Canine anti-nerve growth factor monoclonal antibody for subcutaneous use in dogs only.

Single-Use Vial

CAUTION

Federal law restricts this product to use by or on the order of a licensed veterinarian.

DESCRIPTION

LIBRELA (bedinvetmab injection) is a sterile injectable solution containing 5, 10, 15, 20, or 30 mg/mL of bedinvetmab in 20 mM histidine buffer pH 5.0 (0.0227% w/v L-histidine and 0.382% w/v histidine HCl monohydrate), 8.5% w/v trehalose dihydrate, 0.005% w/v disodium EDTA dihydrate, 0.01% w/v L-methionine, and 0.1% w/v poloxamer 188). Bedinvetmab is a canine IgG monoclonal antibody (mAb), in which the variable regions from canine B cell sequence were joined with canine IgG constant sequences, and is expressed through recombinant DNA techniques in Chinese hamster ovary (CHO) cells. Bedinvetmab binds to nerve growth factor (NGF) to reduce NGF’s effects. Such mAbs are commonly referred to as anti-NGF mAbs.

INDICATION

LIBRELA is indicated for the control of pain associated with osteoarthritis in dogs.

DOSE AND ADMINISTRATION

The minimum target dose of LIBRELA is 0.23 mg/kg (0.5 mg/kg) body weight, administered subcutaneously once a month. Dogs should be dosed by weight range according to the specific dosing information below.

The product does not contain a preservative. The full content of each vial is for single-use only. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

Dogs weighing > 11 lb (5 kg):

Dogs should be dosed by weight range according to the Dosing Table below (Table 1). Dogs are given the full content of 1 or 2 vials of the appropriate concentration based on body weight. Aseptically withdraw the total dose into a single syringe and administer immediately.

Table 1. Dosing Table

<table>
<thead>
<tr>
<th>Body Weight (lb)</th>
<th>Number and Strength (mg/mL) of LIBRELA Vials to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-22.1</td>
<td>5 mg/mL orange 1 vial</td>
</tr>
<tr>
<td>20-38.1</td>
<td>10 mg/mL blue 1 vial</td>
</tr>
<tr>
<td>30-50</td>
<td>15 mg/mL green 1 vial</td>
</tr>
<tr>
<td>50</td>
<td>20 mg/mL orange 2 vials</td>
</tr>
<tr>
<td>60</td>
<td>30 mg/mL purple 1 vial</td>
</tr>
</tbody>
</table>

Dogs < 11 lb:

Aseptically withdraw 0.045 mL/lb (0.1 mL/kg) from a 5 mg/mL vial (orange vial) into a single syringe and administer immediately. Discard the dose after it has been withdrawn.

Effectiveness may not be achieved until after the second dose (see EFFECTIVENESS).

CONTRAINDICATIONS

LIBRELA should not be administered to dogs with known hypersensitivity to bedinvetmab.

LIBRELA should not be used in breeding dogs or in pregnant or lactating dogs. Immunoglobulin G class antibodies such as LIBRELA can pass through the placental blood barrier and be excreted in milk. Fetal abnormalities, increased rates of stillbirths and increased postpartum fetal mortality were noted in rodents and primates receiving anti-NGF monoclonal antibodies.

WARNINGS

User Safety Warnings

Not for use in humans. Keep this and all drugs out of reach of children. For use in dogs only.

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet, vial or carton to the physician.

Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.

The importance of Nerve Growth Factor in ensuring normal fetal nervous system development is well-established and laboratory studies conducted on nonhuman primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity.

PRECAUTIONS

Administration of monoclonal antibodies may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

The safe use of this product with other monoclonal antibodies has not been evaluated. Use with caution in dogs with known hypersensitivity to other immunoglobulin therapy.

Bedinvetmab has been reported in a small number of patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF monoclonal antibody. RPOA has not been characterized or reported in dogs.

The safety and effectiveness of LIBRELA has not been evaluated in dogs less than 12 months of age.

LIBRELA has not been studied in dogs that have a history of cruciate ligament rupture within six months before initial product use as these cases were excluded from the field studies.

Long term effects which may occur more than 9 months after the use of LIBRELA have not been evaluated.

Primates receiving high doses of anti-NGF monoclonal antibodies had anatomical changes in postganglionic cell bodies (reduced size and number of neurons). The change in cell body size returned to normal after anti-NGF monoclonal antibody administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of LIBRELA in young growing dogs.

ADVERSE REACTIONS

The safety of LIBRELA was assessed in a masked, controlled 84-day European field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 272 dogs, 135 dogs treated with LIBRELA and 137 treated dogs with a negative control (sterile saline). The enrolled dogs were at least 1 year of age to 17 years old, weighed between 1.8 to 62.7 kg and were of various breeds and non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 2 below.

Table 2. Number (%) of Dogs with Adverse Reactions Reported in the US Field Study

<table>
<thead>
<tr>
<th>Adverse Reaction*</th>
<th>LIBRELA</th>
<th>Negative Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Total N = 135)</td>
<td>(Total N = 137)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (3.7)</td>
<td>11 (8.0)</td>
</tr>
<tr>
<td>Bacterial skin infection</td>
<td>11 (8.1)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>8 (5.9)</td>
<td>8 (5.8)</td>
</tr>
<tr>
<td>Dermat mass</td>
<td>5 (3.7)</td>
<td>5 (3.7)</td>
</tr>
<tr>
<td>Erythema</td>
<td>6 (4.4)</td>
<td>5 (3.6)</td>
</tr>
<tr>
<td>Dental cyst(s)</td>
<td>4 (3.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Pain on injection</td>
<td>4 (3.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Inappropriate urination**</td>
<td>4 (3.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>4 (3.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Two dogs treated with LIBRELA suffered serious adverse events and were euthanized during or after study completion: A 13-year-old Bichon Frise had pre-existing increased urine protein-creatinine ratio and heart failure that worsened during study; the dog also had an increase in creatinine during the study. The dog was diagnosed with renal failure and was euthanized 3 days after completing the study. An 8-year-old mixed breed dog had pancreatitis and was euthanized on Day 74. The remainder of the dogs that had elevations in the BUN did not have any obvious adverse events associated with this finding.

One dog in the LIBRELA group was diagnosed with pyelonephritis on Day 15; this dog had pre-existing decreased serum BUN and creatinine and a recent history of urinary tract infection that was not confirmed prior to enrollment. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were initiated on Day 7 for osteoartthritis-associated joint pain but NSAIDs were discontinued on Day 10 due to anorexia and gastrointestinal/azotemia worsened at Day 13 and the dog received no further LIBRELA treatment.

One dog in the LIBRELA group with a history of atopy, developed mild alopecia and mild erythema on the injection site on Days 5 and 23. Both episodes of alopecia and erythema resolved with treatment. A total of 89 dogs were enrolled in a 6-month, single arm, open labeled, uncontrolled continuation of the EU field study and received monthly subcutaneous injections of LIBRELA. The study provided additional field safety information.

One dog experienced acute gastroenteritis and recovered following treatment for abdominal pain, fever, vomiting, and anorexia. One large breed dog enrolled for stifle osteoarthritis developed acute forelimb lameness that was diagnosed as elbow dysplasia. Two dogs presented with rear limb paresis of unknown etiology, one of whom responded to ongoing NSAID treatment and one who did not.

CONTACT INFORMATION

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Zoetis Inc. at 1-888-963-8471.

For additional information about reporting adverse drug experience for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalmeds.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bedinvetmab is a recombinant canine monoclonal antibody that binds to nerve growth factor (NGF), reduces NGF binding to the tropomyosin receptor kinase A (TrkA) and p75 neurotrophin receptor (p75NTR) receptors and decreases TrkA signal transduction in cell types involved in pain. In vitro studies suggest that bedinvetmab binds with high affinity to NGF but does not bind to other neurotrophins such as human neurotrophin-3 (NT-3), canine and human NT-4, and human brain-derived neurotrophic factor (BDNF).

NGF has been found to be elevated in the osteoarthritic joints of dogs. Following a noxious stimulus, inflammatory cytokines and NGF are released by tissues of the joint.

NGF binds to TrkA/p75NTR receptors found on peripheral nerves, immune cells, endothelial cells, synovocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception. Bedinvetmab binds to NGF and prevents NGF/TrkA/p75NTR cellular signaling. In in vitro studies, bedinvetmab potently inhibits NGF-mediated signaling as measured by a reduction in TF-1 cell proliferation and functionally blocks NGF-induced neurite outgrowth in rat PC-12 neuronal cells.

NGF binds to TrkA receptors located on immune cells to elicit the release of additional proinflammatory mediators, including NGF itself. These inflammatory mediators lead to further peripheral sensitization involved in pain perception. Bedinvetmab reduces the expression of these inflammatory mediators in rat PC-12 neuronal cells.
**Pharmacokinetics**

In a 6-month laboratory study of healthy, adult Beagles administered LIBRELA at monthly doses ranging from 1-10 mg/kg, the area under the curve (AUC) and the maximum concentration ($C_{max}$) increased nearly in proportion to dose and steady-state was achieved after approximately 2 doses. In a laboratory study to determine immunogenicity, the antibody titre was below the limit of quantitation for all dogs. Serum fibrinogen level. At one of the injection administrations, one dog administered a 4 mg/kg dose had a 4 cm firm erythematous lesion with slight serosanguinous discharge and mild scabs of the shaved cervical area that resolved over 4 days.

**TARGET ANIMAL SAFETY**

6 Month Margin of Safety Study: LIBRELA (bedinvetmab injection) 15 mg/mL and 30 mg/mL concentrations were administered subcutaneously to 11 to 12-month old, healthy Beagles (8 dogs per group) at doses of 1 mg/kg (1X), 3 mg/kg (3X), and 10 mg/kg (10X) every 28 days for seven consecutive doses. The control group (8 dogs) received sterile saline injections. Dogs weighed 5.6-11.7 kg at study initiation.

There were no clinically significant changes noted in neurological examinations, body temperature, heart rate and respiratory rate, blood pressure, electrocardiography, and organ weights. Detailed pathology evaluation revealed no abnormalities of the shoulder, elbow, hip, and knee joints were conducted.

Vomiting and soft stool were noted across all groups throughout the study. Scabbing on the face, neck and thorax was seen across all groups except the 1 mg/kg group. Injection site redness was noted for all groups, except the control group.

**ATTENTION**

The presence of ADA was confirmed in 2 dogs after treatment with LIBRELA (1 dog on Study Visit Day 28). Of the 138 LIBRELA-treated dogs, the presence of ADA was confirmed in 2 dogs after treatment with placebo on (Study Visit Day 56). Of the 138 LIBRELA-treated dogs, the presence of ADA was confirmed in 2 dogs after treatment with LIBRELA (1 dog on Study Visit Day Day 28). Of the 138 LIBRELA-treated dogs, the presence of ADA was confirmed in 2 dogs after treatment with placebo on (Study Visit Day 56). Of the 138 LIBRELA-treated dogs, the presence of ADA was confirmed in 2 dogs after treatment with placebo on (Study Visit Day 56).

**US Field Effectiveness Study**

An 84-day masked, randomized, controlled field study was conducted at 24 US veterinary clinics. The study enrolled 272 client-owned dogs with clinical signs of osteoarthritis confirmed by radiography and orthopedic examination. Enrolled dogs were randomized at an equal ratio into one of two treatment groups: LIBRELA (0.5 mg/kg, n = 137) and LANTUM (0.28 mg/kg, n = 137) treated dogs were characterized by pain and mobility deficits in the shoulder, elbow, hip, and knee joints were conducted. This field study did not provide sufficient data to support a conclusion on the safety of concurrent use of LIBRELA and NSAIDs.

In a 3-month exploratory laboratory safety study using a non-final formulation of bedinvetmab administered by subcutaneous injection monthly for four doses, a dog administered a 4 mg/kg dose had a reddened and/or swollen muzzle abrasion, with an elevated white blood cell count, and elevated globulin level and fibrinogen level. One of the injection administrations, one dog administered a 4 mg/kg dose had a 4 cm 2 cm injection site erythema with an eschar that resolved over 5 days.

**STORAGE CONDITIONS**

LIBRELA (bedinvetmab injection) should be stored in a refrigerator, 2° – 8°C (36° – 46°F). Do not freeze. Store vials in their boxes to protect from prolonged exposure to light. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

**HOW SUPPLIED**

LIBRELA is available in 5 strengths packaged in 4 mL glass vials containing an extractable volume of 1 mL of clear solution. Each strength is available in cartons containing 2 or 6 vials.

**REFERENCES**
