IMRESTOR- pegbovigrastim suspension
Elanco Animal Health

Elanco™
Imrestor™ pegbovigrastim injection

15 mg pegbovigrastim per 2.7 mL single dose syringe

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

Imrestor is a sterile injectable formulation of pegbovigrastim (an immunomodulator, bovine granulocyte stimulating factor) in single-dose syringes. Each syringe of Imrestor contains pegbovigrastim (15 mg), L-arginine hydrochloride (94 mg), L-arginine (40 mg), and citric acid monohydrate (17 mg).

INDICATIONS FOR USE:

For the reduction in the incidence of clinical mastitis in the first 30 days of lactation in periparturient dairy cows and periparturient replacement dairy heifers.

DOSAGE AND ADMINISTRATION:

This is a two-dose regimen. The same dose is used regardless of cow/heifer body weight. Remove surface dirt from the injection site area before injecting. Inject the entire contents of the syringe subcutaneously. Do not reuse the syringe.

Administer the first dose (syringe) 7 days prior to the cow's or heifer's anticipated calving date. If necessary, the first dose may be administered within a range of 4 to 10 days prior to the anticipated calving date to accommodate management schedules. Administer the second dose (syringe) within 24 hours after calving.

Animals that calve either less than or more than 7 days after the first dose should receive the second dose within 24 hours after calving.

Prior to administration, Imrestor should be visually inspected for particulate matter and discoloration. Imrestor is a clear, colorless solution and may contain a few small, translucent or white particles. Imrestor should not be used if it is discolored or cloudy, or if other particulate matter is present. Do not shake or tap the syringe prior to use.

WARNINGS:

RESIDUE WARNING: No withdrawal period or milk discard time is required when used according to the labeling.

HUMAN WARNINGS: Not for use in humans. Keep out of reach of children.

USER SAFETY WARNINGS: In case of accidental self-injection, wash the site of injection thoroughly with clean running water. Foreign proteins such as pegbovigrastim have the potential to cause anaphylactic-type reactions. If you experience swelling or redness at the site of exposure, or more severe reactions such as shortness of breath, seek medical attention immediately and take the package insert with you. Report the event to Elanco Animal Health at 1-800-428-4441. To obtain a Safety Data Sheet, contact Elanco Animal Health at 1-800-428-4441.

PRECAUTIONS:

Do not use Imrestor to treat cows with clinical mastitis because effectiveness has not been demonstrated for this use.

ADVERSE REACTIONS:

Some cases of hypersensitivity-type reactions have been observed in studies outside the United States within five minutes to two hours, occurring most often after the first administration of Imrestor. Clinical signs may include elevated respiratory rate, dyspnea, urticaria, sweating, dependent edema, swollen mucous membranes, and/or hypersalivation, and, rarely death. These reactions resolve within hours of onset with or without therapeutic intervention and have not been shown to reoccur with subsequent injections of Imrestor. Abomasal ulcerations/erosions were observed in the Margin of Safety studies. (See Target Animal Safety section).

To report a suspected adverse drug event, contact Elanco Animal Health at 1-800-428-4441. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

CLINICAL PHARMACOLOGY:

Endogenous granulocyte colony stimulating factor is a protein (cytokine) which induces increased production of mature neutrophils from bone marrow stem cells and activation of the functional capabilities of mature circulating neutrophils. Pegbovigrastim is a modified form of bovine granulocyte colony stimulating factor conjugated to polyethylene glycol (PEG). This PEGylation technology enables sustained biological activity of the protein. In one study, cows treated with 20 µg/kg pegbovigrastim displayed statistically significant increased absolute neutrophil counts relative to the untreated control group beginning 5 hours post-dosing. Absolute neutrophil counts peaked 36 hours post-dosing and remained elevated up to 12 days post-dosing.

EFFECTIVENESS:

The effectiveness of Imrestor for the reduction in the incidence of clinical mastitis was demonstrated in a multi-site natural infection field study conducted at four sites in the U.S. and one site in France. A total of 801 healthy periparturient commercial dairy heifers and cows were enrolled and treated with Imrestor or saline by subcutaneous injection in the neck when they were identified as being approximately 7 days before their anticipated calving date (Day -7), and again within 24 hours after calving (Day 0). Each quarter of each enrolled animal was evaluated at each milking from Days 3

to 30 to monitor the development of clinical mastitis. Animals developing clinical mastitis (using quarter health, milk quality, and California Mastitis Test [CMT] evaluations) through Day 30 were classified as treatment failures. Administration of Imrestor resulted in a statistically significant difference ($p = 0.025$) in the incidence of clinical mastitis (treatment failure rate) across all five sites with a difference in favor of the Imrestor-treated group (failure rate: 60/331 = 18.13%) compared to the saline-treated group (failure rate: 85/338 = 25.15%).

TARGET ANIMAL SAFETY:

Margin of Safety: In the first study, forty primiparous and multiparous Jersey cows were assigned to one of four treatments: saline control, 1X, 2X, or 3X the intended dose of Imrestor administered at Days -7 and -3 prior to anticipated calving date and within 24 hours after calving. Cows and heifers were monitored daily until 4 days postpartum. Calves were monitored daily for 14 days after birth. Measurements on cows included bodyweights, feed consumption, milk production, somatic cell counts, physical examinations, and clinical pathology. A complete postmortem examination was conducted on each adult animal. Measurements in calves included physical examinations, bodyweights, and hematology. There were no test article related findings associated with abnormal clinical observations, feed consumption, milk production, physical examinations, or urinalysis in adult animals. A mature neutrophilia was seen in all treated animals, regardless of dose group. This was considered a test article related change and consistent with the mechanism of action of Imrestor. No test article related hematology changes were observed in the calves. Observations of mastitis, metritis, and abomasal ulcers were documented, with more animals in the treated groups affected compared to the controls. Two animals (one each from 1X and 3X groups) had perforated abomasal ulcers found at necropsy. A second study evaluated the margin of safety of pegbovigrastim in multiparous Holstein dairy cows. Forty-five multiparous Holstein dairy cows were assigned to one of five treatments: saline control, 1X, 2X, 2.5X, or 3X the recommended dose of one syringe of pegbovigrastim administered subcutaneously on Day -7 relative to the anticipated calving date and within 24 hours after calving. Cows were monitored daily until 14 days postpartum. Measurements included bodyweights, feed consumption, milk production, somatic cell counts, physical examinations, and clinical pathology, including reticulocyte counts and fecal occult blood. A postmortem examination that focused on the gastrointestinal tract, uterus, and mammary tissue was conducted on each cow. Calves were not evaluated in this study. There were no test article related findings associated with abnormal clinical observations, feed consumption, milk production, or physical examinations. A mature neutrophilia was observed in all treated animals which was consistent with the Imrestor mechanism of action and was similar to what was observed in the first margin of safety study. Treated animals had a greater number of mild gastrointestinal erosions and small areas of reddened or thinned mucosa along various portions of the gastrointestinal tract as compared to the control animals. No abomasal ulcers were seen on necropsy.

It was concluded from these studies that abomasal ulcerations/erosions could be test article related. However, given the lack of clinical signs associated with such gastrointestinal pathology in conjunction with the mild nature of the erosions in the second study, it was concluded that these findings were not clinically relevant.

Injection Site Safety: Injection site safety was evaluated following the injection of Imrestor into healthy periparturient dairy cows. Results of the injection site toleration study showed that subcutaneous injections of pegbovigrastim administered 14 days prior to slaughter in 6 cows had no gross lesions and would require no carcass trim at slaughter. Additionally, subcutaneous injections of pegbovigrastim administered approximately 12 hours prior to slaughter in 6 cows caused minimal acute local tissue reactions generally characterized by focal hemorrhage and edema and would be removed along with the hide at the time of slaughter and would not result in any carcass trim.

Reproductive Safety: Animals in the effectiveness study were also evaluated for reproductive safety. This study included 801 animals: 401 control animals and 400 treated animals. Variables measured included daily health observations on cows and calves, mortality, gestation length, percent live births, and first service conception rates following treatment. There were no statistically significant differences between treated and control animals for these reproductive variables.

STORAGE INFORMATION:

Store under refrigeration (2° to 8°C; 36° to 46°F). DO NOT FREEZE. Avoid prolonged exposure to sunlight. Excursions of up to 24 hours at room temperature (15° to 30°C; 59° to 86°F) are allowed after receipt.

DISPOSAL:

Dispose of used syringes in a leak-resistant, puncture-resistant container in accordance with applicable Federal, state and local regulations.

HOW SUPPLIED:

10, 50 or 100 single-dose syringe packages with each syringe containing 15 mg of pegbovigrastim.

NADA 141-392. Approved by FDA.

Manufactured for Elanco Animal Health, a Division of Eli Lilly and Company, Indianapolis, IN 46285.

For technical assistance or to report suspected adverse drug events, contact Elanco Animal Health at 1-800-428-4441.

Principal Display Panel - 15 mg Box Label

Elanco™

Imrestor™

pegbovigrastim injection

20 cartons containing
10 single-dose syringes (15 mg pegbovigrastim per syringe)

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Store under refrigeration (2° to 8°C; 36° to 46° F).

Manufactured for:

Elanco Animal Health

A division of Eli Lilly and Company

Indianapolis, IN 46285, USA

Product of the U.K.

NADA 141-392.

Approved by FDA

AH0955

Elanco™

Imrestor™

pegbovigrastim injection

pegbovigrastim para inyección

LOT:

EXP:

20 cajas con 10 jeringas de dosis única (15 mg de pegbovigrastim por jeringa)

20 cartons containing 10 single-dose syringes (15 mg pegbovigrastim per syringe)

Para inyección subcutánea en vacas lecheras periparturientas y vaquillas lecheras periparturientas de reemplazo.

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Almacene refrigerado (2° to 8°C; 36° to 46°F).

Store under refrigeration (2° to 8°C; 36° to 46°F).

Fabricado para:
Elanco Animal Health
Una división de
Eli Lilly and Company
Indianapolis, IN 46285, EE. UU.

Manufactured for:
Elanco Animal Health
A division of
Eli Lilly and Company
Indianapolis, IN 46285, USA

Producto del Reino Unido.

Product of the U.K.

NADA 141-392.
Aprobado por la FDA

NADA 141-392.
Approved by FDA

YL088964AMA

Principal Display Panel - 15 mg Carton Label

Elanco™

Imrestor™

pegbovigrastim injection

Principal Display Panel - 15 mg Syringe Label

***Elanco™* AHO0955**

Imrestor™

pegbovigrastim injection

15 mg pegbovigrastim per
2.7 mL single dose syringe

For subcutaneous injection in periparturient dairy cows
and periparturient replacement dairy heifers.

Manufactured for Elanco Animal Health

A Division of Eli Lilly and Company, Indianapolis, IN 46285

Product of the U.K.

Lot Number: Expiration Date:

BGD90450

pegbovigrastim injection

15 mg pegbovigrastim per
2.7 mL single dose syringe

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Manufactured for Elanco Animal Health
A Division of Eli Lilly and Company, Indianapolis, IN 46285

Product of the U.K.

Lot Number: Expiration Date:

YL088964AMX

Principal Display Panel - 15 mg Box Label

Elanco™

Imrestor™

pegbovigrastim injection

4 cartons containing
50 single-dose syringes (15 mg pegbovigrastim per syringe)

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Store under refrigeration (2° to 8°C; 36° to 46° F).

Manufactured for:

Elanco Animal Health

A division of Eli Lilly and Company

Indianapolis, IN 46285, USA

Product of the U.K.

NADA 141-392.

Approved by FDA

AH0955

Elanco™

Imrestor™

pegbovigrastim injection

pegbovigrastim para inyección

LOT:

EXP:

4 cajas con 50 jeringas de dosis única (15 mg de pegbovigrastim por jeringa)

4 cartons containing 50 single-dose syringes (15 mg pegbovigrastim per syringe)

Para inyección subcutánea en vacas lecheras periparturientas y vaquillas lecheras periparturientas de reemplazo.

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Almacene refrigerado (2° to 8°C; 36° to 46°F).

Store under refrigeration (2° to 8°C; 36° to 46°F).

Fabricado para:
Elanco Animal Health
Una división de
Eli Lilly and Company
Indianapolis, IN 46285, EE. UU.

Manufactured for:
Elanco Animal Health
A division of
Eli Lilly and Company
Indianapolis, IN 46285, USA

Producto del Reino Unido.

Product of the U.K.

NADA 141-392.
Aprobado por la FDA

NADA 141-392.
Approved by FDA

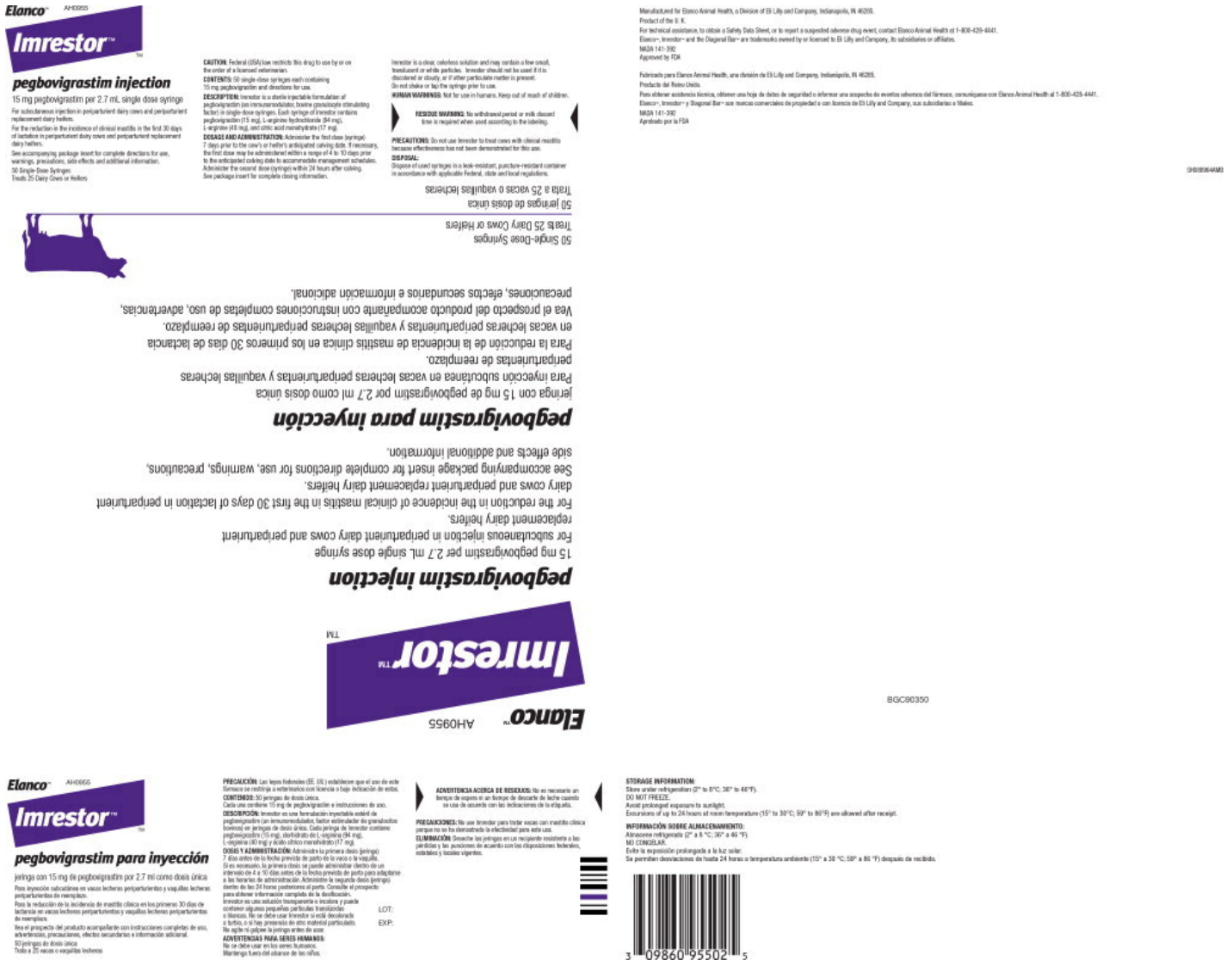
YL088964AMB

Principal Display Panel - 15 mg Carton Label

Elanco™

Imrestor™

pegbovigrastim injection



Principal Display Panel - 15 mg Syringe Label

***Elanco*™ AHO0955**

***Imrestor*™**

pegbovigrastim injection

15 mg pegbovigrastim per
2.7 mL single dose syringe

For subcutaneous injection in periparturient dairy cows
and periparturient replacement dairy heifers.

Manufactured for Elanco Animal Health

A Division of Eli Lilly and Company, Indianapolis, IN 46285

Product of the U.K.

Lot Number: Expiration Date:

Principal Display Panel - 15 mg Box Label

Elanco™

Imrestor™

pegbovigrastim injection

2 cartons containing
100 single-dose syringes (15 mg pegbovigrastim per syringe)

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Store under refrigeration (2° to 8°C; 36° to 46° F).

Manufactured for:

Elanco Animal Health

A division of Eli Lilly and Company

Indianapolis, IN 46285, USA

Product of the U.K.

NADA 141-392.

Approved by FDA

AH0955

Elanco™

Imrestor™

pegbovigrastim injection

pegbovigrastim para inyección

LOT:

EXP:

2 cajas con 100 jeringas de dosis única (15 mg de pegbovigrastim por jeringa)

2 cartons containing 100 single-dose syringes (15 mg pegbovigrastim per syringe)

Para inyección subcutánea en vacas lecheras periparturientas y vaquillas lecheras periparturientas de reemplazo.

For subcutaneous injection in periparturient dairy cows and periparturient replacement dairy heifers.

Almacene refrigerado (2° to 8°C; 36° to 46°F).

Store under refrigeration (2° to 8°C; 36° to 46°F).

Fabricado para:
Elanco Animal Health
Una división de
Eli Lilly and Company
Indianapolis, IN 46285, EE. UU.

Manufactured for:
Elanco Animal Health
A division of
Eli Lilly and Company
Indianapolis, IN 46285, USA

Producto del Reino Unido.

Product of the U.K.

NADA 141-392.
Aprobado por la FDA

NADA 141-392.
Approved by FDA

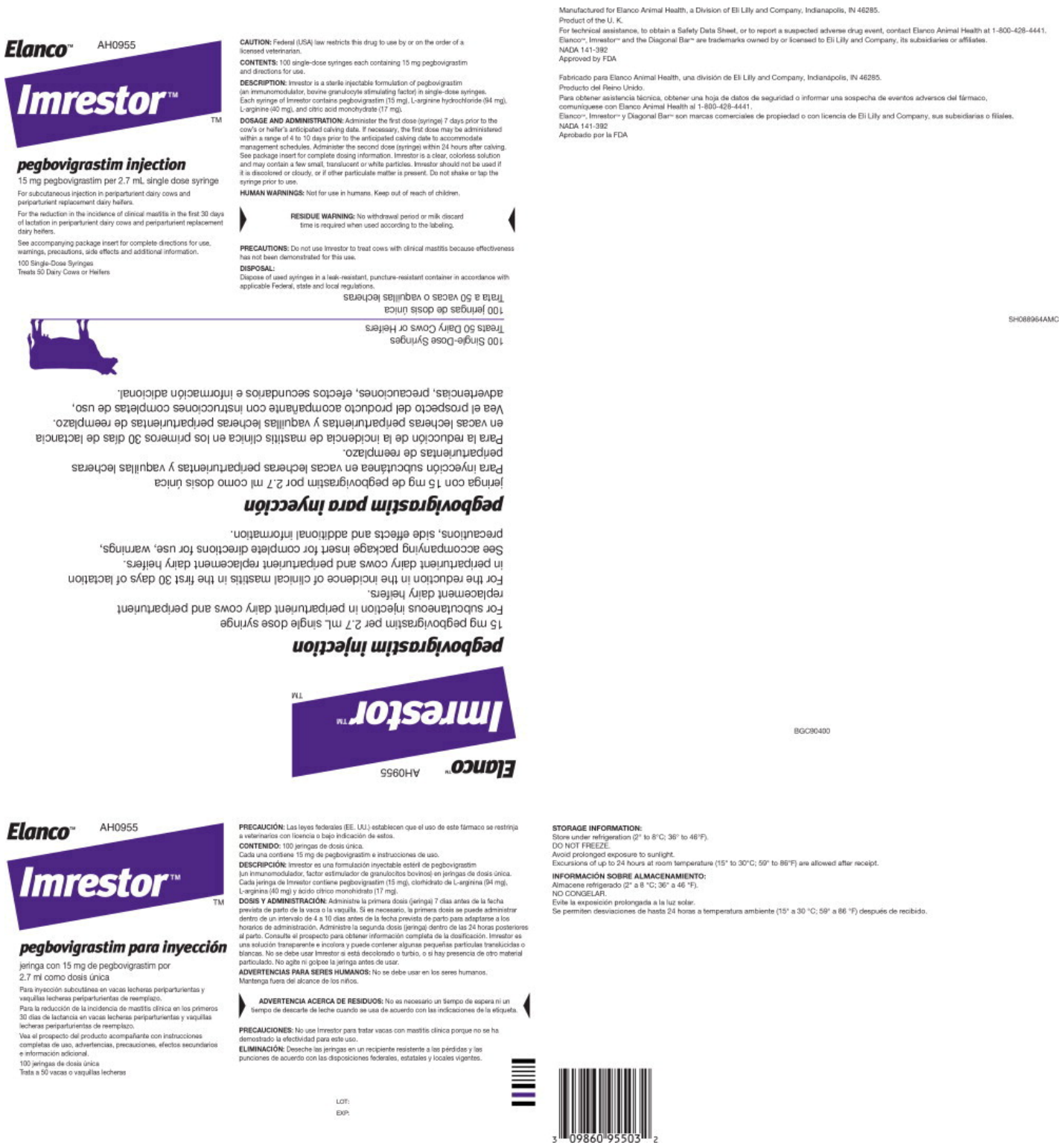
YL088964AMC

Principal Display Panel - 15 mg Carton Label

Elanco™

Imrestor™

pegbovigrastim injection



Principal Display Panel - 15 mg Syringe Label

***Elanco*™ AHO0955**

***Imrestor*™**

pegbovigrastim injection

15 mg pegbovigrastim per
2.7 mL single dose syringe

For subcutaneous injection in periparturient dairy cows
and periparturient replacement dairy heifers.

Manufactured for Elanco Animal Health

A Division of Eli Lilly and Company, Indianapolis, IN 46285

Product of the U.K.

Lot Number: Expiration Date:

IMRESTOR

pegbovigrastim suspension

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:0986-0955
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
pegbovigrastim (UNII: 87M3B1263R) (pegbovigrastim - UNII:87M3B1263R)	pegbovigrastim	15 mg

Inactive Ingredients

Ingredient Name	Strength
citric acid monohydrate (UNII: 2968PHW8QP)	
arginine hydrochloride (UNII: F7LTH1E20Y)	
arginine (UNII: 94ZLA3W45F)	
water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0986-0955-04	20 in 1 BOX		
1		10 in 1 CARTON		
2	NDC:0986-0955-05	4 in 1 BOX		
2		50 in 1 CARTON		
3	NDC:0986-0955-02	2 in 1 BOX		
3		100 in 1 CARTON		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141392	03/11/2016	

Labeler - Elanco Animal Health (807447169)

Establishment

Name	Address	ID/FEI	Business Operations
Elanco Animal Health, a Division of Eli Lilly and Company		155529378	API MANUFACTURE

Establishment

Name	Address	ID/FEI	Business Operations
Eli Lilly and Company Limited		230761368	API MANUFACTURE

Establishment

Name	Address	ID/FEI	Business Operations
Patheon UK Limited		237710418	MANUFACTURE

Establishment

Name	Address	ID/FEI	Business Operations
Catalent		370696762	ANALYSIS, LABEL, MANUFACTURE, PACK