NOVAREL- gonadotrophin, chorionic
Ferring Pharmaceuticals Inc.

Novarel®

(Chorionic Gonadotropin for Injection, USP)

FOR INTRAMUSCULAR USE ONLY

Rx Only

DESCRIPTION

Human chorionic gonadotropin (HCG), a polypeptide hormone produced by the human placenta, is composed of an alpha and a beta subunit. The alpha subunit is essentially identical to the alpha subunits of the human pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as to the alpha subunit of human thyroid-stimulating hormone (TSH). The beta subunits of these hormones differ in amino acid sequence.

Chorionic Gonadotropin is a water soluble glycoprotein derived from human pregnancy urine. The sterile lyophilized powder is stable. When reconstituted with Bacteriostatic Water for Injection preserved with benzyl alcohol 0.9%, the solution should be refrigerated and used within 30 days.

Each **5,000** USP units vial contains:

Chorionic Gonadotropin **5,000** USP Units, Mannitol 100 mg, Dibasic Sodium Phosphate 16 mg, and Monobasic Sodium Phosphate 4 mg.

Each **10,000** USP units vial contains:

Chorionic Gonadotropin **10,000** USP Units, Mannitol 100 mg, Dibasic Sodium Phosphate 16 mg, and Monobasic Sodium Phosphate 4 mg.

CLINICAL PHARMACOLOGY

The action of HCG is virtually identical to that of pituitary LH, although HCG appears to have a small degree of FSH activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone. Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when HCG is discontinued. During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation. HCG can substitute for LH in this function.

During a normal pregnancy, HCG secreted by the placenta maintains the corpus luteum after LH secretion decreases, supporting continued secretion of estrogen and progesterone, and preventing menstruation. HCG HAS NO KNOWN EFFECT ON FAT MOBILIZATION, APPETITE OR SENSE OF HUNGER, OR BODY FAT DISTRIBUTION.

INDICATIONS AND USAGE

HCG HAS NOT BEEN DEMONSTRATED TO BE EFFECTIVE ADJUNCTIVE THERAPY IN THE TREATMENT OF OBESITY. THERE IS NO SUBSTANTIAL EVIDENCE THAT IT INCREASES WEIGHT LOSS BEYOND THAT RESULTING FROM CALORIC RESTRICTION, THAT IT CAUSES A MORE ATTRACTIVE OR "NORMAL" DISTRIBUTION OF FAT, OR THAT IT DECREASES THE HUNGER AND DISCOMFORT ASSOCIATED WITH CALORIE-RESTRICTED DIETS.

1. Prepubertal cryptorchidism not due to anatomic obstruction. In general, HCG is thought to induce testicular descent in situations when descent would have occurred at puberty. HCG thus may help to predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following HCG administration is permanent, in most cases the response is temporary. Therapy is usually instituted between the ages of 4 and 9.
2. Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males.
3. Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with human menotropins.

CONTRAINDICATIONS

Precocious puberty, prostatic carcinoma or other androgen-dependent neoplasm, prior allergic reaction to HCG. HCG may cause fetal harm when administered to a pregnant woman. Combined HCG/PMS (pregnant mare's serum) therapy has been noted to induce high incidences of external congenital anomalies in the offspring of mice, in a dose-dependent manner. The potential extrapolation to humans has not been determined.

WARNINGS

HCG should be used in conjunction with human menopausal gonadotropins only by physicians experienced with infertility problems who are familiar with the criteria for patient selection, contraindications, warnings, precautions, and adverse reactions described in the package insert for menotropins. The principal serious adverse reactions during this use are: (1) Ovarian hyperstimulation, a syndrome of sudden ovarian enlargement, ascites with or without pain, and/or pleural effusion; (2) Enlargement of preexisting ovarian cysts or rupture of ovarian cysts with resultant hemoperitoneum; (3) Multiple births, and (4) Arterial thromboembolism.

The recommended diluent for reconstitution is Bacteriostatic Water for Injection preserved with benzyl alcohol 0.9%. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

Anaphylaxis has been reported with urinary-derived HCG products.

PRECAUTIONS

General

1. Induction of androgen secretion by HCG may induce precocious puberty in patients treated for cryptorchidism. Therapy should be discontinued if signs of precocious puberty occur.
2. Since androgens may cause fluid retention, HCG should be used with caution in patients with cardiac or renal disease, epilepsy, migraine, or asthma.

Drug/Laboratory test

HCG can crossreact in the radioimmunoassay of gonadotropins, especially luteinizing hormone. Each

individual laboratory should establish the degree of crossreactivity with their gonadotropin assay. Physicians should make the laboratory aware of patients on HCG if gonadotropin levels are requested.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been sporadic reports of testicular tumors in otherwise healthy young men receiving HCG for secondary infertility. A causative relationship between HCG and tumor development in these men has not been established. Defects of forelimbs and of the central nervous system, as well as alterations in sex ratio, have been reported in mice on combined gonadotropin and HCG regimens. The dose of gonadotropin used was intended to induce superovulation. No mutagenic effect has been clearly established in humans. Fertility—see " **INDICATIONS AND USAGE**."

Pregnancy

See " **CONTRAINDICATIONS**" section. Combined HCG/PMS (pregnant mare's serum) therapy has been noted to induce high incidences of external congenital anomalies in the offspring of mice, in a dose-dependent manner. The potential extrapolation to humans has not been determined.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HCG is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 4 have not been established.

ADVERSE REACTIONS

(see **WARNINGS**) Headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, pain at the site of injection. Hypersensitivity reactions both localized and systemic in nature, including erythema, urticaria, rash, angioedema, dyspnea and shortness of breath, have been reported. The relationship of these allergic-like events to the polypeptide hormone or the diluent containing benzyl alcohol is not clear.

DOSAGE AND ADMINISTRATION

(Intramuscular Use Only): The dosage regimen employed in any particular case will depend upon the indication for use, the age and weight of the patient, and the physician's preference. The following regimens have been advocated by various authorities.

Prepubertal cryptorchidism not due to anatomical obstruction:

- 4,000 USP Units three times weekly for three weeks.
- 5,000 USP Units every second day for four injections.
- 15 injections of 500 to 1,000 USP Units over a period of six weeks.
- 500 USP Units three times weekly for four to six weeks. If this course of treatment is not successful, another is begun one month later, giving 1,000 USP Units per injection.

Selected cases of hypogonadotropic hypogonadism in males:

- 500 to 1,000 USP Units three times a week for three weeks, followed by the same dose twice a week for three weeks.
- 4,000 USP Units three times weekly for six to nine months, following which the dosage may be reduced to 2,000 USP Units three times weekly for an additional three months.

Table 1. Final Concentration after Reconstitution

Reconstitution volume	10,000 IU Vial Concentration	5,000 IU Vial Concentration	Administration
1 mL	10,000 IU/mL	5,000 IU/mL	Administer entire dose at once
10 mL	1,000 IU/mL	500 IU/mL	Multiple dose administration, refrigerate between doses

Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure and who has been appropriately pretreated with human menotropins (See prescribing information for menotropins for dosage and administration for that drug product).

5,000 to 10,000 USP Units one day following the last dose of menotropins. (A dosage of 10,000 USP Units is recommended in the labeling for menotropins).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Disposing of Needles and Syringes

To safely dispose of medical sharps, place used needles and syringes in a closeable, puncture-resistant container, such as a red biohazard sharps container. Sharps containers should then be taken to a collection center for proper disposal. Ask your physician or pharmacist or reference our website for more information about safely disposing used sharps.

In some states, it is illegal to throw away medical sharps in household garbage, recycling, and compost bins. Needles and other sharps must be placed in an approved sharps container and disposed of at an approved drop-off site.

HOW SUPPLIED

Chorionic Gonadotropin for Injection, USP, is available as individually packaged vials containing 5,000 or 10,000 USP Units per vial.

Each vial of Novarel ® is accompanied by a vial of sterile diluent containing 10 mL of Bacteriostatic Water for Injection, USP containing 0.9% benzyl alcohol.

Novarel ® is available in the following presentations:

- **NDC 55566-1501-1**: 10,000 USP units of Chorionic Gonadotropin injection in 1 vial with blue cap and 1 vial of diluent
- **NDC 55566-1502-1**: 5,000 USP units of Chorionic Gonadotropin injection in 1 vial with aqua cap and 1 vial of diluent

Store dry product at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (between 59° and 86°F) [See USP Controlled Room Temperature].

REFRIGERATE RECONSTITUTED PRODUCT AT 2° to 8°C (36° to 46°F) AND USE WITHIN 30 DAYS.

Manufactured for:

Ferring Pharmaceuticals Inc.

Parsippany, NJ 07054

8109000036

Rev. 05/2018

PRINCIPAL DISPLAY PANEL - Kit Carton - 10,000 USP

NDC 55566-1501-1

Novarel ®
(Chorionic Gonadotropin
for Injection, USP)

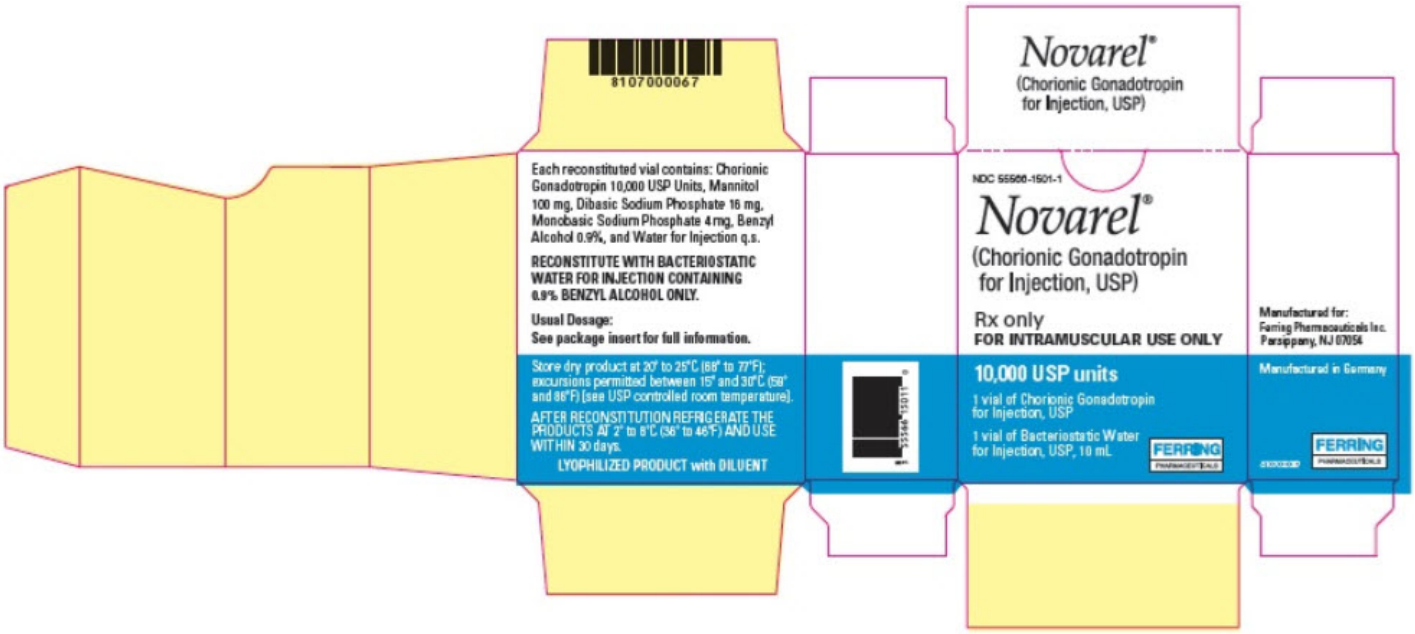
Rx only
FOR INTRAMUSCULAR USE ONLY

10,000 USP units

1 vial of Chorionic Gonadotropin
for Injection, USP

1 vial of Bacteriostatic Water
for Injection, USP, 10 mL

FERRING
PHARMACEUTICALS



PRINCIPAL DISPLAY PANEL - Kit Carton - 5,000 USP

NDC 55566-1502-1

Novarel ®
(Chorionic Gonadotropin
for Injection, USP)

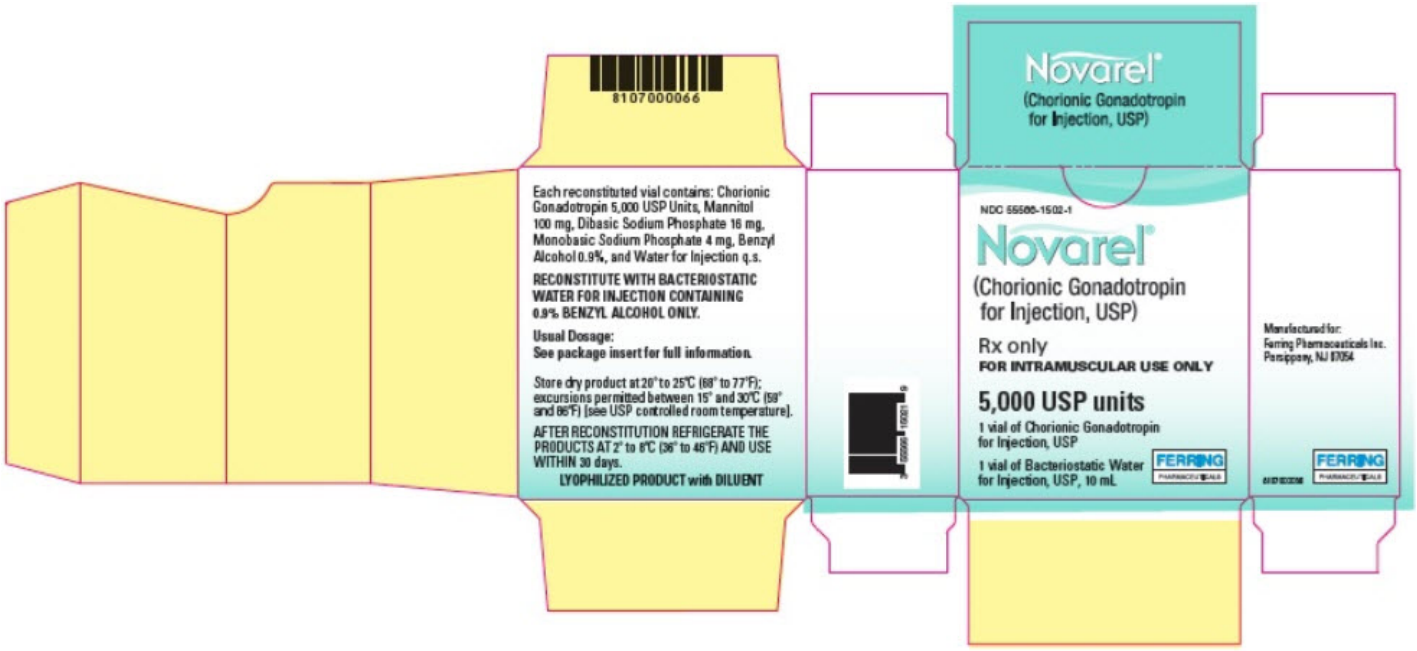
Rx only
FOR INTRAMUSCULAR USE ONLY

5,000 USP units

1 vial of Chorionic Gonadotropin
for Injection, USP

1 vial of Bacteriostatic Water
for Injection, USP, 10 mL

FERRING
PHARMACEUTICALS



PRINCIPAL DISPLAY PANEL - Kit Carton - 5,000 USP - Canada

NDC 55566-1502-1

Novarel ®
(Chorionic Gonadotropin
for Injection, USP)

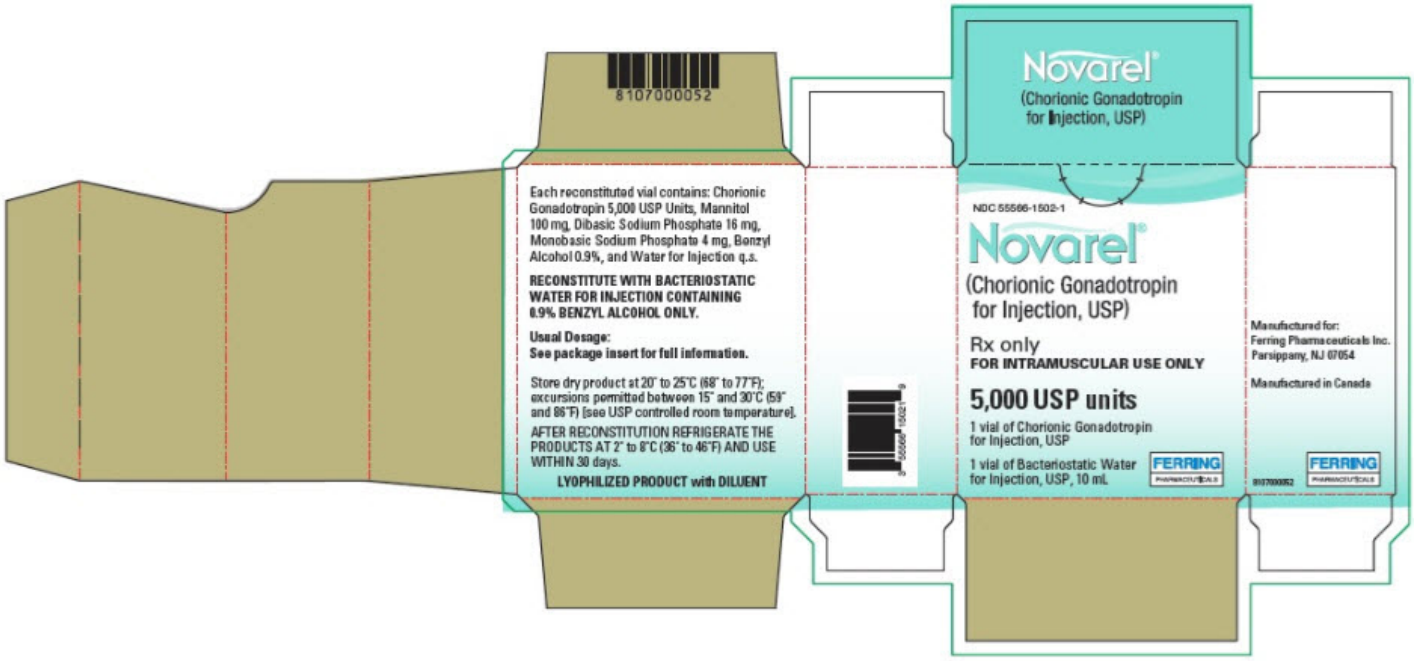
Rx only
FOR INTRAMUSCULAR USE ONLY

5,000 USP units

1 vial of Chorionic Gonadotropin
for Injection, USP

1 vial of Bacteriostatic Water
for Injection, USP, 10 mL

FERRING
PHARMACEUTICALS



NOVAREL

gonadotrophin, chorionic kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55566-1501

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:55566-1501-1	1 in 1 CARTON	01/15/1974	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	1
Part 2	1 VIAL	10 mL

Part 1 of 2

NOVAREL

gonadotrophin, chorionic injection

Product Information	
Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CHORIONIC GONADOTROPIN (UNII: 20ED16GHEB) (CHORIONIC GONADOTROPIN - UNII:20ED16GHEB)	CHORIONIC GONADOTROPIN	10000 [USP'U]

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM (UNII: 3980JIH2SW)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1		1 in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
BLA	BLA017016	06/26/2019	

Part 2 of 2

BACTERIOSTATIC WATER

water solution

Product Information	
Item Code (Source)	NDC:55566-1700
Route of Administration	INTRAMUSCULAR

Inactive Ingredients	
Ingredient Name	**Strength**
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:55566-1700-0	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA017016	01/15/1974	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA017016	01/15/1974	

NOVAREL

gonadotrophin, chorionic kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55566-1502

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55566-1502-1	1 in 1 CARTON	01/15/1974	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	1
Part 2	1 VIAL	10 mL

Part 1 of 2

NOVAREL

gonadotrophin, chorionic injection

Product Information

Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CHORIONIC GONADOTROPIN (UNII: 20ED16GHEB) (CHORIONIC GONADOTROPIN - UNII:20ED16GHEB)	CHORIONIC GONADOTROPIN	5000 [USP'U]

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	

SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM (UNII: 3980JIH2SW)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA017016	01/15/1974	

Part 2 of 2

BACTERIOSTATIC WATER

water solution

Product Information

Item Code (Source)	NDC:55566-1700
Route of Administration	INTRAMUSCULAR

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55566-1700-0	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA017016	01/15/1974	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA017016	01/15/1974	

Labeler - Ferring Pharmaceuticals Inc. (103722955)

Establishment

Name	Address	ID/FEI	Business Operations
Ferring Production Inc.		079510999	manufacture(55566-1502) , pack(55566-1502)

Establishment

Name	Address	ID/FEI	Business Operations
Jubilant HollisterStier General Partnership		246762764	manufacture(55566-1501, 55566-1502) , pack(55566-1501, 55566-1502)

Establishment

Name	Address	ID/FEI	Business Operations
Ferring GmbH		328609615	manufacture(55566-1501) , pack(55566-1501)

Establishment

Name	Address	ID/FEI	Business Operations
Ferring International Center SA		481210362	pack(55566-1501)

Establishment

Name	Address	ID/FEI	Business Operations
Aspen Oss B.V.		491017488	api manufacture(55566-1501, 55566-1502)

Establishment

Name	Address	ID/FEI	Business Operations
F.M. Howell & Company		962888116	pack(55566-1501)

Establishment

Name	Address	ID/FEI	Business Operations
Instituto Massone S.A.		970053831	api manufacture(55566-1501, 55566-1502)