Solensia™
(frunevetmab injection)

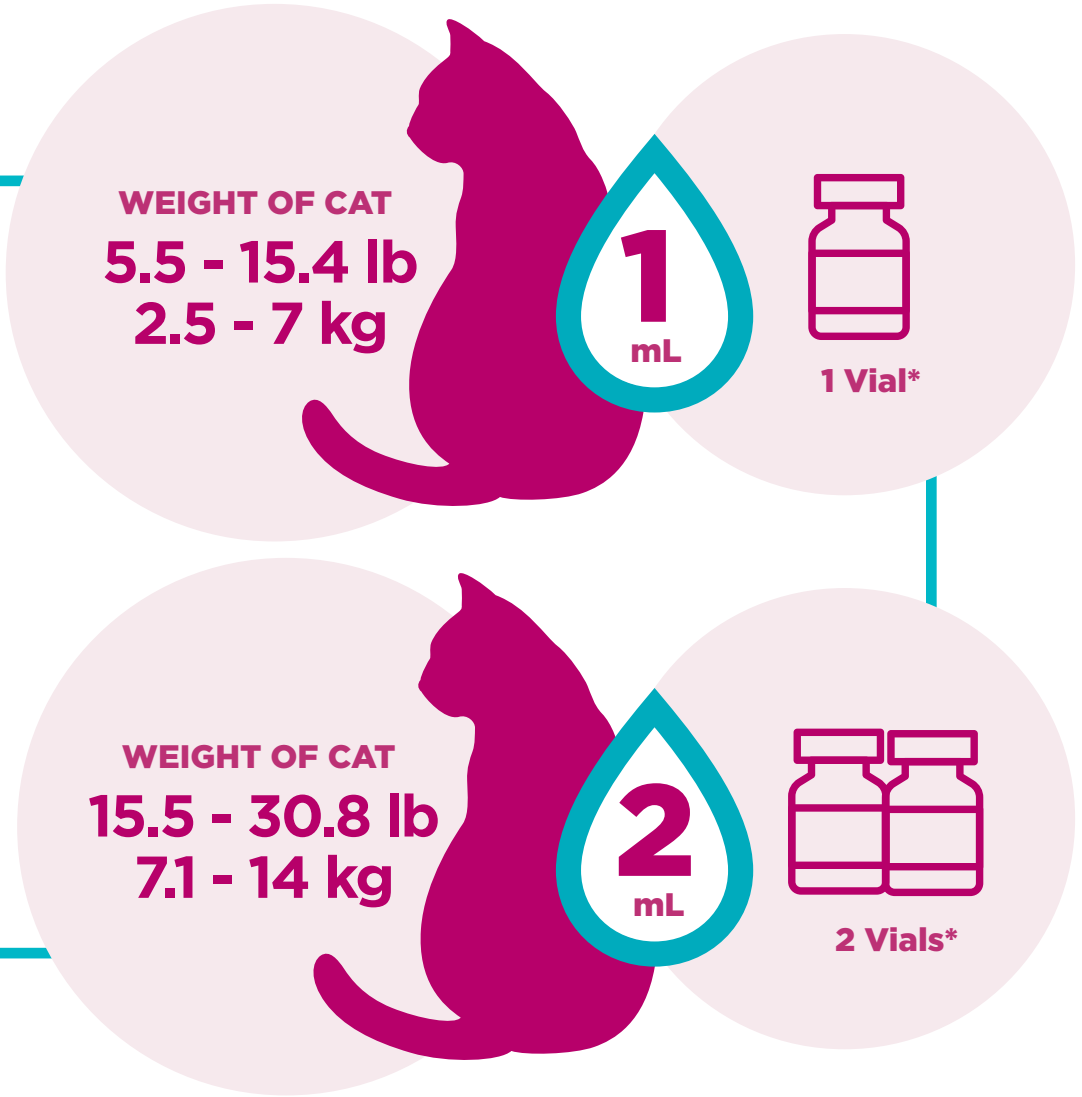
Concentration:
7 mg/mL of frunevetmab

Dose:
0.45 mg/lb (1 mg/kg) body weight

Dosing frequency:
1 month

Administration:
Subcutaneous injection

Storage:
Solensia should be stored in a refrigerator, between 35° to 46°F (2° to 8°C).
Do not freeze.



*1 mL frunevetmab injection per vial.

IMPORTANT SAFETY INFORMATION:
For use in cats only. Women who are pregnant, trying to conceive or breastfeeding should take extreme care to avoid self-injection. Hypersensitivity reactions, including anaphylaxis, could potentially occur with self-injection. Solensia should not be used in breeding cats or in pregnant or lactating queens. Solensia should not be administered to cats with known hypersensitivity to frunevetmab. The most common adverse events reported in a clinical study were vomiting and injection site pain. See full Prescribing Information.

zoetis

Solensia™
(frunevetmab injection)
7 mg/mL

Feline anti-nerve growth factor monoclonal antibody for subcutaneous injection in cats only.

Single-Use Vial

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

DESCRIPTION
SOLENSIA (frunevetmab injection) is a sterile injectable solution containing 7mg/mL of frunevetmab in histidine buffer (10 mM L-histidine monohydrochloride, 5% D-sorbitol, 0.01%polysorbate 20, adjusted to pH 6.0 by HCl/NaOH, quantity sufficient to 1 mL by Water for Injection.). Frunevetmab is a felinized immunoglobulin G monoclonal antibody (mAb), a murine antibody in which all regions of the mouse antibody are replaced with feline counterparts except for the complementarity-determining regions. Frunevetmab binds to nerve growth factor (NGF) to block NGF's effects. Such mAbs are commonly referred to as anti-NGF mAbs.

INDICATION
SOLENSIA is indicated for the control of pain associated with osteoarthritis in cats.

DOSAGE AND ADMINISTRATION
Cats should be dosed by weight range according to the Dosing Chart (Table 1) below. Cats are given the full content of 1 or 2 vials based on body weight to target a minimum dosage of 0.45 mg/lb. (1 mg/kg) body weight, administered subcutaneously once a month. Aseptically withdraw the total dose into a single syringe and administer immediately.

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.

Table 1. Dosing Chart

Weight of Cat (lb.)	Weight of Cat (kg)	Volume	Number of Vials*
5.5-15.4	2.5-7 kg	1 mL	1
15.5-30.8	7.1-14 kg	2 mL	2

*1 mL frunevetmab injection per vial

CONTRAINDICATIONS
SOLENSIA should not be administered to cats with known hypersensitivity to frunevetmab.

SOLENSIA should not be used in breeding cats or in pregnant or lactating queens because it may 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 mAbs.

WARNINGS
User SafetyWarnings
Not for use in humans. Keep out of reach of children.

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 or the label to the physician.

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

The importance of NGF 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 mAbs may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

Administration of SOLENSIA may be associated with scabbing on the head and neck, dermatitis, and pruritus; however, pre-approval data suggest that these signs do not require cessation of SOLENSIA administration (see **ADVERSE REACTIONS** and **TARGET ANIMAL SAFETY**).

Evaluations were not made to determine if interactions occurred between SOLENSIA and veterinary vaccines.

Treatment with SOLENSIA may result in the formation of anti-frunevetmab antibodies and potentially the loss of product effectiveness (see **Immunogenicity**).

The safe use of SOLENSIA with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in cats. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF mAb therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF mAb. RPOA has not been characterized or reported in cats.

SOLENSIA has not been evaluated in cats less than 7 months or 5.5 lbs.

Long term effects, which may occur more than 6 months after the use of SOLENSIA, have not been evaluated. Primates receiving high doses of anti-NGF mAbs had reduced cell size in postganglionic neuronal cell bodies. The change in cell body size returned to normal after anti-NGF mAb 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 SOLENSIA in young growing cats.

The safe use of this product with other mAbs has not been evaluated.

ADVERSE REACTIONS
The safety of SOLENSIA was evaluated in a masked, controlled 112-day field study to evaluate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Enrollment included 275 cats weighing 2.5-to 11.4 kg and 1.6-to 22.4 years old; 182 cats were treated with SOLENSIA and 93 cats were administered a vehicle control. Cats were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the field study are presented below.

Table 2. Adverse Reactions Reported in the Field Study[1]

Adverse Reaction	Solensia N=182 (%)	Vehicle Control N=93 (%)
Vomiting	24 (13.2%)	10 (10.8%)
Injection site pain[2]	20 (10.9%)	13 (14%)
Diarrhea	12 (6.6%)	5 (5.4%)
Abnormal behavior and behavioral disorders[3]	12 (6.6%)[4]	5 (5.4%)[5]
Renal insufficiency[6]	12 (6.6%)	4 (4.3%)
Anorexia	12 (6.6%)	4 (4.3%)
Lethargy	11 (6.0%)	3 (3.2%)
Dermatitis	11 (6.0%)	1 (1.1%)
Alopecia	10 (5.5%)	2 (2.2%)
Dehydration	8 (4.4%)	0 (0.0%)
Lameness[7]	8 (4.4%)	2 (2.2%)
Pruritus	7 (3.8%)	0 (0.0%)
Weight loss	6 (3.3%)	5 (5.4%)
Scabbing on head/neck	6 (3.3%)	1 (1.1%)
Gingival disorder	5 (2.7%)	0 (0.0%)
Bacterial skin infection	4 (2.2%)	1 (1.1%)
Otitis externa	4 (2.2%)	0 (0.0%)

[1] If a cat experienced the same event more than once, only the first occurrence is reported
[2] The control product was the vehicle without active ingredient
[3] Behavior abnormal for the individual cat
[4] Individual cats had at least one of the following behavior changes: anxiety (1), hiding (1), hypersomnia (1), inappropriate urination (5), sleeping with owner (1), vocalization (3), increased aggressive behavior (1)
[5] Individual cats had at least one of the following behavior changes: anxiety (2), disorientation (1), inappropriate urination (2), and vocalization (1)
[6] Worsening of existing disease
[7] New lameness or worsening of previous lameness

The safety of SOLENSIA was also evaluated in a masked, controlled 56-day exploratory field study to evaluate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Enrollment included 126 cats; 85 cats were treated with frunevetmab injection manufactured similar to SOLENSIA and 41 cats were administered a vehicle control. Cats were dosed at 28-day intervals and received up to two injections. The most frequently reported adverse reactions were digestive tract disorders, including vomiting and diarrhea, and skin disorders, including dermatitis/eczema and alopecia that were mostly attributed to irritation by an activity monitor collar required for the study.

Immunogenicity
All therapeutic proteins, including monoclonal antibodies, have the potential for immunogenicity, including the production of antibodies that bind to the therapeutic protein and may decrease effectiveness. Such host-derived antibodies are termed anti-drug antibodies (ADA). SOLENSIA, therefore has the potential to cause the cat to produce ADAs against frunevetmab.

The presence of binding antibodies to frunevetmab in cats was assessed using a screening and confirmatory assay approach. In controlled field effectiveness studies in cats with osteoarthritis (see **EFFECTIVENESS**), four out of 259 cats that received SOLENSIA once monthly developed anti-drug antibodies (ADAs). One cat tested positive for ADAs on Days 0, 28, 56, and 84. This cat had non-detectable plasma drug concentration levels of SOLENSIA on Days 28 and 56, and was a treatment failure in the effectiveness analysis, suggesting that the ADAs may have clinical significance. No assessment for neutralizing antibodies was performed.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOLENSIA with the incidence of antibodies to other products may not be appropriate.

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 experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY
Mechanism of Action
Frunevetmab is a felinized monoclonal antibody that binds to nerve growth factor (NGF), reduces NGF binding to the tropomyosin receptor kinase A (TrkA) and $p75^{NTR}$ receptors, and decreases signal transduction in cell types involved in pain. *In vitro* binding studies suggest that frunevetmab binds with high affinity to NGF, but does not bind to other neurotrophins, including human neurotrophin-3 (NT-3), feline and human neurotrophin-4 (NT-4), and human brain-derived neurotrophic factor (BDNF).

NGF has been found to be elevated in osteoarthritic joints of multiple species. Following a noxious stimulus, inflammatory cytokines and NGF are released by tissues of the joint. NGF binds to TrkA/$p75^{NTR}$ receptors found on peripheral nerves, immune cells, endothelial cells, synoviocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception.

Frunevetmab binds to NGF and prevents NGF/TrkA/$p75^{NTR}$ cellular signaling. In *in vitro* studies, frunevetmab potently inhibits NGF-mediated signaling as measured by reducing proliferation of TF-1 cells, a human erythroleukemia cell line, 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. Frunevetmab reduces the expression of these inflammatory mediators in rat PC-12 neuronal cells.

Pharmacokinetics
In a laboratory safety study in healthy cats administered SOLENSIA (frunevetmab injection) subcutaneously once every twenty-eight days for six consecutive doses (2.8 mg/kg), area under the plasma concentration time curve from time zero to the end of the dose interval (AUC) and maximum plasma concentration (C_{max}) increased in a less than dose proportional manner. Dosing every 28 days resulted in minimal accumulation over the course of five consecutive SOLENSIA doses of 2.8 mg/kg.

Table 3. Mean ± Standard Deviation frunevetmab pharmacokinetic parameters following subcutaneous dosing to laboratory and osteoarthritic cats.

Parameter	Laboratory Cats	Osteoarthritic Cats
Dose (mg/kg)	2.8	3.0
C_{max} (µg/mL)	42.8 ± 10.4	30.2 ± 5.5
T_{max}[#] (day)	3.5 (1-7)	7.0 (3-7)
AUC (day*µg/mL)	596 ± 245	653.0 ± 132
$t_{1/2}$ (day)	9.8 ± 3.1	11.0 ± 2.5
Bioavailability (%)	Not determined	73.2 ± 14.8

[#]Median and range

In a cross-study comparison of the pharmacokinetics in healthy laboratory cats and cats with naturally occurring osteoarthritis, the median time to maximum concentration (T_{max}) was approximately 3.5 days longer in cats with osteoarthritis compared to healthy cats. C_{max} was greater in healthy cats compared to cats with osteoarthritis. Overall drug exposure (AUC) and half-life were similar between healthy cats and cats with osteoarthritis. Compared to an intravenous dose, subcutaneously-administered frunevetmab had a bioavailability of approximately 73% in cats with osteoarthritis.

In a field effectiveness study at the label dose in cats with osteoarthritis, steady-state was achieved after approximately 2 doses.

EFFECTIVENESS

Because of the limitations currently inherent in studies designed to assess chronic pain and the response to drugs intended to control chronic pain in cats, a weight of evidence approach was employed to determine if the overall evidence supported the conclusion that SOLENSIA was effective for the control of pain associated with osteoarthritis in cats. Based on current thinking, the endpoints used to evaluate the effectiveness of SOLENSIA for the control of osteoarthritic pain in cats are observer-reported measures conducted by either owners or veterinarians. When taken together, the results of the two studies described below demonstrate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Additional information related to the evaluation of these studies, including the study endpoints, is available in the Freedom of Information Summary available at https://animaldrugsatfda.fda.gov.

Field Effectiveness Study #1

A 56-day, masked, randomized, controlled field study was conducted at 14 U.S. veterinary clinics. The study enrolled 126 client-owned cats with clinical signs of osteoarthritis (OA) confirmed by radiography and orthopedic examination; enrolled cats weighed 3.3 to 10.5 kg and were over 6 months old. The enrolled cats were randomized to treatment with frunevetmab injection (n=85) manufactured similar to SOLENSIA or vehicle control (n=41), administered subcutaneously on Days 0 and 28 or intravenously on Day 0 and subcutaneously on Day 28. Cats were dosed with frunevetmab injection or vehicle control based on body weight (2.5-7 kg cats received 1 mL, 7.1-14 kg cats received 2 mL).

Outcome measures for the control of pain associated with OA included comparison of the owner's evaluation of Client Specific Outcomes Measures (CSOM) at Days 14, 28, 42, and 56 compared to baseline (Day 0, before treatment); Owner Global Assessments on Days 28 and 56; and total orthopedic pain score completed by the veterinarian at screening and on Days 28 and 56. For the CSOM, treatment success was defined as a reduction of at least 2 in the total CSOM score compared with the score at baseline. Cats that had an increase in any individual CSOM activity score (regardless of the total CSOM score) were considered treatment failures. For the Owner Global Assessment, success was defined as an owner's impression of the response to treatment as Good or Excellent (versus Fair or Poor). Success was not defined for the veterinarian-assessed total orthopedic pain score. The proportion of cats considered treatment successes based on the owner CSOM assessment and the Owner Global Assessment was greater in the frunevetmab injection group compared to the control group for all assessments. The mean total orthopedic pain score was lower in the frunevetmab injection group compared to the control group at all post-dosing assessments.

Table 4. Percent CSOM Success by Assessment Day

Study Day	Frunevetmab Injection (%)	Vehicle Control (%)
14	61.8	60.6
28	68.6	55.9
42	73.5	55.9
56	80.0	47.1

Table 5. Percent Owner Global Assessment Success by Assessment Day

Study Day	Frunevetmab Injection (%)	Vehicle Control (%)
28	63.2	26.3
56	71.1	32.4

Table 6. Mean Veterinarian-Assessed Total Orthopedic Pain Score by Assessment Day

Study Day	Frunevetmab Injection (change from baseline)	Vehicle Control (change from baseline)
Screening	31.88	32.25
28	27.08 (-4.8)	28.03 (-4.22)
56	25.69 (-6.19)	27.75 (-4.5)

Field Effectiveness Study #2

A 112-day, masked, randomized, controlled field study was conducted at 21 U.S. veterinary clinics. The study enrolled 275 client-owned cats with clinical signs of osteoarthritis (OA) confirmed by radiography and orthopedic examination; enrolled cats weighed 2.5 to 11.4 kg and were 1.6 to 22.4 years old. The enrolled cats were randomized to treatment with SOLENSIA (n=182) or vehicle control (n=93), administered subcutaneously on Days 0, 28, and 56. Cats were dosed with SOLENSIA (frunevetmab injection) or vehicle control based on body weight (2.5-7 kg cats received 1 mL, 7.1-14 kg cats received 2 mL).

The primary outcome measure for success for the control of pain associated with OA was comparison of the owner's evaluation of CSOM at Day 56 compared to baseline (Day 0, before treatment). Treatment success was defined as a reduction of at least 2 in the total CSOM score at Day 56 compared with the score at baseline. Cats that had an increase in any individual CSOM activity score (regardless of the total CSOM score) or that received rescue analgesia prior to Day 56 were considered treatment failures. Secondary outcome measures included the total CSOM score on Days 28 and 84; Owner Global Assessments on Days 28, 56, and 84; and total orthopedic pain score completed by the veterinarian on Days 28, 56, and 84. For the Owner Global Assessment, success was defined as an owner's impression of the response to treatment as Good or Excellent (versus Fair or Poor). Success was not defined for the veterinary-assessed total orthopedic pain score. The proportion of cats considered treatment successes based on the owner CSOM assessment and the Owner Global Assessment was greater in the SOLENSIA group compared to the control group for all assessments. The mean total orthopedic pain score was lower in the SOLENSIA group compared to the control group at all post-dosing assessments.

Table 7. Percent CSOM Success by Assessment Day

Study Day	Solensia (%)	Vehicle Control (%)
28	66.9	51.6
56	75.1	64.8
84	76.5	67.3

Table 8. Percent Owner Global Assessment Success by Assessment Day

Study Day	Solensia (%)	Vehicle Control (%)
28	39.3	30.4
56	59.3	48.3
84	64.6	57.8

Table 9. Mean Veterinarian-Assessed Total Orthopedic Pain Score by Assessment Day

Study Day	Solensia (change from baseline)	Vehicle Control (change from baseline)
Screening	34.11	33.6
28	28.68 (-5.43)	29.1 (-4.5)
56	27.52 (-6.59)	28.67 (-4.93)
84	27.29 (-6.82)	28.54 (-5.06)

TARGET ANIMAL SAFETY

Frunevetmab injection was administered subcutaneously to healthy seven to eight-month-old cats (8 cats per group) at doses of 2.8 mg/kg (1X), 8.4 mg/kg (3X), and 14 mg/kg (5X) every 28 days for six consecutive doses. The control group (8 cats) received vehicle control injections. No clinically significant changes related to frunevetmab were observed among the cats for physical examination, lameness evaluation, and body weight.

The most common findings included vomiting and diarrhea observed sporadically in all groups. The highest frequency of vomiting occurred in the 1X group. Clinically relevant skin findings included abrasions, alopecia, or scabs mostly around the face and ears. These findings were noted in three 1X cats, three 3X cats, and one 5X cat. Another 1X cat developed a 2 cm ventral neck lesion following clipping and blood collection on Day 87. Although the initial irritation appeared related to the clipping, the unexpectedly severe and persistent pruritus and prolonged recovery were deemed possibly drug-related. The ulcerated skin lesion healed when self-trauma was prevented including the placement of an e-collar for the remainder of the study.

Flinching was occasionally associated with injections, most frequently noted during the first dosing in all dosing groups. Occasionally, scabs, small abrasions, or spot of alopecia were observed at the injection sites in all dosing groups. A few cats had transient swelling at injection sites.

Body tremors and shivering were noted in one 3X cat on Day 28.

Serum creatinine values in females were significantly higher in the 5X group compared to controls ($P < 0.10$). Creatinine values on Day 28 were significantly higher ($P= 0.0239$) in the 1X group compared to the control group. On Day 112, values were significantly higher ($P = 0.0443$) in the 5X group compared to the control group. Creatinine values did not exceed the reference ranges in cats of either sex at any time point.

There was one 1X cat with mild focal discoloration of the left tibiofemoral joint cruciate ligament on gross pathology. There was no correlative pathology on microscopic examination. No lameness was reported in this cat or any cat over the course of this study.

One 1X cat had a small amount of bilirubinuria on Day 43. This cat had dark urine and hematuria on Days 43-45 with no evidence of UTI on urinalysis. The cat responded to a canned prescription urinary diet and recovered. This cat also vomited food, bile or hair on three days and had diarrhea or dark, tarry stools on two days. Another 3X cat had a small amount of bilirubinuria on Day 83 and orange colored urine. This cat also had elevated serum lactate dehydrogenase activity at three time points.

There was one 5X cat that had a small amount of bilirubinuria at the end of the study with lipid sediment. This cat also had focal hepatic lipidosis on histopathology.

STORAGE CONDITIONS

SOLENSIA should be stored upright in a refrigerator, between 35°– 46°F (2°– 8°C). Do not freeze. Protect from light. See in-use instructions provided in the **DOSAGE AND ADMINISTRATION** section.

HOW SUPPLIED

SOLENSIA is supplied as a sterile buffered solution of 7mg/mL of frunevetmab in single-use 4 mL glass vials containing an extractable volume of 1mL of clear solution with a butyl rubber stopper and aluminum overseal. Vials are available in cartons containing 2 or 6 vials.

Approved by FDA under NADA # 141-546

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Distributed by:
Zoetis Inc.
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