

Ganirelix Acetate

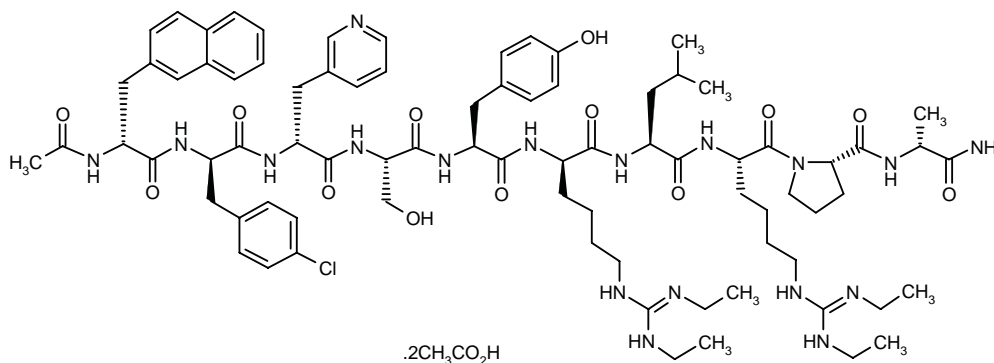
Rec INM; USAN; BAN

*GnRH Antagonist
Treatment of Female Infertility*

Org-37462
RS-26306
Orgalutran®

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-*N*⁶-[(ethylamino)(ethylimino)methyl]-D-lysyl-L-leucyl-*N*⁶-[(ethylamino)(ethylimino)methyl]-L-lysyl-L-prolyl-D-alaninamide diacetate

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-*N*^ω,*N*^ω-diethyl-D-homoarginyll-L-leucyl-*N*^ω,*N*^ω-diethyl-L-homoarginyll-L-prolyl-D-alaninamide diacetate



C₈₀H₁₁₃ClN₁₈O₁₃·2C₂H₄O₂

Mol wt: 1690.442

CAS: 129311-55-3

CAS: 124904-93-4 (as free base)

EN: 180634

Synthesis

The synthesis of ganirelix was performed using usual solid-state peptide synthesis with a Beckman 990 (1-3) or a 5.0 L Vega 296 (4) automated solid-phase peptide synthesizer. The synthesis was initiated by condensation of chloromethylated polystyrene/divinylbenzene resin (Merrifield resin) (II) with Boc-D-alanine (I) by means of cesium carbonate, giving Boc-D-ala-RESIN (III), which was submitted to successive cycles of deprotection with TFA or HCl and addition of a new protected amino acid by means of DCC or HOBt. The following amino acids were added successively: Boc-L-proline (IV), *N*^α-Boc-*N*^ω,*N*^ω-diethyl-L-homoarginine (VI), Boc-L-leucine (VIII), *N*^α-Boc-*N*^ω,*N*^ω-diethyl-D-homoarginine (X), Boc-L-tyrosine (XII), *N*-Boc-*O*-benzyl-L-serine (XIV), Boc-(3-pyridyl)-D-alanine (XVI), Boc-4-chloro-D-phenylalanine (XVIII) and Boc-(2-naphthyl)-D-alanine (XX), yielding successively the pep-

tide resins (V), (VII), (IX), (XI), (XIII), (XV), (XVII), (XIX) and (XXI). When the integration of amino acids was completed, the peptide resin (XXI) was deprotected with TFA, acetylated with acetic anhydride and finally treated with ammonia in methanol in order to eliminate the resin matrix and form the final amide group (1). Schemes 1-3.

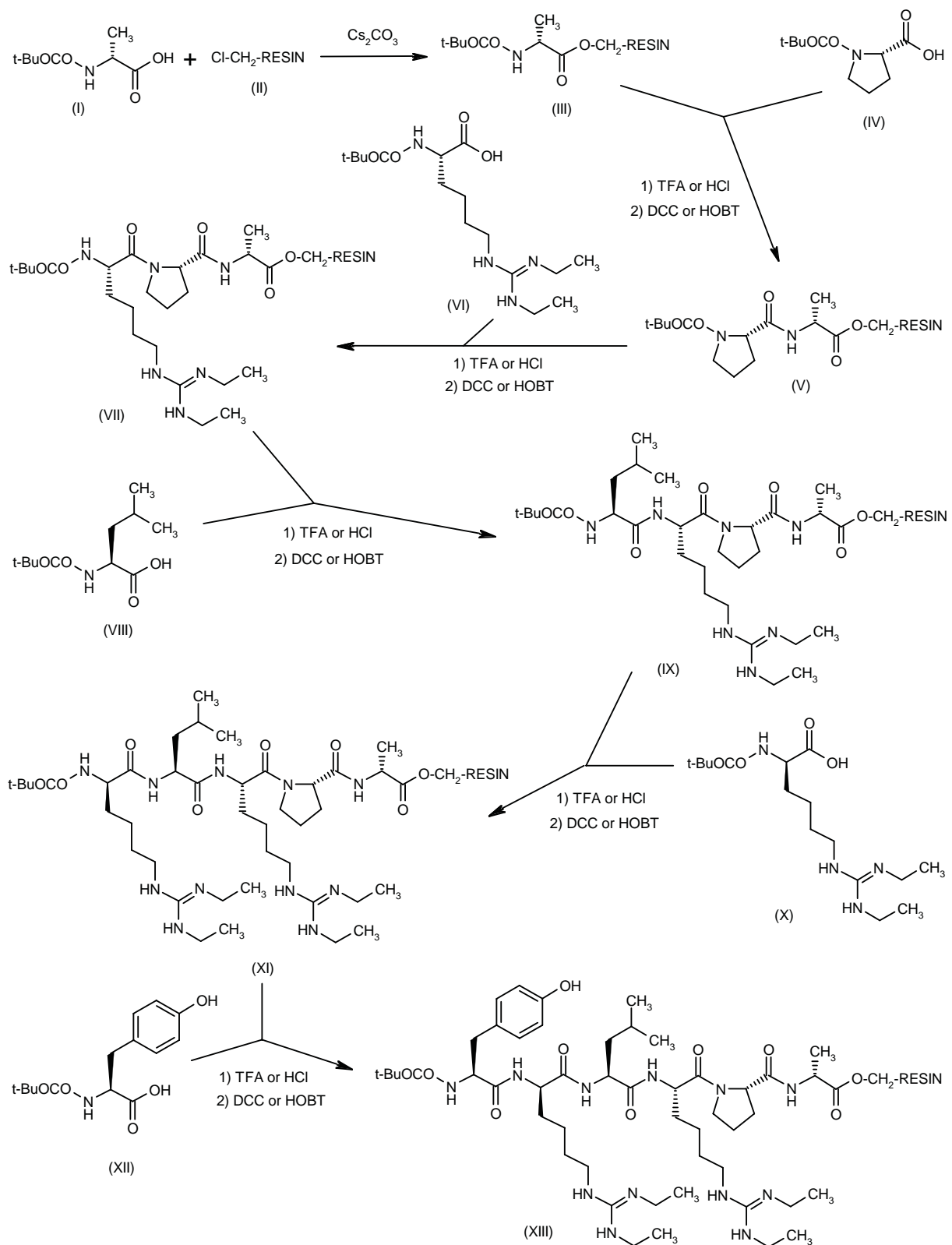
The preceding synthesis can also be performed using *N*-Boc-*O*-t-Bu-L-serine or *N*-Boc-L-serine instead of *N*-Boc-*O*-benzyl-L-serine (XIV) (3, 4).

Introduction

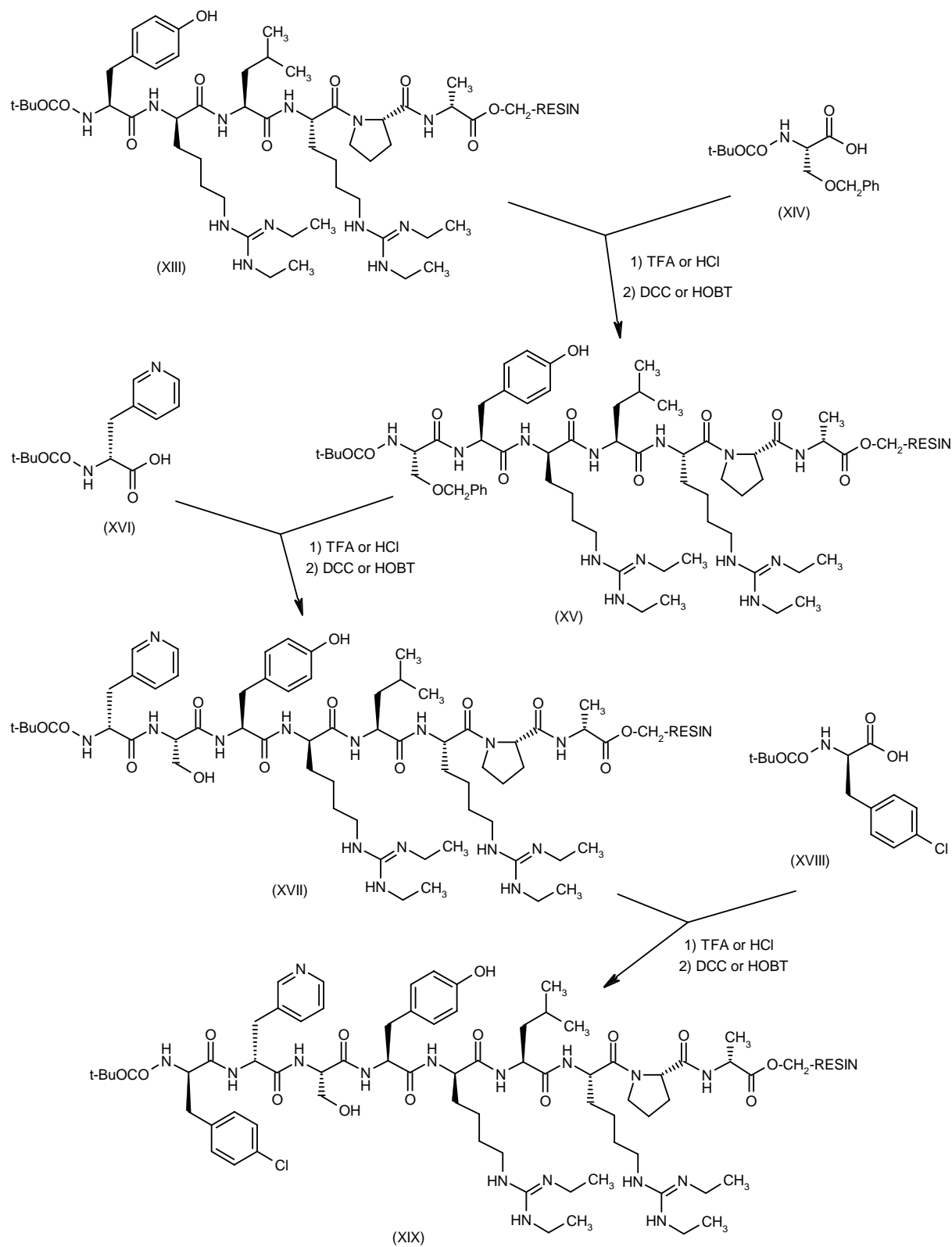
Gonadotropin-releasing hormone (GnRH; pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂), also called luteotropic hormone-releasing hormone (LHRH), is the hypothalamic decapeptide factor that controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the pituitary.

FSH is produced by the anterior pituitary and released into the circulation, where it stimulates the differentiation

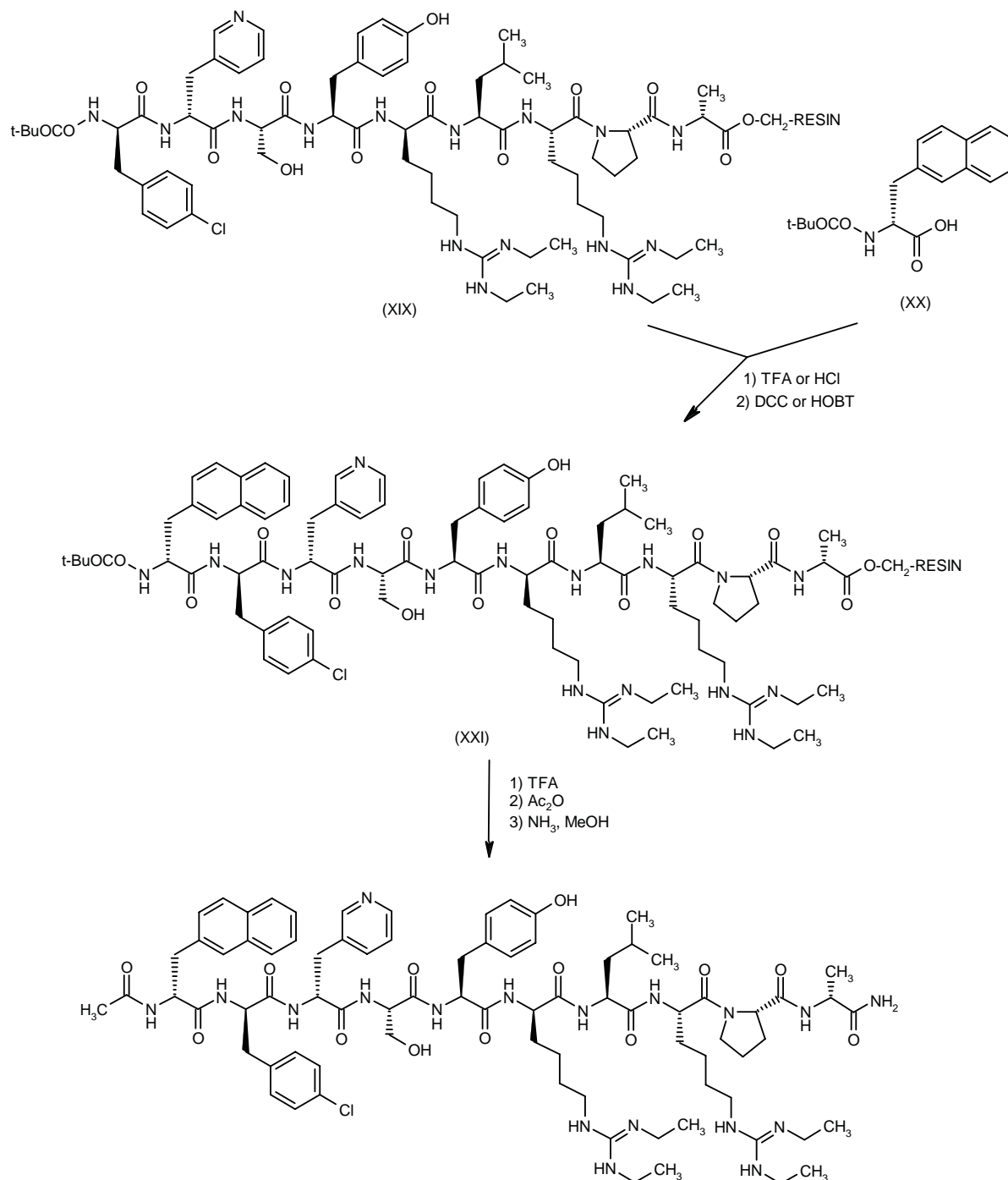
Scheme 1: Synthesis of Ganirelix Acetate



Scheme 2: Synthesis of Ganirelix Acetate (Cont.)



Scheme 3: Synthesis of Ganirelix Acetate (Cont.)



and maturation of developing follicles by binding to specific membrane receptors on granulosa and Sertoli's cells. After activating the adenylate cyclase system, FSH enhances the synthesis of cytochrome P450 aromatase, which converts androgens into estrogens. It also controls

other morphological events, such as the formation of the antral cavity and the induction of LH receptors on granulosa cells. FSH has a dimeric structure composed of α - and β -subunits linked by oligosaccharide chains. The α -subunit is common to other glycoprotein hormones such

as LH, chorionic gonadotropin and thyroid-stimulating hormone (TSH). Recombinant FSH (folliculin β) potentiates ovarian growth and follicular development in immature hypophysectomized rats and has been used as an ovulation inducer for the treatment of infertility by assisted conception (5).

Attempts to replace or delete different amino acids within the LHRH led to the discovery of superagonists (compounds much more effective in the release of LH and FSH than LHRH itself) and antagonists, which exert high binding affinities but do not activate the second messenger system, and thus are not functional in releasing LH or FSH.

Chronic treatment with LHRH superagonists led to desensitization and downregulation of pituitary receptors, and LHRH agonists showed remarkable activity in the treatment of idiopathic precocious puberty and endometriosis, and were deemed to be useful in the treatment of hormone-sensitive tumors.

Antagonist analogs, which were initially developed for contraception, exerted these effects with a single administration. However, severe side effects (edematogenic reactions due to histamine release) were observed with the first LHRH antagonists to be clinically evaluated, such

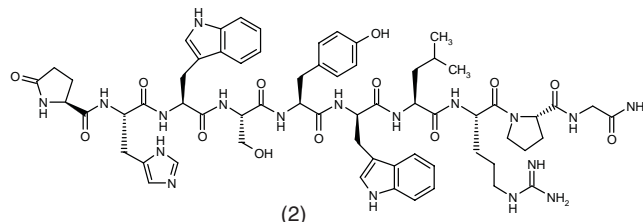
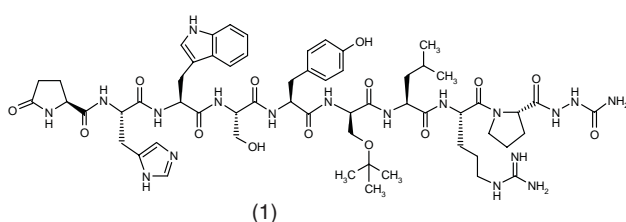
as Nal-Glu, which were found to be too expensive and/or to cause an unacceptable level of local or systemic adverse reactions. A new group of LHRH antagonists devoid of these adverse reactions emerged with the synthesis of cetorelix, albeit at the expense of antagonistic potency, probably due to its very low solubility (6).

Subsequent efforts concentrated on synthesizing a molecule which would retain the antagonistic potency of Nal-Glu but lack its histamine-releasing effects and possess high water solubility. This led to the third-generation LHRH antagonist, ganirelix.

According to current knowledge, LHRH antagonists are useful inhibitors of gonadotropin secretion by the pituitary gland and of steroid hormone release by the gonads, and have potential in the treatment of a range of clinical conditions including hormone-dependent breast, ovarian and prostate cancer, endometriosis, amenorrhea or as contraceptive agents (suppressors of ovulation and inhibitors of ova implantation). Some of these drugs are used in the management of female infertility. The chemical structures and description of LHRH modulators currently under investigation or in use as therapeutics are shown in Table I.

Table I: LHRH antagonists launched or under investigation (from Prous Science Ensemble database).

Compound/Manufacturer	Description
1. Goserelin (Astra Zeneca)	LHRH analog marketed for treatment of cancer, endometriosis, female infertility and uterine fibroids
2. Triptorelin (Ferring)	LHRH analog marketed for treatment of prostate cancer and endometriosis
3. Abarelix (Praecis)	LHRH antagonist in phase III clinical trials for hormone-responsive prostate cancer and phase II clinical trials for endometriosis
4. Cetorelix (Asta Medica)	LHRH antagonist preregistered for controlled ovulation stimulation and in phase II clinical trials for benign prostatic hyperplasia, uterine myoma and prostate and ovarian cancer
5. Ganirelix acetate (Organon; licensed from Roche)	LHRH antagonist preregistered for treatment of female infertility
6. Antarelix (Asta Medica)	LHRH antagonist in phase I clinical trials for treatment of prostate cancer
7. Ramorelix (Hoechst Marion Roussel)	LHRH antagonist in phase I clinical trials for treatment of prostate cancer
8. Iturelix (Ares-Serono)	LHRH antagonist in phase II clinical trials for treatment of endocrine-related fertility disorders
9. A-84861 (Abbott)	LHRH antagonist in preclinical development for treatment of prostate cancer and other hormone-dependent disorders
10. AN-207 (Asta Medica)	LHRH analog linked to doxorubicin in preclinical development for treatment of breast, ovarian and prostate cancers
11. AN-152 (Asta Medica)	Cytotoxic LHRH analog containing doxorubicin in preclinical development for treatment of breast, ovarian and prostate cancers
12. FE-200486* (Ferring)	Potent, long-acting and water-soluble LHRH antagonist with high affinity for the LHRH receptor that dose-dependently and reversibly suppresses plasma LH and testosterone levels
13. TX-54*	LHRH antagonist in preclinical development by the Tiankin Municipal Research Institute for Family Planning in China as a male contraceptive
14. Gonadimmune; (Aphton; SmithKline Beecham)	Anti-LHRH vaccine in phase I/II clinical trials for treatment of prostate cancer. Gonadimmune is an immunogen against LHRH that does not act on LHRH receptor but has similar pharmacological effects as an LHRH antagonist



*Structure not yet detected

(Continued)

Table 1: LHRH antagonists launched or under investigation (from Prous Science Ensemble database) (continued).

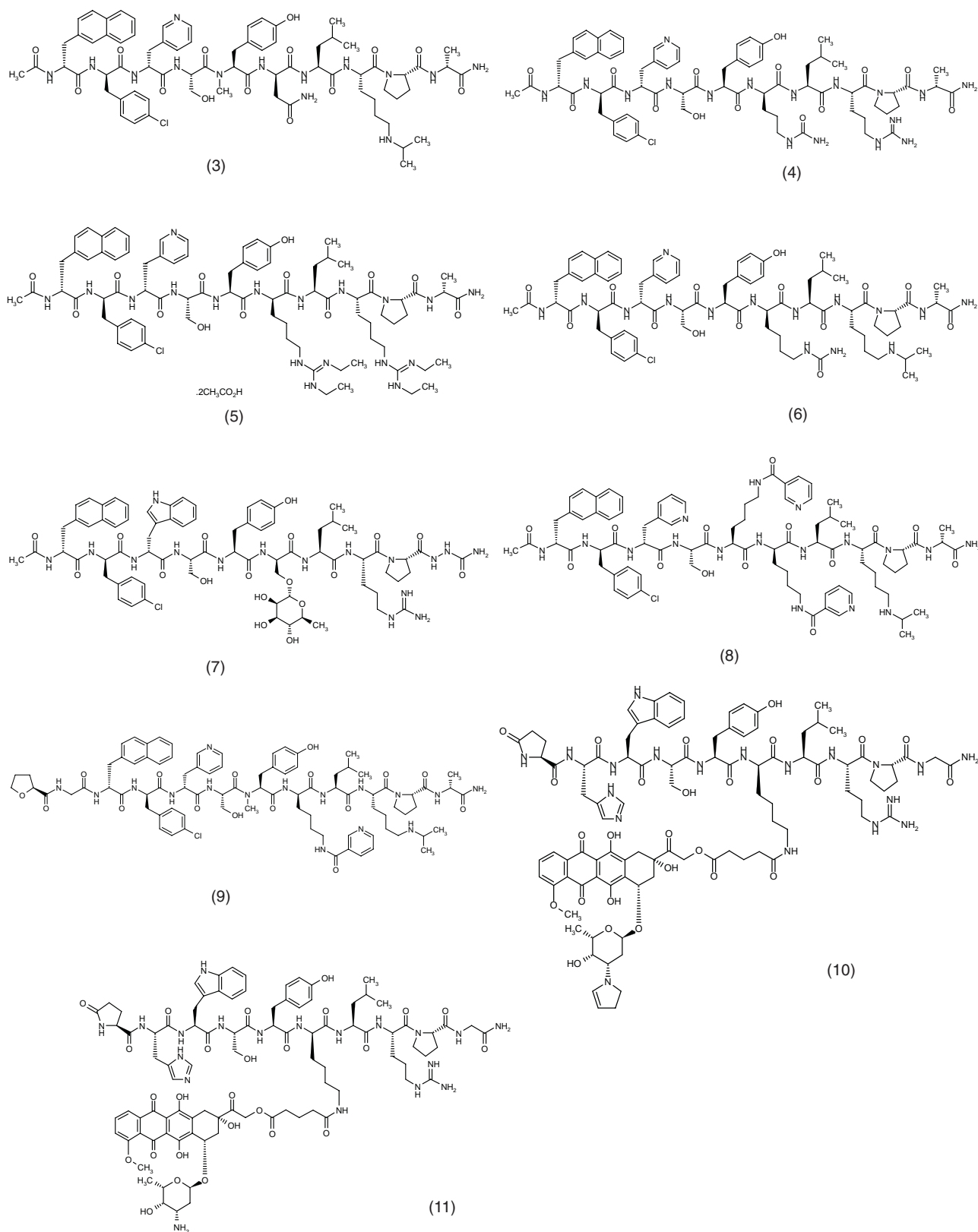


Table II: Pharmacology of ganirelix and other LHRH antagonists (7-9, 11).

Compound	Affinity for LHRH receptor ¹	Inhibition or leuprolide-induced LH release ²	Induction of histamine release ³	Ovulation suppression ⁴
Ganirelix	10.8	11.4	5.3-13	0.3
Iturelix	10.2	10.6	261- ≥300	1.5
Cetrorelix	9.9	10.5	1.1	
Detirelix			0.2	0.4
A-75998	10.5	11.2	10.0-22	
Nal-Glu	10.3	11.1	1.1-1.8	

¹Displacement of [¹²⁵I]-leuprolide in rat pituitary LHRH receptor (pK_i values). ²Inhibition of leuprolide-induced LH release in cultured rat pituitary cells (pA₂ values). ³Induction of histamine release in rat peritoneal mast cells (EC₅₀ values in µg/ml). ⁴Suppression of ovulation in rats (ED₅₀ values in mg s.c.)

LHRH Antagonists in Female Infertility

Infertility is the inability to conceive, but many "infertile" couples can be helped by assisted conception treatment. However, before assisted conception is attempted, the causes of infertility should be assessed; only about 20% of infertility cases remain unexplained after evaluating ovulation, quality of the fallopian tubes, hormone levels in women and sperm production in men.

Therapeutic options for female infertility include ovulation induction, *in vitro* fertilization (IVF), gamete intrafallopian transfer (GIFT), artificial insemination and egg donation. Ovulation induction involves ovary stimulation with fertility drugs and is used to treat infertility resulting from hormonal disorders and polycystic ovary syndrome. IVF refers to the extracorporeal fertilization of induced ova with subsequent transvaginal implantation into the uterine cavity. In GIFT, the ova with a sample of sperm are transferred back to the fallopian tube almost immediately after collection. Artificial insemination is performed after ovulation is induced by fertility drugs. For egg donation, ova from the donor are fertilized *in vitro* and implanted into a female recipient.

For standard IVF, the ova are stimulated to mature with gonadotropins (such as natural FSH obtained from the urine of postmenopausal women or recombinant FSH). However, prior to FSH administration, the patient's natural hormone cycle must be suppressed with LHRH agonists, which need to be given for approximately 2 weeks, as well as during the 10-14 days of FSH administration. Eggs are then obtained through the vagina, fertilized and transvaginally transferred to the womb. LHRH agonists shut down the natural reproductive system by a slow, complex downregulation process, whereas LHRH antagonists immediately block the receptors which regulate the release of gonadotropins from the pituitary. Thus, LHRH antagonists may be more convenient than LHRH agonists for both patients and physicians, as they eliminate the need for pretreatment before IVF stimulation. LHRH antagonists can be given for just 4-5 days during FSH administration. One such LHRH antagonist in development is ganirelix.

Pharmacological Actions

Ganirelix displaces [¹²⁵I]-leuprolide from LHRH receptors in the rat pituitary with a pK_i value of 10.78, thus binding to the receptor with more than twice the potency of [Ac-Δ³Pro¹,D⁵Fpa²,D⁶Trp^{3,6}]LHRH, which is the current LHRH experimental standard. In cultured rat pituitary cells, ganirelix competitively inhibited leuprolide-induced LH release with a pA₂ value of 11.37 (7, 8).

In experimental studies, ganirelix inhibited ovulation in 90% of rats treated with 1 µg and in 100% of the animals receiving 2 µg of the drug. The standard compound inhibited ovulation in 50% of the animals at 0.5 µg and in all of the animals at 1.5 µg (8). The calculated ED₅₀ value for ganirelix in female rats at noon of proestrus was 1.4 µg/kg (9).

However, ganirelix induced histamine release in cultured rat mast cells with an EC₅₀ value of 5.3-11 µg/ml, whereas the corresponding value for the standard was 1.8 µg/ml, showing that ganirelix is more than 6 times less potent as a histamine release inducer (7, 8). More importantly, *in vivo* anaphylactoid potency, assessed by hypotensive effect in anesthetized male rats, is very low with ganirelix (ED₅₀ = 0.9 mg/kg i.v.) compared to values obtained with earlier LHRH antagonists (20-40 µg/kg i.v.), leading to a very favorable ratio of antigonadotropic *versus* anaphylactoid potency (9, 10).

The comparative pharmacology of ganirelix and other peptide LHRH antagonists is summarized in Table II.

As ganirelix is designed as an LHRH antagonist to be used with FSH for controlled ovarian stimulation before IVF or intracytoplasmic sperm injection, the effect of the drug on oocyte morphology and quality has been assessed. In patients undergoing ovarian stimulation, no difference in nuclear maturity, ooplasmic morphology and oolemma elasticity was found after treatment with ganirelix or the LHRH agonist leuporelin. Furthermore, no differences in fertilization or cleavage rates were noted, and the number of embryos with sufficient quality for transfer was similar after both treatments (12).

Table III: Pharmacokinetic properties of ganirelix (13, 15-17).

Species	Dose	C _{max} (µg/ml)	t _{max} (h)	AUC (µg.h/ml)	t _{1/2} (h)	Cl (ml/min/kg)	V _D (l/kg)
Rats	1 mg/kg i.v.	3.8		6.6	1.4	2.5	0.3
	1 mg/kg s.c.	0.5	4	4.3	3.6		
	10 mg/kg s.c.	1.1	12	30.8	15.2		
Monkeys	1 mg/kg i.v.	9.5		25.1	5.1	0.8	0.3
	1 mg/kg s.c.	1.2		12.3			
Humans	0.25 mg i.v.			105*	12.7		
	0.125 mg s.c.	5.2*					
	0.25 mg s.c.	11.2-14.8*	1	96*	12.8		
	0.5 mg s.c.	22.2*					
	1 mg s.c.	37.2*	1.2	348*	15.0		
	3 mg s.c.	68.1*	1.9	1141*	22.8		
	6 mg s.c.	152*	1.8	2290*	26.9		
	1 mg i.n.	5.7*	0.5	19.1*			
	3 mg i.n.	14.7*	0.7	55.0*			
	6 mg i.n.	30.0*	0.5	140.4*			

*Data in ng

Pharmacokinetics

In rats and monkeys, ganirelix is rapidly eliminated (Cl = 2.5 and 0.8 ml/min/kg, respectively), giving t_{1/2} values of 1.4 and 5.1 h, respectively, after i.v. administration. The drug is systemically bioavailable after s.c. administration, with C_{max} and t_{max} values of 0.5 µg/ml and 4 h in rats after a 1 mg/kg dose and 1.1 µg/ml and 12 h after a 10 mg/kg dose. Respective t_{1/2} values after s.c. administration of 1 mg/kg and 10 mg/kg were 3.6 and 15.2 h. In monkeys, s.c. administration of a 1 mg/kg dose gave a C_{max} of 1.2 µg/ml at a t_{max} of 0.5 h, with a t_{1/2} value of at least 19 h. Plasma protein binding was calculated at 82-84% for both species (13).

Excretion of ganirelix is mainly biliary, with 12-25% and 55-84% of the dose being recovered in urine and feces, respectively. Three truncated peptide metabolites of the parent decapeptide have been identified in rat bile, but only one in monkey plasma (13). Ganirelix is very resistant to hydrolysis. The major circulatory and excretory component is the intact parent drug. The high stability of ganirelix is responsible for its high oral and subcutaneous bioavailability compared to similar compounds (9, 14).

Human pharmacokinetics show a dose-proportional profile. In women undergoing controlled ovarian hyperstimulation, the absolute bioavailability of ganirelix after a dose of 0.25 mg s.c. was 91%, with a C_{max} of 14.8 ng/ml at a t_{max} of 1 h. After multiple-dose administration, steady state was reached within 2-3 days. C_{max} was dose-dependent after doses of 0.125-0.5 mg administered s.c. for 7 days (15).

The main pharmacokinetic properties of ganirelix are summarized in Table III.

There is a direct correlation between circulating levels of ganirelix and its therapeutic effect. In animals, reproductive function was suppressed at circulating levels

above 1 ng/ml, but this effect was reversible; when circulating levels dropped below 1 ng/ml reproductive function rapidly returned (18).

A liquid crystal gel for sustained delivery of ganirelix was developed for the treatment of endometriosis and prostate cancer during an extended period of time. The gel can be administered s.c. or i.m., with the capability of a high drug loading, and displays little variation in release rate, with a low initial peptide burst release (19-21).

Clinical Studies

Subcutaneous doses of ganirelix effectively suppressed the production of LH, FSH and the α-subunit of LH, FSH and TSH. Doses of 1-6 mg s.c. reduced the production of LH by 70.1-73.9% for 24-72 h, the production of FSH by 32.9-42.3% for 48-72 h and the production of alpha-subunit by 56.0-74.6% for >72 h in a clinical study in 5 healthy postmenopausal women. Ganirelix also suppressed testosterone production, but did not affect prolactin serum concentrations (16). In two other open clinical studies in women with documented ovulatory menstrual cycles, ganirelix rapidly decreased serum levels of gonadotropins and estradiol (50-74% reduction at 1-6 mg s.c. or i.n.), with rapid return of ovarian function after the last dose of the drug (17, 22).

Use in controlled ovarian hyperstimulation

In a multicenter, randomized, double-blind, dose-finding clinical study in 329 women undergoing controlled ovarian hyperstimulation, the optimal dose of ganirelix was established at 0.25 mg o.d. s.c. Women received ganirelix (up to 2 mg/day for 6 days) at daily doses ranging from 0.0625-2 mg s.c. from day 7 of menstrual cycle

Box 1: Ganirelix in controlled ovarian hyperstimulation (23, 24).

Design	Multicenter, randomized, double-blind, dose-finding clinical study
Population	Women undergoing controlled ovarian hyperstimulation (n = 329)
Interventions	Ganirelix (G), 0.0625, 0.125, 0.25, 0.5, 1.0, 2.0 mg s.c from day 7 of menstrual cycle + rFSH, 150 IU o.d. on days 2-6 of menstrual cycle → 150-183 IU o.d. (31 patients on 0.0625 mg, 65 on 0.125 mg, 69 on 0.25 mg, 69 on 0.5 mg, 65 on 1 mg and 30 on 3 mg)
Withdrawals [causes]	An independent committee recommended discontinuation of the lowest and highest dose groups during the study
Adverse events	Possibly/probably drug-related: 11/329 (3.3%) [asthenia, nausea, malaise]. 8/329 (2.4%) patients presented with ectopic pregnancy (3), ovarian hyperstimulation syndrome (2), miscarriage (1) or fever (1)
Results	Ganirelix dose-dependently decreased LH and estradiol rises LH increase (≥ 10 IU/l) rate: G0.0625 (16.1%) > G0.125 (9.2%) > G0.25 (1.4%) \geq G1 = G2 (0%) Implantation rate: G0.0625 (14.2%) = G0.125 (16.6%) \equiv G0.25 (21.9%) > G0.5 (9.0%) = G1.0 (8.8%) > G2.0 (1.5%) Vital pregnancy rate (per embryo transfer) at 5-6 wk: G0.0625 (25.9%) = G0.125 (25.0%) \equiv G0.25 (37.1%) > G0.5 (13.0%) = G1.0 (15.3%) > G2.0 (0%)
Conclusions	Ganirelix at daily doses of 0.25 mg s.c. effectively prevented LH surges and resulted in good clinical outcome in women undergoing controlled ovarian hyperstimulation for IVF

along with recombinant FSH at a fixed daily dose of 150 IU for 5 days starting on day 2. Ganirelix dose-dependently decreased serum LH and estradiol levels, with no effect on the number and size of follicles, the number of recovered oocytes or embryo quality and implantation rate. The daily dose of 0.25 mg effectively prevented LH surges and resulted in a good clinical outcome; treatment was safe and well tolerated (23, 24) (Box 1).

Other pilot studies in women undergoing controlled ovarian hyperstimulation have shown ganirelix to decrease serum LH, FSH and estradiol levels by 74, 32 and 25%, respectively, after a subcutaneous dose of 0.25 mg. Maximal reductions were seen after 4-16 h of injection and returned to baseline within 2 days after last injection (15).

Results of a multicenter, comparative, open, randomized clinical trial in 730 women undergoing controlled ovarian hyperstimulation have been reported. Subjects received stimulation with recombinant FSH at day 2 or 3 of menses plus ganirelix (0.25 mg s.c.) once daily from stimulation on day 6 and thereafter to prevent premature LH surges. Intranasal buserelin plus recombinant FSH was used as reference treatment. Overall, ganirelix was safe and well tolerated, with an incidence of ovarian hyperstimulation syndrome of 2.4% compared to 5.9% in the reference group, although the incidence of increases in LH increased slightly with ganirelix (2.8%) compared to buserelin (1.3%). Mean duration of LHRH antagonist treatment was 5 days with ganirelix and 26 days with buserelin, whereas median total FSH dose was 1500 and 1800 IU, respectively. The mean number of mature follicles at ovulation triggering was comparable in both groups (10.7 and 11.8, respectively), with lower estradiol levels in the ganirelix group (1190 vs. 1700 pg/ml).

Fertilization, implantation and ongoing pregnancy rates were similar in both groups (25). No information is available on withdrawals from this study, but in a subset of 60 patients corresponding to a single center, 2/40 (5%) ganirelix patients were excluded (1 due to spontaneous pregnancy and 1 for personal reasons) and 2/20 (10%) women receiving buserelin due to failure of downregulation (26). This suggests that ganirelix is more suitable, with patients preferring the shorter duration of treatment, making the drug a convenient treatment option (Box 2).

The first case of established pregnancy after controlled ovarian hyperstimulation with recombinant FSH combined with ganirelix was described in detail in 1998. The pregnancy progressed normally and resulted in the birth of a healthy boy and a girl after elective cesarean intervention at 37 weeks (27).

Safety

Evaluation of safety data of approximately 800 patients treated with ganirelix in clinical trials has shown no discontinuation due to hypersensitivity reaction or drug-related adverse events, which makes ganirelix a very safe treatment for patients undergoing controlled ovarian hyperstimulation (14). In the clinical trials reviewed, no subject had evidence of systemic histamine release or anaphylactoid reaction. The most common adverse events have been vasodilation/hot flushes, emotional lability and menstrual disorder, which are a direct result of hypoestrogenism and are reactions expected from the action of ganirelix. No clinically significant changes in serum chemistries or hematologic parameters have been noted.

Box 2: Ganirelix in controlled ovarian hyperstimulation (25, 26).

Design	Multicenter, comparative, open, randomized clinical study
Population	Women undergoing controlled ovarian hyperstimulation (n = 730)
Interventions	Ganirelix (G), 0.25 mg s.c. from stimulation on day 6 onwards x 5 days (median) + rFSH, 1500 IU (median total) starting on day 2-3 of menses Buserelin (B), from stimulation on day 6 onwards x 26 days (median) + rFSH, 1800 IU (median total) starting on day 2-3 of menses
Withdrawals [causes]	G, 2/40 (5%) patients due to spontaneous pregnancy and personal reasons B, 2/20 (10%) patients due to failure of downregulation
Adverse events	G, ovarian hyperstimulation syndrome in 2.4%; LH rise in 2.8% B, ovarian hyperstimulation syndrome in 5.9% LH rise (≥ 10 IU/l) rate: G (2.8%) \equiv B (1.3%)
Results	Mean number of mature follicles: G (10.7) = B (11.8) Serum estradiol levels: G (1190 pg/ml) < B (1700 pg/ml) Fertilization rate: G = B (62.1%) Implantation rate: G (15.7%) \equiv B (21.8%) Pregnancy rate: G (20.3%) \equiv B (25.7%)
Conclusions	Ganirelix was convenient, safe and well tolerated in controlled ovarian hyperstimulation and resulted in good clinical outcome

Conclusions

LHRH antagonists are useful when immediate, reversible suppression of the pituitary-gonadal axis is desired, such as during ovary stimulation to prevent LH surges. However, clinical development of first- and second-generation compounds was unsuccessful due to histamine-releasing activity, low solubility or low biological potency. Ganirelix is a third-generation LHRH antagonist which induces a rapid, profound, reversible suppression of endogenous gonadotrophins by competitively binding to LHRH receptor in the pituitary gland. It is highly water-soluble, has a high absolute bioavailability and a short elimination half-life that leads to an immediate recovery of the pituitary-gonadal function after discontinuation. It is indicated for the prevention of LH surges during controlled ovarian hyperstimulation with FSH before IVF or similar reproductive techniques for infertile women. Ganirelix reduces the exposure to LHRH analogs to less than 3 weeks, offering a short treatment regimen that will simplify treatment, make it more convenient, reduce total drug requirements and reduce costs of medical supervision and assistance (28).

Manufacturer

NV Organon (NL), licensed from Roche Bioscience (US).

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