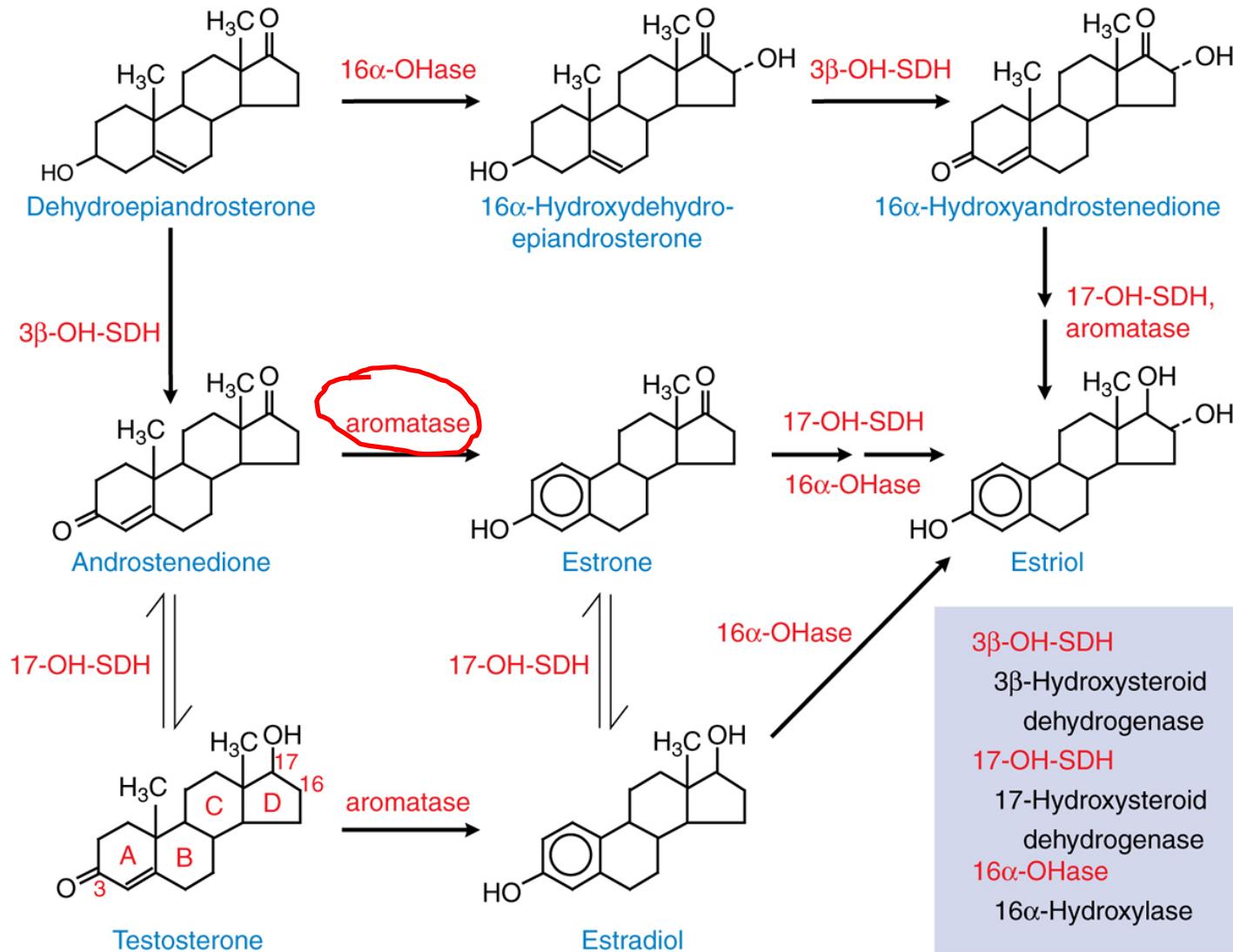
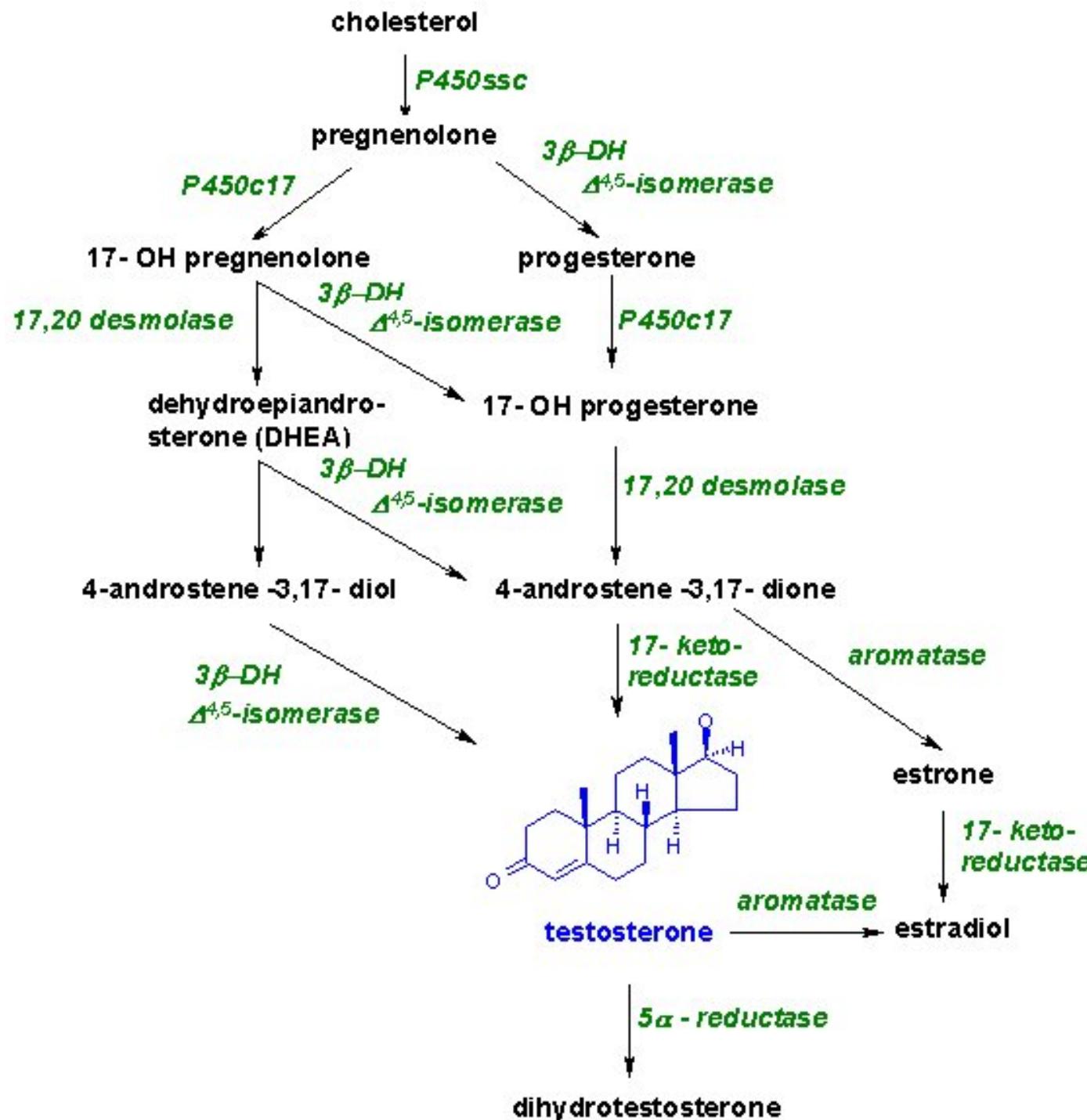


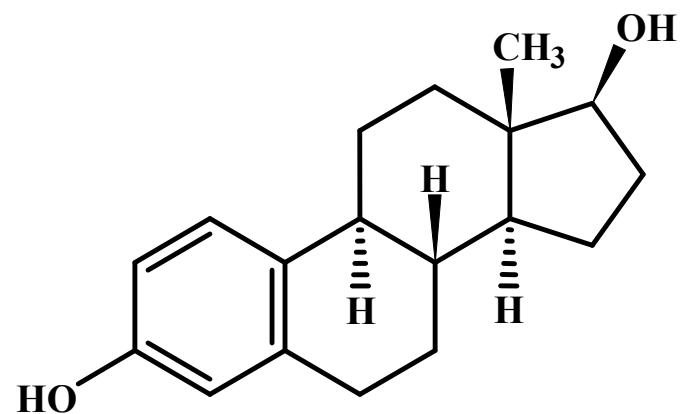
Sexual steroid pharmacology



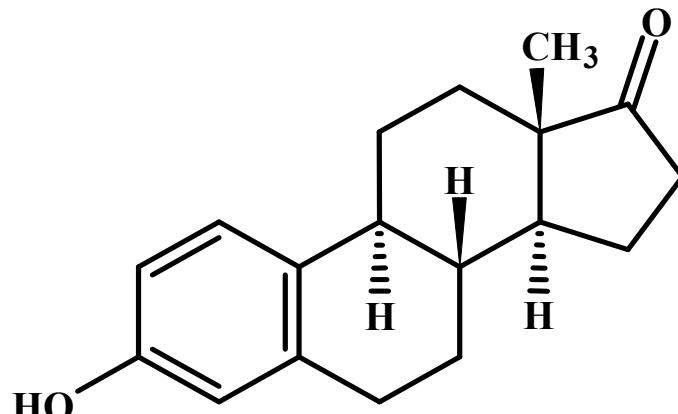
Biosynthetic pathways of estrogens



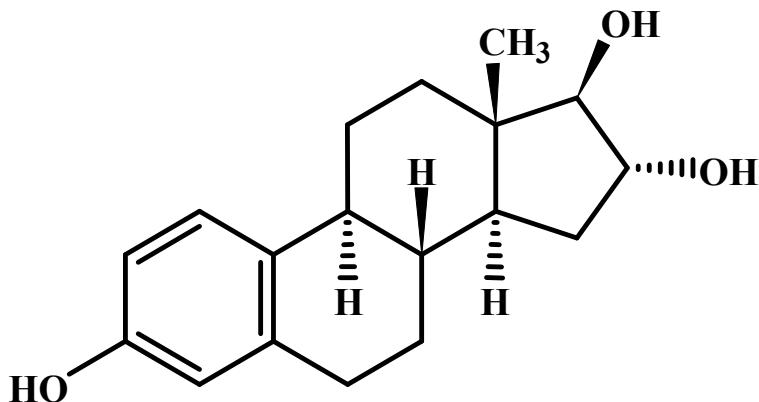




ESTRADIOL



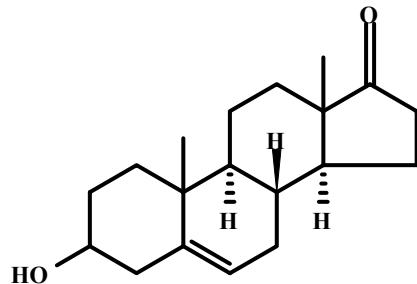
ESTRONE



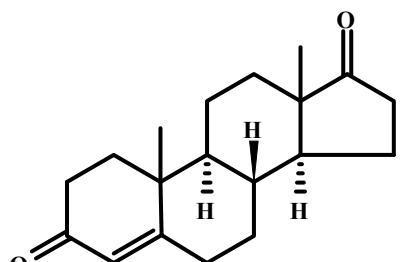
ESTRIOL

natural mammalian estrogens; plants also produce estrogenic substances (isoflavones)

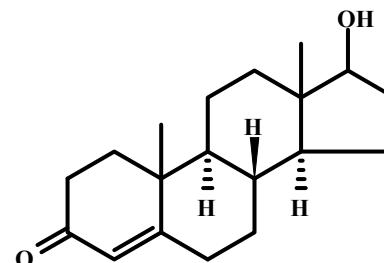




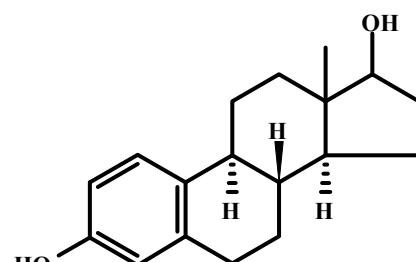
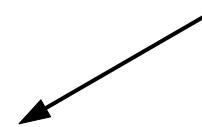
DEHYDROEPIANDROSTERONE



ANDROSTENEDIONE



TESTOSTERONE



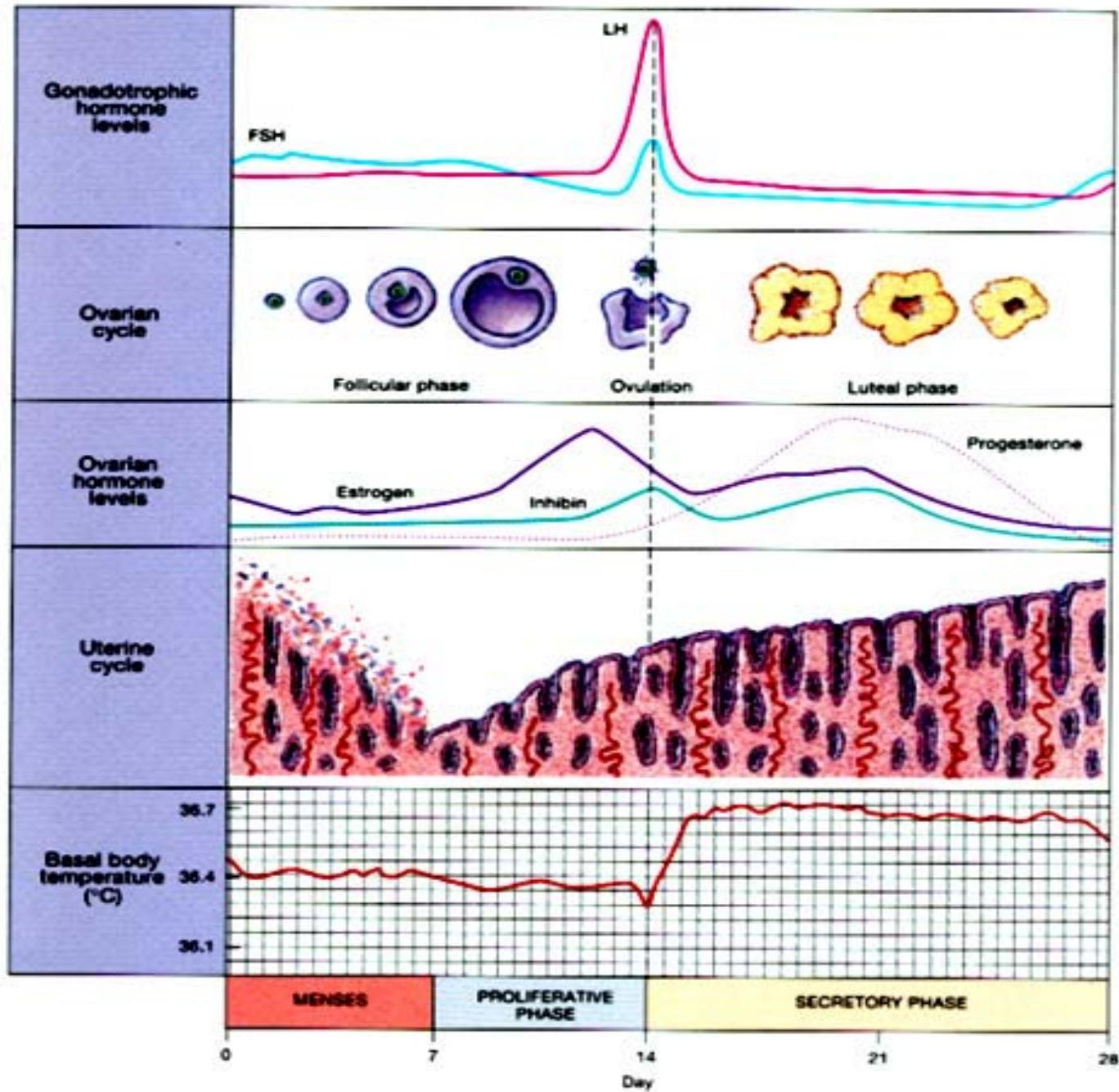
ESTRADIOL

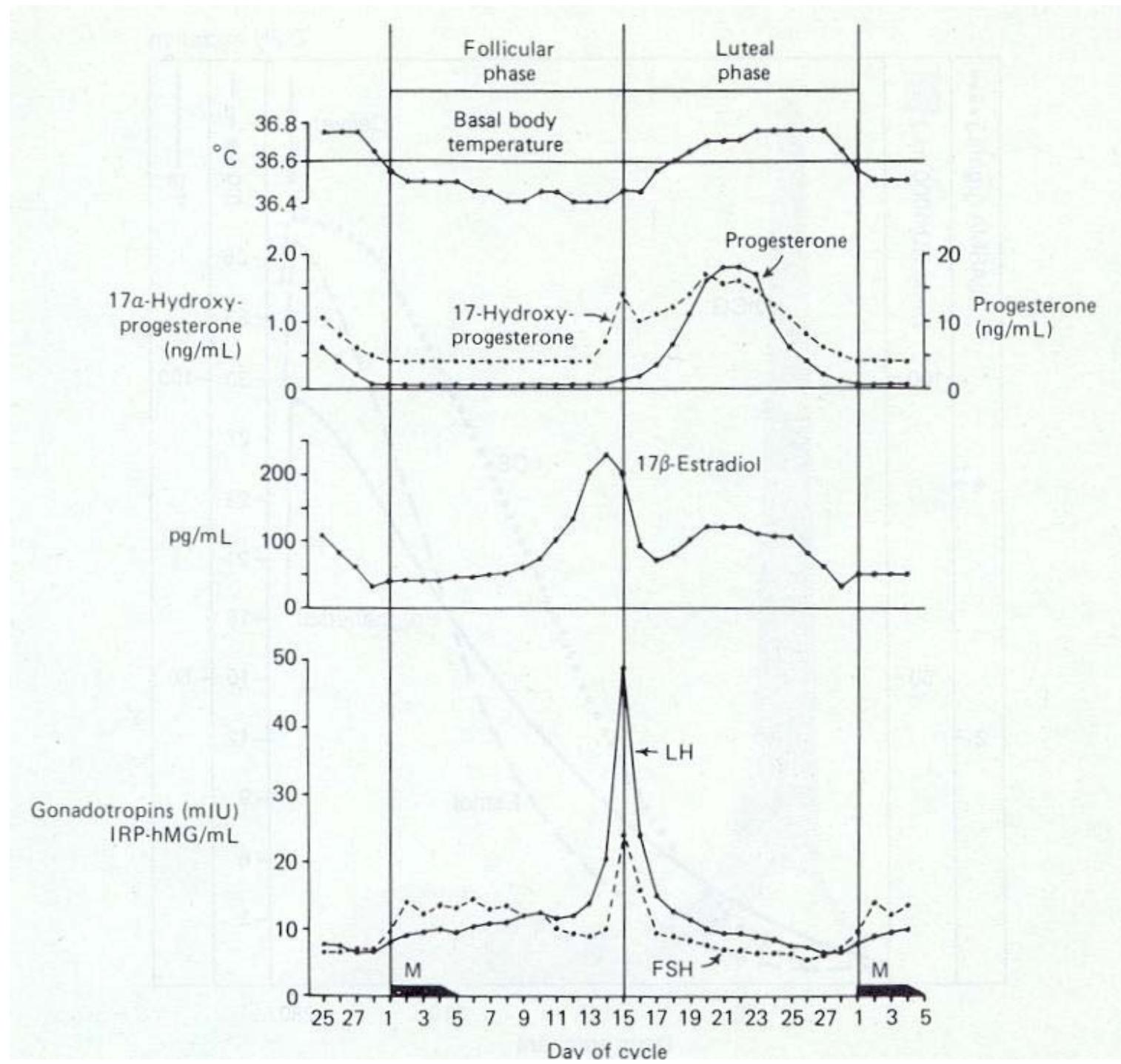


ESTROGENS

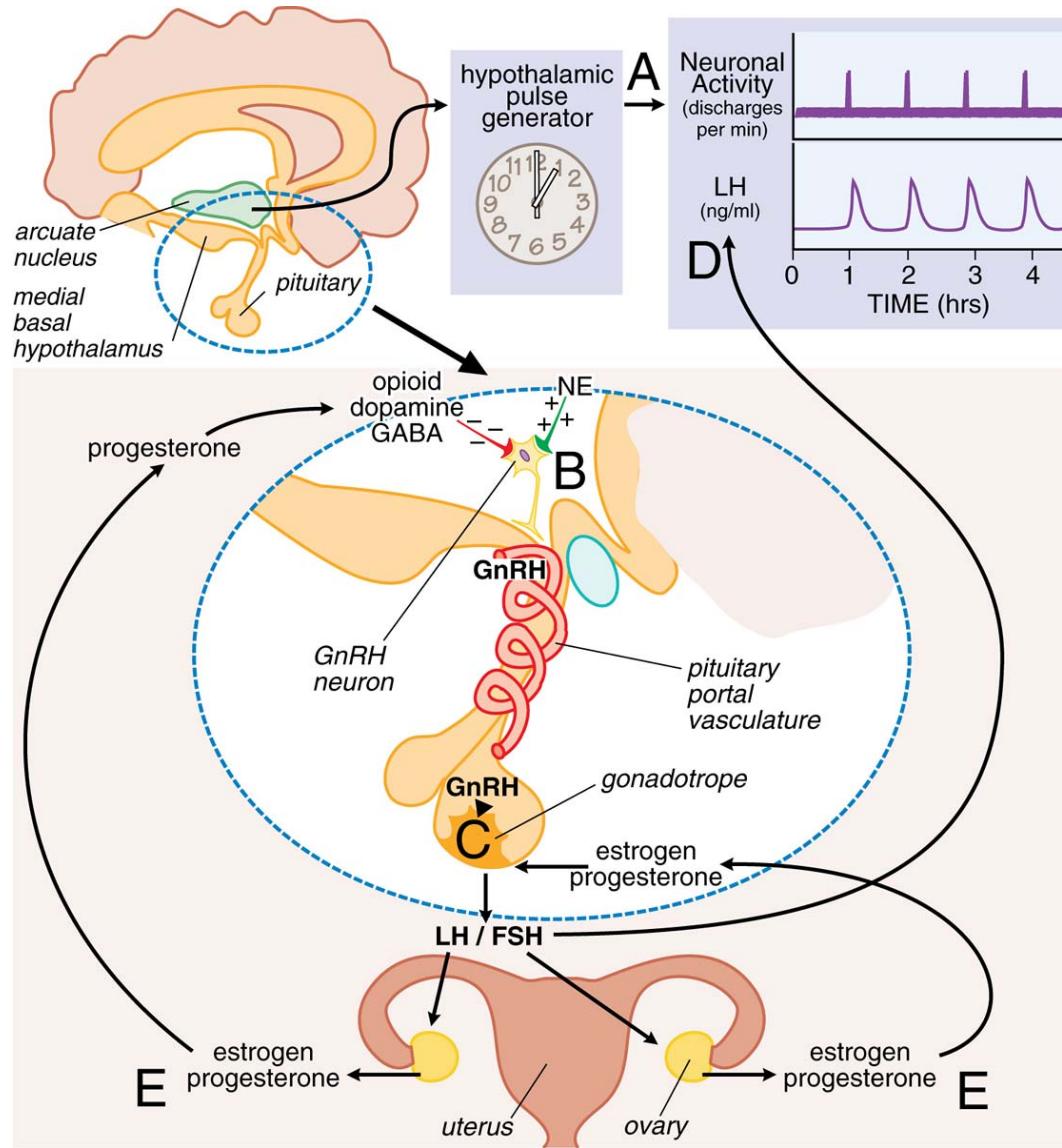
- Estrogens include the natural hormones as well as semi-synthetic and synthetic (stilbene) agents
- Estrogens are used as hormone-replacement therapy (menopause), in oncology and as contraceptives
- Most estrogen in the female is produced in the ovaries by the theca interna and the granulosa cells of the follicles







Neuroendocrine control of gonadotropin secretion in females



Inhibin:

- Secreted by the granulosa cells in the ovaries.
- Inhibit the secretion of follicle-stimulating hormone by the anterior pituitary gland.
- Typical negative feedback servomechanism.
- Small amounts of inhibin are produced by the Sertoli cells in the testes of men.

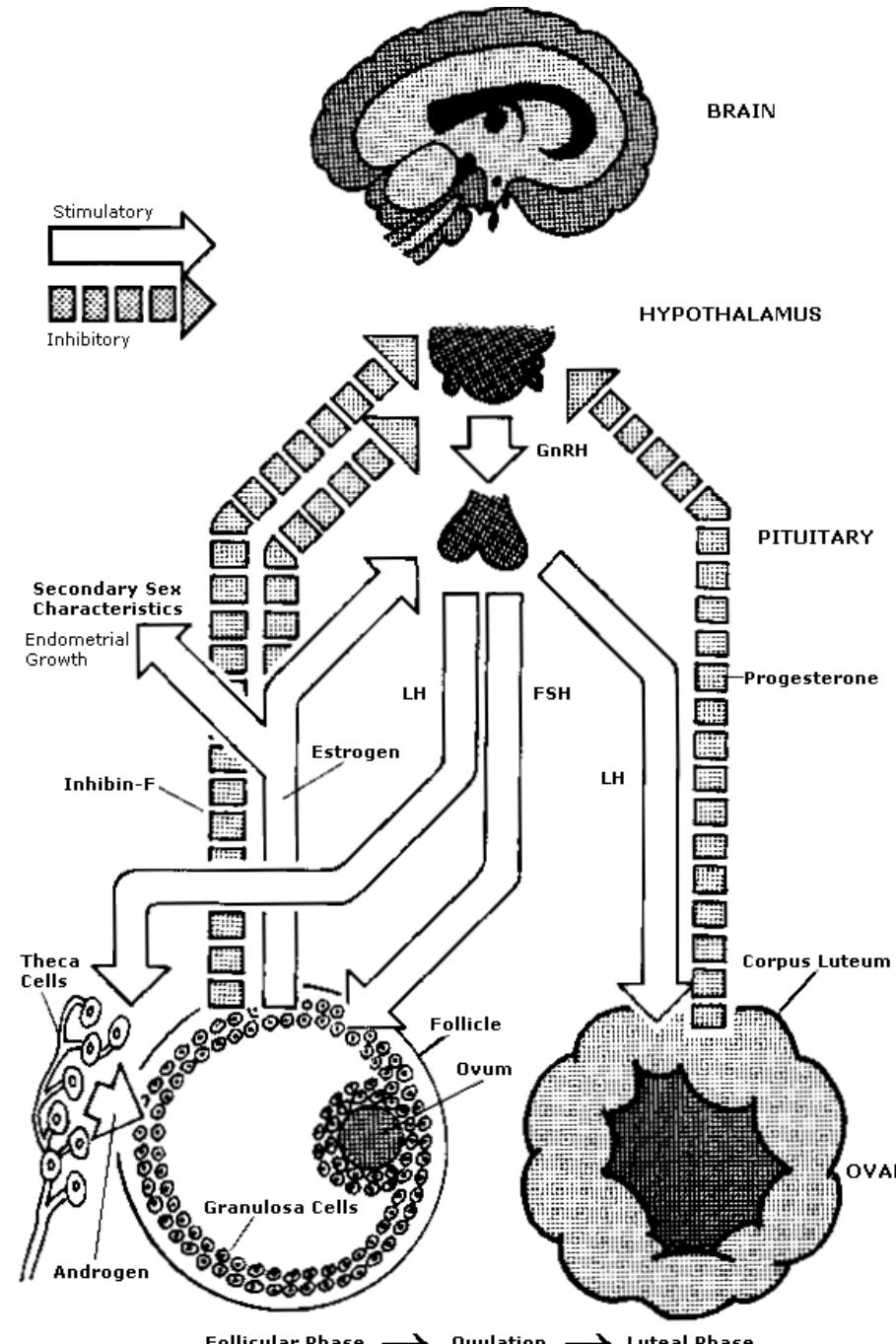
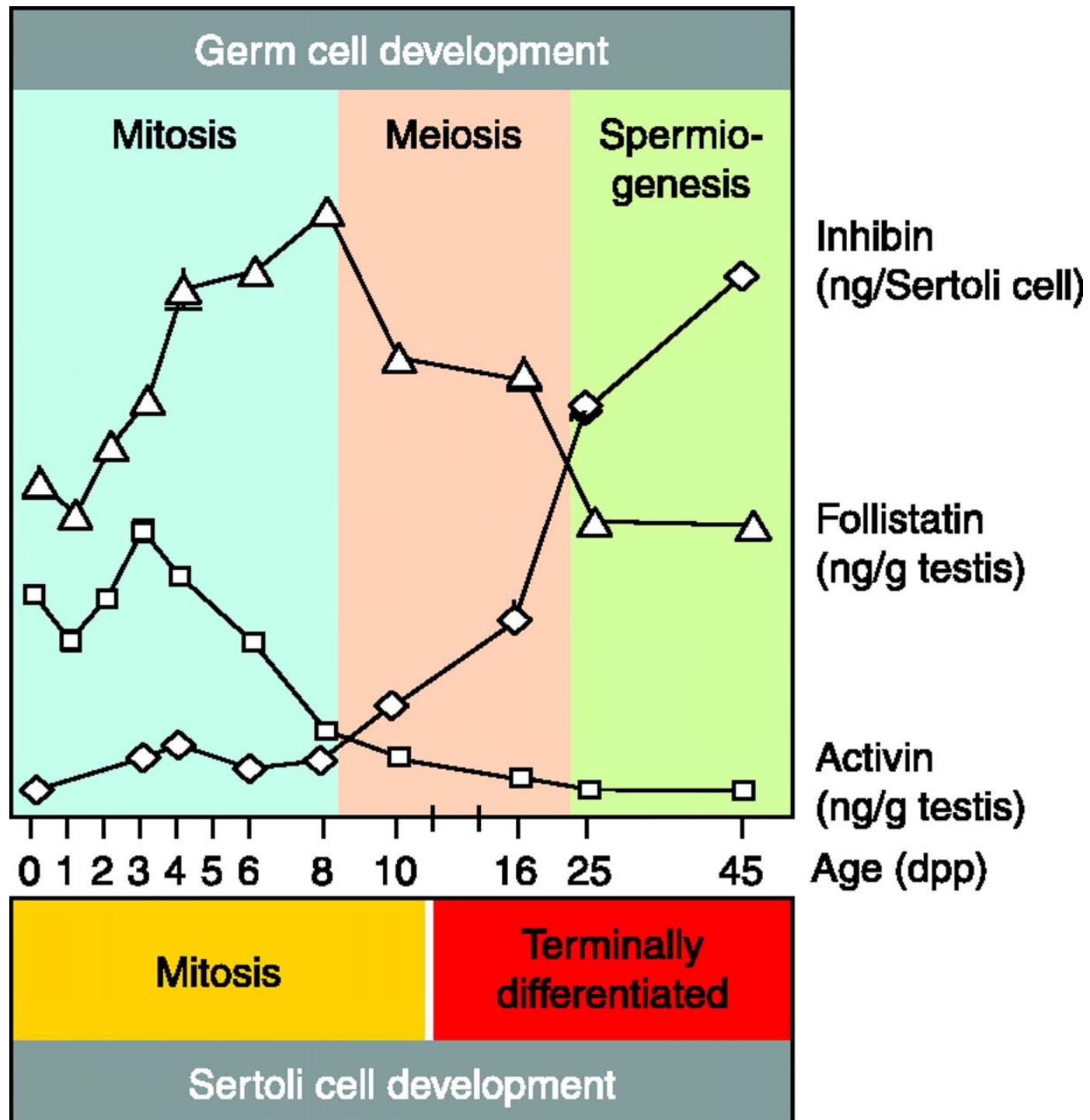


Figure 11-1. The Female Hormone System





Actions of estrogens

- on sexual organs (primary and secondary sexual characteristics)
 - ovaries: stimulate follicular growth; small doses cause an increase in weight of ovary; large doses cause atrophy
 - uterus: endometrial growth
 - vagina: cornification of epithelial cells with thickening and stratification of epithelium
 - cervix: increase of cervical mucous with a lowered viscosity (favoring sperm access)
 - breast: cause enlargement of the breasts, shaping the body contours and the skeleton
 - Induces the growth of axillary and pubic hair and pigmentation of the genital tract.



Actions of estrogens

- Development and maintenance of internal (fallopian tubes, uterus, vagina), and external genitalia
- skin: increase in vascularization, development of soft, textured and smooth skin
- bone: increase osteoblastic activity
- electrolytes: retention of Na^+ , Cl^- and water by the kidney
- cholesterol: hypcholesterolemic effect



Metabolic effects of estrogens

- Decrease stromal cell production of IL-1, IL-6, TNFalpha
- Increase the production of Insulin-like growth factor (IGF)-1, bone morphogenic protein (BMP)-6 and transforming growth factor (TGF)-beta which are antiresorptive.
- Increase osteoblast production of the cytokine osteoprotegerin (OPG). OPG antagonizes the binding of osteoprotegrin-ligand to its receptor (termed RANK, or receptor activator of NF-Kappa B) and prevents the differentiation of osteoclast precursors to mature osteoclasts.
- Estrogens increase the osteoclast apoptosis.
- Estrogen affects bone growth and epiphyseal closure in both sexes.

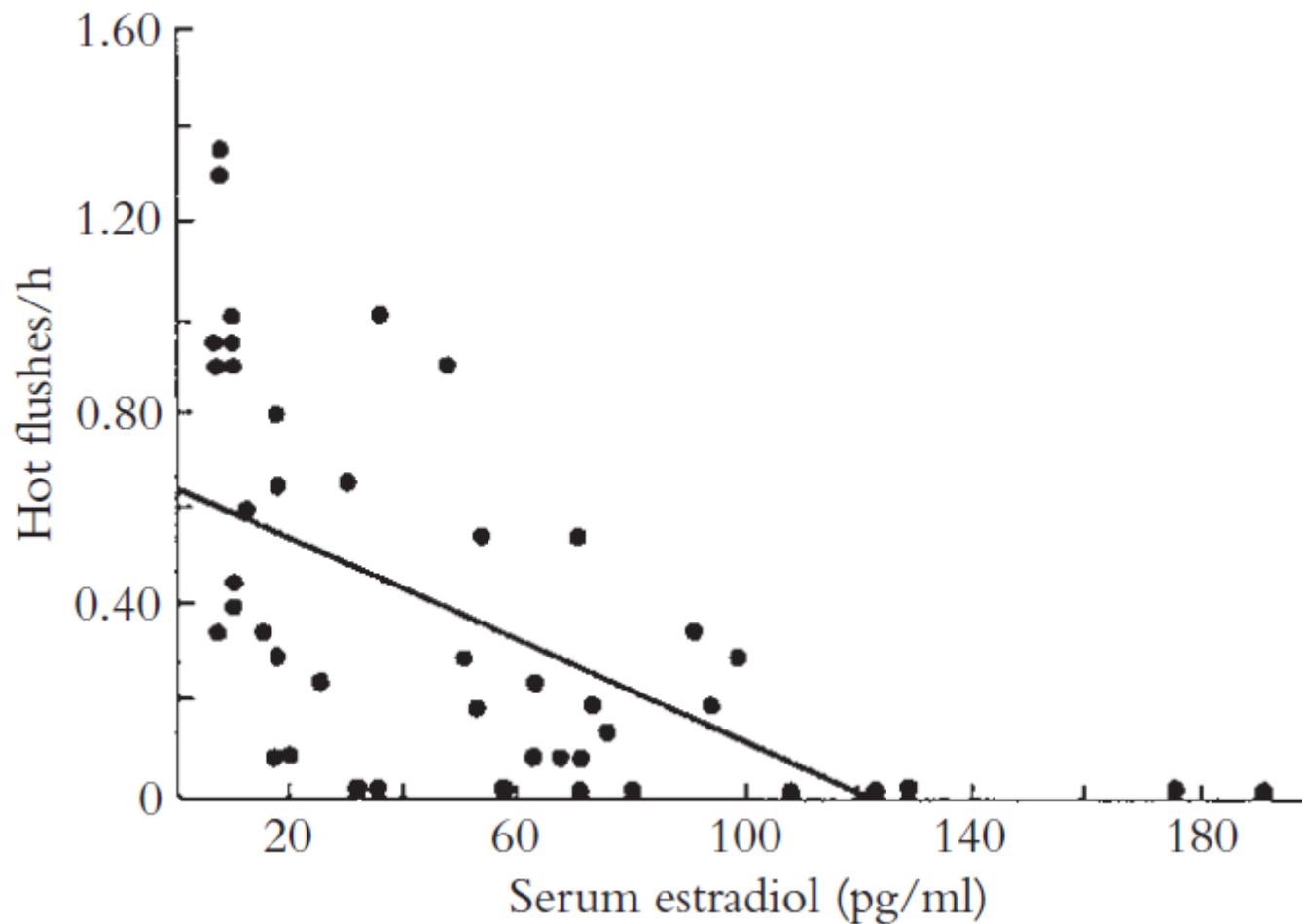


Effect on lipid metabolism and coagulation

- Elevates HDL and decreases LDL and Lp(a)
- Alter bile composition by increasing cholesterol secretion and decreasing bile acid secretion. → Gallstone formation.
- Estrogens increase plasma levels of CBG, TBG, SSBG.
- Cause an increase in coagulation factor VII and XII. Decrease the anticoagulation factors protein C, protein S and antithrombin III. → Thrombosis
- Increase the fibrinolysis.
- In high concentration have antioxidant activity.
- Long-term administration of estrogens decrease the plasma renin, ACE, ET-1 production.
- Increase production of nitric oxide in the vascular wall.
- Increase melanin cc in the skin (chloasma gravidarum)



Correlation between the number of hot flushes per hour and the serum levels of estradiol during transdermal treatment of postmenopausal women



Estrogen receptors

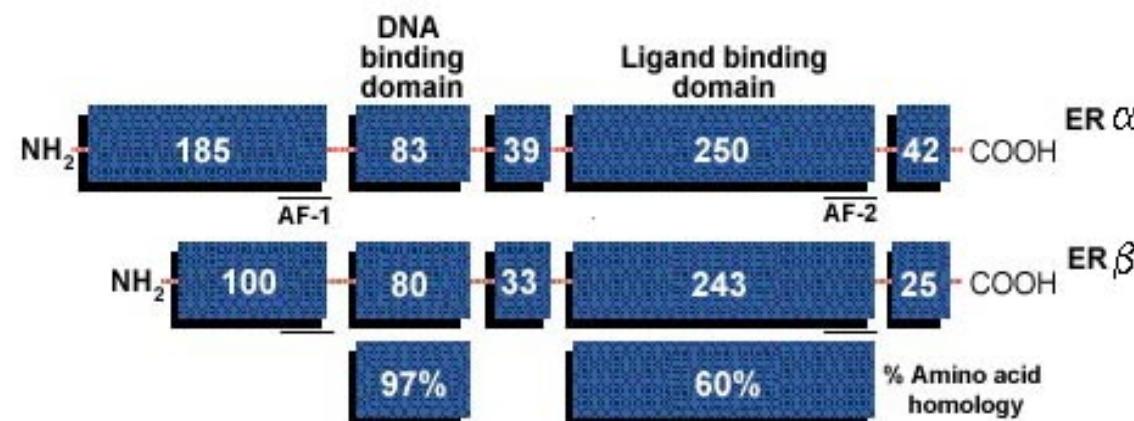
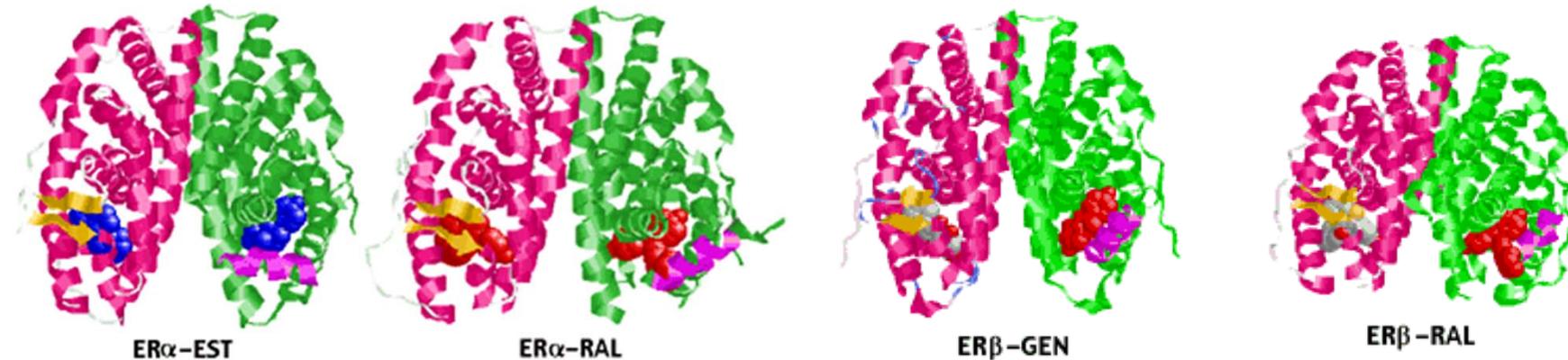


Table 1 Distribution of estrogen receptors ER α and ER β in various tissues^{4–8}

Target tissue	ER α	ER β
Ovary	+ (theca cells)	+ (granulosa cells)
Uterus	+	+ (stromal cells)
Vagina	+ (pre- and postmenopause)	+ (premenopause)
Urinary tract	(–)	+
Mammary gland	+	+
Placenta	+	(–)
Ventral prostate	(–)	+
Central nervous system	+	+
Cardiovascular system	+	+
Bone	+	+
Muscle	(–)	+
Adipose tissue	+	+
Intestinal tract	(–)	+
Immune system	(–)	+
Hematopoiesis	+	+
Liver	+	(–)
Lung	(–)	+
Adrenals	(–)	
Pineal gland	(–)	
Thyroid gland	(–)	
Parathyroids	(–)	
Pancreas	(–)	
Gallbladder	(–)	
Skin	+ (sebaceous glands)	+

+, high expression and important function; (–) no or low expression



Table 2 Relative binding affinity (RBA) of various estrogens for *in vitro* synthesized human estrogen receptors ER α and rat ER β as determined by competition experiments (ratio of concentration at 50% inhibition (IC₅₀) values of estradiol:competitor)⁹

<i>Steroid</i>	<i>RBA for ERα</i>	<i>RBA for ERβ</i>
Estradiol-17 β	100	100
Estrone	60	37
Estrone-3-sulfate	<1	<1
Estriol	14	21
Estradiol-17 α	58	11
4-Hydroxy-estradiol	13	7
2-Hydroxy-estradiol	7	11
Diethylstilbestrol	468	295
Tamoxifen	7	6
4-Hydroxy-tamoxifen	178	339
Clomiphene	25	12
Nafoxidine	44	16
5-androstenediol	6	17
3 β -androstanediol	3	7
Coumestrol	94	185
Genistein	5	36



Natural estrogens

- Conjugated estrogenic substances:
 - an amorphous preparation containing water soluble conjugated forms of mixed estrogens from the urine of pregnant mares (Premarin, Cenestin - synthetic conjugated estrogens)
- estradiol :
 - oral : Estrace
 - transdermal: Climara, Alora, Vivelle, Vivelle-Dot, Estraderm, FemPatch



Natural estrogens

- estrone:
 - Kestrone 5 (injectable only)
- esterified estrogen
 - (75-85% sodium estrone sulfate and 6-15% sodium equilin sulfate)
 - Estratab; Menest
- estropipate (piperazine estrone sulfate)
 - Ogen; Ortho-Est



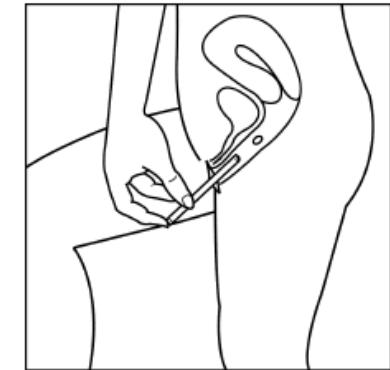
Natural estrogens

- Sustained-release injectables:
 - estradiol valerate in oil (Delestrogen; Valergen)
 - estradiol cypionate in oil (depGynogen; DepoGen)
 - duration of action from 3 to 8 weeks
 - esterified at C-17 hydroxyl group

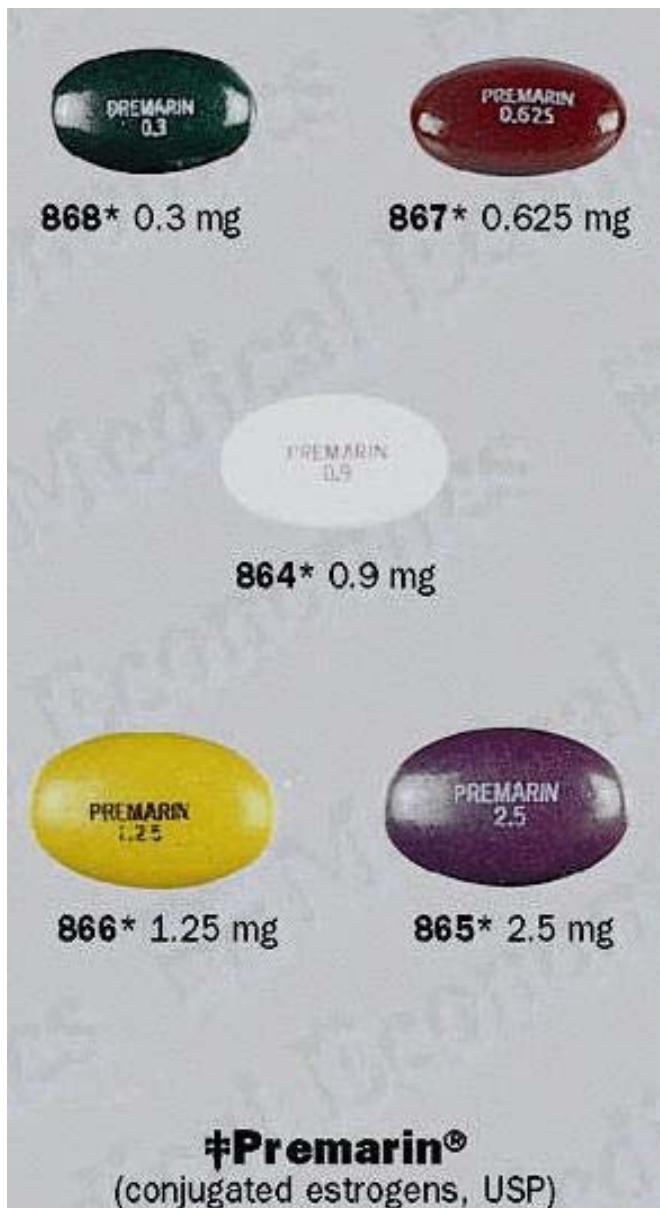


Estrogen products in Hungary

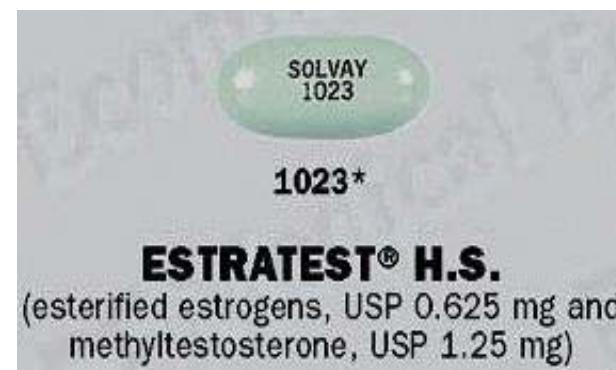
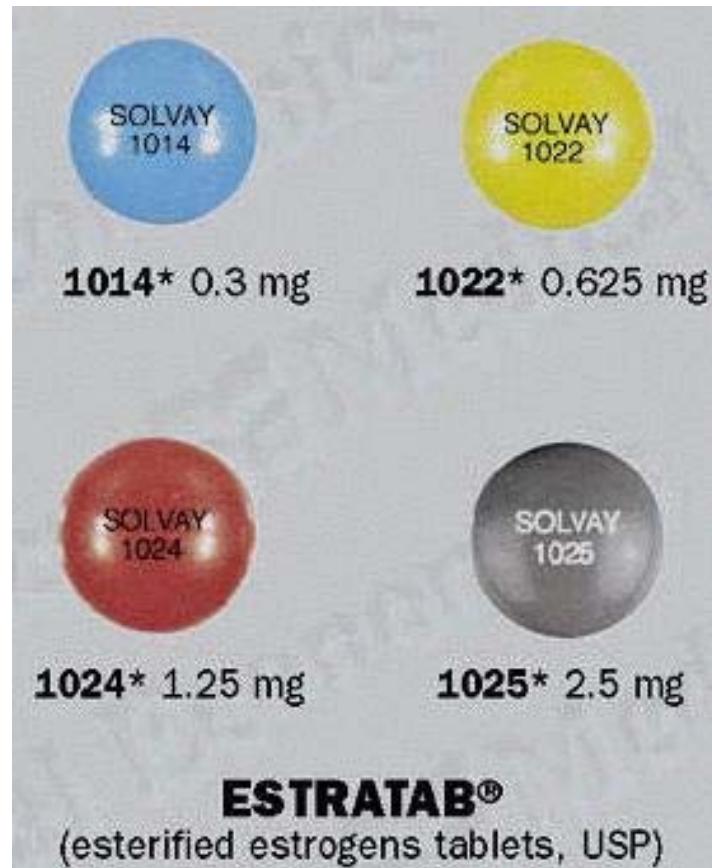
- Estradiol
 - Dermestril
 - Divigel
 - Estrimax
 - Estrofem
 - Linoladiol
 - Vagifem
- Estriol
 - Estrokad
 - Ortho-Gynest D
 - Ovestin
- Tibolon
 - Livial

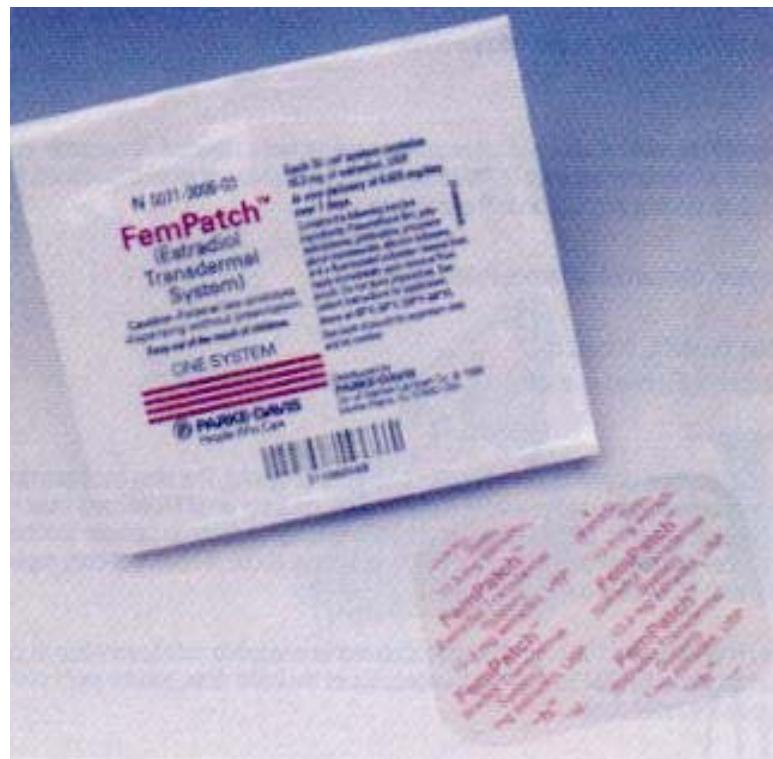


Estrogen products



Estrogen products





Estrace® Vaginal Cream
(estradiol vaginal cream USP, 0.01%)

25 μ g

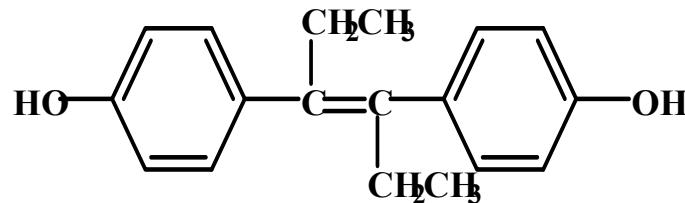
VAGIFEM®

estradiol vaginal tablets

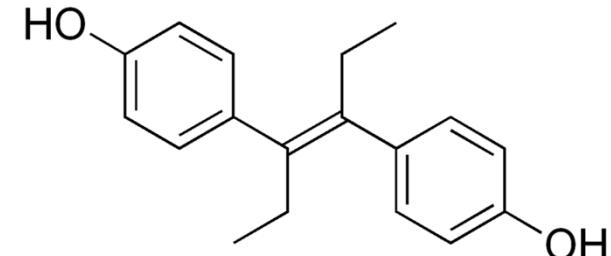
**CONVENIENT, COMFORTABLE
RELIEF WITHOUT THE MESS**

A large advertisement for Vagifem estradiol vaginal tablets. The product name is prominently displayed in blue. A purple banner below it contains the slogan "CONVENIENT, COMFORTABLE RELIEF WITHOUT THE MESS".

DIETHYLDIESTROL



DIETHYLDIESTROL (DES)



Synthesized in 1938.

From about 1940 to 1970, DES was given to pregnant women under the mistaken belief it would reduce the risk of pregnancy complications and losses. In 1971, DES was shown to cause a rare vaginal tumor (adenocarcinoma) in girls and women who had been exposed to this drug in utero. In male babies: testicular hypoplasia, cryptorchism, epididymal cysts. Breast cancer development in the mothers.

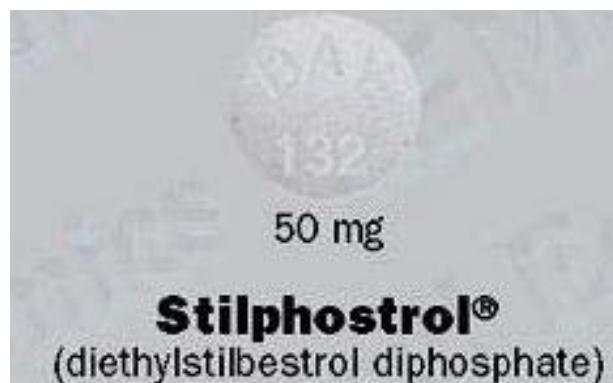


Table 3 Relative potency of various estrogens concerning several clinical (relief of hot flushes) and metabolic parameters (suppression of follicle stimulating hormone (FSH) levels; increase in the serum levels of high density lipoprotein (HDL) cholesterol, sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and angiotensinogen). The values are estimated on a weight basis^{12–14}

<i>Estrogen</i>	<i>Hot flushes</i>	<i>FSH</i>	<i>HDL cholesterol</i>	<i>SHBG</i>	<i>CBG</i>	<i>Angiotensinogen</i>
Estradiol-17 β	100	100	100	100	100	100
Estriol	30	30	20			
Estrone sulfate		90	50	90	70	150
CEE	120	110	150	300	150	500
Equilin sulfate			600	750	600	750
Diethylstilbestrol		340		2 560	2 450	1 950
Ethinylestradiol	12 000	12 000	40 000	50 000	60 000	35 000

CEE, conjugated equine estrogens



Table 7 Effects of oral and transdermal estrogen replacement therapy on the cardiovascular system and various surrogate parameters. The effects may vary according to the type and dose of the estrogens, and may be modulated by the addition of progestogens

<i>Parameter</i>	<i>Oral estrogens</i>	<i>Transdermal estrogens</i>
Risk of thrombosis	increase	possibly smaller increase
Hemostasis	procoagulatory effect	minor effect
APC resistance	increase	minor increase
Atherosclerosis	prevention	prevention
Triglycerides	increase	minor decrease
HDL cholesterol, triglycerides, Apo A	increase	minor increase
LDL cholesterol, remnants, Apo B	reduction	minor reduction
Size of LDL particles	decrease	increase
Activity of metalloproteinases	increase	no effect
Vasodilation	increase	increase
Release of NO, prostacyclin	increase	increase
Release of endothelin-1	reduction	reduction
Angiotensinogen	increase	no effect
C-reactive protein	increase	no effect
Adhesion molecules	decrease	decrease
Cytokines (IL-1, IL-6, TNF- α)	no effect	no effect
PAI-1	decrease	no effect
IGF-1, IGFBP-3	decrease	no effect
IGFBP-1, GH, GHBP	increase	no effect

APC, activated protein C; HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor; PAI-1, plasminogen activator inhibitor-1; IGF, insulin-like growth factor; IGFBP; insulin-like growth factor-binding protein; GH, growth hormone; GHBP, growth hormone-binding protein



Therapeutic use of estrogens

1. Hormone replacement therapy: Conjugated estrogens: 0.625 mg/day for replacement (oral potency is lower than ethinyl estradiol. Means around 5-10 µg.)
2. Contraceptive: Ethinyl estradiol (EOD): 20-35 µg/day
3. Postmenopausal hormone-replacement therapy: prevention of bone loss and amelioration of vasomotor systems.
4. Vasomotor symptoms: hot flashes may alternate with chilly sensations, inappropriate sweating and paresthesias. Instead of estrogen medroxyprogesterone acetate can be administered.
5. Prevention of cardiovascular diseases, but thrombembolic disease and the incidence of gallstones are increased.
6. Neuroprotective effect: Delay the onset of Alzheimer's disease. The trial result is controversial.
7. Urogenital atrophy: dryness and itching of the vagina, pain during urination and intercourse, a need to urinate urgently and often, incontinence. Estrogen orally, vaginal cream, ring device.
8. Treatment of testosterone-dependent prostate carcinoma



SERMs

Selective estrogen-receptor modulators

Common feature: variable actions depending on target tissue:

Agonist in bone

Partial agonist in endometrium

Antagonist in breast



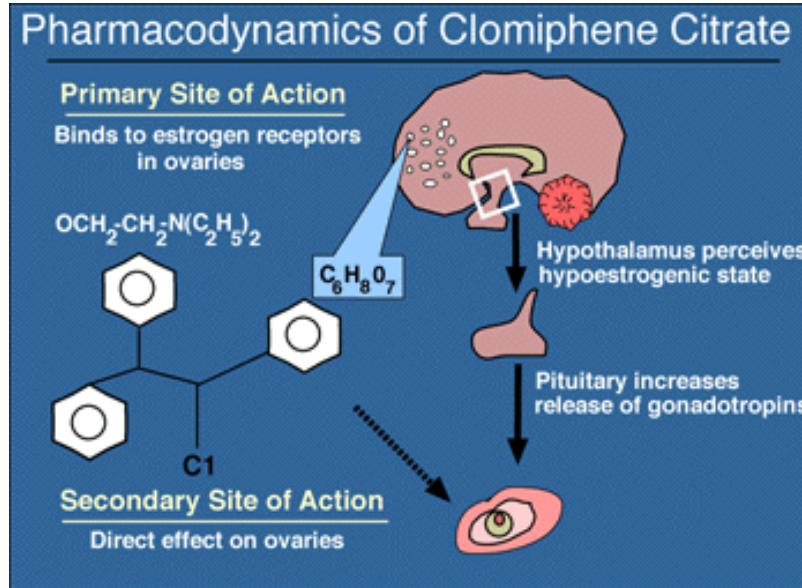
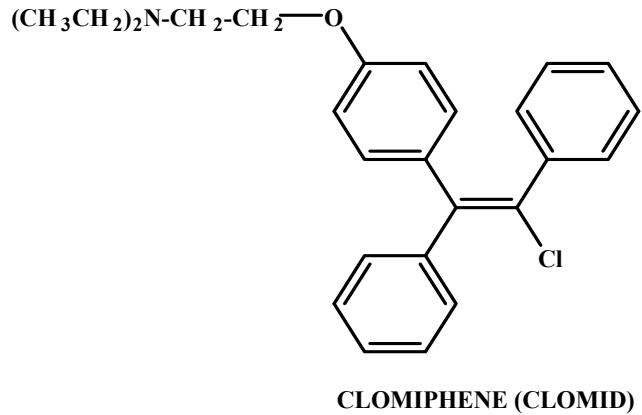
- Clomiphene (Clomid, Omiphin), exception!!
- Tamoxifen
- Toremifén (Fareston)
- Raloxifén (Evista)
- Centchroman/Ormeloxifene (Saheli, Novex-DS, Centron, Sevista)

Under development

- Droloxifén
- Idoxifén
- Nafoxidén



CLOMIPHENE CITRATE

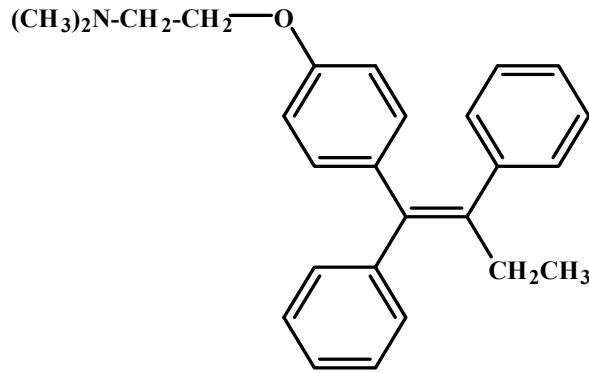


Adverse effects:

vasomotor flushes (or hot flashes)
abdominal discomfort
visual blurring (dose-dependent)
reversible ovarian enlargement and cyst formation
twin formation!!!

Fertility pill!!!





TAMOXIFEN (NOLVADEX)

TAMOXIFEN

Tamoxifen competitively binds to ER (on tumors)
 Nonsteroidal
 Causes cells to remain in the G0 and G1 phases
 Cytostatic rather than cytocidal
 Prodrug (2D6, 3A4)

Side effects:

Bone

Cardiovascular and metabolic

CNS

Premature growth plate fusion

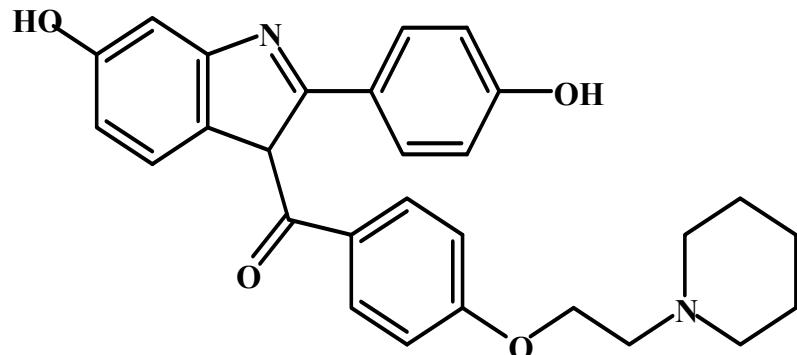
Agonist at bone

Partial agonist at uterus (cancer risk)

Antagonist at breast

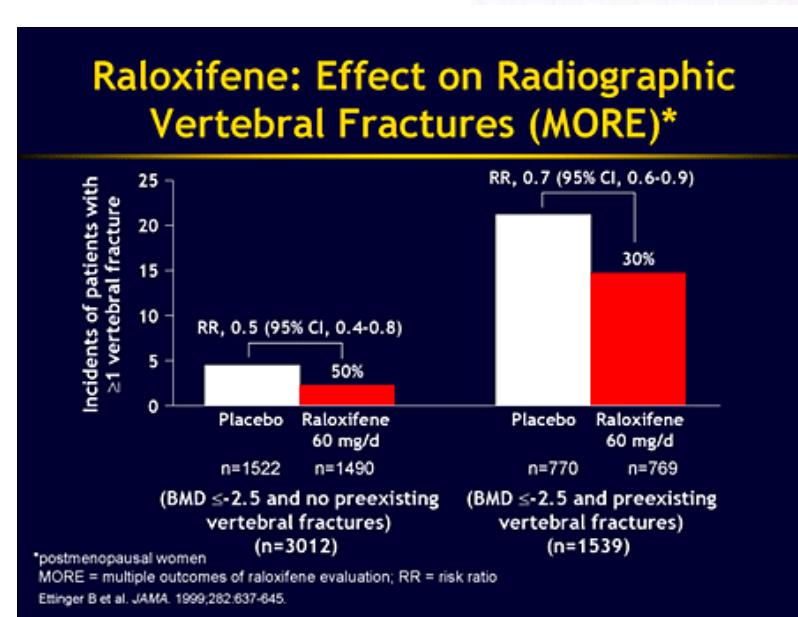


RALOXIFENE (Evista)



RALOXIFENE (EVISTA)

Agonist at bone
Antagonist at breast and uterus
no increased cancer risk



Known as a SERM (selective estrogen receptor modulator) –currently used to modify/ prevent postmenopausal osteoporosis



Raloxifene (Evista)

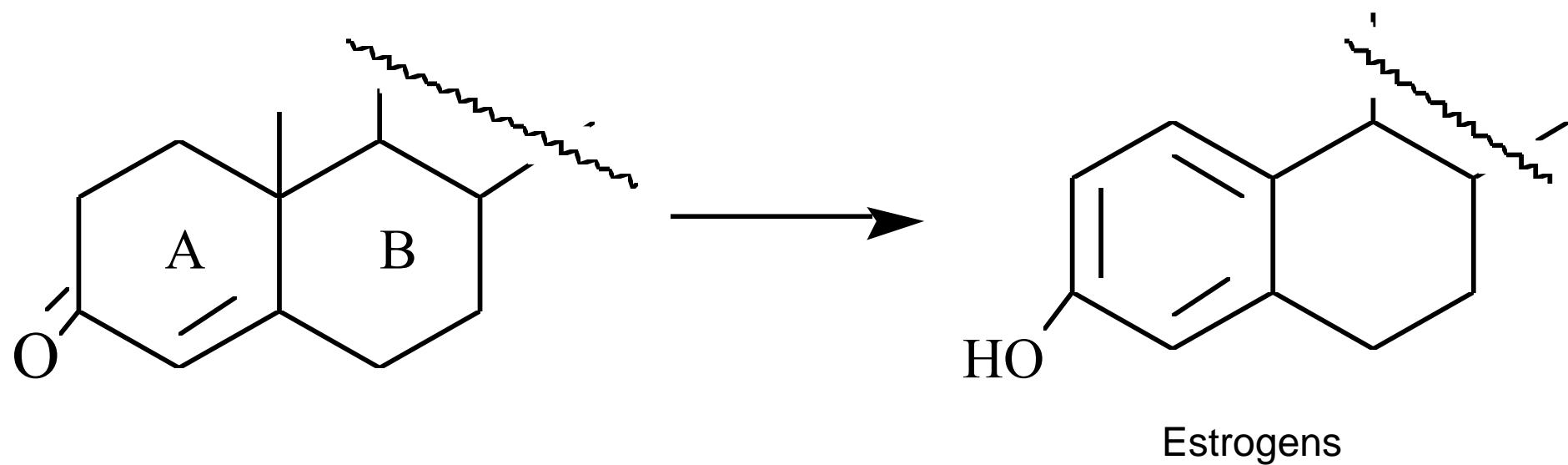


Estrogen receptor antagonists

- Fulvestrant (Faslodex)
 - 30 x stronger than tamoxifen
 - Ind: breast cancer



Steroid Aromatase

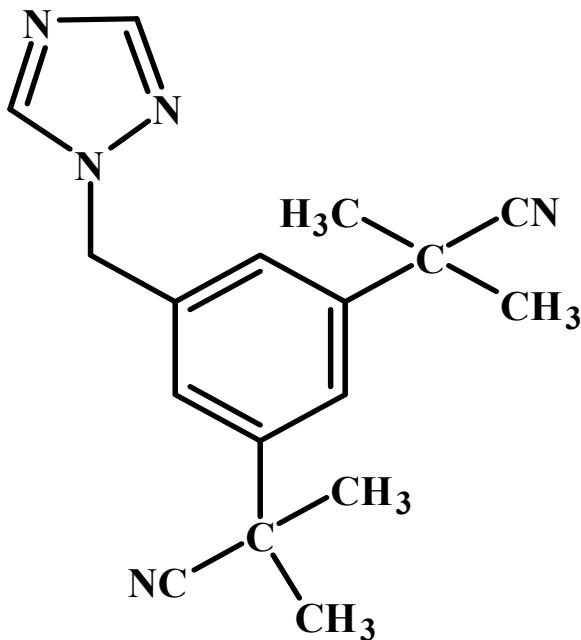


AROMATASE INHIBITORS

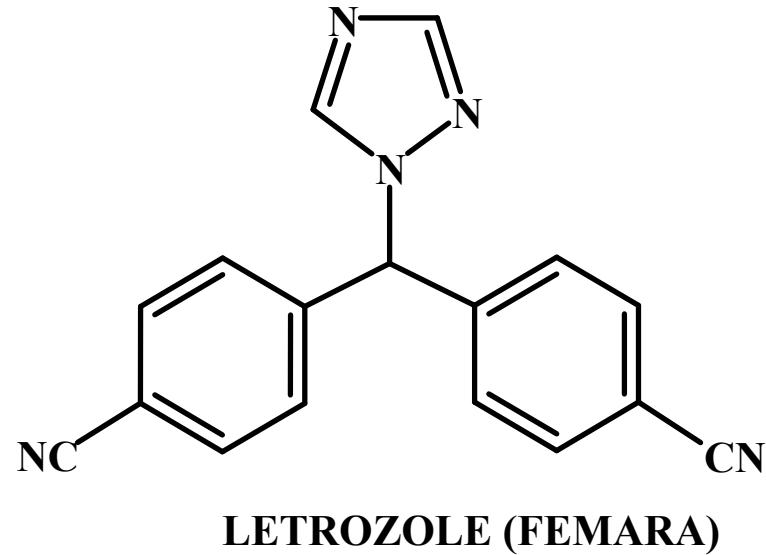
- Aromatase is a cytochrome P450 enzyme that catalyzes the conversion of adrenal androgen androstenedione to estrone in both pre- and post menopausal women
- Reaction occurs in the liver, muscle, adipose and breast tissue
- In post-menopausal women, aromatization is responsible for the majority of circulating estrogen
- Aminoglutethimide was used but has now been replaced by more selective drugs
- Drugs may be steroidal (formestan, exemestane) or non-steroidal (anastrozole, letrozole, vorozole)
- Estrogen deprivation through aromatase inhibition is an effective and selective treatment for some post-menopausal patients with hormone-dependent breast cancer
- Second line drugs in the treatment of breast cancer



AROMATASE INHIBITORS



ANASTROZOLE (ARIMIDEX)

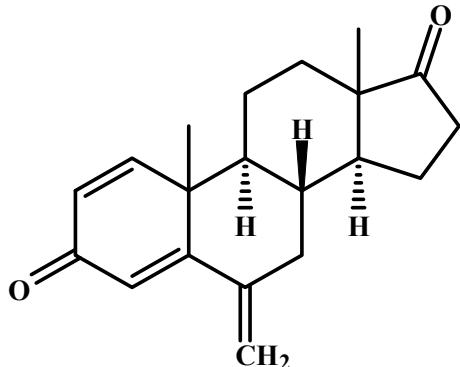


LETROZOLE (FEMARA)

both of these drugs are used in the treatment of advanced breast cancer in post-menopausal women with disease progression following tamoxifen therapy



EXEMESTANE (Aromasin)

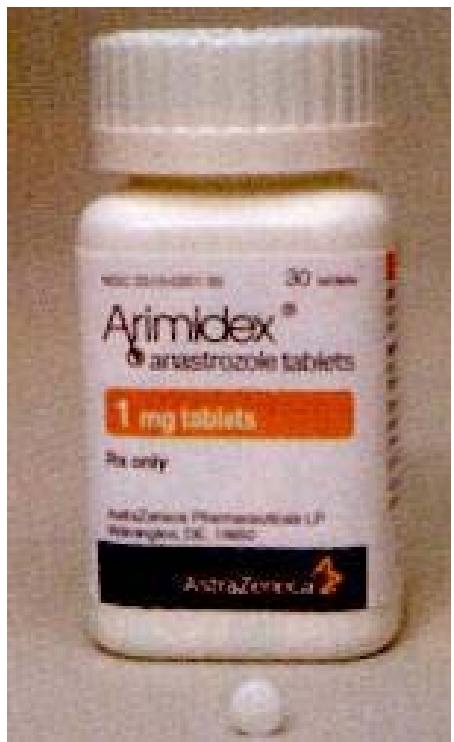


EMESTANE (AROMASIN)

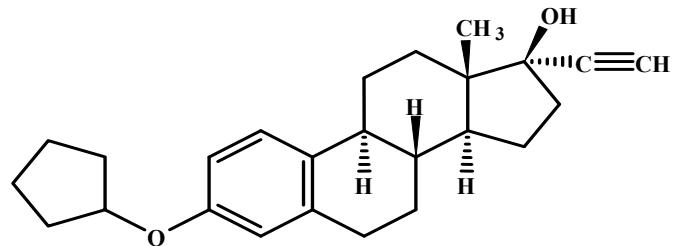


- 6-methylenandrosta-1,4-diene-3,17-dione
- structurally related to androstenedione
- acts as an irreversible (suicide) inhibitor of aromatase
- has no effect on other enzymes involved in steroidogenesis
- indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy





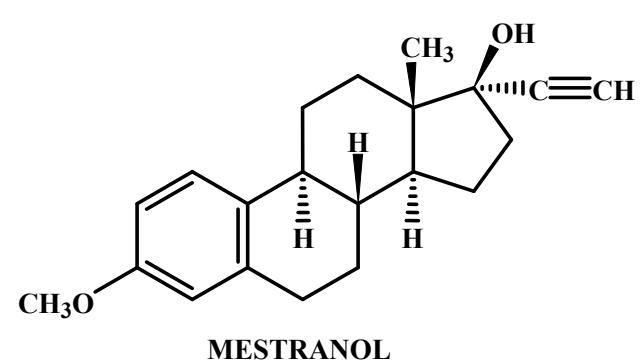
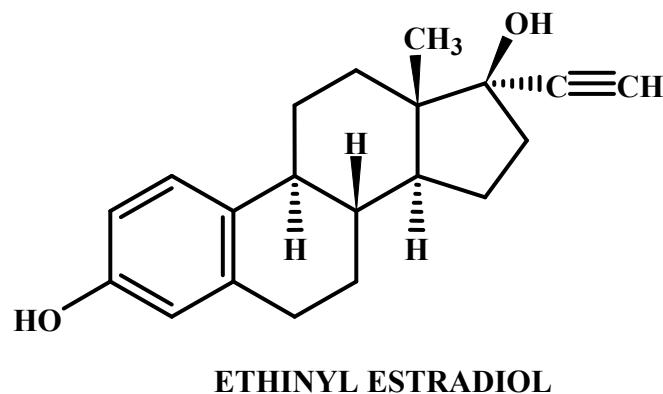
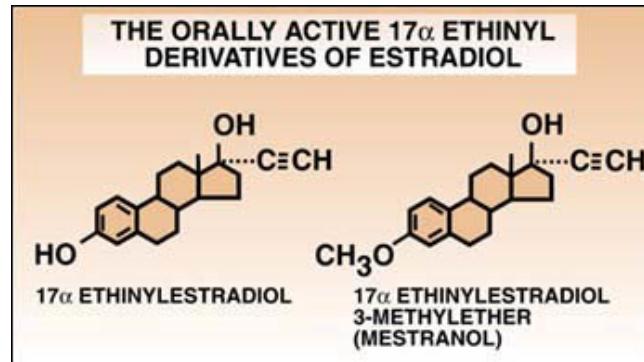
QUINESTROL



QUINESTROL



Semi-synthetic estrogens



Very commonly utilized in oral contraceptive products
ethinyl estradiol is more potent than mestranol



PROGESTERONE AND PROGESTINS

- Drugs which mimic the action of progesterone
- complement the action of estrogen on primary and secondary sex characteristics
- many are used as oral contraceptives:
 - norgestrel, levonorgestrel, norethindrone, norethindrone acetate, norethynodrel, ethynodiol diacetate, desogestrel and norgestimate



Effects of progestins

Reproductive tract

- Decreases the frequency of the hypothalamic pulse generator.
- Endocervical glands: scant, viscid material, helps to block the penetration of sperms.
- Suppress menstruation and uterine contractility.
- Breakthrough bleeding can occur!

Mammary Gland

- With estrogen causes the proliferation of the acini of mammary gland.

CNS effects

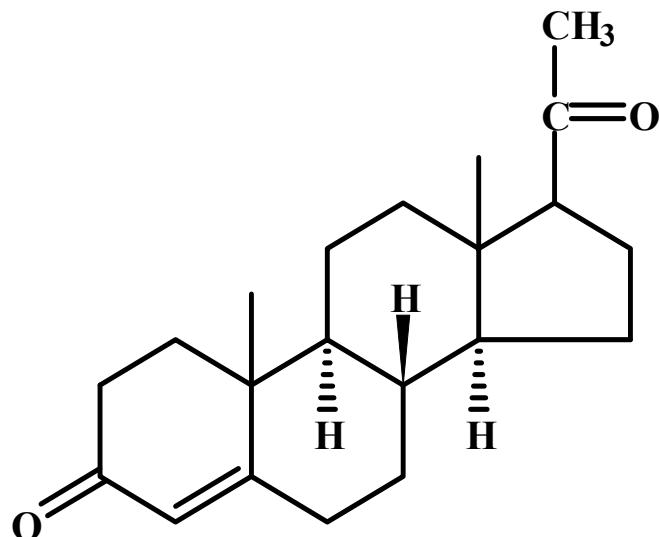
- At midcycle the body core temperature is elevated by 0.5 C° . \rightarrow ovulation.
Temperature increase is persists until the onset of menstruation.
- Depressant and hypnotic effect.

Metabolic effects

- Increase the basal insulin level. Long-term administration of potent progestins (norgestrel) **decrease glucose tolerance**.
- Increase LPL and fat deposition. Increase LDL level.
- $\downarrow \text{HDL}$ and $\uparrow \text{LDL}$
- **Hirsutism and acne (androgenic effect)**



PROGESTERONE



PROGESTERONE

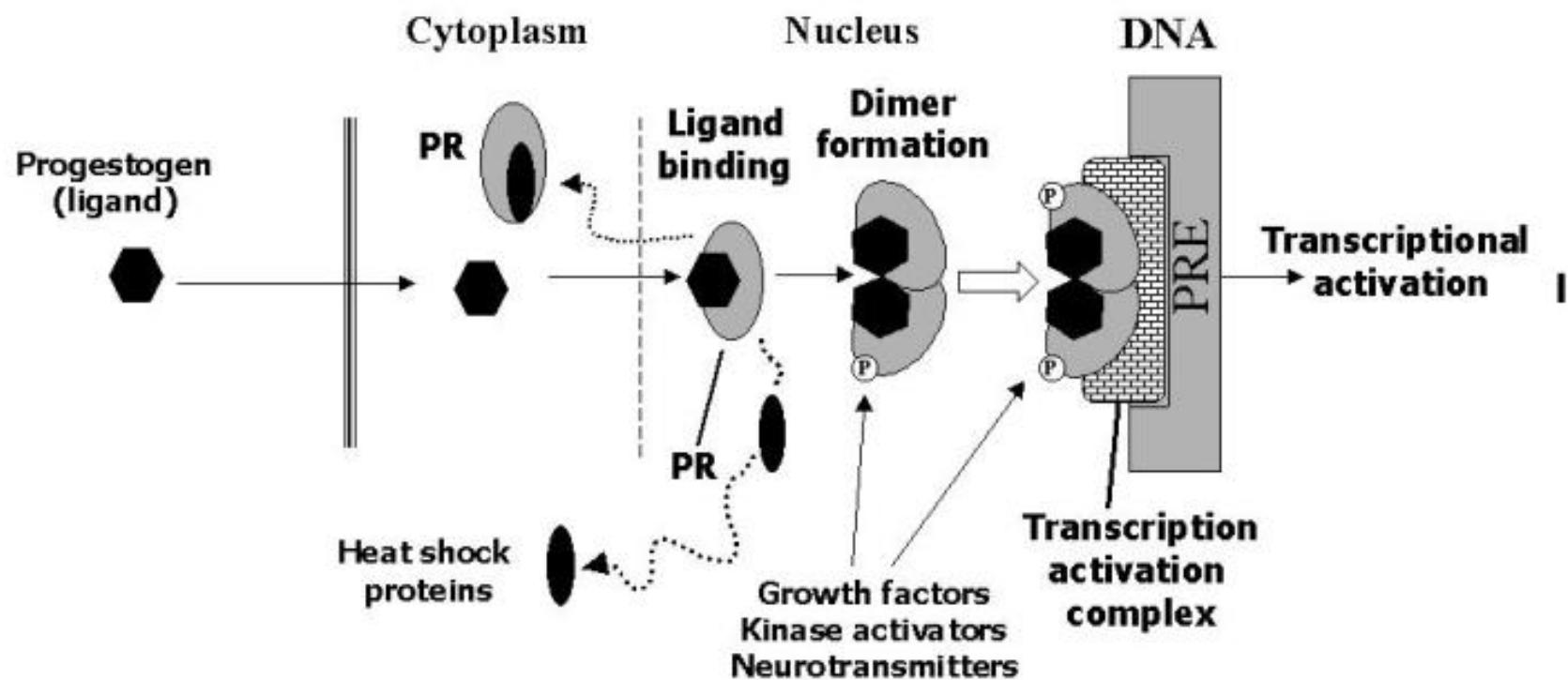
Natural hormone secreted by the corpus luteum and the placenta (a C-21 steroid).

It is also an important intermediate in steroid biogenesis in all tissues that produce steroids (testes, adrenal cortex).

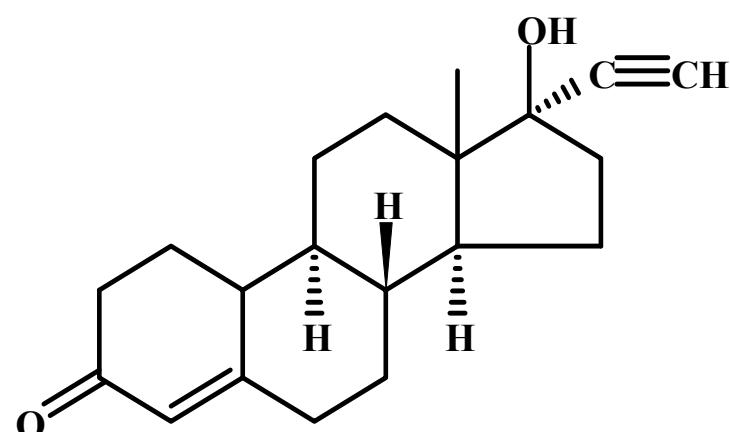
Intestinal absorption is quite erratic; must be micronized for most effective absorption (Prometrium)



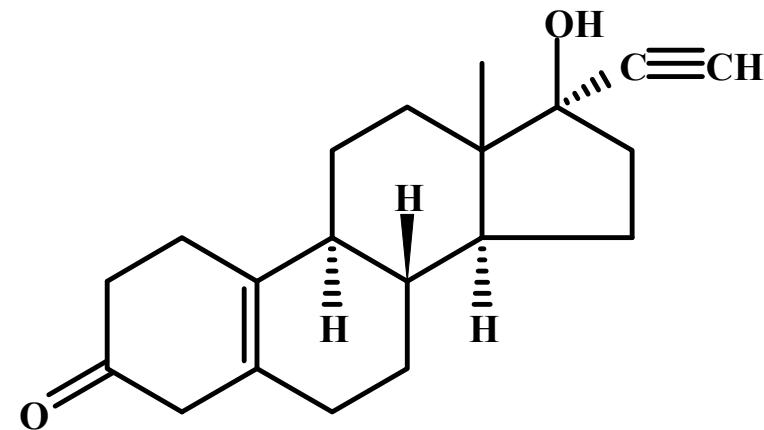
Schematic representation of progesterone receptor binding and transactivation



19-NOR STEROIDS



NORETHINDRONE

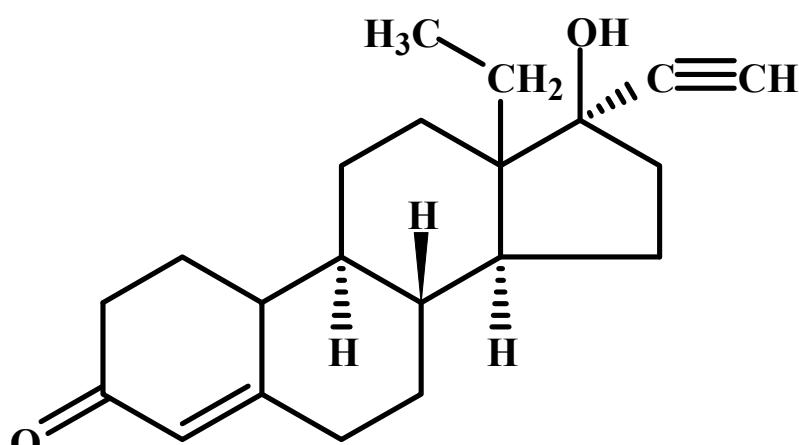


NORETHINODREL

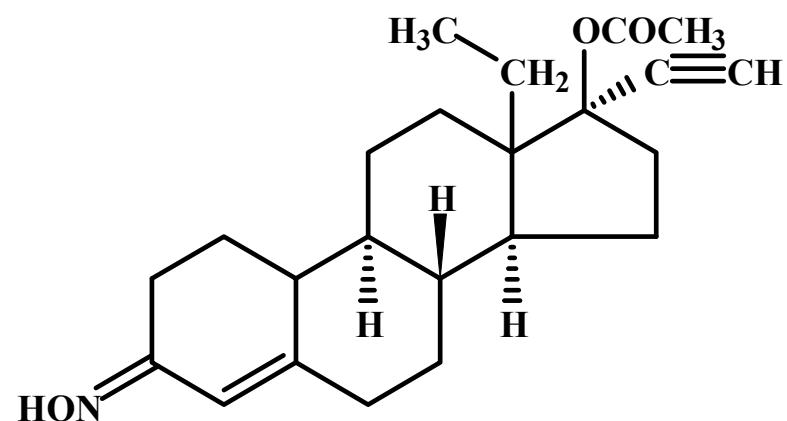
Chemical analogues of testosterone - some retain some androgenic activity such as norethindrone



19-NOR STEROIDS



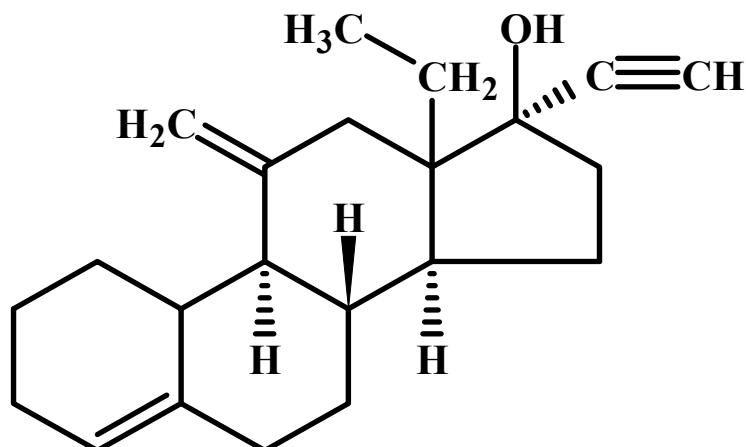
NORGESTREL



NORGESTIMATE

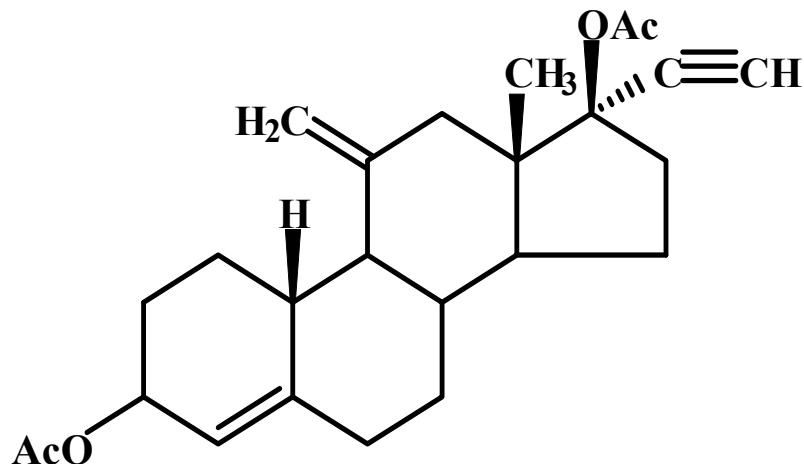


19-nor steroids



DESOGESTREL

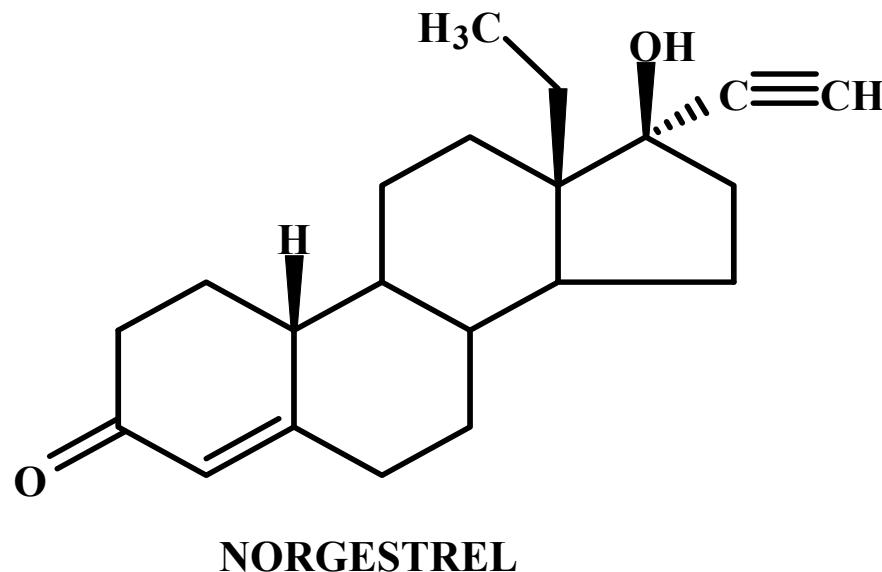
Devoid of androgenic and
anti-estrogenic activities!!!



ETHYNODIOL DIACETATE



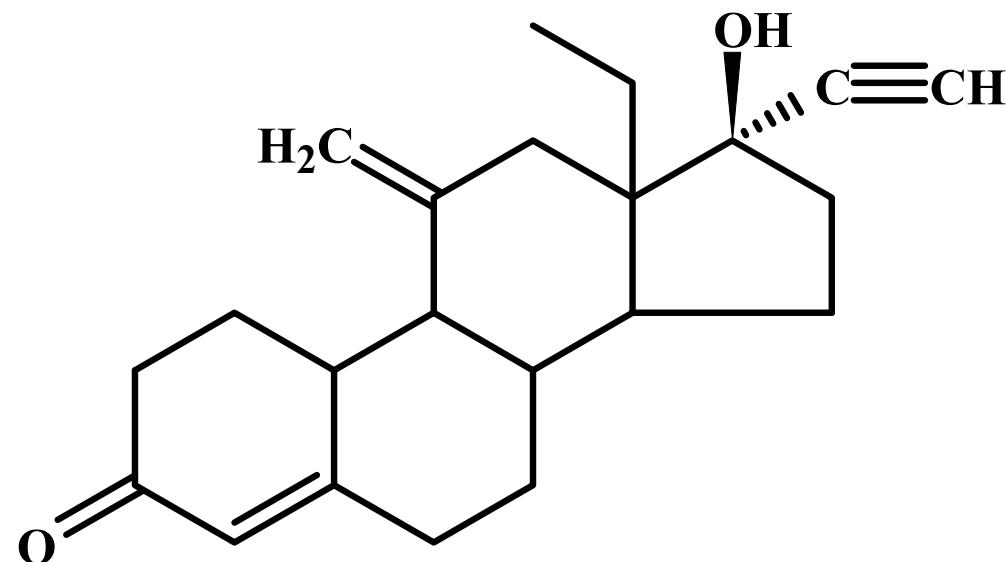
19-nor steroids



Both the racemic and the optically pure (levonorgestrel)
are used in oral contraceptive products



Etonorgestrel



ETONORGESTREL (NUVARING)

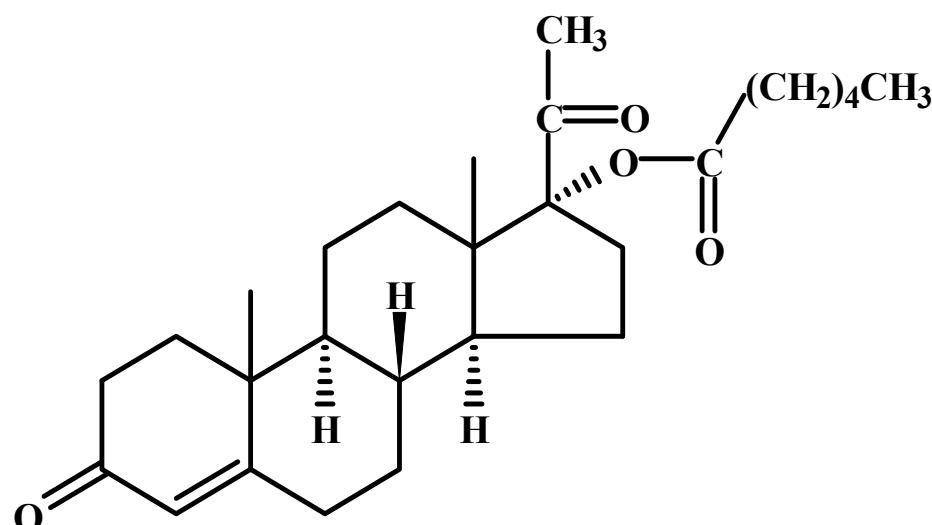


19-nor steroids

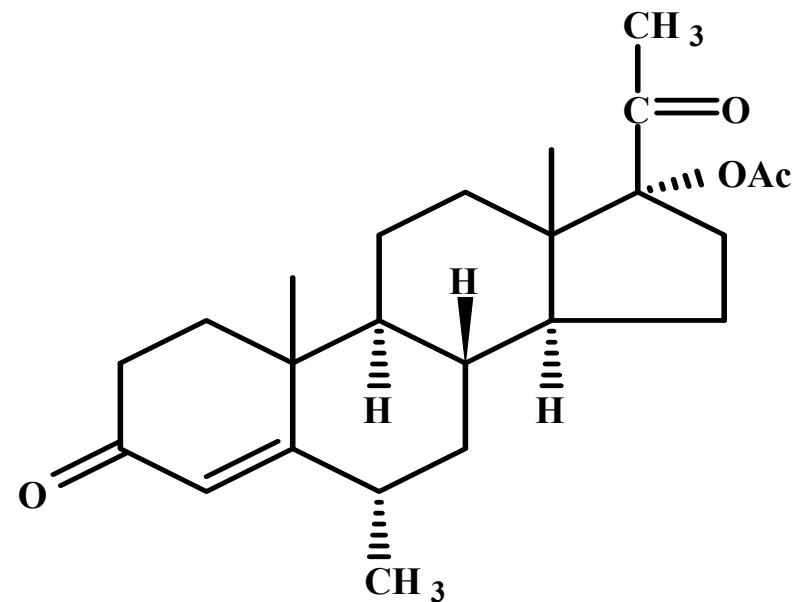
- Some 19-nor steroids can be metabolized to estrogenic compounds
- these progestins then exhibit estrogenic activity
 - norethynodrel and ethynodiol diacetate have estrogenic activity



17-hydroxy esterified progestins



HYDROXYPROGESTERONE CAPROATE



MEDROXYPROGESTERONE ACETATE

Medroxyprogesterone acetate is a very popular orally effective progestin (Provera)



Progesterins available in Hungary

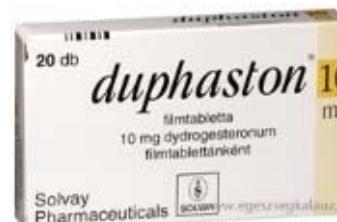
Medroxyprogesterone (PROVERA)



Progesterone (CRINONE, UTROGESTAN)



Dydrogesterone (DUPHASSTON)



Norethisterone (NORCULUT)





50* 10 mg



64* 2.5 mg



286* 5 mg

Provera® (medroxyprogesterone acetate)



Act-O-Vial®
Systems

1 gram vial



Sterile aqueous suspension

Depo-Medrol®

(sterile methylprednisolone acetate, USP)



Combined estrogens and progestins

- Currently very popular forms for HRT
- combine an estrogen (natural or semi-synthetic) with an orally effective progestin
 - Prempro and Premphase
 - FemHRT
 - Combipatch



RX

PARKE-DAVIS
A WARNER-LAMBERT DIVISION
A PFIZER COMPANY



1 mg/5 mcg

Femhrt®

(norethindrone acetate/ethinyl estradiol)

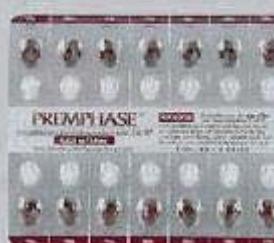


867*



867**

Card 1 consists of 14 maroon tablets,
each containing 0.625 mg of Premarin®
brand of conjugated estrogens.
This card is to be used first



867*

Card 2 consists of 14 maroon tablets,
each containing 0.625 mg of Premarin®
brand of conjugated estrogens, and 14
light-purple tablets, each containing 5.0 mg
of medroxyprogesterone acetate.

Each blister card consists of 14 maroon
tablets, each containing 0.625 mg of
Premarin® brand of conjugated estrogens,
and 14 white tablets, each containing
2.5 mg of medroxyprogesterone acetate.

Prempro™

(conjugated estrogens tablets/
medroxyprogesterone acetate tablets, USP)
0.625 mg / 2.5 mg

Premphase™

(conjugated estrogens tablets/
medroxyprogesterone acetate tablets, USP)
0.625 mg / 5.0 mg



Gonadotropins for ovulation stimulation (Drugs in Hungary)

- Chorionic gonadotrophin (CHORAGON, PREGNYL)
- Human menopausal gonadotrophin (MENOPUR, MERIONAL)
- Urofollitropin (FOSTIMON)
- Follitropin alpha (GONAL)
- Follitropin beta (PUREGON)
- Lutropin (LUVERIS)
- Choriogonadotripin alpha (OVITRELLE)
- Corifollitropin alpha (ELONVA)



Progestin antagonist

- Mifepristone
 - Glucocorticoid receptor antagonist as well
 - Abortifacient (used with PGs)



CONTRACEPTIVES



Therapeutic use of progestins

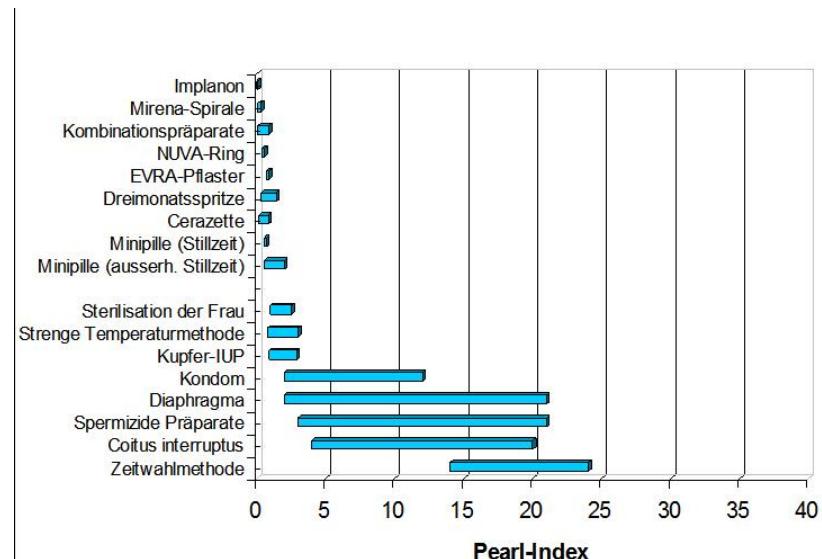
1. Contraception with or without estrogen.
2. Hormone replacement therapy.
3. Secondary amenorrhoea, bleeding disorders
4. Luteal-phase support to treat infertility
5. Premature labour
6. Progestins have been used as palliative measure for metastatic endometrial carcinoma, and is used as a second line treatment of metastatic carcinoma.
7. Diagnostic uses: to test endometrial responsiveness with or without estrogen.



Perl index

Number of unwanted pregnancies X 1200
Application time in months

Without protection	80
Vaginal lavage	25-45
Coitus interruptus	12-42
Vaginal tablets	10-42
Ogino-Knaus	12-40
Vaginal, cervical pessarium	6-32
Condom	6-28
IUD	0.8-8
Minipill	2-8
Classic combinational	0.2-1.5



History

- **Ludwig Haberlandt** (1885-1932) in 1927, rodents are fed ovarian and placental extracts – inhibition of ovulation.
- Nem sokon múlott, hogy az első fogamzásgátló tabletát a hazai gyógyszergyártás megalapítójának, a hormongyártásban kiemelkedő tevékenységet kifejtő Richter Gedeonnak a budapesti vegyészeti gyárában állítsák elő az 1930-as évek végén, vagyis közel húsz évvel azelőtt, hogy a ma használatos fogamzásgátlók prototípusa feltűnt a piacon. Richter ugyanis jó szakmai és baráti kapcsolatot ápolt az Innsbruckban, majd Bécsben élő Ludwig Haberlandt élettanprofesszorral, akivel közösen a teherbeesés elkerülésére utaló Infecundin néven humán fogamzásgátló tabletta előállítását tervezte. A végső kivitelezés azonban az értelmi szerző osztrák tudós korai halála és a második világháborút megelőző esztendők kedvezőtlen körülményei, főként az 1938-ban bekövetkezett Anschluss miatt meghiúsult.
- Haberlandt apja (Gottlieb) Mosonmagyaróváron született és túlélte fiát.



Oral Contraceptives

- 4 types:
 - monophasic: Loestrin, Levlen, Levora, Levlite, Desogen, Lo/Ovral, Ortho-Cept, Nordette, Demulen, Ovcon, Modicon, Zovia, Loestrin, Aprि, Microgestin, Yasmin, Ortho-Cept, Levora, Alesse
 - biphasic: Ortho-Novum 10/11, Nelova 10/11, Necon 10/11, Jenest-28, Mircette
 - triphasic: Ortho-Novum 7/7/7, Tri-Norinyl, Tri-Levlen, Triphasil, Trivora-28, Estrostep
 - progestin-only: Micronor, Nor-QD, Ovrette



Estragen and progestagene fix combinations

•		Ethinylestradiol	levonorgestrel
•OVIDON	0.05 mg		0.25 mg
•RIGEVIDON	0.03 mg		0.15 mg
•LOETTE	0.02 mg		0.10 mg
•			desogestrel
•MARVELON	0.03 mg		0.15 mg
•MERCILON	0.02 mg		0.15 mg
•NOVYNETTE	0.02 mg		0.15 mg
•REGULON	0.03 mg		0.15 mg
•			gestodenum
•FEMODEN	0.03 mg		0.075 mg
•HARMONET	0.02 mg		0.075 mg
•MELIANE	0.02 mg		0.075 mg
•MINULET	0.03 mg		0.075 mg
•TRI-MINULET	0.03 mg	0.05 mg	beige
	0.04 mg	0.07 mg	brown
	0.03 mg	0.1 mg	white
•LINDYNETTE	0.02 v. 0.03 mg	0.075 mg	
•MINESSE	0.015 mg	0.06 mg	
•CILEST	0.035 mg	norgestimate 0.25 mg	
•BELARA	0.03 mg	chlormadinon 1.71 mg	
•			drospirenone
•YADINE	0.03 mg		3.0 mg
•YASMINELLE	0.02 mg		3.0 mg



Estrogen and progestagen sequential combinations

•	EOD	levonorgestrel
•ANTEOVIN	0.05 mg	0.05 mg white
•	0.05 mg	0.125 mg pinkish
•TRINORDIOL	0.03 mg	0.05 mg purplebrown
•	0.04 mg	0.075 mg white
•	0.03 mg	0.125 mg okkeryellow
•TRIQUILAR	0.03 mg	0.05 mg
•	0.04 mg	0.075 mg
•	0.03 mg	0.125 mg
•TRIREGOL	0.03 mg	0.05 mg pinkish
•	0.04 mg	0.075 mg white
•	0.03 mg	0.125 mg okkeryellow
•		
•		
•GRACIAL	0.04 mg	desogestrel
•	0.03 mg	0.025 mg blue
•		0.125 mg white
•		
•TRIODENA	0.03 mg	gestodenum
•	0.04 mg	0.05 mg beige
•	0.03 mg	0.07 mg darkbrown
•MILLIGEST	0.03 mg	0.1 mg white
•	0.04 mg	0.05 mg
•	0.03 mg	0.07 mg
•		0.01 mg



Progestagen only contraceptives

- CONTINUIN (etinodiol diacetát 0.5 mg)
- DEPO PROVERA (medroxyprogesteron 150 mg) 3 hónaponta 1 inj.
- MIRENA levonorgestrel tartalmú intrauterin eszköz
- IMPLANON (etonogestrel 68 mg) implantátum, 3 évig tart!
- CERASSETTE (desogestrel 0.075 mg) 28 tbl. (Minipill!)
- Postcoitalis, esemény utáni elsősegély contraceptívumok
- RIGESOFT (0.75 mg levonorgestrel)
- POSTINOR (0.75 mg levonorgestrel)
- ESCAPELLE (1.5 mg levonorgestrel)



Generics

Examples of Generic Oral Contraceptives

- Apri (same as Desogen and Ortho-Cept 28)
- Aviane (same as Alesse-28)
- Lessina (same as Levlite 28)
- Necon (same as Ortho-Novum 1/35)
- Ogestrel (same as Ovral)
- Sprintec (same as Ortho-Cyclen-28)
- Microgestin Fe (same as Loestrin Fe)
- Kariva (same as Mircette)
- Enpresse (same as Triphasil-28)



OTHER CONTRACEPTIVE PRODUCTS

- Levonorgestrel implants (Norplant system)
- intrauterine progesterone contraceptive system (Progestasert)
- medroxyprogesterone contraceptive injection (Depo-Provera)
- nonoxynol contraceptive creams and gels



2564* 36 mg

Norplant® System (levonorgestrel implants)

Progestasert®





Emergency contraceptives

- drugs used for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure
- to be effective these must be taken within 72 hours of intercourse
- two products are available:
 - Plan B: 0.75 mg levonorgestrel
 - Preven: 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol
(this product includes a pregnancy test kit)





Table 9 Spectrum of hormonal activities of progestogens. The data are mainly based on animal experiments and are compiled from the literature^{202,204,236–244}. The clinical effects of the progestogens are dependent on their tissue concentrations

<i>Progestogen</i>	<i>A-E</i>	<i>EST</i>	<i>AND</i>	<i>A-A</i>	<i>GLU</i>	<i>A-M</i>
Progesterone	+	–	–	(+)	+	+
Chlormadinone acetate	+	–	–	+	+	–
Cyproterone acetate	+	–	–	+	+	–
Medroxyprogesterone acetate	+	–	(+)	–	+	–
Medrogestone	+	–	–	–	?	–
Dydrogesterone	+	–	–	–	?	(+)
Norethisterone	+	+	+	–	–	–
Levonorgestrel	+	–	+	–	–	–
Gestodene	+	–	+	–	(+)	+
Etonogestrel (3-keto-desogestrel)	+	–	+	–	(+)	–
Norgestimate	+	–	+	–	?	?
Dienogest	+	–	–	+	–	–
Tibolone metabolites	+	+	++	–	–	–
Drospirenone	+	–	–	+	–	+
Trimegestone	+	–	–	(+)	–	(+)
Promegestone	+	–	–	–	+	–
Nomegestrol acetate	+	–	–	+	–	–
Nestorone	+	–	–	–	–	–

A-E, antiestrogenic; EST, estrogenic; AND, androgenic; A-A, antiandrogenic; GLU, glucocorticoid; A-M, antimineralocorticoid activity

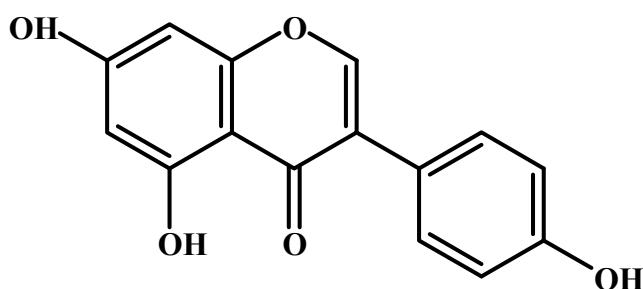
++, strongly effective; +, effective; (+) weakly effective; -, not effective; ?, unknown



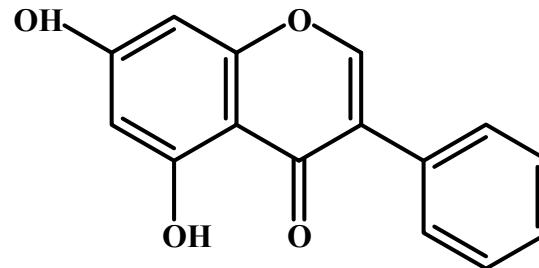
Plant estrogens: phytoestrogens

- A variety of compounds exist in plant which possess estrogenic activity
- Soy products contain flavonoids and lignin derived compounds which have estrogenic activity
- Extractum agni casti fructus (illatos barátcsereje termés kivonat)
- Extractum cimicifugae rhizomae (black cohosh, poloskavész, indiánasszonygyökér kivonat)

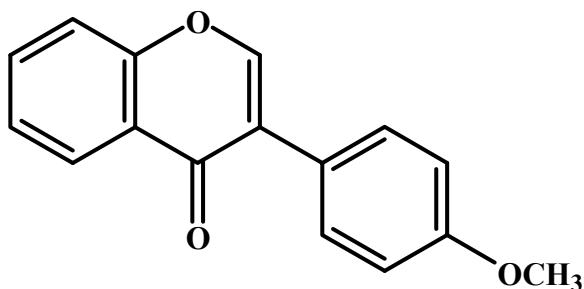




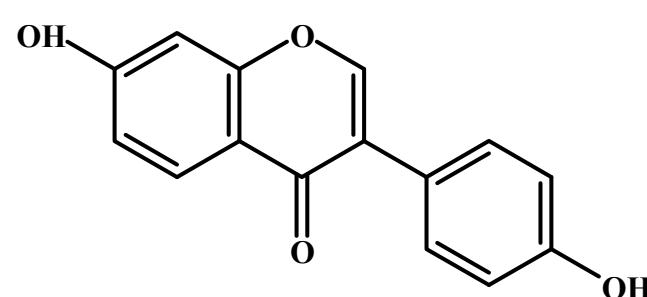
GENISTEIN



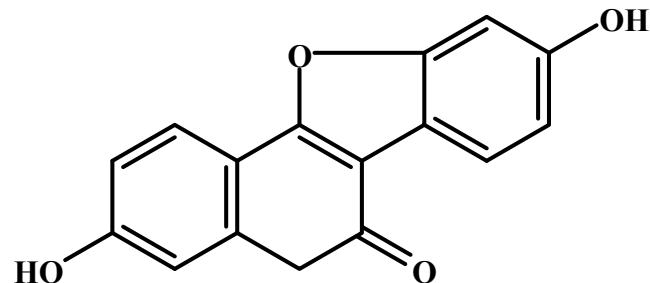
BIOCHANIN A



FORMONONETIN



DAIDZIN



COUMESTROL



Black cohosh (Remifemin)

- *Cimicifuga racemosa*
- medicinally used parts: dried rhizomes and roots
- used for the symptoms of PMS and climacteric complains
- active ingredients:
 - triterpenes: cimifugoside, actein, 27-deoxyactein
 - Quinolizine alkaloids: cytisine, methyl cytisine
 - Other: isoferulic acid
- binding to estrogen receptor causes a suppression of LH release





Side effects of oral contraceptives

Estrogen component (EOD)

Mastalgia, bloating, headache, nausea, vomitus, gall stone formation

Progestin component

Hirsutism, weight gain, acne, tiredness, depression, ↓HDL, ↑LDL



ANDROGENS

- prototype is testosterone (produced by interstitial cells of testis)
- main function: development and maintenance of primary and secondary sex characteristics in males (androgenic)
- protein retention (anabolic action)
- other naturally occurring androgens: androsterone, isoandrosterone, dehydroandrosterone, dehydroisoandrosterone

Uses:

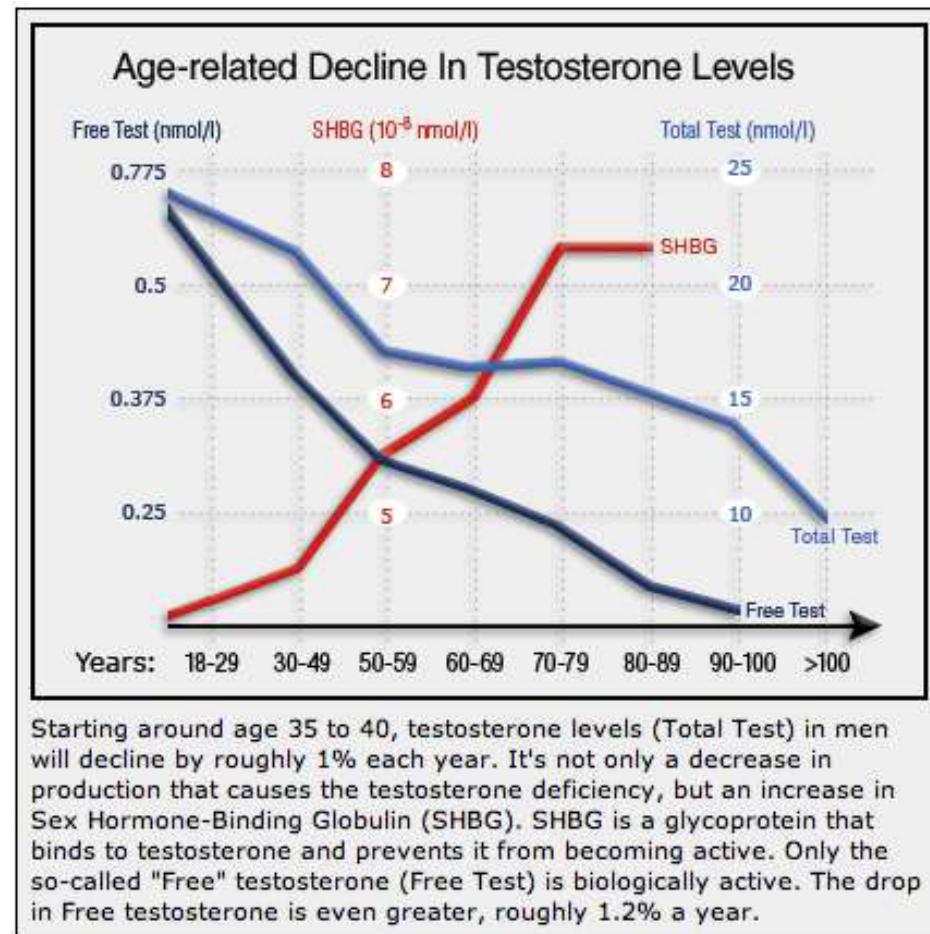
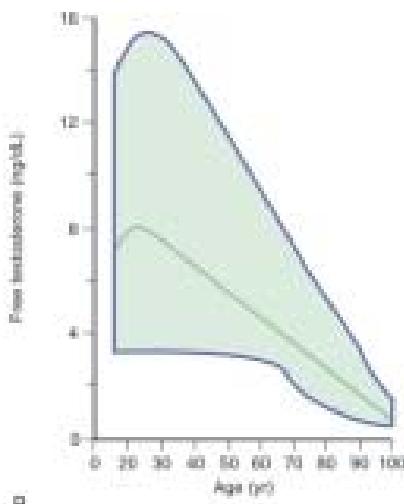
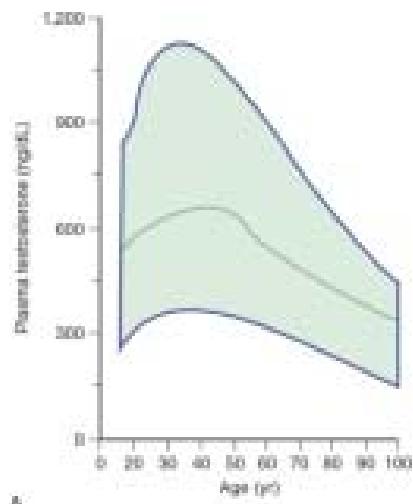
- Male hypogonadism
- Anabolic actions
- Illicit use in athletics



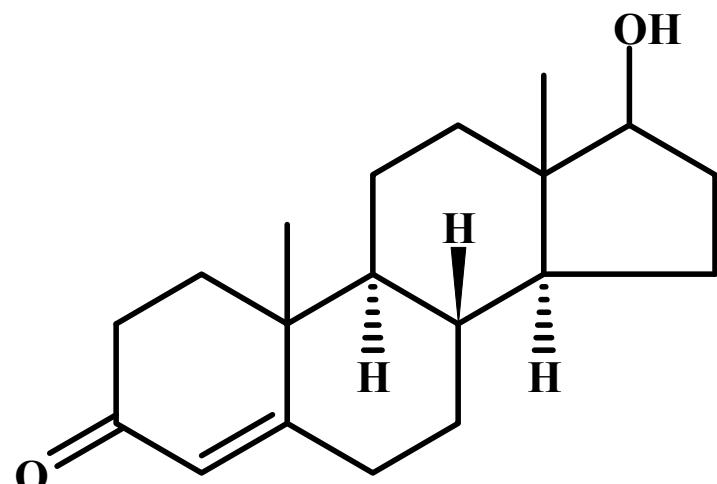
Physiological effects of testosterone

- pubertal transformation:
 - enlargement of testes, penis and scrotum
 - pubic and axillary hair
 - bone growth
 - red cell mass increase
 - skeletal muscle mass increase
 - larynx enlarges - deepening of the voice
 - increase in sebaceous glands - often cause of acne
 - beard development

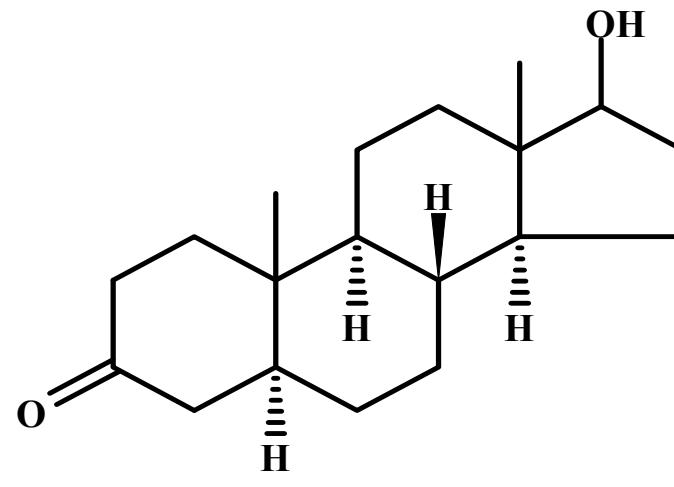




Natural androgens

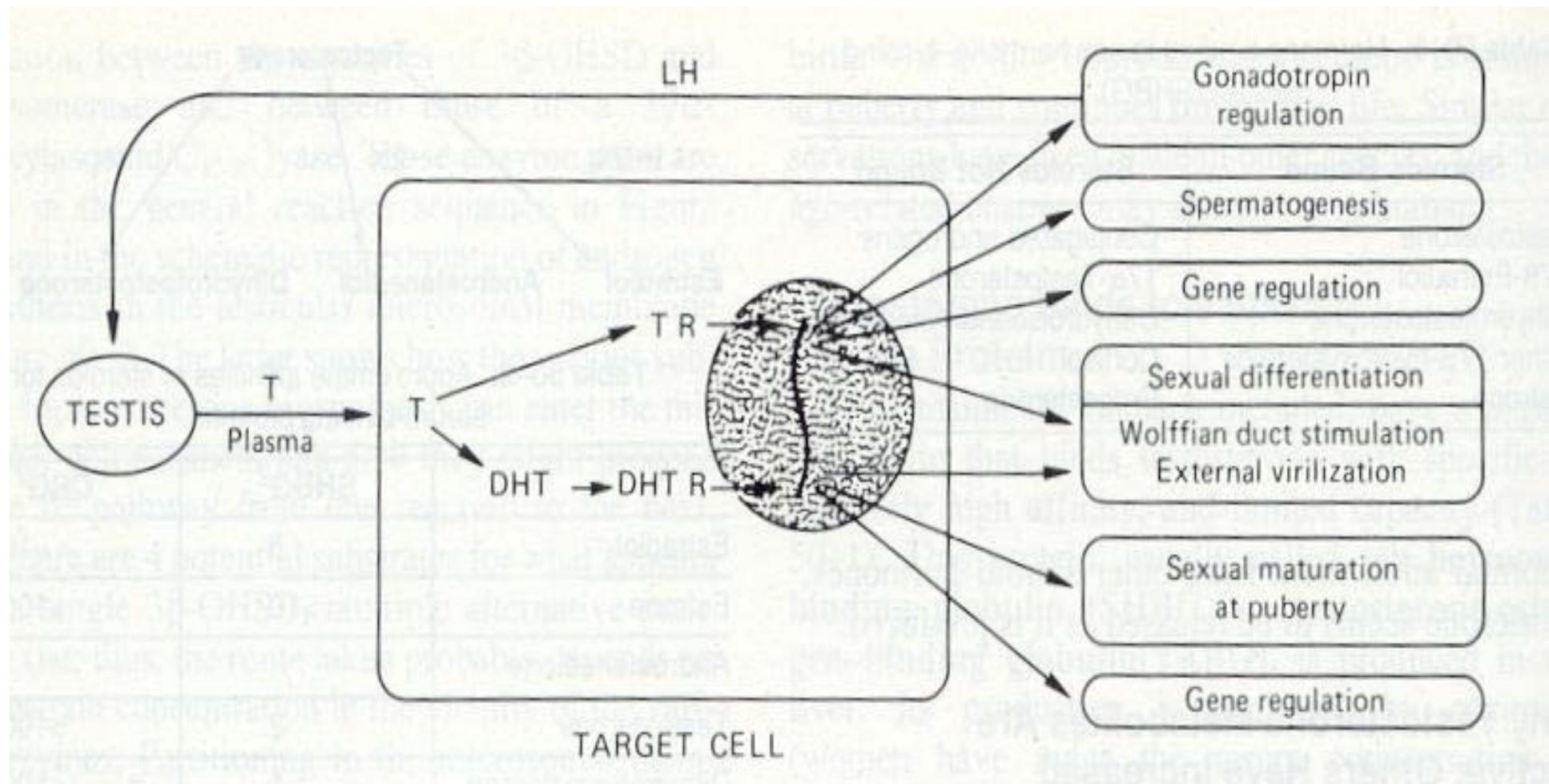


TESTOSTERONE



DIHYDROTESTOSTERONE





Testosterone products

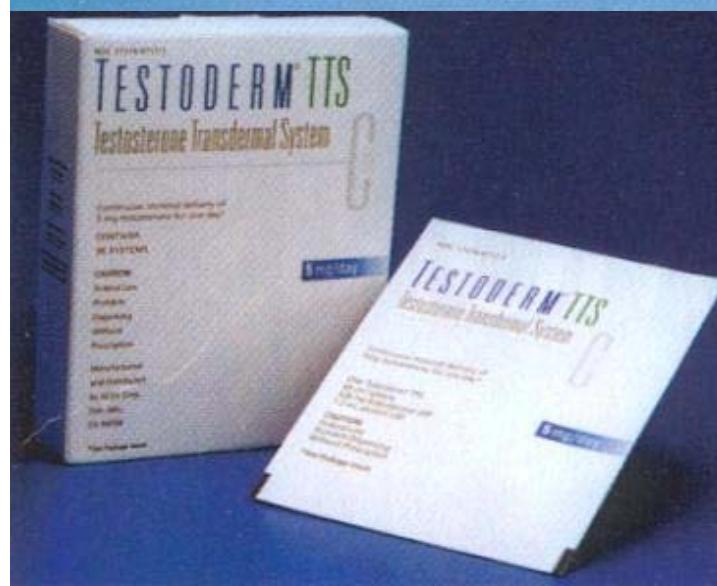
- testosterone in aqueous suspension (short-acting)
- testosterone propionate in oil
- testosterone enanthate in oil (Delatestryl)
- testosterone cypionate in oil (Depotest)
- testosterone pellets (Testopel)
- testosterone transdermal system (Androderm)



Androgen products in Hungary

- Testosterone
 - ANDRIOL
 - ANDROGEL
 - NEBIDO
 - TOSTRAN
- Mesterolone
 - PROVIRON





Uses for Androgens

- Replacement therapy in hypogonadism
- delayed puberty
- cryptorchidism
- metastatic breast cancer in women
- postpartum breast pain/engorgement
- male climacteric



Side effects of androgens

Excessive masculinization (virilization in the baby as well)

Cholestatic jaundice

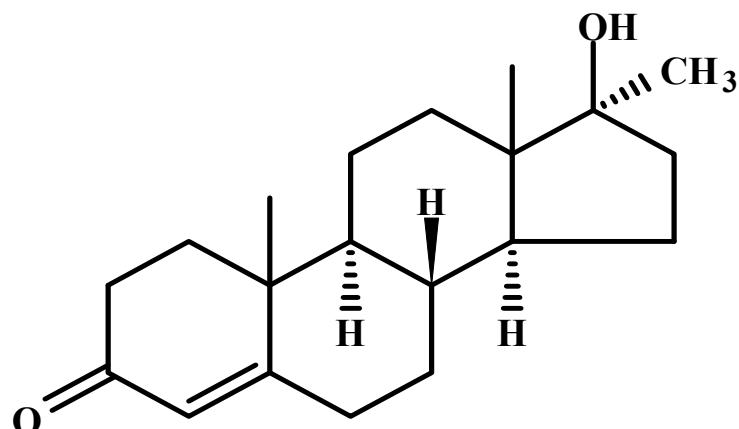
Premature closure of epiphyses

Aggression ((Ste)roid rage)

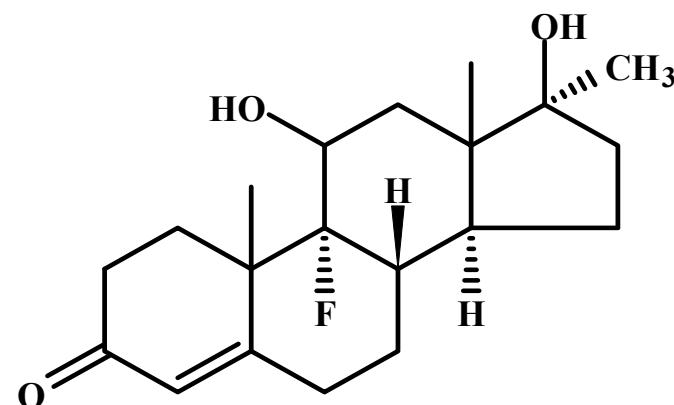
Dependence



Semi-synthetic androgens



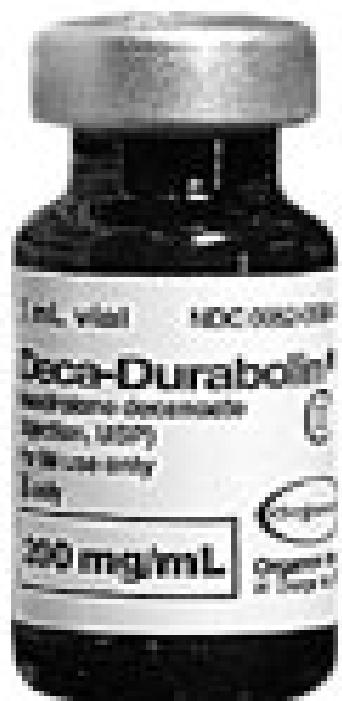
METHYLTESTOSTERONE



FLUOXYMESTERONE (HALOTESTIN)

Frequently classified as 17-alpha alkylated androgens;
alkylation confers more oral effectiveness





Up to 20 mg/day

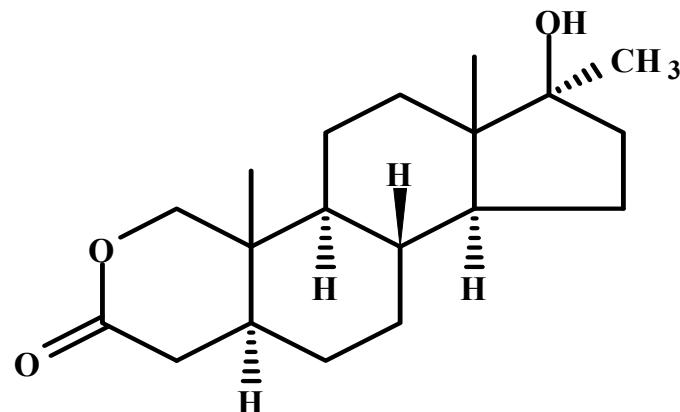
OXANDRIN®

oxandrolone, USP @
2.5 mg tablets

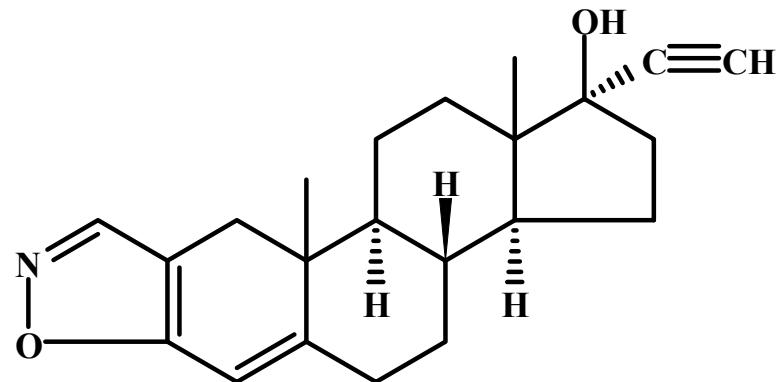
Co-marketed by Ross Products
Division, Abbott Laboratories
Manufactured for BTG Pharmaceuticals
For more information:
www.oxandrin.com



ANABOLIC STEROIDS



OXANDROLONE (OXANDRIN)



DANAZOL (DANOCRINE)

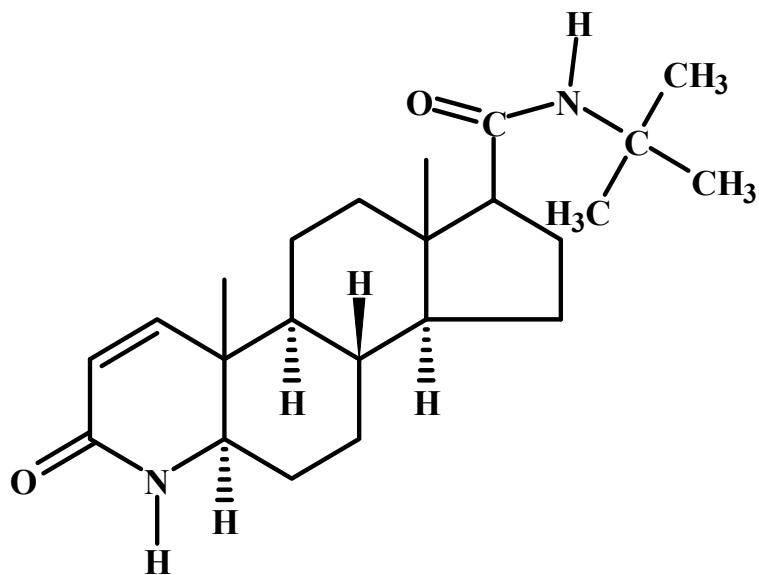
Also classified as 17-alpha alkylated androgens



FINASTERIDE (PROSCAR, PROPECIA)



An anti-androgen used
in the treatment of BPH
(benign prostatic hypertrophy)
also used to manage male pattern
baldness (Propecia)
Can be teratogenic!



FINASTERIDE (PROSCAR)

MOA: Inhibits 5^α-reductase enzyme →
Testosterone-DHT formation is inhibited

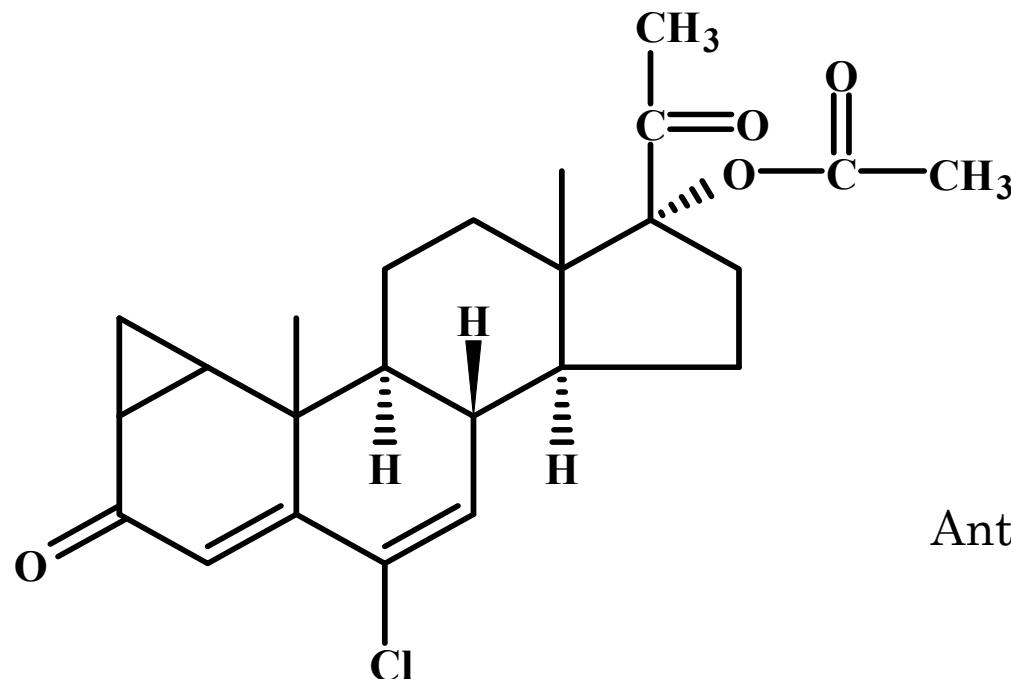




Finasteride : Proscar and Propecia



CYPROTERONE ACETATE

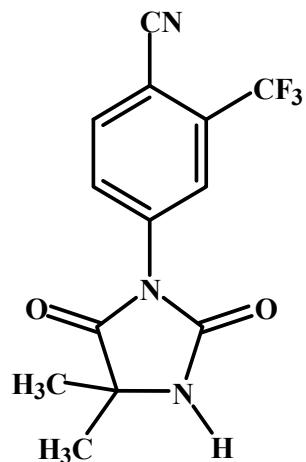


Antiandrogenic properties

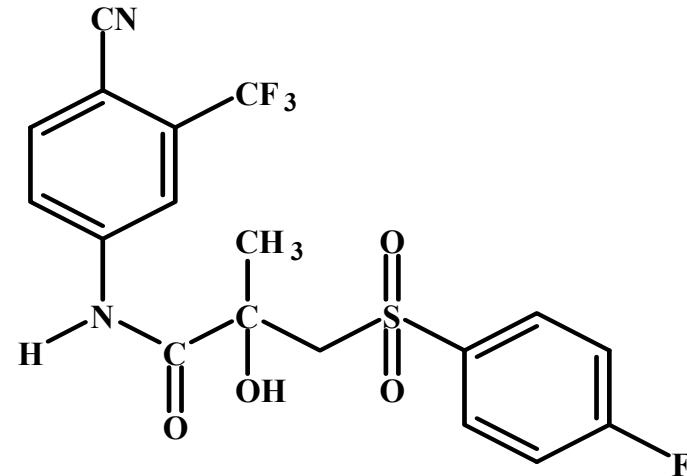
CYPROTERONE ACETATE (ANDROCUR)



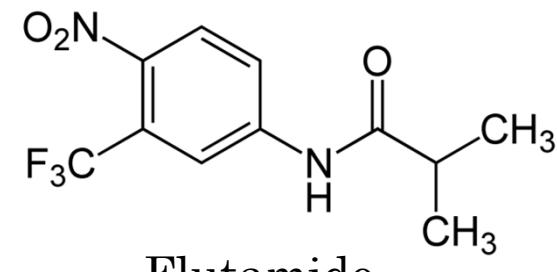
ANTIANDROGENS (SARMs)



NILUTAMIDE (NILANDRON)



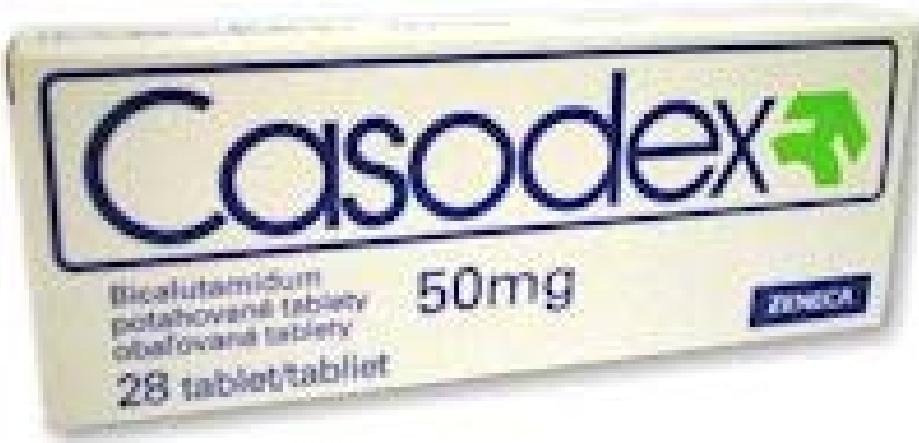
BICALUTAMIDE (CASODEX)



Flutamide

Use in metastatic prostate carcinoma





RX SCHERING CORPORATION



525* 125 mg

Eulexin®
(flutamide)

RX AVENTIS PHARMACEUTICALS



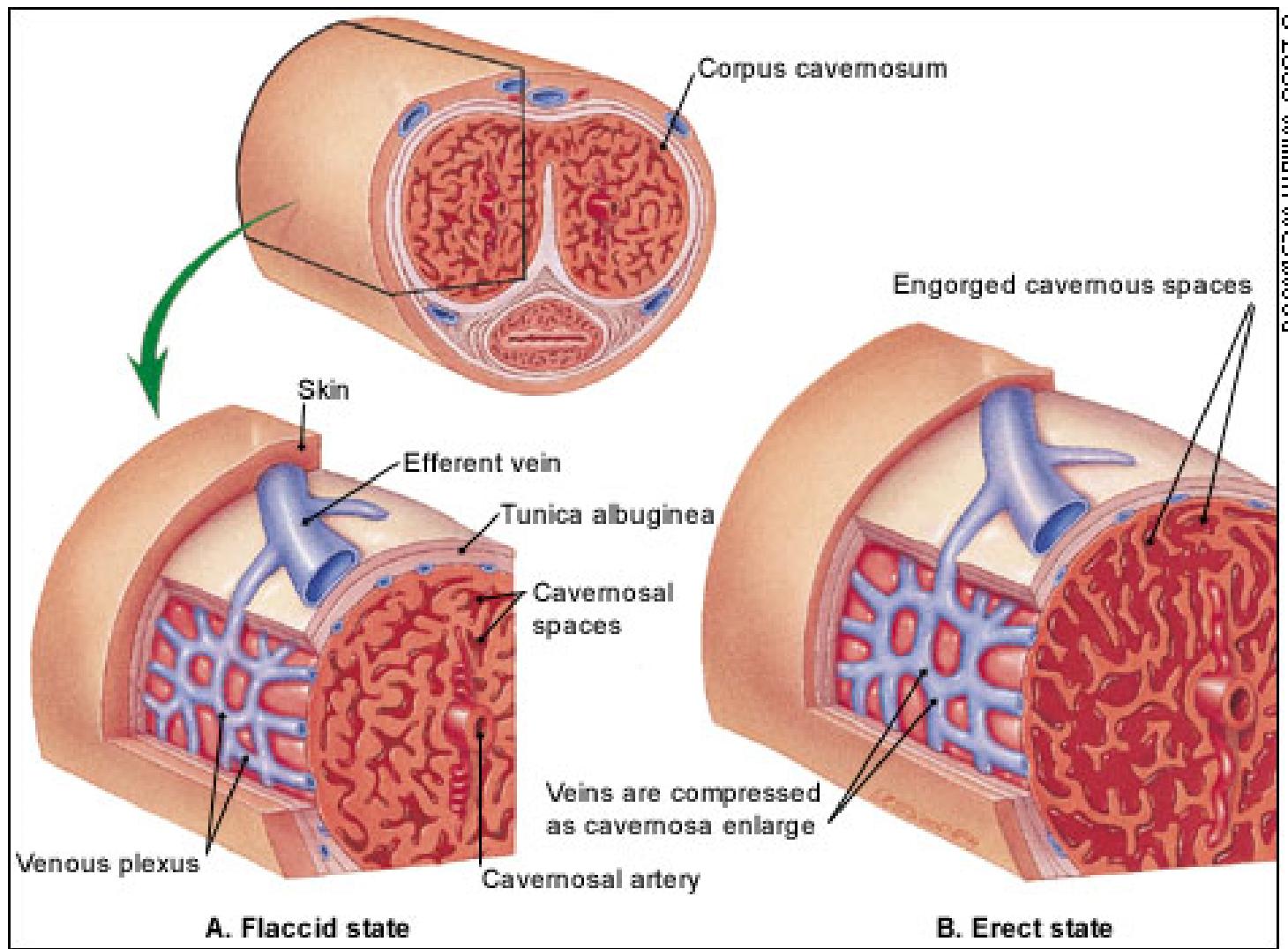
50 mg

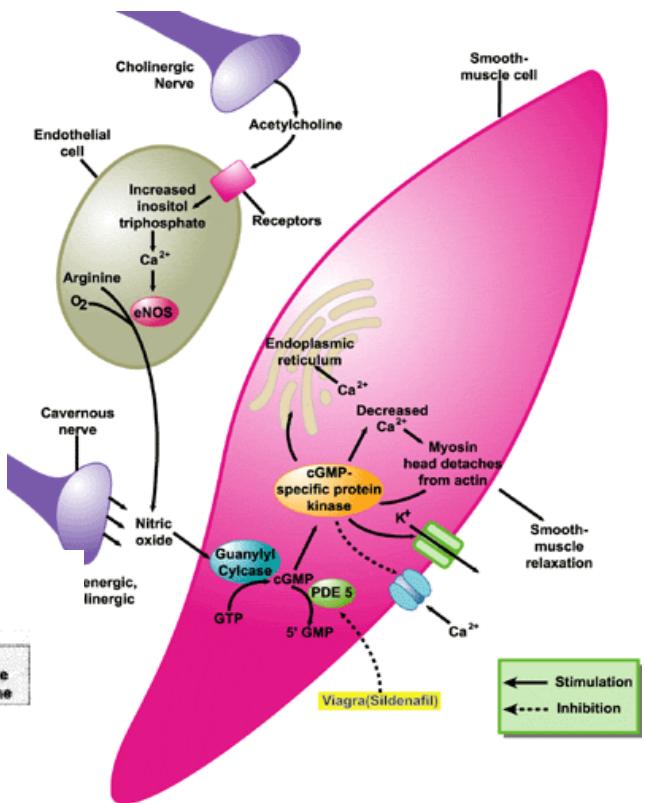
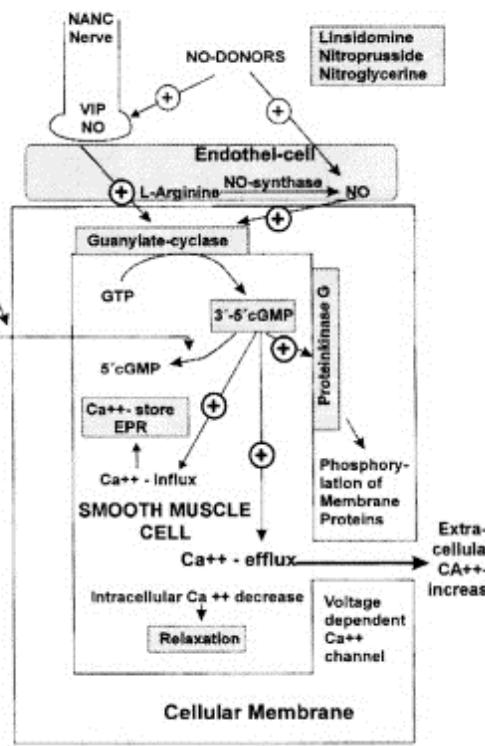
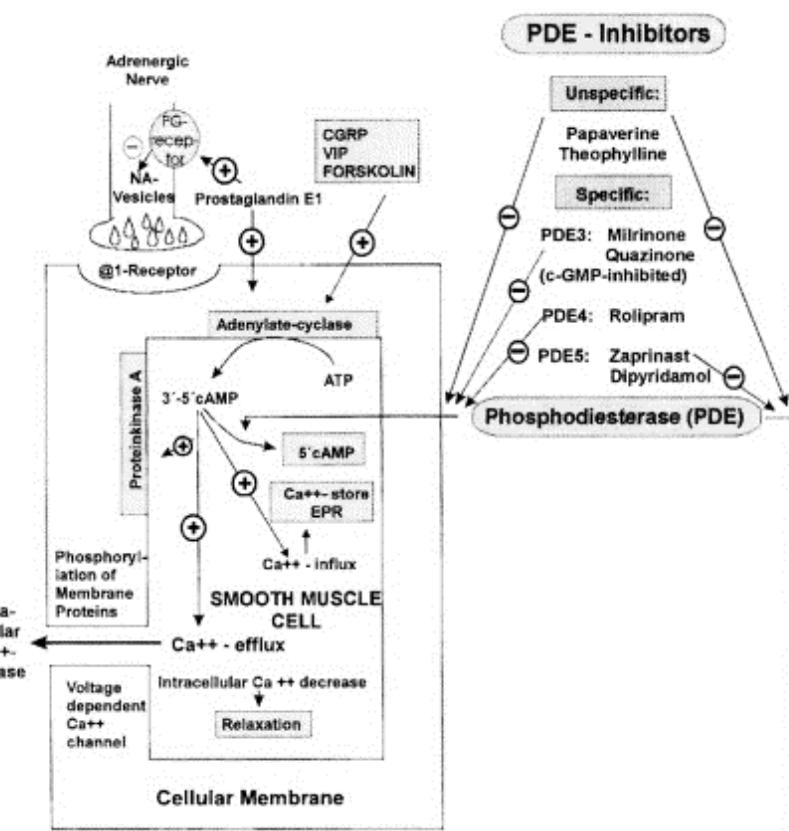
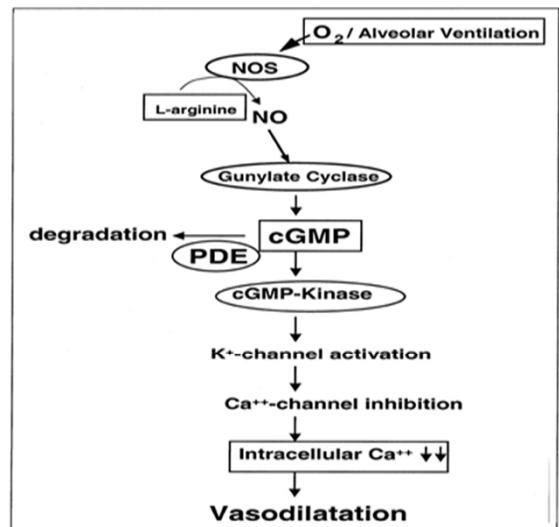
Nilandron®
(nilutamide)

Antiandrogen drugs



Treatment of erectile dysfunction





PDE5 inhibitors

Sildenafil (VIAGRA)

Tadalafil (CIALIS)

Vardenafil (LEVITRA)

Alprostadiol (CAVERJECT)

Phentolamin

Papaverin

Contraindicated to co-administer with nitrates!!! (Severe hypotension may occur.)



PDE5 inhibitors are used in the treatment of pulmonary hypertension as well!

<http://circ.ahajournals.org/content/122/1/88.full#T1>

