CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21057

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-057

DATE REVIEWED: 7-20-99

REVIEW #: 3

REVIEWER: Swapan K. De

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Correspondence	07-19-99	07-19-99	07-20-99(Fax copy)

NAME & ADDRESS OF APPLICANT:

Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME

Proprietary:	Antagon
Established:	Ganirelix acetate
Code Name/#:	Org 37462
Chem.Type/Ther.Class:	1 P

DOSAGE FORM:	Pre-filled syringe
STRENGTHS:	250 µg/0.5 ml
ROUTE OF ADMINISTRATION:	Subcutaneous
Rx/OTC:	_X_ Rx __ OTC

ITEM REVIEWED:

Labeling of Carton (hand revised):

Following changes were made in the carton labeling in response to FDA's Query:

Satisfactory

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from the standpoint of chemistry and manufacturing controls.

/S/ 7/20/99

Swapan K. De, Ph.D.
Review Chemist

cc:
Org. NDA 21-057
HFD-580/Division File
HFD-580/SDe/4/12/99
HFD-580/DMoore
HFD-580/MRhee
HFD-820/JGibbs/Koepke (NMEs only)
R/D Init by: Moo-Jhong Rhee, Ph. D. 7/20/99

filename: NDA21057.3

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-057

DATE REVIEWED: 07-14-99

REVIEW #: 2

REVIEWER: Swapan K. De

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-01-99	29-01-99	03-02-99
AMENDMENT	07-01-99	07-02-99	07-06-99
CORRESPONDENCE	07-09-99	07-09-99	07-12-99

NAME & ADDRESS OF APPLICANT:

Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME

Proprietary:	Antagon
Established:	Ganirelix acetate
Code Name/#:	Org 37462
Chem.Type/Ther.Class:	1 P

TYPE OF SUBMISSION: Response to FDA Letter dated 5/26/99 and a fax following a t-con on 7/8/99

PHARMACOL. CATEGORY/INDICATION: Prevention of Premature LH Surges in Woman Undergoing Controlled Ovarian Hyperstimulation

DOSAGE FORM: Pre-filled syringe
STRENGTHS: 250 µg/0.5 ml
ROUTE OF ADMINISTRATION: Subcutaneous
Rx/OTC: _X_ Rx __ OTC
SPECIAL PRODUCTS: ___ Yes _X_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

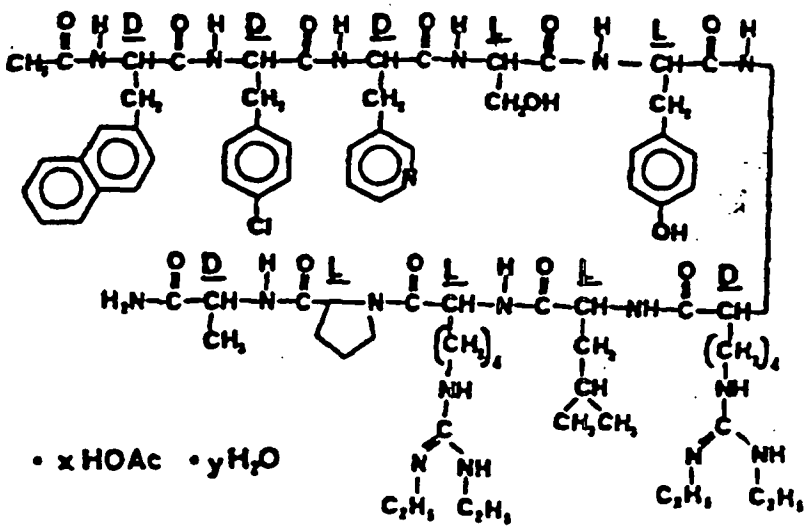
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical names: 1. 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 (IUPAC)

2. N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N^5-[bis(ethylamino)methylene]-D-lysyl-L-leucyl-N^5-[bis(ethylamino)methylene]-L-lysyl-L-prolyl-D-alaninamide acetate(CAS)

CAS number: 124904-93-4

Structural Formula:



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF			Reviewed Not adequate Responses to deficiencies Adequate	5/3/99 7/14/99	5/3/99 N/A
			Reviewed by S. De Adequate	6/15/99	N/A
			4432/50- Reviewed by S. De Adequate Reviewed by J. Sieczkowski Adequate	5/20/99 1/22/99	N/A N/A
IND	Indication: Prevention of LH surges in controlled ovarian hyperstimulation	Organon Inc. 375 Mt. Pleasant Avenue West Orange, NJ 07052			N/A

CONSULTS:

Microbiologist has reviewed the microbiology section of the NDA. The Office of Compliance has completed EERs of all the facilities associated with the chemistry, manufacturing and controls. All facilities were found acceptable except one, which is still pending.

REMARKS/COMMENTS:

Org 37462 (ganirelix acetate) is a new molecular entity, a decapeptide, and acts as an antagonist of gonadotropin releasing hormone and induces rapid, profound, reversible suppression of the pituitary-gonadal axis. Drug substance Org 37462 is unique because of the use of several modified amino acids. method is used to synthesize Ganirelix acetate.

Drug product is a pre-filled syringe and composed of Org 37462, acetic acid, mannitol and water buffered with acetic acid and sodium hydroxide and will be administered subcutaneously.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from the standpoint of chemistry and manufacturing controls. The drug substance was found to be satisfactory from the recent DMF holder's correspondence of 7/14/99.

/S/ 7/15/99

Swapan K. De, Ph.D.
Review Chemist

cc:
Org. NDA 21-057
HFD-580/Division File
HFD-580/SDe/4/12/99
HFD-580/DMoore
HFD-580/MRhee
HFD-820/JGibbs/Koepke (NMEs only)
R/D Init by: Moo-Jhong Rhee, Ph. D.
filename: NDA21057.2

/S/ 7/16/99

MAY

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

DATE REVIEWED: 5-25-99

NDA #: 21-057

REVIEWER: Swapan K. De

REVIEW #: 1

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-01-99	29-01-99	03-02-99

NAME & ADDRESS OF APPLICANT: Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME
Proprietary: Antagon
Established: Ganirelix acetate
Code Name/#: Org 37462
Chem.Type/Ther.Class: 1 P

PHARMACOL. CATEGORY/INDICATION: Prevention of Premature LH Surges in Woman Undergoing Controlled Ovarian Hyperstimulation

DOSAGE FORM: Pre-filled syringe
STRENGTHS: 250 µg/0.5 ml
ROUTE OF ADMINISTRATION: Subcutaneous
Rx/OTC: X Rx __ OTC
SPECIAL PRODUCTS: __ Yes X No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

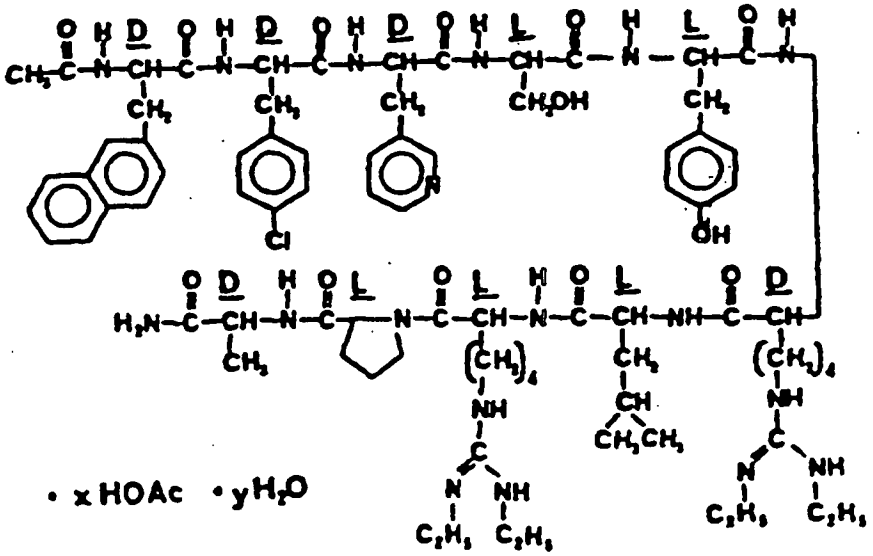
Chemical names:

1. 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 (IUPAC)

2. N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N^5-[bis(ethylamino)methylene]-D-lysyl-L-leucyl-N^5-[bis(ethylamino)methylene]-L-lysyl-L-prolyl-D-alaninamide acetate(CAS)

CAS number: 124904-93-4

Structural Formula:



Molecular Formula: $C_{80}H_{113}N_{18}O_{13}Cl$, anhydrous free base

$C_{80}H_{113}N_{18}O_{13}Cl$. XCH_3CO_2H. yH_2O, hydrated salt where $2 \leq x \leq 3$ and $y \leq 10$

Relative molecular mass: 1570.4, anhydrous free base
1690.5 anhydrous diacetate
1750.6 anhydrous triacetate

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF			Reviewed Not adequate	5/3/99	5/3/99
			Pending		
			Reviewed by S. De Adequate Reviewed by J. Sieczkowski Adequate	5/20/99 1/22/99	N/A N/A
IND	Indication: Prevention of LH surges in controlled ovarian hyperstimulation	Organon Inc. 375 Mt. Pleasant Avenue West Orange, NJ 07052			N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS:

The division of microbiology will review the microbiology section of the NDA. Compliance division has been consulted for EER, and the Labeling and Nomenclature Committee (LNC) had been consulted for the tradename, Antagon. On 11-Nov-98, LNC forwarded a decision and it was 'unacceptable' due to the reason that 'it may be misleading and inaccurate unless it antagoni all gonadotropins'. The sponsor appealed against the LNC's decision. However, the division has finally decided to allow the name 'Antagon' as proposed on 4-May-99

REMARKS/COMMENTS:

Org 37462 (ganirelix acetate) is a new molecular entity, a decapeptide, and acts as an antagonist of gonadotropin releasing hormone and induces rapid, profound, reversible suppression of the pituitary-gonadal axis. Drug substance Org 37462 contains 10 chiral centers. Org 37462 is unique because of the use of several modified amino acids which includes a napthyl group in D-ala, a chloro group in D-Phe, a pyridyl group in D-Ala and use of 5 D-amino acids. method is used to synthesize Ganirelix acetate. F-moc-D-Ala-OH is coupled to a resin (Wangresin) to get F-moc-D-Ala-Wangresin. F-moc-D-Ala-Wangresin is then placed in the reaction vessel of an automated synthesizer and each amino acid or modified amino acid (well characterized) is attached to the resin in successive coupling cycles.

Not enough information on the starting materials is included in the DMF . Amino acids used in the synthesis should be qualified by test results including the optical rotation, melting point and chiral purity. In addition to the limit of total impurities, major individual impurity should be identified and limits should be specified.

Drug product is a pre-filled syringe and composed of Org 37462, mannitol and water buffered with acetic acid and sodium hydroxide and will be administered subcutaneously.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from the standpoint of chemistry and manufacturing controls. The application contain some deficiencies which are included in the draft letter needs to be addressed. The drug substance contains a number of deficiencies, which has been sent to the DMF holder and need to be addressed before approval. EER is pending.

/S/ 5/25/99

Swapan K. De, Ph.D.
Review Chemist

/S/

cc:
Org. NDA 21-057
HFD-580/Division File
HFD-580/SDe/4/12/99
HFD-580/DMoore
HFD-580/MRhee
HFD-820/JGibbs/Koepke (NMEs only)
R/D Init by: Moo-Jhong Rhee, Ph. D. /S/ 5/25/99

filename: NDA21057.1

NDA 21-057
Antagon™ (ganirelix acetate) 250 µg/mL injection
Organon, Inc.

Environmental Assessment

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b), and it is accepted (see Chemistry Review #1).