Synovetin OA®

Homogeneous Tin (^{117m}Sn) Colloid Veterinary Device for Use in Dogs

NAME: Synovetin OA®

Tin (^{117m}Sn) stannic colloid in ammonium salt. It is supplied as a 2–8 mCi (74–296 MBq)/mL suspension for intra-articular (IA) injection.

NET QUANTITY

Vials contain a prescribed dose per dog to be administered on the treatment date. The prescribed dose is restricted by the treating facility's Radioactive Materials (RAM) license. Confer with the treating veterinarian to understand the treating facility's dose limit per dog.

1 mL of suspension contains 2–8 mCi (74–296 MBq) of tin (^{117m}Sn) stannic colloid in ammonium salt at the date and time of end use.

PRODUCT DESCRIPTION

Synovetin OA® is a conversion electron therapeutic veterinary device comprising a colloidal, sterile suspension with a pH between 6.5 and 9.0 where at least 90% of the particles have a size between 1.5 µm and 20 µm (HORIBA light scatter instrument). The ^{117m}Sn emits monoenergetic conversion electrons (significant energies 127–158 keV; emission probability 113%) and imageable gamma radiation (159 keV, 86% abundant). Accompanying low-energy emissions are Auger electrons (<22 keV) and X-rays (<30 keV). The half-life of ^{117m}Sn is 14 days. ^{117m}Sn decays by isomeric transition to stable ^{117}Sn.

Excipients include phosphate buffered saline (NaCl), iodine (I_2), ammonium carbonate ($(NH_4)_2CO_3$), ammonium chloride (NH_4Cl), ammonium iodide (NH_4I), and trace tin (Sn) salts.

MECHANISM OF ACTION

Synovetin OA® is a veterinary device consisting of a homogeneous tin colloid which emits discrete (<300 µm) low-energy conversion electrons confined to the joint space. The colloid is composed of microparticles (1.5 µm to 20 µm) that are retained in the joint space of the dog. The particles are absorbed and retained by macrophages, synoviocytes, and other phagocytic cells in the joint, resulting in apoptosis and reduction of inflammatory cells. Reduction of the pro-inflammatory cells and associated cytokines helps reduce the drivers of inflammation, pain, and progression of OA. This procedure, termed radiosynoviorthesis (restoration of the synovium using a radioisotope), has been used in humans with different isotopes, and has been shown to stop or delay OA progression in people.[1]

CAUTION

Federal law restricts this device to sale by or on the order of a licensed veterinarian trained in the use of radioactive veterinary medical products.

Use of this product is restricted to facilities with a compatible Radioactive Materials (RAM) license.

INTENDED USE

Synovetin OA® is intended for the durable relief of chronic canine elbow osteoarthritis pain through the reduction of synovial inflammation.

WARNINGS

Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental injection or ingestion by humans.

PRECAUTIONS

Injection should be performed only by a licensed veterinarian skilled in the delivery of intra-articular (IA) injections who is located at a facility that has a RAM license.

Rigorous aseptic technique must be ensured during injection.

DIRECTIONS FOR USE

Use the chart below to determine the appropriate dose. Doses were determined using the elbow joint.

For example, a dog weighing 25 lbs. receives an IA dose of 0.9 mCi in each elbow to be treated.

Dog Weight (lbs.)	Synovetin OA® Dose per Elbow Joint (mCi)*
10–19 lbs.	0.6
20–29 lbs.	0.9
30–39 lbs.	1.2
40–49 lbs.	1.5
50–59 lbs.	1.7
60–69 lbs.	1.9
70–79 lbs.	2.2
80–89 lbs.	2.4
90–99 lbs.	2.6
100–109 lbs.	2.8
110 lbs. and over	3.0

***Dose will be limited to 3.0 mCi/elbow joint when weight exceeds 110 lbs., with the total body dose not exceeding the limit listed on the treating facility's Radioactive Materials (RAM) license.**

PREPARATION FOR USE

Synovetin OA® is provided in a 2, 3, 5 or 10 mL glass vial within a lead container (PIG). Vials are for use in a single dog or for multiple dogs (bulk) as indicated.

The product should be stored in the cardboard shipping container until needed for use. The **prescribed dose** should be **administered on the date noted** on the certificate accompanying the Synovetin OA®; however, it can be administered the day before or the day after if circumstances require injection on a different day. Always use proper personal protection equipment and precautions for handling radioactive medical products, including nitrile gloves, splash shield, safety goggles, back-fastening gowns, head covers, booties, and surgical masks.

STEP 1: When ready to withdraw the dose into a syringe, vigorously **shake the lead PIG for approximately 10 seconds to ensure proper mixing** of the product.

STEP 2: Remove/Unscrew the lead PIG lid and gently remove the glass vial from inside the lead PIG. Confirm that there is **no white particulate** remaining in the bottom of the glass vial.

STEP 3: If there is **no white particulate**, replace the glass vial back into the PIG and continue to STEP 4. If there **is white particulate**, replace the glass vial back in the lead PIG with original packing material protecting the vial, replace and secure the lid on the lead PIG and repeat STEPS 1 and 2 until the residue is dissolved.

STEP 4: Remove the colored flip cap from the vial and retain for placement on the vial after the dose is withdrawn.

STEP 5: Attach a plastic syringe (3 mL or other appropriate volume) to a 22-ga. needle. Where practical, use a syringe shield to maintain operator radiation doses as low as reasonably achievable and to meet existing license conditions.

STEP 6: While holding the container at an approximate 45° angle, insert the needle through the septum.

STEP 7: **Draw the prescribed volume into the syringe** for an individual elbow. **Under no circumstances should the volume be modified**. If designated, repeat immediately for the second elbow dose in a dog. If both elbows are to be treated, both doses will be contained in the same vial. Bulk dog vials contain product to treat joints for multiple dogs as indicated. If there are any questions or concerns, contact Exubrion Therapeutics® Customer Service at 866-364-7786.

STEP 8: The dose should be resuspended by gently inverting the syringe if more than 10 minutes has elapsed since dose was drawn into the syringe.

STEP 9: Following use of Synovetin OA®, replace the colored flip cap on the vial, then place the lid on the lead PIG. Mark the vial with a tentative

disposal date 5 months from the present date. After 5 months, the vial should be measured with a handheld rate meter (GM detector) to verify that radioactivity has decayed. If the vial is less than or equivalent to background radiation, it can then be disposed of as regular trash. All waste disposals should be documented according to your radioactive materials license and federal or state regulations. Do not return the vial, any packaging components, or supplies to the manufacturer.

The shielded syringe or syringes and needles that are used for administration should be placed in shielded sharps containers for radionuclides of similar half-lives (two weeks) and disposed of according to local, state, and federal regulations.

ROUTE OF ADMINISTRATION

Intra-articular injection. The product must NOT be administered by any other route. Confirmation of needle placement is recommended, whether by anatomical landmarks, fluoroscope, C-arm, ultrasound, or radiography.

DIRECTIONS FOR ADMINISTRATION

Dogs should be appropriately anesthetized or deeply sedated prior to administration to prevent vocalization and resistance to dosing. Select an appropriate needle size based on the target joint. For example, a 22-ga. needle can be used to inject Synovetin OA® directly into the elbow joint. Pain during and after treatment may occur. Administration of non-steroidal anti-inflammatory agents at the labeled dose may help any post-treatment pain.

FREQUENCY OF ADMINISTRATION

If needed, Synovetin OA® can be readministered to a previously treated elbow 12 months after the last treatment.

EFFECTIVENESS AND DURATION OF RESPONSE[2,3]

In clinical trials, 71% of dogs with severe OA, and 92% of dogs with mild-moderate OA were considered treatment successes. Positive response is durable for up to 12 months following a single treatment in dogs with naturally occurring OA of the elbow.

MAXIMUM ANNUAL DOSE

Total mCi dose should not exceed the limit listed on the treating facility's Radioactive Materials (RAM) license.

ADVERSE REACTIONS

Dogs participating in clinical studies to evaluate safety and effectiveness (n=74 dogs, 97 elbow joints) exhibited no significant adverse reactions when administered Synovetin OA®. Discomfort in the treated elbow has been reported in some dogs up to 72 hours after treatment. If adverse events are observed or suspected, please report them by calling Exubrion Therapeutics® Customer Service at 866-364-7786.

POST-INJECTION CARE

Following administration of Synovetin OA®, the dog can recover with other post-operation animals in the general clinic population. Once the dog has fully recovered from anesthesia, it can be discharged to go home with the approval of the facility radiation safety officer or authorized user. All treatment site policies and license requirements should be observed

FACILITY CONTAMINATION ASSESSMENT

Removable radioactive contamination is assessed by using filter paper or something similar (i.e., tissue paper) to wipe a known area (typically 100 cm^2), then count the number of interactions on the paper using a radiation detector with a known efficiency for counting the specific isotope in question. Empirical data using a Ludlum model 3 rate meter and 44-9 GM probe show the efficiency for ^{117m}Sn detection to be approximately 20% under 2D geometry. With a background rate of 100 counts per minute (cpm), this radiation detection system has a minimum detectable activity (MDA) of approximately 400 disintegrations per minute (dpm). The standard regulatory threshold for removable contamination in an unrestricted area is 2000 dpm for similar isotopes. Therefore, a Ludlum rate meter and GM is an adequate instrument to use for compliance measurements of removable contamination.

Note, ^{117m}Sn has a similar gamma emission as the commonly used medical radioisotope ^{99m}Tc along with several low-energy conversion electron emissions which would only aid in the detection efficiency of contamination.

EXPOSURE RATE MEASUREMENTS

Radioactive materials licenses require daily closeout surveys of all areas where unsealed radioactive material was used. These surveys can be completed with any rate meter capable of detecting the type of radiation emitted by the radioactivity. Further, license conditions require that release exposure rate measurements be completed prior to releasing animals who have been administered radioactivity. Most license conditions require the measurement taken not exceed 0.5 mR/h at 1 meter from the treatment site. The exposure rate release measurement and daily closeout surveys can be completed with either a standard volume ion chamber such as the Ludlum 9DP or Victoreen 451P, a Ludlum Model 3 rate meter and energy compensated GM probe 44-38, or a Ludlum 26-1 DOSE with energy flattening cover. While the ion chamber is the gold standard for exposure rate measurements, the Ludlum model 26-1 DOSE is the most practical because it can satisfy both contamination and exposure rate measurements (with dose flattening cover).

OWNER INSTRUCTIONS FOR POST-TREATMENT CARE

When the level of radiation is determined to be below the established levels for release, the dog can be discharged. The dog will, however, retain a low level of radioactivity in the treated joint(s) for a short period of time. Specific written instructions based on the post-treatment radiation dosimetry for care and proximity to the treated dog will be provided by the radiation safety officer (RSO) or authorized user (AU) of a radioactive materials (RAM)-licensed veterinary hospital to the dog owner. These instructions include information on limiting proximity to the dog in the post-treatment period. If in the judgement of the veterinarian, the dog owners are not likely to comply with the release instructions, the product should not be administered. A RAM-licensed veterinary hospital RSO or AU should contact Exubrion Therapeutics® if there are specific questions. Apart from the proximity requirements to protect in the release instructions, there are no requirements for restraint of the dog itself, and the dog can resume normal level of activity subject to the distance requirements.

MANUFACTURED BY Telix IsoTherapeutics Group, Inc. for Exubrion Therapeutics®

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STORAGE INSTRUCTIONS

Store in the shipping container at controlled room temperature (10°–30°C or 50°–86°F) until ready to use.

CITATIONS

1: Szerb I, Gál T, Kiss D, Nagy V, Hangody L. Efficacy assessment of radiosynoviorthesis on the progression of radiological osteoarthritic features of hip and ankle joint in patients with osteoarthritis and rheumatoid arthritis. Nuklearmedizin. 2020 Jun;59(3):269-275. English. doi: 10.1055/a-1108-1187. Epub 2020 Feb 19. PMID: 32074661.

2: Aulakh KS, Lopez MJ, Hudson C, Gaschen L, Fabiani M, Beale B, Andrews FM, Liu CC, Lattimer J. Prospective Clinical Evaluation of Intra-Articular Injection of Tin-117m (117mSn) Radiosynoviorthesis Agent for Management of Naturally Occurring Elbow Osteoarthritis in Dogs: A Pilot Study. Vet Med (Auckl). 2021 Jun 4;12:117-128. doi: 10.2147/VMRR.S295309. PMID: 34113552; PMCID: PMC8187093.

3: Donecker J, Fabiani M, Gaschen L, Aulakh KS. Treatment response in dogs with naturally occurring grade 3 elbow osteoarthritis following intra-articular injection of 117mSn (tin) colloid. PLoS One. 2021 Jul 19;16(7):e0254613. doi: 10.1371/journal.pone.0254613. PMID: 34280212; PMCID: PMC8289027.

EXUBRION® THERAPEUTICS

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