

As with other 17 $\alpha$ -alkylated compounds fluoxymesterone may cause hepatotoxicity, and is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

### Uses and Administration

Fluoxymesterone has androgenic properties (see Testosterone, p.2131). It is effective when given orally and is more potent than methyltestosterone.

In the treatment of male hypogonadism (p.2079), fluoxymesterone has been given in a dosage of 5 to 20 mg daily. For the use of fluoxymesterone in boys with delayed puberty, see Administration in Children, below. In the palliation of inoperable neoplasms of the breast in postmenopausal women (p.661) it has been given in daily doses of up to 40 mg. Fluoxymesterone has also been used in the treatment of aplastic anaemia.

**Administration in children.** In the treatment of delayed puberty (p.2079) in boys fluoxymesterone has been given orally in usual daily doses of 2.5 to 10 mg, adjusted according to response (doses up to 20 mg daily have been used). Care is necessary because of the risk of epiphyseal closure and treatment is generally only given for 4 to 6 months.

### Preparations

**USP 31:** Fluoxymesterone Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Hong Kong:** Halotestin†; **Mex.:** Stenox; **Thai:** Halotestin†; **USA:** Androxy.

**Multi-ingredient:** **Arg.:** Ferona.

## Follicle-stimulating Hormone ⊗

Follitropin; FSH.

ATC Vet — QG03GA90.

### Follitropin Alfa (BAN, rINN) ⊗

Follitropin Alfa; Follitropina alfa; Follitropine Alfa; Follitropinum Alfa.

Фоллитропин Альфа

$C_{437}H_{682}N_{122}O_{134}S_{13} = 10\ 206$  ( $\alpha$ -subunit);  
 $C_{538}H_{833}N_{145}O_{171}S_{13} = 12\ 485$  ( $\beta$ -subunit).

CAS — 9002-68-0 (follitropin alfa); 56832-30-5 ( $\alpha$ -subunit); 110909-60-9 ( $\beta$ -subunit); 146479-72-3 (follitropin alfa).

ATC — G03GA05.

ATC Vet — QG03GA05.

### Follitropin Beta (BAN, rINN) ⊗

Follitropin Beta; Follitropina beta; Follitropine Bêta; Follitropinum Beta; Org-32489.

Фоллитропин Бета

$C_{437}H_{682}N_{122}O_{134}S_{13} = 10\ 206$  ( $\alpha$ -subunit);  
 $C_{538}H_{833}N_{145}O_{171}S_{13} = 12\ 485$  ( $\beta$ -subunit).

CAS — 169108-34-3 (follitropin beta); 150490-84-9 (follitropin beta); 56832-30-5 ( $\alpha$ -subunit); 110909-60-9 ( $\beta$ -subunit).

ATC — G03GA06.

ATC Vet — QG03GA06.

### Units

80 units of human pituitary follicle-stimulating hormone are contained in about 4.17 micrograms (with 5 mg of mannitol and 1 mg human serum albumin) in one ampoule of the first International Standard (1986).

138 units of recombinant human follicle-stimulating hormone for bioassay are contained in one ampoule of the first International Standard (1995).

### Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p.2109.

**Spongiform encephalopathies.** In a few countries, gonadotrophins derived from cadaver pituitary glands have been used in the treatment of infertility, and a small number of patients are reported to have acquired Creutzfeldt-Jakob disease from such preparations.<sup>1</sup> However, most countries have preferred to use gonadotrophins derived from urine,<sup>1</sup> and these in their turn are being replaced with recombinant products;<sup>2</sup> such preparations appear to carry negligible risk of transmitting prion disease.<sup>3-5</sup>

1. Healy DL, Evans J. Creutzfeldt-Jakob disease after pituitary gonadotrophins. *BMJ* 1993; **307**: 517-18.
2. Eshkol A, Page ML. Human gonadotrophin preparations. *BMJ* 1994; **308**: 789.
3. Matorras R, Rodríguez-Escudero FJ. Bye-bye urinary gonadotrophins? The use of urinary gonadotrophins should be discouraged. *Hum Reprod* 2002; **17**: 1675.
4. Balen A. Is there a risk of prion disease after the administration of urinary-derived gonadotrophins? *Hum Reprod* 2002; **17**: 1676-80.
5. Jansen C. Bye-bye urinary gonadotrophins? Reply to debate. *Hum Reprod* 2003; **18**: 895-6.

### Pharmacokinetics

Follitropins alfa and beta are slowly absorbed after subcutaneous or intramuscular injection, with an absolute bioavailability of about 70 to 80%. Peak plasma concentrations of follitropin beta have been stated to occur about 12 hours after subcutaneous or intramuscular injection. Accumulation occurs with repeated doses, reaching a steady state within 3 to 5 days. Follitropins are slowly eliminated from the body, with a terminal half-life ranging from 12 to 70 hours. About one-eighth of a dose of follitropin alfa is reported to be excreted in the urine.

◇ References.

1. Karlsson MO, *et al.* The population pharmacokinetics of recombinant- and urinary-human follicle stimulating hormone in women. *Br J Clin Pharmacol* 1998; **45**: 13-20.

### Uses and Administration

Follicle-stimulating hormone is secreted by the anterior lobe of the pituitary gland, with another gonadotrophin, luteinising hormone (p.2112).

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova; in men it has a role in spermatogenesis.

Recombinant human follicle-stimulating hormones (follitropins alfa or beta) are used in the treatment of female infertility due to anovulation, in women who have not responded to clomifene therapy. Follitropins are also used for the stimulation of spermatogenesis in the management of male infertility caused by hypogonadotropic hypogonadism (see Infertility, p.2080).

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. In menstruating patients treatment should be started within the first 7 days of the menstrual cycle.

- Treatment is usually begun with 75 to 150 units daily by subcutaneous or intramuscular injection for 7 or 14 days; if there is no response, dosage is increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation.

It has been suggested in UK licensed product information for follitropin alfa that a daily dose of 225 units is the usual maximum, and that if a patient fails to respond adequately after 4 weeks of treatment that cycle should be abandoned and the patient should subsequently begin the next cycle at a higher starting dose.

Follitropins are also used as part of IVF or other assisted reproductive technologies.

- For this purpose doses of 150 to 225 units daily are generally given, for at least 4 days, commencing on the second or third day of the menstrual cycle. Thereafter the dose may be adjusted individually based on ovarian response to a usual maximum of about 450 units; adequate follicular development generally occurs within about 5 to 10 days of treatment.
- Pituitary downregulation with a gonadorelin analogue may be used with follitropin therapy, in which case the gonadorelin analogue is generally begun about 2 weeks before follitropin, and the 2 are then continued together until follicular development is adequate.
- A single dose of up to 10 000 units of chorionic gonadotrophin is then given to induce final follicular maturation and oocyte retrieval performed about 35 hours later.

Follitropins are used for the stimulation of spermatogenesis in the management of **male infertility** caused by hypogonadotropic hypogonadism. Before

starting follitropin therapy, chorionic gonadotrophin is given to raise serum testosterone concentrations to the normal range, which may take 3 to 6 months. A dose of follitropin alfa or beta of 150 units subcutaneously three times weekly is then used, with continued chorionic gonadotrophin; doses of follitropin alfa up to 300 units three times weekly may be required. Treatment is continued for at least 4 months, and more than 18 months of treatment may be needed. A dose of follitropin beta 75 units daily or two or three times weekly, by subcutaneous or intramuscular injection, has been used similarly.

Other substances with follicle-stimulating activity are used similarly: these include human menopausal gonadotrophins (p.2109), which have both luteinising and follicle-stimulating activity, and urofollitropin (p.2136).

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Gonalf; **Puregon;** **Austral.:** Gonalf; **Puregon;** **Austria:** Gonalf; **Puregon;** **Belg.:** Gonalf; **Puregon;** **Braz.:** Gonalf; **Puregon;** **Canada:** Gonalf; **Puregon;** **Chile:** Gonalf; **Puregon;** **Cz.:** Gonalf; **Puregon;** **Denm.:** Gonalf; **Puregon;** **Fin.:** Gonalf; **Puregon;** **Fr.:** Gonalf; **Puregon;** **Ger.:** Gonalf; **Puregon;** **Gr.:** Gonalf; **Puregon;** **Hong Kong:** Gonalf; **Puregon;** **Hung.:** Gonalf; **Puregon;** **India:** Gonalf; **Puregon;** **Indon.:** Gonalf; **Puregon;** **Israel:** Gonalf; **Puregon;** **Ital.:** Gonalf; **Puregon;** **Malaysia:** Gonalf; **Puregon;** **Mex.:** Gonalf; **Puregon;** **Neth.:** Gonalf; **Puregon;** **Norw.:** Gonalf; **Puregon;** **NZ:** Gonalf; **Puregon;** **Philipp.:** Gonalf; **Puregon;** **Pol.:** Gonalf; **Puregon;** **Port.:** Gonalf; **Puregon;** **Rus.:** Gonalf (Гонал-Ф); **Puregon;** **S.Afr.:** Gonalf; **Puregon;** **Singapore:** Gonalf; **Puregon;** **Spain:** Gonalf; **Puregon;** **Swed.:** Gonalf; **Puregon;** **Switz.:** Gonalf; **Puregon;** **Thai:** Gonalf; **Puregon;** **Turk.:** Gonalf; **Puregon;** **UK:** Gonalf; **Puregon;** **USA:** Follistim; **Gonalf;** **Puregon;** **Venez.:** Gonalf; **Puregon.**

**Multi-ingredient:** **Cz.:** Pergoveris; **Port.:** Pergoveris; **UK:** Pergoveris.

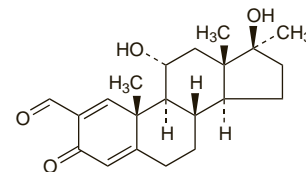
### Formebolone (BAN, rINN) ⊗

Formebolona; Formébolone; Formebolonom; Formyldienolone. 11 $\alpha$ ,17 $\beta$ -Dihydroxy-17 $\beta$ -methyl-3-oxoandrosta-1,4-diene-2-carbaldehyde.

Формеболол

$C_{21}H_{28}O_4 = 344.4$ .

CAS — 2454-11-7.



### Profile

Formebolone has been used for its anabolic properties (see Testosterone, p.2129). It appears to be widely abused by body-builders.

### Fosfestrol (BAN, rINN)

Diethylstilbestrol Diphosphate; Fosfestrol; Fosfestrolum; Phosphoestrolum; Stilboestrol Diphosphate. (E)- $\alpha,\alpha'$ -Diethylstilbene-4,4'-diol bis(dihydrogen phosphate); (E)-4,4'-(1,2-Diethylvinylene)bis(phenyl dihydrogen orthophosphate).

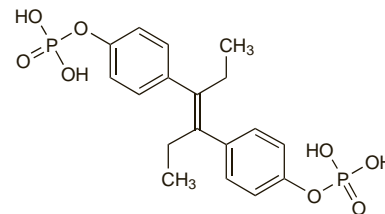
Фосфэстрол

$C_{18}H_{22}O_8P_2 = 428.3$ .

CAS — 522-40-7.

ATC — L02AA04.

ATC Vet — QL02AA04.



### Pharmacopoeias. In Jpn and US.

**USP 31** (Diethylstilbestrol Diphosphate). An off-white, odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol and in dilute alkali. Store in airtight containers at a temperature not exceeding 21°.