Western Pacific	0	1 625	2 577
Total	15 493	139 751	89 363
Oral anti-acne preparations			
Africa	10 015	12 875	15 901
Eastern Mediterranean	3 684	7 312	11 576
Europe	447 961	495 803	627 266
North America	5 995	15 219	36 054
South America	80 570	129 686	254 244
South-East Asia	28 711	31 593	63 107
Western Pacific	17 838	41 116	87 877
Total	594 773	733 603	1 096 026

From IMS Health (2005)

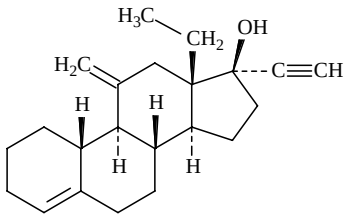
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

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 O'Neil (2001) and Sweetman (2005)
(*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° (in chloroform)

2.3.4 *Technical products and impurities*

Desogestrel is available commercially only in combination with ethinylestradiol in tablets for monophasic and triphasic regimens (IPPF, 2002; British Medical Association/ Royal Pharmaceutical Society of Great Britain, 2004; American Hospital Formulary Service, 2005; Editions du Vidal, 2005; Sweetman, 2005).

Reported impurities include: 13-ethyl-16-[13-ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-16-ylidene]-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17β-ol, 13-ethyl-11-methylene-18,19-dinor-5α,17α-pregn-3-en-20-yn-17-ol (desogestrel D^3-isomer) and 11-methylene-19-nor-17α-pregn-4-en-20-yn-17-ol; 13-ethyl-11-methylenegon-4-en-17-one (British Pharmacopoeial Commission, 2004).

2.3.5 *Use*

Desogestrel is a synthetic progestene that is structurally related to levonorgestrel, has actions and uses similar to those of progestogens in general and has 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 oral dose of 150 μg is used as the progestogenic component of combined oral contraceptive preparations. An oral dose of 75 μg daily is used as a progestogen-only contraceptive (Editions du Vidal, 2005; Sweetman, 2005).

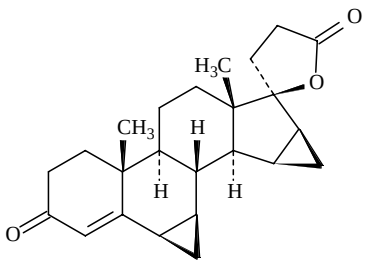
Table 11 presents comparative global data on sales of desogestrel in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

2.4 Drospirenone

2.4.1 *Nomenclature*

Chem. Abst. Services Reg. No.: 67392-87-4
Chem. Abstr. Name: (2′S,6R,7R,8R,9S,10R,13S,14S,15S,16S)-1,3′,4′,6,7,8,9,10,11,12,13,14,15,16,20,21-Hexadecahydro-10,13-dimethyl-spiro[17H-dicyclopropa-[6,7:15,16]cyclopenta[a]phenanthrene-17,2′ (5′H)-furan]-3,5′ (2H)-dione
Synonyms: Dihydrospirorenone; 1,2-dihydrospirorenone; drospirenona; spiro[17H-dicyclopropa[6,7:15,16]cyclopenta[a]phenanthrene-17,2′ (5′H)-furan]-3,5′ (2H)-dione, 1,3′,4′,6,7,8,9,10,11,12,13,14,15,16,20,21-hexadecahydro-10,13-dimethyl-, [6R-(6α, 7α,8β,9α,10β,13β,14α,15α,16α,17β)]-

2.4.2 *Structural and molecular formulae and relative molecular mass*



$C_{24}H_{30}O_3$ Relative molecular mass: 366.5

2.4.3 *Chemical and physical properties*

From O'Neil (2001)
(*a*) *Melting-point*: 201.3 °C
(*b*) *Optical rotation*: $[\alpha]_D^{22}$, –182° (in chloroform)

Table 11. Desogestrel used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 µg estrogen)			
Africa	287	231	223
Eastern Mediterranean	495	841	1 129
Europe	65 347	51 877	53 550
North America	9 875	11 326	15 764
South America	7 675	9 952	8 295
South-East Asia	1 618	4 078	5 933
Western Pacific	2 320	2 122	2 237
Subtotal	87 617	80 426	87 131
Monophasic preparations (≥ 50 µg estrogen)			
North America	0	0	19
South America	1	0	0
Subtotal	1	0	19
Biphasic preparations			
Eastern Mediterranean	0	0	148
Europe	3 430	3 893	4 774
North America	0	1 879	5 620
South America	0	732	1 298
South-East Asia	0	1	2
Western Pacific	0	3	46
Subtotal	3 430	6 508	11 888
Triphasic preparations			
Europe	0	120	1 690
North America	0	0	880
Subtotal	0	120	2 571
Total	91 048	87 054	101 609
Combined hormonal menopausal therapy			
Europe	10 563	3 992	2 532
Total	10 563	3 992	2 532

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.4.4 *Technical products and impurities*

Drospirenone is available as capsules that contain 3.0 mg drospirenone and 0.030 mg ethinylestradiol as part of an oral contraceptive regimen (IPPF, 2002).

2.4.5 *Use*

Drospirenone is a progestogen with anti-mineralo-corticoid and anti-androgenic activities; it is used as the progestogenic component of a combined oral contraceptive at doses of 3 mg daily (Sweetman, 2005). Its use in hormonal menopausal therapy has also been reported very recently (IMS Health, 2005).

Table 12 presents comparative global data on sales of drospirenone in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 12. Drospirenone used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 μg estrogen)			
Africa	0	0	293
Eastern Mediterranean	0	0	601
Europe	0	0	25 422
North America	0	0	11 996
South America	0	0	4 129
South East Asia	0	0	92
Western Pacific	0	0	1 087
Total	0	0	43 620
Combined hormonal menopausal therapy			
Africa	0	0	209
Europe	0	0	3 191
Total	0	0	3 400

From IMS Health (2005)

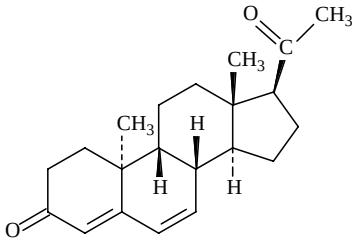
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.5 Dydrogesterone

2.5.1 *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

2.5.2 *Structural and molecular formulae and relative molecular mass*



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

2.5.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*a*) *Description*: White to pale yellow, 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)

2.5.4 *Technical products and impurities*

Dydrogesterone is available commercially as tablets and capsules, either alone or in combination with estradiol (British National Formulary, 2004; APPCo, 2005; Editions du Vidal, 2005).

2.5.5 *Use*

Dydrogesterone is a progestogen that is structurally related to progesterone, but does not have estrogenic or androgenic properties. Together with cyclic or continuous estrogen, dydrogesterone is also given cyclically in oral doses of 10 mg once or twice daily, or continuously in doses of 5 mg daily, for endometrial protection during hormonal menopausal therapy. It is also given orally in the treatment of menstrual disorders such as menorrhagia, usually in a dose of 10 mg twice daily in a cyclical regimen, and for the treatment of endometriosis at a dose of 10 mg two or three times daily cyclically or continuously (British Medical Association, 2004; Sweetman, 2005).

Table 13 presents comparative global data on sales of dydrogesterone in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 13. Dydrogesterone used in a combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Africa	0	0	87
Eastern Mediterranean	0	1 226	2 283
Europe	0	51 054	115 892
South America	0	0	2 429
South-East Asia	0	104	3 352
Western Pacific	0	368	570
Total	0	52 752	124 613

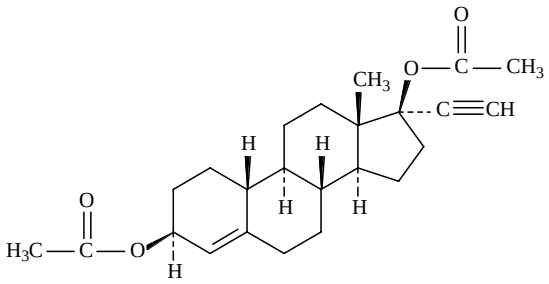
From IMS Health (2005)
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.6 Ethynodiol diacetate

2.6.1 *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

2.6.2 *Structural and molecular formulae and relative molecular mass*



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

2.6.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005), unless otherwise noted
(*a*) *Description:* White, odourless, crystalline powder
(*b*) *Melting-point:* ~126–127 °C

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

(*d*) *Optical rotation*: $[\alpha]_D^{20}$, –70° to –76° (in chloroform) (Pharmacopeial Commission, 2004)

2.6.4 *Technical products and impurities*

Ethynodiol diacetate is available commercially alone or as a component of a combination tablet that contains ethynodiol diacetate plus ethinylestradiol or mestranol (Sweetman, 2005).

2.6.5 *Use*

Ethynodiol diacetate is a progestogen that is used as the progestogenic component of combined oral contraceptives and also alone as an oral progestogen-only contraceptive. Typical daily doses are 1–2 mg in combination products and 500 µg for progestogen-only contraceptives (Sweetman, 2005).

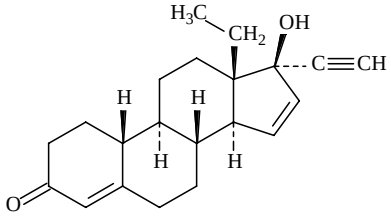
Table 14 presents comparative global data on sales of ethynodiol diacetate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

2.7 Gestodene

2.7.1 *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

2.7.2 *Structural and molecular formulae and relative molecular mass*



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

Table 14. Ethynodiol diacetate used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 μg estrogen)			
Europe	65	28	0
North America	3 904	4 363	3 239
Western Pacific	32	0	26
Subtotal	4 000	4 390	3 265
Monophasic preparations (≥ 50 μg estrogen)			
Africa	26	0	0
Europe	127	0	0
North America	533	232	40
South America	299	176	62
South-East Asia	778	655	448
Western Pacific	69	6	2
Subtotal	1 832	1 069	551
Biphasic preparations			
South America	9	7	0
Subtotal	9	7	0
Total	5 841	5 466	3 816
Combined hormonal menopausal therapy			
Europe	0	49	0
Western Pacific	2 427	1 283	598
Total	2 427	1 332	598

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.7.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001)

(*a*) *Description*: Crystals

(*b*) *Melting-point*: 197.9 °C

2.7.4 *Technical products and impurities*

Gestodene is available commercially as a component of combination tablets with ethinylestradiol (IPPF, 2002; Editions du Vidal, 2005).

2.7.5 *Use*

Gestodene is used as the progestogenic component of combined oral contraceptives; a typical daily dose is 75 µg in monophasic preparations and 50–100 µg in triphasic preparations (Sweetman, 2005).

Table 15 presents comparative global data on sales of gestodene in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 15. Gestodene used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptive			
Monophasic preparations (< 50 µg estrogen)			
Africa	416	580	778
Eastern Mediterranean	305	1 118	2 103
Europe	42 138	49 100	59 460
North America	1 232	1 873	1 864
South America	9 939	16 905	22 829
South-East Asia	1 932	1 661	2 686
Western Pacific	1 111	1 359	1 633
Subtotal	57 072	72 595	91 352
Biphasic preparations			
Europe	1	0	0
Subtotal	1	0	0
Triphasic preparations			
Africa	155	136	84
Europe	11 958	15 204	9 695
South America	0	121	69
Western Pacific	0	53	1
Subtotal	12 113	15 514	9 849
Total	69 186	88 109	101 201
Combined hormonal menopausal therapy			
Europe	0	0	4 980
South America	0	0	1 412
North America	0	0	428
Total	0	0	6 821

From IMS Health (2005)

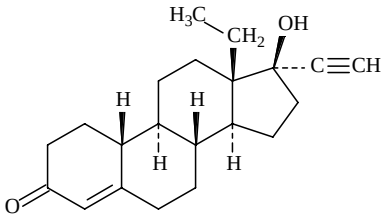
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.8 Levonorgestrel

2.8.1 *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

2.8.2 *Structural and molecular formulae and relative molecular mass*



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

2.8.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*a*) *Description*: White or almost white, odourless, crystalline powder
(*b*) *Melting-point*: 235–237 °C
(*c*) *Solubility*: Practically insoluble in water; slightly soluble in ethanol; sparingly soluble in dichloromethane; soluble in chloroform
(*d*) *Specific rotation*: $[\alpha]_D^{20}$, –32.4° (in chloroform)

2.8.4 *Technical products and impurities*

Levonorgestrel is available commercially as a single-ingredient tablet and in combined tablets with estradiol, estradiol valerate, estriol and ethinylestradiol for hormonal therapy (British Pharmacopaeial Commission, 2004). It is also available as an intrauterine system and as a flexible, closed-capsule implant made of silicone rubber tubing (Sweetman, 2005).

Reported impurities include: 13-ethyl-3,4-diethynyl-18,19-dinor-17α-pregn-5-en-20-yn-3β,4α,17-triol, 13-ethyl-3,4-diethynyl-18,19-dinor-17α-pregn-5-en-20-yn-3α,4α,17-triol 13-ethyl-18,19-dinor-17α-pregn-4-en-20-yn-17-ol, 13-ethyl-3-ethynyl-18,19-dinor-

17α-pregna-3,5-dien-20-yn-17-ol, 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,8(14)-dien-20-yn-3-one and 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-5(10)-en-20-yn-3-one (British Pharmacopoeial Commission, 2004).

2.8.5 *Use*

Levonorgestrel is D-(–)-norgestrel, the active levorotatory form of norgestrel.

Levonorgestrel is more commonly used as a hormonal contraceptive than norgestrel (and is twice as potent) and has androgenic activity. The typical daily dose of levonorgestrel is 30 or 37.5 µg when used as an oral progestogen-only contraceptive, 150–250 µg when used as a combined oral contraceptive in monophasic preparations, and 50–125 µg when used as a combined oral contraceptive in triphasic preparations. Levonorgestrel is also used as a long-acting (up to 5 years) progestogen-only contraceptive administered by subcutaneous implantation. A long-acting intrauterine device is also available for contraception or menorrhagia (Sweetman, 2005).

Levonorgestrel is used as the progestogenic component of hormonal menopausal therapy. A typical oral regimen is 75–250 µg levonorgestrel for 10–12 days of a 28-day cycle. Levonorgestrel may also be given via a combined transdermal patch, applied once weekly for 2 weeks of a 4-week cycle, that releases 10 µg per 24 h together with an estrogen. Alternatively, a patch that releases 7 µg per 24 h together with an estrogen is applied once weekly for continuous hormonal therapy (Sweetman, 2005).

Table 16 presents comparative global data on sales of levonorgestrel in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

2.9 Lynestrenol

2.9.1 *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

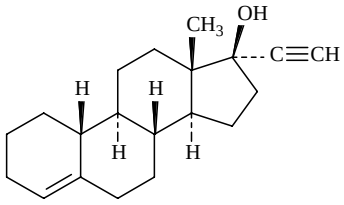
Table 16. Levonorgestrel used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2001
Combined hormonal contraceptives			
Monophasic preparations (< 50 µg estrogen)			
Africa	1 854	2 142	2 584
Eastern Mediterranean	5 501	6 636	3 364
Europe	31 996	61 292	79 164
North America	10 928	16 583	22 538
South America	34 863	42 064	46 906
South-East Asia	3 640	19 803	42 426
Western Pacific	5 858	9 167	18 916
Subtotal	94 638	157 686	215 897
Monophasic preparations (≥ 50 µg estrogen)			
Africa	30	15	5
Eastern Mediterranean	318	286	66
Europe	7 637	4 679	2 706
North America	1 132	671	537
South America	15 709	15 387	13 050
South-East Asia	238	8 734	3 962
Western Pacific	1 439	1 304	753
Subtotal	26 502	31 077	21 079
Biphasic preparations			
Africa	313	336	400
Eastern Mediterranean	70	59	69
Europe	14 814	13 302	10 835
Western Pacific	312	200	49
Subtotal	15 508	13 896	11 352
Triphasic preparations			
Africa	4 181	5 150	4 353
Eastern Mediterranean	1 586	965	1 860
Europe	43 499	47 396	39 636
North America	21 673	18 226	11 415
South America	13 418	11 908	10 607
South-East Asia	352	2 232	3 389
Western Pacific	8 329	7 545	6 718
Subtotal	93 037	93 421	77 977
Total	229 685	296 080	326 305
Combined hormonal menopausal therapy			
Europe	187 978	231 661	85 112
North America	0	0	790
South America	20 543	20 553	10 889
South-East Asia	0	428	2 054
Western Pacific	354	300	95
Total	208 875	252 942	98 941

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.9.2 *Structural and molecular formulae and relative molecular mass*



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

2.9.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*a*) *Description*: White, crystalline powder
(*b*) *Melting-point*: 158–160 °C
(*c*) *Solubility*: Practically insoluble in water; soluble in ethanol, acetone and diethyl ether; freely soluble in chloroform
(*d*) *Specific rotation*: $[\alpha]_D$, –13° (in chloroform)

2.9.4 *Technical products and impurities*

Lynestrenol is available commercially as a single-ingredient tablet and as a component of combination tablets that contain ethinylestradiol or mestranol (Reynolds, 1996; IPPF, 2002; Editions du Vidal, 2005).

2.9.5 *Use*

Lynestrenol is used alone or as the progestogenic component of oral contraceptives. Typical oral daily doses for contraception are 0.5 mg when used as a progestogen-only preparation and 0.75–2.5 mg when combined with an estrogen. When used alone for menstrual disorders, doses of 5 to 10 mg daily are given, frequently as cyclical regimens (Sweetman, 2005).

Table 17 presents comparative global data on sales of lynestrenol in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

2.10 *Medroxyprogesterone acetate*

2.10.1 *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

Table 17. Lynoestrenol used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

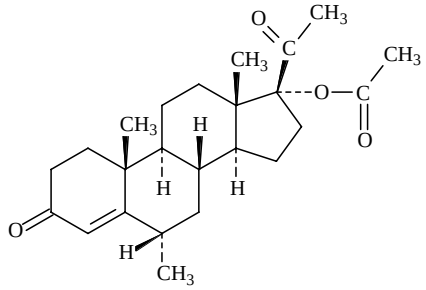
Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 μg estrogen)			
Europe	1197	658	538
South America	0	0	13
South-East Asia	23	0	0
Subtotal	1220	658	551
Monophasic preparations (≥ 50 μg estrogen)			
Africa	8	0	0
Eastern Mediterranean	10	0	0
Europe	1619	842	0
North America	114	0	0
South America	1644	1570	581
South-East Asia	1684	2156	2374
Western Pacific	82	76	0
Subtotal	5162	4643	2956
Biphasic preparations			
Africa	7	7	0
Europe	1839	1088	310
South America	41	0	0
Subtotal	1887	1095	310
Total	8269	6396	3817
Combined hormonal menopausal therapy			
Europe	986	407	0
Western Pacific	6676	4373	2344
Total	7662	4780	2344

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

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

2.10.2 *Structural and molecular formulae and relative molecular mass*



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

2.10.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

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

(*b*) *Melting-point*: 207–209 °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 and dichloromethane

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

2.10.4 *Technical products and impurities*

Medroxyprogesterone acetate is available commercially as single-ingredient tablets, as combination tablets with conjugated estrogens, estradiol or estradiol cypionate and as sterile suspensions (IPPF, 2002; American Hospital Formulary Service, 2005; Editions du Vidal, 2005).

Reported impurities include: 6α,17a-dimethyl-3,17-dioxo-*D*-homoandrost-4-en-17aα-yl acetate, 6β-hydroxy-6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6β-hydroxymedroxyprogesterone acetate), 17-hydroxy-6α-methylpregn-4-ene-3,20-dione (medroxyprogesterone), 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate, 6α-methyl-3,20-dioxo-5β-pregnan-17-yl acetate (4,5β-dihydromedroxyprogesterone acetate), 6β-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epimedroxyprogesterone acetate) and 6-methylene-3,20-dioxopregn-4-en-17-yl acetate (6-methylenehydroxyprogesterone acetate) (British Pharmacopoeial Commission, 2004).

2.10.5 *Use*

Medroxyprogesterone acetate is given by intramuscular injection as a contraceptive. A combined contraceptive injection that contains 25 mg medroxyprogesterone acetate

with 5 mg estradiol cypionate is given monthly. As a progestogen-only contraceptive, a dose of 150 mg is given every 12 weeks.

When used as the progestogen component of hormonal menopausal therapy, medroxyprogesterone acetate is administered orally in a variety of regimens that include 2.5 or 5 mg daily continuously, 5 or 10 mg daily for 12–14 days of a 28-day cycle and 20 mg daily for 14 days of a 91-day cycle (Sweetman, 2005).

It is also used for the treatment of menorrhagia and secondary amenorrhoea and in the palliative treatment of some hormone-dependent malignant neoplasms (Sweetman, 2005).

Table 18 presents comparative global data on sales of medroxyprogesterone acetate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 18. Medroxyprogesterone acetate used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Africa	0	1 068	2 669
Eastern Mediterranean	0	514	511
Europe	54 980	298 081	167 948
North America	0	1 031 863	219 035
South America	23 322	131 139	41 098
South-East Asia	4 782	6 691	13 091
Western Pacific	6 364	101 908	31 230
Total	89 447	1 571 264	475 583

From IMS Health (2005)

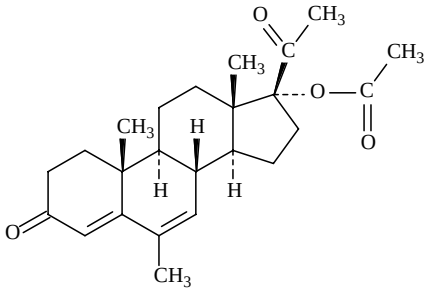
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.11 Megestrol acetate

2.11.1 *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

2.11.2 *Structural and molecular formulae and relative molecular mass*



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

2.11.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*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)

2.11.4 *Technical products and impurities*

Megestrol acetate is available commercially as tablets and as an oral suspension (IPPF, 2002; Editions du Vidal, 2005).

Reported impurities include: 6,17a-dimethyl-3,17-dioxo-*D*-homoandrosta-4,6-dien-17aα-yl acetate (*D-homo* megestrol acetate), 6α-methyl-3,20-dioxopregn-4-en-17-yl acetate (medroxyprogesterone acetate), 6-methyl-3,20-dioxopregna-1,4,6-trien-17-yl acetate, 6-methylene-3,20-dioxopregn-4-en-17-yl acetate (6-methylene hydroxyprogesterone acetate) and 6-methyl-17-hydroxypregna-4,6-diene-3,20-dione (megestrol) (British Pharmacopoeial Commission, 2004).

2.11.5 *Use*

Megestrol acetate has been used in a few countries as an oral contraceptive, usually in combination with ethinylestradiol, although it is believed that such usage has been discontinued. It is used for the palliative treatment of carcinoma of the breast or endometrium, in the treatment of acne, hirsutism and sexual infantilism in women and in the treatment of anorexia and cachexia in patients with acquired immunodeficiency syndrome or cancer (Reynolds, 1996; Sweetman, 2005).

Table 19 presents comparative global data on sales of megestrol acetate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 19. Megestrol acetate used in combined oestrogen–progestogen contraceptives (thousands of standard units[a])

Region	1994	1999	2004
Monophasic preparations (≥ 50 μg estrogen)			
South America	185	87	0
Total	185	87	0

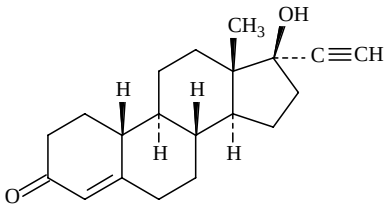
From IMS Health (2005)
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.12 Norethisterone

2.12.1 *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

2.12.2 *Structural and molecular formulae and relative molecular mass*



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

2.12.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)
(*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° (in chloroform)

2.12.4 *Technical products and impurities*

Norethisterone is available commercially as single-ingredient tablets or as a component of combination tablets with ethinylestradiol or mestranol (IPPF, 2002).

2.12.5 *Use (norethisterone and its acetate and enanthate esters)*

Norethisterone and its acetate and enanthate esters are progestogens that have weak estrogenic and androgenic properties. They are commonly used as hormonal contraceptives in monophasic, biphasic and triphasic regimens (Sweetman, 2005).

Norethisterone and norethisterone acetate are both given orally. Typical daily doses are 0.35 mg for norethisterone and 0.6 mg for norethisterone acetate when used alone, or 0.5–1 mg for norethisterone and 1–1.5 mg for norethisterone acetate when used with an estrogen. Norethisterone enanthate is given by intramuscular injection; a dose of 200 mg provides contraception for 8 weeks (Sweetman, 2005).

Norethisterone and norethisterone acetate are used as the progestogen component of hormonal menopausal therapy. Typical regimens have included either continuous daily doses of 0.7 mg norethisterone or 0.5–1 mg norethisterone acetate, or cyclical regimens of 1 mg norethisterone or norethisterone acetate daily for 10–12 days of a 28-day cycle. Norethisterone acetate is also available as transdermal patches that supply 170 or 250 μg in 24 h and are applied twice weekly for 2 weeks of a 4-week cycle; the lower dose may also be applied twice weekly on a continuous basis (Sweetman, 2005).

Table 20 presents comparative global data on sales of norethisterone in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

2.13 Norethisterone acetate

2.13.1 *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

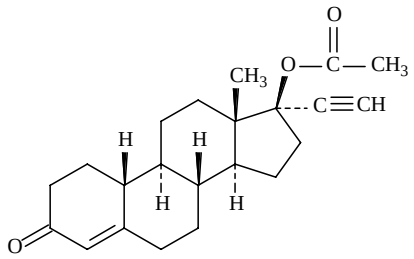
Table 20. Norethisterone used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 μg estrogen)			
Africa	7	2	0
Eastern Mediterranean	52	0	0
Europe	4 462	6 107	4 654
North America	20 035	20 682	17 720
South America	8	85	59
South-East Asia	6 421	0	0
Western Pacific	1 094	1 819	1 698
Subtotal	32 079	28 696	24 132
Monophasic preparations (≥ 50 μg estrogen)			
Africa	94	92	42
Eastern Mediterranean	1 185	11	0
Europe	1 827	930	202
North America	3 734	1 889	1 193
South America	75	23	13
South-East Asia	1 439	892	650
Western Pacific	181	163	181
Subtotal	8 535	4 000	2 281
Biphasic preparations			
Africa	119	87	74
Europe	2 778	1 867	1 117
North America	574	250	70
South America	167	71	0
Western Pacific	0	9	0
Subtotal	3 637	2 283	1 260
Triphasic preparations			
Africa	111	63	34
Europe	6 587	4 995	3 134
North America	16 279	12 882	7 908
South America	138	135	24
Western Pacific	284	231	532
Subtotal	23 399	18 306	11 632
Total	67 650	53 285	39 305
Combined hormonal menopausal therapy			
Africa	8 687	12 325	12 960
Eastern Mediterranean	15	632	1 008
Europe	390 651	702 960	444 352
North America	409	16 506	159 294
South America	16 951	60 481	75 382
South-East Asia	4 520	8 229	22 067
Western Pacific	21 123	42 462	37 686
Total	442 356	843 594	752 747

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.13.2 *Structural and molecular formulae and relative molecular mass*



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

2.13.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White or creamy white, odourless, crystalline powder (Sweetman, 2005)

(*b*) *Melting-point*: 161–162 °C (O'Neil, 2001)

(*c*) *Solubility*: Practically insoluble in water (1 g in > 10 L); soluble in ethanol (1 part in 10), chloroform (1 part in < 1), dioxane (1 part in 2) and diethyl ether (1 part in 18) (Sweetman, 2005)

(*d*) *Specific rotation*: $[\alpha]_D^{25}$, –32° to –38° (Pharmacopeial Convention, 2004)

2.13.4 *Technical products and impurities*

Norethisterone acetate is available commercially as single-ingredient tablets or as a component of combination tablets with ethinylestradiol. For hormonal postmenopausal therapy, norethisterone acetate is used in combination with estradiol or estradiol hemihydrate. It is also available as a percutaneous patch with estradiol (IPPF, 2002; British Medical Association, 2004; Editions du Vidal, 2005).

Reported impurities include: 6β-acetyl-3-oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate, 3,20-dioxo-19-nor-17α-pregn-4-en-17-yl acetate, 6β-hydroxy-3-oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate, 3,6-dioxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate, norethisterone, 3-oxo-19-nor-17α-pregn-5(10)-en-20-yn-17-yl acetate and 3-oxo-19-nor-17α-pregn-5-en-20-yn-17-yl acetate (British Pharmacopoeial Commission, 2004).

2.13.5 *Use*

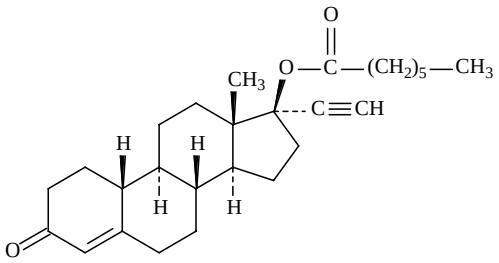
See norethisterone.

2.14 Norethisterone enanthate

2.14.1 *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

2.14.2 *Structural and molecular formulae and relative molecular mass*



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

2.14.3 *Chemical and physical properties of the pure substance*

No information was available to the Working Group.

2.14.4 *Technical products and impurities*

Norethisterone enanthate is available commercially in an oily solution for depot injection (IPPF, 2002).

2.14.5 *Use*

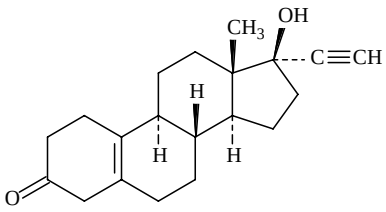
See norethisterone.

2.15 Norethynodrel

2.15.1 *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

2.15.2 *Structural and molecular formulae and relative molecular mass*



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

2.15.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005)

(*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)

2.15.4 *Technical products and impurities*

Norethynodrel was available commercially as a component of a combination tablet with mestranol. Information available in 2005 indicated that there is no usage of norethynodrel at any dose in any form of drug (Sweetman, 2005).

2.15.5 *Use*

Norethynodrel is a progestogen that is structurally related to norethisterone, which has been given orally in conjunction with an estrogen such as mestranol for the treatment of various menstrual disorders and endometriosis (Sweetman, 2005). Available information indicates that it is no longer produced or used.

Table 21 presents comparative global data on sales of norethynodrel in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 21. Norethynodrel used in combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Western Pacific	18	0	0
Total	18	0	0

From IMS Health (2005)

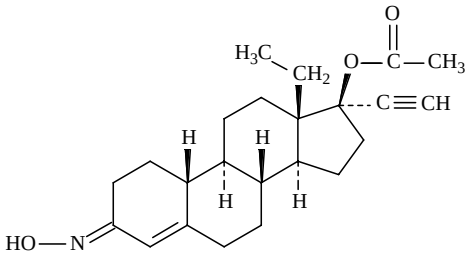
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.16 Norgestimate

2.16.1 *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

2.16.2 *Structural and molecular formulae and relative molecular mass*



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

2.16.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005), unless otherwise noted

(*a*) *Description*: White to pale yellow powder (a mixture of (E)- and (Z)-isomers that has a ratio of (E)- to (Z)-isomer of between 1.27 and 1.78)
(*b*) *Melting-point*: 214–218 °C
(*c*) *Solubility*: Insoluble in water; sparingly soluble in acetonitrile; freely to very soluble in dichloromethane
(*d*) *Specific rotation*: $[\alpha]_D^{25}$, +110°; $[\alpha]_D$, +40° to +46° (in chloroform) (Pharmacopeial Commission, 2004)

2.16.4 *Technical products and impurities*

Norgestimate is available commercially as a component of a combination tablet with ethinylestradiol (British Medical Association, 2004; IPPF, 2004; Editions du Vidal, 2005).

2.16.5 *Use*

Norgestimate is structurally related to levonorgestrel (to which it is partly metabolized) and is used as the progestogenic component of combined oral contraceptives and

in hormonal menopausal therapy. A typical daily dose is 250 µg in monophasic contraceptive preparations and 180–250 µg in triphasic preparations. For hormonal menopausal therapy, a regimen of estradiol daily for 3 days followed by estradiol combined with 90 µg norgestimate daily for 3 days is used; this 6-day cycle is repeated continuously without interruption (Sweetman, 2005).

Table 22 presents comparative global data on sales of norgestimate in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 22. Norgestimate used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 µg estrogen)			
Africa	0	0	4
Eastern Mediterranean	0	133	258
Europe	13 748	19 133	16 355
North America	2 865	6 091	5 562
South America	60	359	204
South-East Asia	0	0	172
Subtotal	16 673	25 717	22 554
Triphasic preparations			
Africa	0	12	6
Europe	907	1 421	1 732
North America	1 599	16 973	30 846
South America	56	236	171
Subtotal	2 562	18 642	32 755
Total	19 235	44 359	55 309
Combined hormonal menopausal therapy			
North America	0	0	14 095
South America	0	0	6 364
Total	0	0	20 459

From IMS Health (2005)

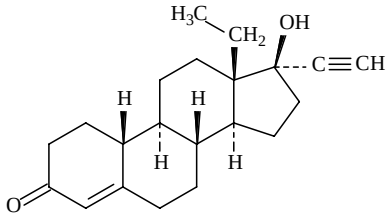
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.17 Norgestrel

2.17.1 *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

2.17.2 *Structural and molecular formulae and relative molecular mass*



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

2.17.3 *Chemical and physical properties of the pure substance*

From O'Neil (2001) and Sweetman (2005), unless otherwise noted
(*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° (in chloroform) (Pharmacopeial Convention, 2004)

2.17.4 *Technical products and impurities*

Norgestrel is available commercially as a single-ingredient tablet and as a component of combination tablets with ethinylestradiol, estradiol valerate or as combined injectable solution with ethinylestradiol (IPPF, 2002; Editions du Vidal, 2005).

2.17.5 *Use*

Uses of norgestrel in oral contraception and menopausal hormonal therapy are similar to those of levonorgestrel, with the exception of applications of the levo-enantiomer in subcutaneous implants and intrauterine devices (Sweetman, 2005).

Table 23 presents comparative global data on sales of norgestrel in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 23. Norgestrel used in combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (thousands of standard units[a])

Region	1994	1999	2004
Combined hormonal contraceptives			
Monophasic preparations (< 50 µg estrogen)			
Eastern Mediterranean	0	0	3 075
Europe	227	193	361
North America	6 751	7 185	7 007
South America	8	10	52
South-East Asia	120	3 746	7 103
Western Pacific	0	0	8
Subtotal	7 105	11 134	17 605
Monophasic preparations (≥ 50 µg estrogen)			
Africa	1 912	1 539	1 359
Eastern Mediterranean	430	530	60
Europe	4 285	3 024	2 019
North America	1 814	1 165	928
South America	7 141	3 948	1 339
South-East Asia	762	1 074	1 010
Western Pacific	541	615	615
Subtotal	16 886	11 895	7 330
Total	23 991	23 029	24 935
Combined hormonal menopausal therapy			
Africa	3 308	3 213	1 797
Eastern Mediterranean	6 545	15 656	19 387
Europe	338 968	237 793	91 053
North America	14 787	13 048	12 237
South America	31 690	24 458	21 968
South East Asia	5 821	10 489	11 395
Western Pacific	53 391	49 259	29 457
Total	454 510	353 916	187 294

From IMS Health (2005)

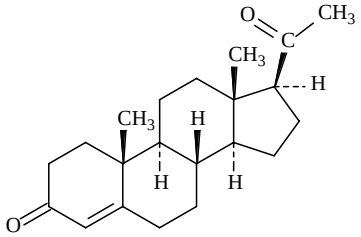
[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.18 Progesterone

2.18.1 *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

2.18.2 *Structural and molecular formulae and relative molecular mass*



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

2.18.3 *Chemical and physical properties*

From O'Neil (2001) and Sweetman (2005), unless otherwise noted

(*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*) *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
(*d*) *Optical rotation*: α form — $[\alpha]_D^{20}$, +192°; β form — $[\alpha]_D^{20}$, +172° to +182° (in dioxane)

2.18.4 *Technical products and impurities*

Progesterone is available in an oily solution for injection, as pessaries or suppositories and as an intrauterine device (IPPF, 2002; British Medical Association, 2004; Editions du Vidal, 2005).

Reported impurities include: 21-(cyclohex-1-enyl)pregn-4-ene-3,20-dione, 21-(cyclohexylidene)pregn-4-ene-3,20-dione, (20*R*)-20-hydroxypregn-4-en-3-one, (20*S*)-20-hydroxypregn-4-en-3-one, (20*R*)-3-oxopregn-4-en-20-yl acetate, (20*S*)-3-oxopregn-4-en-20-yl acetate and pregna-4,14-diene-3,20-dione (British Pharmacopoeial Commission, 2004).

2.18.5 *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 is used in human medicine for the treatment of secondary amenorrhoea and dysfunctional uterine bleeding, although progestational agents that are active orally are generally preferred to progesterone (Reynolds, 1996). Progesterone is usually administered as an oily intramuscular injection, a vaginal gel or pessaries or as suppositories. An oral micronized preparation of progesterone is also available. In dysfunctional uterine bleeding or amenorrhoea, 5–10 mg progesterone daily may be given by intramuscular injection for about 5–10 days until 2 days before the anticipated onset of menstruation. Alternatively, progesterone may be administered as a vaginal gel at a usual dose of 45 mg on alternate days from day 15 to 25 of the cycle or orally at a dose of 400 mg daily for 10 days (Sweetman, 2005).

Progesterone gel may be administered intravaginally at a dose of 45 mg on alternate days for 12 days of a 28-day cycle as the progestogen component of menopausal hormonal therapy. A progesterone-releasing intrauterine device has also been used as a hormonal contraceptive; the device contains 38 mg of progesterone and is effective for up to 12 months (Sweetman, 2005).

In women with a history of recurrent miscarriage and proven progesterone deficiency, twice-weekly intramuscular injections (increased to daily if necessary) of 25–100 mg progesterone, from approximately day 15 of the pregnancy until 8–16 weeks, has been used. A similar schedule has been used in in-vitro fertilization or gamete intra-fallopian transfer techniques (Sweetman, 2005).

Table 24 presents comparative global data on sales of progesterone in 1994, 1999 and 2004 (IMS Health, 2005). The regions are broadly as those defined by WHO.

Table 24. Progesterone used for combined estrogen–progestogen menopausal therapy (thousands of standard units)

Region	1994	1999	2004
Africa	837	827	1 143
Eastern Mediterranean	1 255	729	979
Europe	2 844	1 946	1 415
North America	2 824	1 438	1 005
South America	3 122	2 402	897
South-East Asia	1 231	1 764	1 806
Western Pacific	465	6 253	1 298
Total	12 578	15 358	8 543

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

2.19 Regulations and guidelines

Guidelines for the use of progestogens are those found in national and international pharmacopoeias (Secretaría de Salud, 1994, 1995; Society of Japanese Pharmacopoeia, 2001; British Pharmacopoeial Commission, 2004; Pharmacopeial Convention, 2004; Swiss Pharmaceutical Society, 2004; Council of Europe, 2005; Sweetman, 2005).

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