FOR IMMEDIATE RELEASE

Elanco Animal Health Announces U.S. Food and Drug Administration (FDA) Approval of Imrestor™ (pegbovigrastim injection)

Greenfield, Ind. (March 17, 2016) — Today, Elanco Animal Health, a division of Eli Lilly and Company (NYSE: LLY), announced the approval of Imrestor™ (pegbovigrastim injection) – the first product of its kind for the dairy industry.

Available only by veterinary prescription, Imrestor is now FDA approved 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. Imrestor is a protein that helps support the natural function of a dairy cow’s immune system during the critical time around calving, when she is most vulnerable to mastitis.

“Imrestor is an innovative new approach for reducing clinical mastitis by proactively helping to restore the function of a cow’s immune system,” explained Paul Rapnicki, DVM, MBA, Associate Technical Advisor, Elanco Animal Health.

Pivotal efficacy studies conducted for FDA approval showed a 28 percent reduction in clinical mastitis incidence among cows and heifers that received Imrestor compared with control animals.\(^1\) Mastitis is the most common disease among dairy cows, affecting as many as 1 in 4 cows.\(^2\) Clinical mastitis affects each cow’s potential leading to reduced conception rates\(^3\), an increased risk for another case of mastitis\(^4\), and lost milk production potential throughout the lactation\(^5\).

Dairy Cows Experience Immune Suppression At Calving

Immune suppression at calving can leave cows vulnerable to infection and an increased risk of mastitis.\(^6\) Dairy cows and heifers are in need of protection particularly at calving due to a decline in neutrophils – the primary type of white blood cell that recognizes and destroys harmful bacteria. Imrestor helps restore the function\(^7\) and increase the number\(^1,7\) of neutrophils at calving which helps the cow to fight invading bacteria that cause mastitis.

“We know that even the best producers need a little help protecting their dairy herds. Imrestor is a proactive approach that can help keep cows healthy and help reduce the frustration, financial strain and stress associated with treating mastitis,” added Rapnicki.
Elanco shared news of the Imrestor approval today during a U.S. Department of Agriculture (USDA) meeting where antibiotic alternatives for use in food animals were discussed. Mastitis is the most common illness treated with antimicrobials in dairy cows.

The launch of Imrestor is aligned with Elanco’s eight-point antibiotic stewardship plan that ensures the responsible use of antibiotics, reduces shared-class antibiotic use and replaces antibiotics with alternatives. The plan was outlined by Elanco President Jeff Simmons at a White House antibiotic stewardship forum last year.

Available in pre-filled, single-dose syringes, Imrestor is administered with two injections – one seven days prior to the anticipated date of calving and the other within 24 hours after calving – thus helping to protect the cow against mastitis when she needs it most.

Imrestor does not require a meat or milk withdrawal period. Imrestor will be available for purchase in 10, 50, and 100 dose pack sizes. The product availability date will be announced at a later time. Dairy producers are encouraged to contact their veterinarian to discuss incorporating Imrestor into their herd health program.

**IMPORTANT SAFETY INFORMATION**
Not for use in humans. Keep out of reach of children. 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. No withdrawal period or milk discard time is required when used according to the labeling. Do not use Imrestor to treat cows with clinical mastitis because effectiveness has not been demonstrated for this use. 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. These reactions resolve within hours of onset with or without therapeutic intervention and have not been shown to reoccur with subsequent injections of Imrestor. For complete safety information, see product label attached.

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*The clinical significance of this data has not been demonstrated

**4-10 days to accommodate management schedules

**ABOUT ELANCO**
Elanco provides comprehensive products and knowledge services to improve animal health and food-animal production in more than 70 countries around the world. We value innovation, both in scientific research and daily operations, and strive to cultivate a collaborative work environment for more than 6,500 employees worldwide. Together with our customers, we are committed to raising awareness about global food security, and celebrating and supporting the human-animal bond. Founded in 1954, Elanco is a division of Eli Lilly and Company. Our worldwide headquarters and research facilities are located in Greenfield, Indiana. Visit us at Elanco.com.
1 Elanco Animal Health, Data on File.


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© 2016 Eli Lilly and Company, its subsidiaries or affiliates. USDBURS00026
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: ImrHor is a sterile injectable formulation of pegbovigrastim (an immunomodulator, bovine granulocyte stimulating factor) in single-dose syringes. Each syringe of ImrHor 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, ImrHor should be visually inspected for particulate matter and discoloration. ImrHor is a clear, colorless solution and may contain a few small, translucent or white particles. ImrHor 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: Do not withdraw period or milk discard time is required when used according to the labeling.


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 anaphylactiic-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 ImrHor 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 ImrHor. 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 ImrHor. 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 ImrHor 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 dairy heifers and cows were enrolled and treated with ImrHor 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 ImrHor 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 ImrHor-treated group (failure rate: 60/331 = 18.13%) compared to the saline-treated group (failure rate: 85/338 = 25.19%).

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 ImrHor 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 bodyweight, 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 ImrHor. No test article related hematologic 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 ImrHor 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 mucoa 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 ImrHor 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.

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Los animales que desarrollaron mastitis clínica (usando las evaluaciones de los cuartiles salud, calidad de la leche y Prueba de Mastitis de California (California Mastitis Test, CMT)) hasta el Día 30 se clasificaron como fracasos del tratamiento. La administración de Imrestror produjo una diferencia significativa desde el punto de vista estadístico ($p = 0.005$) en la incidencia de mastitis clínica (fase de fracaso del tratamiento) en los cinco centros con una diferencia a favor del grupo tratado con Imrestror (fase de fracaso: 60/331 = 18.13 %) en comparación con el grupo tratado con solución salina (fase de fracaso: 85/338 = 25.15 %).

**SEGURIDAD ANIMAL OBJETIVO:**

**Margen de seguridad:** En el primer estudio, se asignaron cuatro vacas Jersin primigenia y mulipar a uno de cuatro tratamientos: control con solución salina y 1, 2 o 3 veces la dosis prevista de Imrestror administrada los Días 7 - 13. Los animales se mantuvieron durante 14 días después del parto. Los animales que presentaron mastitis fueron considerados como positivos. Las vacas que recibieron soluciones salina, poso corporal, alimentación, leche, recuentes de células somáticas, exámenes físicos y patología clínica. Se llevó a cabo una autopsia completa en cada animal. El examen de las vacas mostró que todos los animales tenían mastitis, independientemente del grupo de dosis. Se consideró como un cambio relacionado con el uso de la prueba asociada con observaciones clínicas anormales, consumo de alimentos, producción de leche, exámenes físicos o análisis de orina en animales adultos. Se observó una neumofilia y en todos los animales tratados, independientemente del grupo de dosis. En este estudio se evaluó el margen de seguridad de Imrestror en vacas lecheras Holstein multiparas. Se asignaron cuatro vacas lecheras Holstein multiparas a uno de cinco tratamientos: control con solución salina y 1, 2, 2,5 y 3 veces la dosis recomendada de una jeringa de pegbivostim administrada por vía subcutánea el Día 1, y luego a la fecha prevista de parto. Los animales fueron desmamados dentro de la primera semana del parto. Se monitorizaron las vacas a diario hasta 14 días después del parto. Las mediciones incluyeron poso corporal, consumo de alimentos, producción de leche, recuentes de células somáticas, exámenes físicos y patología clínica. El recuento de retículo a los 4 días, y la prueba de sangre oculta en heces. Se llevó a cabo una autopsia en cada vaca que se controló en el tracto gastrointestinal, el útero y el tejido mamario. No se encontraron hallazgos relacionados con el uso de la prueba asociados con observaciones clínicas anormales, consumo de alimentos, producción de leche o exámenes físicos. Se observó una neumofilia en todos los animales, que fue considerado por el mecanismo de acción de Imrestror y fue similar a lo que se observó en el primer margen del estudio de seguridad. Los animales tratados tenían una mayor cantidad de erosiones gastrointestinales leves y áreas pequeñas de mucosa enzimática o más deglata en varias porciones del tracto gastrointestinal, en comparación con los animales de control. En la necropsia no se observaron úlceras abombadas. A partir de estos estudios, se concluyó que las úlceras o erosiones abombadas podrían estar relacionadas con el uso de la prueba. Sin embargo, debido a la falta de signos clínicos asociados con esta patología gastrointestinal junto con la naturaleza leve de las erosiones en el segundo estudio, se concluyó que estos hallazgos no eran clínicamente relevantes.

**Seguridad en el lugar de la inyección:** Se evaluó la seguridad en el lugar de la inyección de Imrestror en vacas lecheras periparturientes salubres. Los resultados del estudio de tolerancia en el lugar de la inyección mostraron que las inyecciones subcutáneas de pegbivostim administradas 14 días antes del sacrificio en vacas que no necesitaban la inyección, no requerían un tiempo de resolución más largo que el requerido para que las úlceras se recuperaran en el momento del sacrificio. Además, las inyecciones subcutáneas de pegbivostim administradas aproximadamente 12 horas antes del sacrificio en vacas provocaron reacciones agudas mínimas en el tejido local, por lo general caracterizadas por edema y hemorragia, y se eliminaron junto con el cuento en el momento del sacrificio sin provocar ningún recorte de la res muerta.

**Seguridad para la reproducción:** También se evaluó la seguridad para la reproducción en los animales que estaban en el estudio de efectividad. Este estudio incluyó 801 animales: 401 animales de control y 400 animales tratados. Las variables que se midieron incluyeron observaciones de salud diarias en vacas y toros, mortalidad, duración de la gestación, porcentajes de nacimientos vivos con el primer nacimiento y los cuidados de reproducción después del tratamiento. No hubo diferencias significativas desde el punto de vista estadístico entre los animales tratados y los animales de control para estas variables reproductivas.

**INFORMACIÓN SOBRE ALMACENAMIENTO:** Almacene refrigerado (2 °C a 8 °C, 36 °F a 46 °F). NO CONGELAR. Evite la exposición prolongada a la luz solar. Se permiten desvases de hasta 24 horas a temperatura ambiental (15 °C a 30 °C, 59 °F a 86 °F) después de recibir.

**PRESENTACIÓN:** Paquetes de 10, 50 o 100 jeringas de dosis única. Cada jeringa contiene 15 mg de pegbivostim.

NADA 141-392, Aprobado por la FDA.

Fabricado para Elanco Animal Health, a división de Eli Lilly and Company, Indianapolis, IN 46285.

Para obtener asistencia técnica o informar una sospecha de eventos adversos del producto, comuníquese con Elanco Animal Health al 1-800-428-4441.

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