

1 Antagon™ (ganirelix acetate) Injection

2 FOR SUBCUTANEOUS USE ONLY

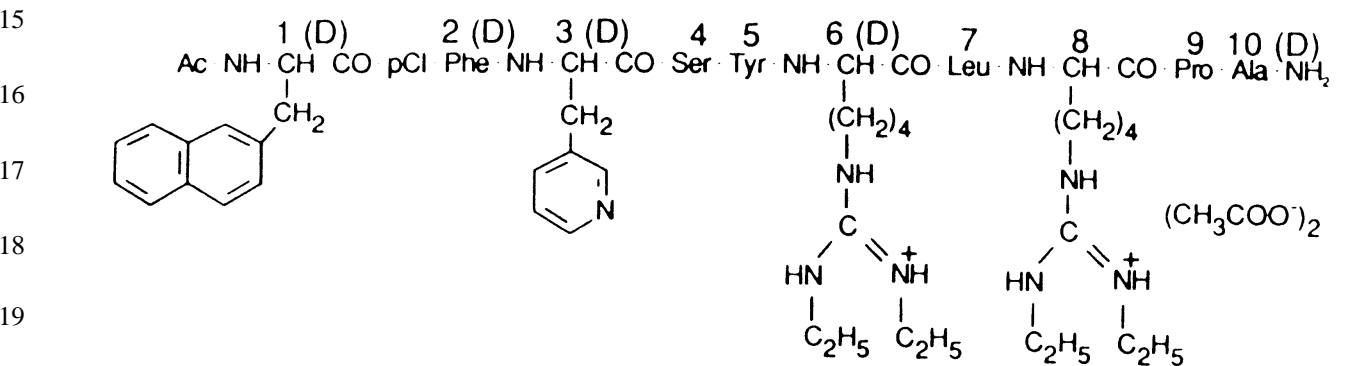
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4 **DESCRIPTION**

5 Antagon™ (ganirelix acetate) Injection is a synthetic decapeptide with high antagonistic
6 activity against naturally occurring gonadotropin-releasing hormone (GnRH). Ganirelix
7 acetate is derived from native GnRH with substitutions of amino acids at positions 1, 2, 3,
8 6, 8, and 10 to form the following molecular formula of the peptide: N-acetyl-3-(2-
9 naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-
10 N⁹,N¹⁰-diethyl-D-homoarginyl-L-leucyl-N⁹,N¹⁰-diethyl-L-homoarginyl-L-prolyl-D-
11 alanylamide acetate. The molecular weight for ganirelix acetate is 1570.4 as an anhydrous
12 free base. The structural formula is as follows:

13 Ganirelix acetate

14



21 Antagon™ is supplied as a colorless, sterile, ready-to-use, aqueous solution intended for

22 SUBCUTANEOUS administration only. Each sterile, pre-filled syringe contains 250

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

25 **CLINICAL PHARMACOLOGY**

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

40 **Pharmacokinetics**

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

45

46 **TABLE I:** Mean (SD) pharmacokinetic parameters of 250 µg of Antagon™ following a
 47 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)

48 t_{max} Time to maximum concentration
 49 t_{1/2} Elimination half-life
 50 C_{max} Maximum serum concentration
 51 AUC Area under the curve; Single dose: AUC_{0-∞}; multiple dose AUC₀₋₂₄
 52 V_d Volume of distribution
 53 † Based on intravenous administration
 54 CL Clearance = Dose/AUC_{0-∞}
 55 F Absolute bioavailability
 56

57 Absorption

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

62 Distribution

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

66 Metabolism

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

72 Excretion

73 On average, 97.2% of the total radiolabeled Antagon™ dose is recovered in the feces and
74 urine (75.1% and 22.1%, respectively) over 288 h following intravenous single dose
75 administration of 1 mg [¹⁴C]-ganirelix acetate. Urinary excretion is virtually complete in
76 24 h, whereas fecal excretion starts to plateau 192 h after dosing.

77 **Special Populations**

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

81 Drug-Drug Interactions

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

86 **Clinical Studies**

87 The efficacy of Antagon™ (ganirelix acetate) Injection was established in two adequate
88 and well-controlled clinical studies which included women with normal endocrine and
89 pelvic ultrasound parameters. The studies intended to exclude subjects with polycystic
90 ovary syndrome (PCOS) and subjects with low or no ovarian reserve. One cycle of study
91 medication was administered to each randomized subject. For both studies, the
92 administration of exogenous recombinant FSH [Follistim® (follitropin beta for injection)]
93 150 IU daily was initiated on the morning of Day 2 or 3 of a natural menstrual cycle.
94 Antagon™ was administered on the morning of Day 7 or 8 (Day 6 of recombinant FSH

95 administration). The dose of recombinant FSH administered was adjusted according to
 96 individual responses starting on the day of initiation of Antagon™. Both recombinant
 97 FSH and Antagon™ were continued daily until at least three follicles were 17 mm or
 98 greater in diameter at which time hCG [Pregnyl® (chorionic gonadotropin for injection,
 99 USP)] was administered. Following hCG administration, Antagon™ and recombinant
 100 FSH administration were discontinued. Oocyte retrieval, followed by *in vitro* fertilization
 101 (IVF) or intracytoplasmic sperm injection (ICSI), was subsequently performed.
 102 In a multicenter, double-blind, randomized, dose-finding study, the safety and efficacy of
 103 Antagon™ were evaluated for the prevention of LH surges in women undergoing COH
 104 with recombinant FSH. Antagon™ doses ranging from 62.5 µg to 2000 µg and
 105 recombinant FSH were administered to 332 patients undergoing COH for IVF (see
 106 Table II). Median serum LH on the day of hCG administration decreased with increasing
 107 doses of Antagon™. Median serum E₂ (17β-estradiol) on the day of hCG administration
 108 was 1475, 1110, and 1160 pg/mL for the 62.5, 125, and 250 µg doses, respectively.
 109 Lower peak serum E₂ levels of 823, 703, and 441 pg/mL were seen at higher doses of
 110 Antagon™ 500, 1000, and 2000 µg, respectively. The highest pregnancy and implantation
 111 rates were achieved with the 250 µg dose of Antagon™ as summarized in Table II.

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

115

	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 \geq 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)

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* 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.

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

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

138 **TABLE III:** Results from the multicenter, open-label, randomized study to assess the
 139 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 [‡] 5 th -95 th percentiles	1190 373-3105
Serum LH (mIU/mL) on day of hCG [‡] 5 th -95 th 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)

140 (Protocol 38607)

141

142 * Following initiation of Antagon™ therapy

143 ‡ Median values

144 § Restricted to subjects with hCG injection

145 ¥ Mean (standard deviation)

146 † ET: Embryo Transfer

147 Ω As evidenced by ultrasound at 12-16 weeks following ET

148 λ Includes one patient who achieved pregnancy with intrauterine induction.

149 Some centers were limited to the transfer of ≤ 2 embryos based on local practice standards

150

151 The mean number of days of Antagon™ treatment was 5.4(2-14). There was no

152 incidence of drug related allergic reactions within the adequate and well-controlled clinical

153 studies.

154 LH Surges

155 The midcycle LH surge initiates several physiologic actions including: ovulation,

156 resumption of meiosis in the oocyte, and luteinization. In 463 subjects administered

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

160 **INDICATIONS AND USAGE**

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

163 **CONTRAINDICATIONS**

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

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

168 **WARNINGS**

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

173 **PRECAUTIONS**

174 **General**

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

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

181 **Information for Patients**

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

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

186 **Laboratory Tests**

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

192 **Drug Interactions**

193 No formal drug/drug interaction studies have been performed.

194 **Carcinogenesis and Mutagenesis, Impairment of Fertility**

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

199 **Pregnancy**

200 Pregnancy Category X

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

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

212 **Nursing Mothers**

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

215 **Geriatric Use**

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

218 **ADVERSE REACTIONS**

219 The safety of Antagon™ (ganirelix acetate) Injection was evaluated in two randomized,
220 parallel-group, multicenter controlled clinical studies. Treatment duration for Org 37462
221 ranged from 1 to 14 days. Table IV represents adverse events (AEs) from first day of
222 Antagon™ administration until confirmation of pregnancy by ultrasound at an incidence of
223 ≥1% in Antagon™ treated subjects without regard to causality.

224 **TABLE IV:** Incidence of common adverse events (Incidence $\geq 1\%$ in AntagonTM-treated
 225 subjects)
 226 Completed controlled clinical studies (All-subjects-treated group).
 227

Adverse Events Occurring in $\geq 1\%$	Antagon TM 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)

228

229 Congenital Anomalies

230

231 Ongoing clinical follow-up studies of 283 newborns of women administered AntagonTM

232 (ganirelix acetate) Injection were reviewed. There were three neonates with major

233 congenital anomalies and 18 neonates with minor congenital anomalies. The major

234 congenital anomalies were: hydrocephalus/meningocele, omphalocele, and Beckwith-

235 Wiedemann Syndrome. The minor congenital anomalies were: nevus, skin tags, sacral

236 sinus, hemangioma, torticollis/ asymmetric skull, talipes, supernumerary digit finger, hip

237 subluxation, torticollis/high palate, occiput/abnormal hand crease, hernia umbilicalis,

238 hernia inguinalis, hydrocele, undescended testis, and hydronephrosis. The causal

239 relationship between these congenital anomalies and AntagonTM is unknown. Multiple

240 factors, genetic and others (including, but not limited to ICSI, IVF, gonadotropins,

241 progesterone) may confound ART (Assisted Reproductive Technology) procedures.

242 **OVERDOSAGE**

243 There have been no reports of overdosage with AntagonTM (ganirelix acetate) Injection in

244 humans.

245 **DOSAGE AND ADMINISTRATION**

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

255 **Directions for using Antagon™ (ganirelix acetate) Injection**

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

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

280 **HOW SUPPLIED**

281 Antagon™ (ganirelix acetate) Injection is supplied in:

282 Disposable, sterile, pre-filled 1 mL glass syringes containing 250 µg/0.5 mL
283 of ganirelix acetate. Each Antagon™ sterile, pre-filled syringe is affixed
284 with a 27 gauge x 1/2 inch needle and is blister-packed.

285 Single syringe NDC 0052-0301-51

286 Box of 5 NDC 0052-0301-61

287 Box of 50 NDC 0052-0301-71

288 **Storage**

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

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

291 R only



292

Manufactured for Organon Inc.

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West Orange, NJ 07052

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by Vetter Pharma-Fertigung GmbH & Co. KG

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Ravensburg, Germany

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and packaged by Organon (Ireland) Ltd, Swords Co.

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Dublin, Ireland

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