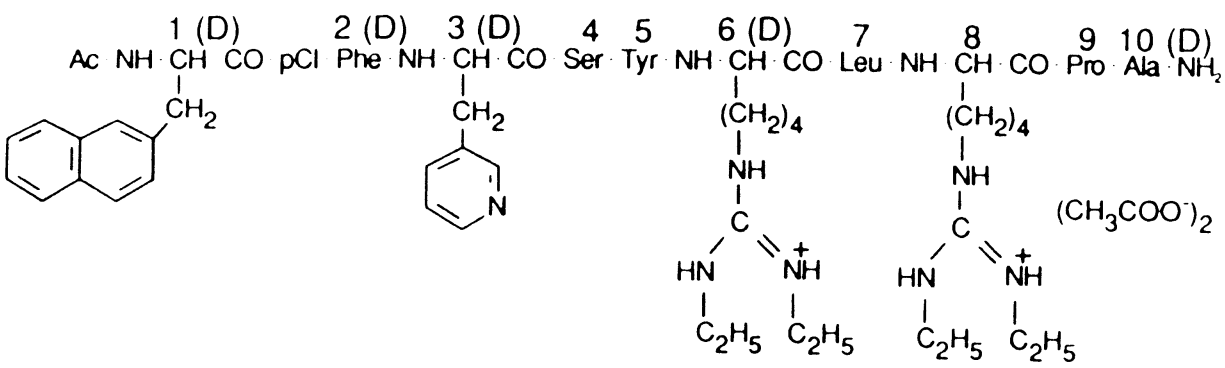
Antagon™ (ganirelix acetate) Injection

FOR SUBCUTANEOUS USE ONLY

DESCRIPTION

Antagon™ (ganirelix acetate) Injection is a synthetic decapeptide with high antagonistic activity against naturally occurring gonadotropin-releasing hormone (GnRH). Ganirelix acetate is derived from native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, 8, and 10 to form the following molecular formula of the peptide: N-acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^9,N^{10}-diethyl-D-homoarginyl-L-leucyl-N^9,N^{10}-diethyl-L-homoarginyl-L-prolyl-D-alanylamide acetate. The molecular weight for ganirelix acetate is 1570.4 as an anhydrous free base. The structural formula is as follows:

Ganirelix acetate



Antagon™ is supplied as a colorless, sterile, ready-to-use, aqueous solution intended for SUBCUTANEOUS administration only. Each sterile, pre-filled syringe contains 250

μg/0.5 mL of ganirelix acetate, 0.1 mg glacial acetic acid, 23.5 mg mannitol, and water for injection adjusted to pH 5.0 with acetic acid, NF and/or sodium hydroxide, NF.

CLINICAL PHARMACOLOGY

The pulsatile release of GnRH stimulates the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The frequency of LH pulses in the mid and late follicular phase is approximately 1 pulse per hour. These pulses can be detected as transient rises in serum LH. At midcycle, a large increase in GnRH release results in an LH surge. The midcycle LH surge initiates several physiologic actions including: ovulation, resumption of meiosis in the oocyte, and luteinization. Luteinization results in a rise in serum progesterone with an accompanying decrease in estradiol levels. Antagon™ (ganirelix acetate) Injection acts by competitively blocking the GnRH receptors on the pituitary gonadotroph and subsequent transduction pathway. It induces a rapid, reversible suppression of gonadotropin secretion. The suppression of pituitary LH secretion by Antagon™ is more pronounced than that of FSH. An initial release of endogenous gonadotropins has not been detected with Antagon™, which is consistent with an antagonist effect. Upon discontinuation of Antagon™, pituitary LH and FSH levels are fully recovered within 48 hours.

Pharmacokinetics

The pharmacokinetic parameters of single and multiple injections of Antagon™ (ganirelix acetate) Injection in healthy adult females are summarized in Table I. Steady state serum concentrations are reached after 3 days of treatment. The pharmacokinetics of ganirelix acetate are dose-proportional in the dose range of 125 to 500 μg.

TABLE I: Mean (SD) pharmacokinetic parameters of 250 µg of Antagon™ following a single subcutaneous (SC) injection (n=15) and daily SC injections (n=15) for seven days.

	t_{max} h	$t_{1/2}$ h	C_{max} ng/mL	AUC ng·h/mL	CL/F L/hr	V_d/F L
Antagon™ single dose	1.1(0.3)	12.8(4.3)	14.8(3.2)	96(12)	2.4 (0.2)†	43.7(11.4)†
Antagon™ multiple dose	1.1(0.2)	16.2 (1.6)	11.2(2.4)	77.1(9.8)	3.3 (0.4)	76.5(10.3)

t_{max} Time to maximum concentration
$t_{1/2}$ Elimination half-life
C_{max} Maximum serum concentration
AUC Area under the curve; Single dose: $AUC_{0-\infty}$; multiple dose AUC_{0-24}
V_d Volume of distribution
† Based on intravenous administration
CL Clearance = $Dose/AUC_{0-\infty}$
F Absolute bioavailability

Absorption

Ganirelix acetate is rapidly absorbed following subcutaneous injection with maximum serum concentrations reached approximately one hour after dosing. The mean absolute bioavailability of Antagon™ following a single 250 µg subcutaneous injection to healthy female volunteers is 91.1%.

Distribution

The mean (SD) volume of distribution of Antagon™ in healthy females following intravenous administration of a single 250 µg dose is 43.7(11.4) liters (L). *In vitro* protein binding to human plasma is 81.9%.

Metabolism

Following single dose intravenous administration of radiolabeled Antagon™ to healthy female volunteers, Antagon™ is the major compound present in the plasma (50-70% of total radioactivity in the plasma) up to 4 hours and urine (17.1-18.4% of administered dose) up to 24 hours. Antagon™ is not found in the feces. The 1-4 peptide and 1-6 peptide of Antagon™ are the primary metabolites observed in the feces.

Excretion

On average, 97.2% of the total radiolabeled Antagon™ dose is recovered in the feces and urine (75.1% and 22.1%, respectively) over 288 h following intravenous single dose administration of 1 mg [^{14}C]-ganirelix acetate. Urinary excretion is virtually complete in 24 h, whereas fecal excretion starts to plateau 192 h after dosing.

Special Populations

The pharmacokinetics of ganirelix acetate have not been determined in special populations such as geriatric, pediatric, renally impaired and hepatically impaired patients (see PRECAUTIONS).

Drug-Drug Interactions

Formal *in vivo* or *in vitro* drug-drug interaction studies have not been conducted (see PRECAUTIONS). Since Antagon™ can suppress the secretion of pituitary gonadotropins, dose adjustments of exogenous gonadotropins may be necessary when used during controlled ovarian hyperstimulation (COH).

Clinical Studies

The efficacy of Antagon™ (ganirelix acetate) Injection was established in two adequate and well-controlled clinical studies which included women with normal endocrine and pelvic ultrasound parameters. The studies intended to exclude subjects with polycystic ovary syndrome (PCOS) and subjects with low or no ovarian reserve. One cycle of study medication was administered to each randomized subject. For both studies, the administration of exogenous recombinant FSH [Follistim® (follitropin beta for injection)] 150 IU daily was initiated on the morning of Day 2 or 3 of a natural menstrual cycle. Antagon™ was administered on the morning of Day 7 or 8 (Day 6 of recombinant FSH

administration). The dose of recombinant FSH administered was adjusted according to individual responses starting on the day of initiation of Antagon™. Both recombinant FSH and Antagon™ were continued daily until at least three follicles were 17 mm or greater in diameter at which time hCG [Pregnyl® (chorionic gonadotropin for injection, USP)] was administered. Following hCG administration, Antagon™ and recombinant FSH administration were discontinued. Oocyte retrieval, followed by *in vitro* fertilization (IVF) or intracytoplasmatic sperm injection (ICSI), was subsequently performed.

In a multicenter, double-blind, randomized, dose-finding study, the safety and efficacy of Antagon™ were evaluated for the prevention of LH surges in women undergoing COH with recombinant FSH. Antagon™ doses ranging from 62.5 μg to 2000 μg and recombinant FSH were administered to 332 patients undergoing COH for IVF (see Table II). Median serum LH on the day of hCG administration decreased with increasing doses of Antagon™. Median serum E_2 (17β-estradiol) on the day of hCG administration was 1475, 1110, and 1160 pg/mL for the 62.5, 125, and 250 μg doses, respectively. Lower peak serum E_2 levels of 823, 703, and 441 pg/mL were seen at higher doses of Antagon™ 500, 1000, and 2000 μg, respectively. The highest pregnancy and implantation rates were achieved with the 250 μg dose of Antagon™ as summarized in Table II.

TABLE II: Results from the multicenter, double-blind, randomized, dose-finding study to assess the efficacy of Antagon™ to prevent premature LH surges in women undergoing COH with recombinant FSH.

	Daily dose (μg) of Antagon™					
	62.5 μg	**125 μg**	**250 μg**	**500 μg**	**1000 μg**	**2000 μg**
No. subjects receiving Antagon™	31	66	70	69	66	30

No. subjects with ET†	27	61	62	54	61	27
No of subjects with LH rise ≥ 10 mIU/mL*	4	6	1	0	0	0
Serum LH (mIU/mL) on day of hCG‡	3.6	2.5	1.7	1.0	0.6	0.3
5^{th}-95^{th} percentiles	0.6-19.9	0.6-11.4	<0.25-6.4	0.4-4.7	<0.25-2.2	<0.25-0.8
Serum E_2 (pg/mL) on day of hCG‡	1475	1110	1160	823	703	441
5^{th}-95^{th} percentiles	645-3720	424-3780	384-3910	279-2720	284-2360	166-1940
Vital pregnancy rate Ω						
per attempt, n (%)	7(22.6)	17(25.8)	25(35.7)	8(11.6)	9(13.6)	2(6.7)
per transfer, n (%)	7(25.9)	17(27.9)	25(40.3)	8(14.8)	9(14.8)	2(7.4)
Implantation rate (%)ϒ	14.2(26.8)	16.3(30.5)	21.9(30.6)	9.0(23.7)	8.5(21.7)	4.9(20.1)

(Protocol 38602)

* Following initiation of Antagon™ therapy. Includes subjects who have complied with daily injections.
‡ Median values
§ Restricted to subjects with hCG injection
ϒ Mean (standard deviation)
† ET: Embryo Transfer
Ω As evidenced by ultrasound at 5-6 weeks following ET.

Transient LH rises alone were not deleterious to achieving pregnancy with Antagon™ at doses of 125 µg (3/6 subjects) and 250 µg (1/1 subjects). In addition, none of the subjects with LH rises ≥ 10 mIU/mL had premature luteinization indicated by a serum progesterone above 2 ng/mL.

A multicenter, open-label, randomized study was conducted to assess the efficacy and safety of Antagon™ in women undergoing COH. Follicular phase treatment with Antagon™ 250 µg was studied using a luteal phase GnRH agonist as a reference treatment. A total of 463 subjects were treated with Antagon™ by subcutaneous injection once daily starting on Day 6 of recombinant FSH treatment. Recombinant FSH was maintained at 150 IU for the first 5 days of ovarian stimulation and was then adjusted by the investigator on the sixth day of gonadotropin use according to individual responses. The results for the Antagon™ arm are summarized in Table III.

TABLE III: Results from the multicenter, open-label, randomized study to assess the efficacy and safety of Antagon™ in women undergoing COH.

	Antagon™ 250 μg
No. subjects treated	463
Duration of GnRH analog (days)[§¥]	5.4(2.0)
Duration of recombinant FSH (days)[§¥]	9.6(2.0)
Serum E_2 (pg/mL) on day of hCG[‡] 5th-95th percentiles	1190 373-3105
Serum LH (mIU/mL) on day of hCG[‡] 5th-95th percentiles	1.6 0.6-6.9
No. of subjects with LH rise ≥ 10 mIU/mL[*]	13
No. of follicles >11mm[¥§]	10.7(5.3)
No. of subjects with oocyte retrieval	440
No. of oocytes[¥]	8.7(5.6)
Fertilization rate	62.1%
No. subjects with ET[†]	399
No. of embryos transferred[¥]	2.2(0.6)
No. of embryos[¥]	6.0(4.5)
Ongoing pregnancy rate [Ω§]	
per attempt, n (%)[λ]	94(20.3)
per transfer, n (%)	93(23.3)
Implantation rate (%)[¥]	15.7(29)

(Protocol 38607)

* Following initiation of Antagon™ therapy
‡ Median values
§ Restricted to subjects with hCG injection
¥ Mean (standard deviation)
† ET: Embryo Transfer
Ω As evidenced by ultrasound at 12-16 weeks following ET
λ Includes one patient who achieved pregnancy with intrauterine induction.
Some centers were limited to the transfer of ≤ 2 embryos based on local practice standards

The mean number of days of Antagon™ treatment was 5.4(2-14). There was no incidence of drug related allergic reactions within the adequate and well-controlled clinical studies.

LH Surges

The midcycle LH surge initiates several physiologic actions including: ovulation, resumption of meiosis in the oocyte, and luteinization. In 463 subjects administered

Antagon™ 250 μg, a premature LH surge prior to hCG administration, (LH rise ≥ 10 mIU/mL with a significant rise in serum progesterone > 2 ng/mL, or a significant decline in serum estradiol) occurred in less than 1% of subjects.

INDICATIONS AND USAGE

Antagon™ (ganirelix acetate) Injection is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation.

CONTRAINDICATIONS

Antagon™ (ganirelix acetate) Injection is contraindicated under the following conditions:

- Known hypersensitivity to Antagon™ or to any of its components.
- Known hypersensitivity to GnRH or any other GnRH analog.
- Known or suspected pregnancy (see PRECAUTIONS).

WARNINGS

Antagon™ (ganirelix acetate) Injection should be prescribed by physicians who are experienced in infertility treatment. Before starting treatment with Antagon™, pregnancy must be excluded. Safe use of Antagon™ during pregnancy has not been established (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Caution is advised in patients with hypersensitivity to GnRH. These patients should be carefully monitored after the first injection. Anaphylactic reactions or ganirelix antibody formation have not been reported in the clinical trials for Antagon™ (ganirelix acetate) Injection.

The packaging of this product contains natural rubber latex which may cause allergic reactions.

Information for Patients

Prior to therapy with Antagon™ (ganirelix acetate) Injection, patients should be informed of the duration of treatment and monitoring procedures that will be required. The risk of possible adverse reactions should be discussed (see ADVERSE REACTIONS).

Antagon™ should not be prescribed if the patient is pregnant.

Laboratory Tests

A neutrophil count ≥ 8.3 (x 10^9/L) was noted in 11.9% (up to 16.8 x 10^9/L) of all subjects treated within the adequate and well-controlled clinical trials. In addition, downward shifts within the Antagon™ (ganirelix acetate) Injection group were observed for hematocrit and total bilirubin. The clinical significance of these findings was not determined.

Drug Interactions

No formal drug/drug interaction studies have been performed.

Carcinogenesis and Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed with Antagon™ (ganirelix acetate) Injection to evaluate the carcinogenic potential of the drug. Antagon™ did not induce a mutagenic response in the Ames test (S. typhimurium and E. coli) or produce chromosomal aberrations in *in vitro* assay using Chinese Hamster Ovary cells.

Pregnancy

Pregnancy Category X

Antagon™ (ganirelix acetate) is contraindicated in pregnant women. When administered from day 7 to near term to pregnant rats and rabbits at doses up to 10 and 30 μg/day (approximately 0.4 to 3.2 times the human dose based on body surface area), Antagon™ increased the incidence of litter resorption. There was no increase in fetal abnormalities. No treatment related changes in fertility, physical, or behavioral characteristics were observed in the offspring of female rats treated with Antagon™ during pregnancy and lactation.

The effects on fetal resorption are logical consequences of the alteration in hormonal levels brought about by the antigonadotrophic properties of this drug and could result in fetal loss in humans. Therefore, this drug should not be used in pregnant women (see CONTRAINDICATIONS).

Nursing Mothers

Antagon™ (ganirelix acetate) Injection should not be used by lactating women. It is not known whether this drug is excreted in human milk.

Geriatric Use

Clinical studies with Antagon™ (ganirelix acetate) Injection did not include a sufficient number of subjects aged 65 and over.

ADVERSE REACTIONS

The safety of Antagon™ (ganirelix acetate) Injection was evaluated in two randomized, parallel-group, multicenter controlled clinical studies. Treatment duration for Org 37462 ranged from 1 to 14 days. Table IV represents adverse events (AEs) from first day of Antagon™ administration until confirmation of pregnancy by ultrasound at an incidence of ≥1% in Antagon™ treated subjects without regard to causality.

TABLE IV: Incidence of common adverse events (Incidence ≥1% in Antagon™-treated subjects)
Completed controlled clinical studies (All-subjects-treated group).

Adverse Events Occurring in ≥ 1%	Antagon™ N=794 %(n)
Abdominal Pain (gynecological)	4.8 (38)
Death Fetal	3.7 (29)
Headache	3.0 (24)
Ovarian Hyperstimulation Syndrome	2.4 (19)
Vaginal Bleeding	1.8 (14)
Injection Site Reaction	1.1 (9)
Nausea	1.1 (9)
Abdominal Pain (gastrointestinal)	1.0 (8)

Congenital Anomalies

Ongoing clinical follow-up studies of 283 newborns of women administered Antagon™ (ganirelix acetate) Injection were reviewed. There were three neonates with major congenital anomalies and 18 neonates with minor congenital anomalies. The major congenital anomalies were: hydrocephalus/meningocele, omphalocele, and Beckwith-Wiedemann Syndrome. The minor congenital anomalies were: nevus, skin tags, sacral sinus, hemangioma, torticollis/ asymmetric skull, talipes, supernumerary digit finger, hip subluxation, torticollis/high palate, occiput/abnormal hand crease, hernia umbilicalis, hernia inguinalis, hydrocele, undescended testis, and hydronephrosis. The causal relationship between these congenital anomalies and Antagon™ is unknown. Multiple factors, genetic and others (including, but not limited to ICSI, IVF, gonadotropins, progesterone) may confound ART (Assisted Reproductive Technology) procedures.

OVERDOSAGE

There have been no reports of overdosage with Antagon™ (ganirelix acetate) Injection in humans.

DOSAGE AND ADMINISTRATION

After initiating FSH therapy on Day 2 or 3 of the cycle, Antagon™ (ganirelix acetate) Injection 250 μg may be administered subcutaneously once daily during the early to mid follicular phase. By taking advantage of endogenous pituitary FSH secretion, the requirement for exogenously administered FSH may be reduced. Treatment with Antagon™ should be continued daily until the day of hCG administration. When a sufficient number of follicles of adequate size are present, as assessed by ultrasound, final maturation of follicles is induced by administering hCG. The administration of hCG should be withheld in cases where the ovaries are abnormally enlarged on the last day of FSH therapy to reduce the chance of developing OHSS.

Directions for using Antagon™ (ganirelix acetate) Injection

1. Antagon™ is supplied in a sterile, pre-filled syringe and is intended for SUBCUTANEOUS administration only.
2. Wash hands thoroughly with soap and water.
3. The most convenient sites for SUBCUTANEOUS injection are in the abdomen around the navel or upper thigh.
4. The injection site should be swabbed with a disinfectant to remove any surface bacteria. Clean about two inches around the point where the needle will be inserted and let the disinfectant dry for at least one minute before proceeding.
5. Remove needle cover.
6. Pinch up a large area of skin between the finger and thumb. Vary the injection site a little with each injection.

7. The needle should be inserted at the base of the pinched-up skin at an angle of 45 - 90° to the skin surface.
8. When the needle is correctly positioned, it will be difficult to draw back on the plunger. If any blood is drawn into the syringe, the needle tip has penetrated a vein or artery. If this happens, withdraw the needle slightly and reposition the needle without removing it from the skin. Alternatively, remove the needle and use a new, sterile, prefilled syringe. Cover the injection site with a swab containing disinfectant and apply pressure; the site should stop bleeding within one or two minutes.
9. Once the needle is correctly placed, depress the plunger slowly and steadily, so the solution is correctly injected and the skin is not damaged.
10. Pull the syringe out quickly and apply pressure to the site with a swab containing disinfectant.
11. Use the sterile, pre-filled syringe only once and dispose of it properly.

HOW SUPPLIED

Antagon™ (ganirelix acetate) Injection is supplied in:

Disposable, sterile, pre-filled 1 mL glass syringes containing 250 µg/0.5 mL of ganirelix acetate. Each Antagon™ sterile, pre-filled syringe is affixed with a 27 gauge x ½ inch needle and is blister-packed.

Single syringe	NDC 0052-0301-51
Box of 5	NDC 0052-0301-61
Box of 50	NDC 0052-0301-71

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

[see USP Controlled Room Temperature]. Protect from light.

℞ only

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West Orange, NJ 07052

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