

Vivos, Inc.
719 Jadwin Ave.
Richland, WA 99352

IsoPet[®]

Instructions for Use

Yttrium – 90 (Y-90) IsoPet[®] - Rx Only

Sterile, Single Use

Do Not Use if sterile packaging is damaged

Caution: Veterinary Product - Not for Human Use – For Animals Only

Caution: Radioactive Material



Caution: Federal law restricts this device to sale by or on the order of a veterinarian.

IsoPet[®] should only be handled in authorized, licensed facilities by experienced personnel who are fully trained and qualified in the safe use of radioactive material by the appropriate regulatory agency. All radiation and contamination surveys should be performed using calibrated equipment. Personnel monitoring for radiation exposure is required, (e.g. film badge, thermal luminescent dosimeter, finger rings, etc.)

IsoPet[®] is supplied in two separate solution vials: a sterilized vial 1.2 ml Yttrium-90 Phosphate (⁹⁰YPO₄) particles suspension in water for injection and a vial of Hydrogel delivery vehicle comprised of an injectable, sterile, phosphate-buffered saline solution containing a dissolved co-polymer of PLGA, (poly-(DL-lactic acid-co-glycolic acid)), and PEG, (poly-ethylene glycol)), referred to as PLGA-g-PEG. Note: the hydrogel delivery vehicle has been prepared by aseptic processing and the Yttrium-90 Phosphate suspension is sterilized by steam.

Physical Characteristics:

Principle Radionuclide: Yttrium-90 (Y-90)

Half-life of Y-90: 2.7 Days

Radiation Energy: β-emitting, 2.3 MeV maximum

Indications:

Yttrium-90 (Y-90) IsoPet[®] is a brachytherapy device for delivering therapeutic radiation to cancerous tissue or sarcomas occurring in canine, feline, and equine animals.

Contraindications:

Y-90 IsoPet is not intended for use for melanomas. Y-90 IsoPet may be contraindicated in patients who have disseminated extra-tumoral malignant disease (distant metastases). Y-90 IsoPet is contraindicated for use in

anatomical sites that pose substantial risk for migration of the Y-90 particles beyond the administration site to other parts of the body, e.g. spongy tissues such as in the lung, friable tissues such as in the pancreas, or highly vascularized tissues.

Device Description & Technological Characteristics:

Y-90 IsoPet[®] is a brachytherapy device designed for radiation treatment of cancerous tissue or solid tumors as defined in the Indications for Use above. The product comprises highly insoluble, microscopic, (nominally < 2.0 μm diameter), ⁹⁰yttrium phosphate, (⁹⁰YPO₄), crystalline particles suspended in a sterile phosphate-buffered saline-polymer delivery vehicle, (hydrogel), that is liquid at room temperature. These two components are supplied to the user in separate vials and mixed together just prior to injection. The Y-90 IsoPet[®] /Hydrogel mixture is injected directly and uniformly into tumors. The Y-90 IsoPet[®] perfuses tumor tissue via interstitial fluid spaces to distribute the microscopic Y-90 particles within the extracellular interstitial fluid spaces. As the delivery vehicle approaches body temperature within the interstitial fluid spaces, (within approximately 10 – 15 seconds), the solution gels in place. The gelation solidifies extracellular fluid channels and inhibits migration of the insoluble ⁹⁰YPO₄ particles suspended in the gel away from the placement site, thereby precluding their re-distribution to other parts of the body. Direct placement of the Y-90 IsoPet[®] particles within the tumor maximizes the radiation dose to target cancer tissue while minimizing to a near zero dose of any radiation delivered to other healthy organs and tissues. This manner of brachytherapy achieves a high therapeutic index and radiation therapy with no discernable side effects. Test data show the crystalline ⁹⁰YPO₄ particles placed in tissue do not migrate away from the treatment area.

Y-90 IsoPet[®] employs the high energy (2.3) MeV maximum), short-path length, (11 mm maximum), pure beta-particle-emitting radio nuclide yttrium-90, (physical half-life of 2.7 days), which effectively delivers a pre-determined highly localized radiation absorbed dose to the target cancer cells. The average Y-90 beta particle path length of 4 to 5 mm optimizes the local delivery of therapeutic radiation to cancerous tissue while effectively minimizing radiation dose to nearby healthy tissues. The Y-90 (⁹⁰YPO₄) particles within the Y-90 IsoPet[®] are highly insoluble to effectively minimize Y-90 release from particles by dissolution in body fluids. The

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hydrogel delivery for the Y-90 (⁹⁰YPO₄) particles comprises an injectable, sterile, phosphate-buffered saline solution containing a dissolved co-polymer of PLGA, (poly-DL-lactic acid-co-glycolic acid), and PEG, (poly-ethylene glycol), referred to as PLGA-g-PEG. The sequence of PLGA and PEG separated by the “g” is a standard notation that indicates that hydrophobic PLGA is the backbone.

Instructions for Use:

Prior to Treatment:

Patient Information:

For each animal, all pertinent data should be recorded in the patient's chart, including any observational comments after the procedure has been completed.

Estimate the size of the tumor and adjacent margins based on physical examination, ultrasound, x-ray or CT. NOTE: a common practice for quantifying tumor size is to measure length, width, and depth and report the results in centimeters (cm). Unless otherwise specified the tumor volume will be calculated assuming ellipsoid geometry. Margins represent potentially significant volume and are to be included or identified separately. Photos provide useful information on tumor morphology and incorporating a scale (e.g. ruler or tape measure) in the image allows for more precise estimation of tumor dimensions.

Select the target tissue absorbed dose. (Note that prescription doses from 170 Gy to 400 Gy have been administered successfully for feline and canine sarcomas). Since the beta radiation from Y-90 travels a relatively short distance in tissue the absorbed dose is directly proportional to the activity implanted per gram of tumor/tissue. The equilibrium dose constant for Y-90 is 1.99 g-cGy/microcurie-hour or 1.48×10^{-13} Gy·kg·Bq⁻¹·s⁻¹.⁽⁸⁾ For continuously decaying sources the total dose delivered through complete decay is proportional to the mean life of the isotope, $T_{Avg} = T_{1/2}/\ln(2)$. For Y-90 it follows that $D_{total} = D_o \times (64.1/0.6932)\text{hr} = 1.99 \text{ g-cGy/uCi-hr} \times (92.48 \text{ hr}) = 184 \text{ g-cGy/uCi}$. Thus, when decay energy is completely absorbed, 54 uCi of Y-90 delivers 100 Gy absorbed dose to 1 g of target tissue.

Y-90 IsoPet is available in activities ranging from <1 mCi to about 30 mCi (37 to 1110 MBq).^(9,10) AAPM guidelines for brachytherapy practice may be followed for independent verification of source output.⁽⁵⁾ A

certificate of analysis is provided with each shipment that includes: customer order number, patient name/ID, total activity, reference date, implant date, and total volume of Y-90 IsoPet supplied. The total activity is determined using a Y-90 standard traceable to NIST (National Institute for Standards and Technology).

Monte Carlo dosimetry studies have shown that good distribution of radiation dose can be achieved by administering multiple small volumes of Y-90 IsoPet throughout the tumor volume. Approximately 0.15 ml of IsoPet per gram of tumor is recommended to promote perfusion of the Y-90 particles and hydrogel within the tumor volume. Parallel injections spaced 5 – 8 mm apart are recommended to achieve the prescribed average dose to the tumor while minimizing hot spots and cold spots.

Good practice for dose planning entails first determining the size and shape of the tumor volume via imaging or manual palpitation/measurement techniques then constructing a 3-dimensional grid of Y-90 IsoPet injections as close as possible to the recommended 5 - 8 mm nominal spacing. A template or grid of fiducial markers may be used to guide the injections during Y-90 IsoPet administration. As each individual injection is placed, the veterinarian may pause for several seconds after the IsoPet has been injected to allow the gel to solidify and thereby minimize potential for backflow of liquid from the injection site.

Once all injections have been administered the actual distribution of Y-90 IsoPet within the tumor volume may be confirmed via CT scan to verify the spatial distribution of the Y-90 phosphate particles. Alternatively, dose distribution may be determined via PET/CT imaging of Y-90 positron emissions.

Select the treatment date and time. Typical lead time for ordering IsoPet[®] is two weeks.

Communicate the above information to Vivos, Inc. in the form of a written directive (prescription product order). It is common practice to order extra material to be delivered with the product order. This is to account for possible variations in tumor size and morphology. Typical practice is to order 10 – 15% extra product for this purpose.

Product Order and Delivery through Vivos:

Vivos, Inc. transmits the order to Vivos' contract manufacturing facility for Y-90 IsoPet[®] and will confirm

their ability to produce the correct volume and activity of IsoPet® for implant on the prescribed date.

NOTE: Before the product can be shipped to the user's facility the shipping facility must be provided a copy of the Radioactive Material License for the receiving facility and verify that the facility is authorized to receive and possess the quantity and form of Y-90 ordered.

The product will be overnight shipped in two vials, hydrogel and the Y-90 particle suspension, in DOT approved containers. The product will be calibrated at the time of shipment to ensure accuracy and provide sufficient activity for achieving the prescribed dose after allowing for decay with the 2.7-day half-life. Typically, the product will be shipped to arrive one day prior to the scheduled therapy. This allows an extra day for delivery in case a shipment is delayed for unforeseen reasons.

The Radiation Safety Officer or designee assumes responsibility for receipt of the package and for transferring the radioactive portion to a secure storage area at the authorized use location. The product will be stored in a locked and posted radioactive material storage area until just prior to the therapy. The hydrogel is shipped in temperature-controlled packaging and must be transferred to refrigerated storage (2° - 4°C) as soon as practical. Do not store hydrogel below 0°C or allow it to freeze.

Preparation for Administration:

The therapy room should be prepared prior to treatment to ensure that the animal is kept anesthetized for the least time possible. Confirm that the necessary materials are readily available, including finger ring dosimeters for the veterinarians and veterinary technicians that will handle the product, lab coats/smocks, safety glasses, surgical gloves (multiple pair), indelible marking pen, magnetic stirrer, plastic holder for the IsoPet vials, 22 or 25-gauge needles, 1 cc syringes, and an ice bath.

For radiation safety purposes place absorbent pads on the therapy table and on surfaces where the product is to be dispensed. A bench-top acrylic radiation shield (12 mm thick) is recommended to minimize personnel dose. Syringe shields are recommended for minimizing hand dose when drawing and administering the product. Pre-stage radioactive waste containers, absorbent wipes, sterile cotton-tipped swabs, and alcohol for swabbing the treatment zone at the end of the procedure.

An important aspect of the therapy is to determine the amount of activity implanted. A convenient and reliable method is to measure the activity of the IsoPet® product before and after the procedure using a dose calibrator. Procedures for calibrating commonly available dose calibrator instruments - including calibration setting, linearity, and constancy, are available from Vivos, Inc. Alternatively, the IsoPet® components, vials, and syringes may be weighed before and after the procedure and the weight difference used to calculate the administered volume and activity. (See Attachment A for details)

Pre-stage radiation and contamination survey meters for convenient access during the administration procedure. It is a good practice for users to survey their hands frequently during the procedure to minimize the potential for contamination spread. It is further good practice to wrap the survey probe with thin plastic to avoid contaminating the probe itself and to shield the waste container with 3 - 6 mm of plastic to reduce background dose during post-procedure radiation surveys.

Users may choose to incorporate a small volume of sterile blue dye when combining the radioactive particle suspension and the hydrogel components. The blue dye provides visual indication of any drips as the syringes are loaded and any backflow from the individual injection sites. A target of 0.25 mg Erioglaucine disodium salt (FD&C blue) per ml of final IsoPet® volume is recommended for good visualization.

IsoPet® Administration Procedure:

Immediately prior to the actual procedure it is a good practice to stage and combine the IsoPet® components; the Y-90 particle solution, hydrogel, and blue dye if used. The components should be pre-conditioned under refrigeration or placed in an ice-water bath. Then place the Y-90 particle solution in a vial holder atop a magnetic stir plate.

The hydrogel is extracted via a needle and syringe and injected into the particle solution vial, which has a magnetic stir bar placed within the vial. Typical practice is to use a 5 – 10 ml syringe with a 22 gauge needle to transfer the hydrogel. Position the syringe and vial to minimize both void areas when filling the syringe and potential for contamination of the area. It is important to measure the hydrogel volume as accurately as possible to achieve the desired final volume of hydrogel.

CAUTION: The magnetic stir bar and stir plate are provided to keep the Y-90-phosphate microparticles uniformly distributed within the hydrogel solution. The individual particles are approximately one micron in size and will remain suspended in solution for several minutes without agitation. If particle settling is observed or suspected do not administer the product. Return any unused product to the product vial and do not proceed unless mixing/agitation of the product can be re-established.

NOTE: Some procedures may require that the product be supplied in more than one set of vials. For example, 5 mL of IsoPet® will treat a 33 cc tumor using typical injection volumes and spacing. For larger tumors multiple product vials may be supplied to provide sufficient product volume to treat the entire tumor. Specific instructions will be provided for combining the non-radioactive hydrogel with the radioactive particle solution. Do not attempt to combine radioactive particle solutions in a single vial. Combining solutions increases risk of spreading radioactive contamination as well as exceeding vial capacity when the prescribed amount of hydrogel is added.

When preparations are complete the animal is anesthetized and the region near the tumor is shaved with a wide margin to ensure that the hair is not inadvertently contaminated. The skin at and around the designated injection site is sanitized with an alcohol wash. Optional surgical tape may be applied to the skin over the tumor site and the individual injection sites are marked with dots using an indelible ink pen. Typical grid spacing is 5 -8 mm between injection points to achieve near-uniform distribution of IsoPet within the treatment volume. A surgical drape may be placed over the animal with an opening directly above the treatment zone.

The IsoPet® is then extracted from the IsoPet® vial using a 22 or 25-gauge needle with a 1-cc syringe. Syringe shields should be used during filling and administration of the IsoPet® product to minimize hand dose. A typical practice is to fill the syringe with sufficient material for up to five injections (e.g. 0.5 to 1.0 ml at 0.1 to 0.2 ml per injection). This is done repeatedly with a series of syringes until the total planned volume of IsoPet has been administered. To reduce the time of the procedure, an assistant can be filling the syringes for the veterinarian who is performing the injections. NOTE: It is a good practice for an assistant to keep a tally of the number of syringes used, the number and location of

injections administered, and the total volume of IsoPet administered. This will serve as a confirmatory check of the total activity administered for post-implant dosimetry purposes.

Small tumors < 1cc can be treated with one or two injections, but larger tumors are treated with multiple injections through the fiducial grid in order to achieve adequate dose distribution. A successful technique is to insert the needle through the fiducial mark to near the base or end point of the tumor then gradually inject the product while withdrawing the needle. Then pause briefly prior to withdrawing the needle completely from the tumor to allow the product to warm and solidify. This will minimize the potential for surface contamination. A small volume of material may ooze from the needle puncture site and may be easily absorbed with a cotton-tipped swab.

After all injections have been administered the surgical tape (if used) is removed and the skin of the animal is wiped as a precaution to absorb any residual IsoPet® that may remain on the surface. An effective technique is to use sterile gauze or wipes soaked with alcohol to clean the surface. See Attachment B for additional techniques for removing excess product from the treatment site.

The wipes used for cleaning the treatment site may be used to survey for residual contamination. Two or three wipes with alcohol followed by a final wipe with a dry gauze or pad are typically adequate to remove any residual contamination.

A protective bandage is applied to the treatment site. A K-collar is strongly advised to prevent the animal from disturbing the treatment site. External radiation dose measurements may be obtained at this point while the animal is still anesthetized.

The animal is revived from the anesthesia and checked for general welfare. The life support equipment is surveyed for potential contamination.

All attending personnel are given a final radiation survey by the Radiation Safety Officer or designated personnel before leaving the therapy room.

The activity of residual unused IsoPet® may be measured at any time after the administration is completed. This quantity will be decay-corrected to a common reference date/time and subtracted from the pre-implant reading to determine the total activity that

was administered. Any significant residual activity in needles and syringes may also be measured and subtracted to assure an accurate estimate of the activity administered.

The protective covering in the treatment room is collected and surveyed or discarded in the radioactive waste container. The prep area, floor and all support equipment are surveyed and documented.

Post Procedure Activities:

The animal is placed in a cage in a designated radiation area, which is posted as containing radioactive material. Any personnel feeding or caring for the animal should be debriefed on the current state of the animal. The health assessment protocols are followed.

The IsoPet product is not soluble in bodily fluids and does not migrate from the injection site. Therefore, it is not necessary to collect and survey urine or feces. The isolation area where the animal is housed shall be surveyed and cleared after the animal is released. The animal is housed for sufficient time to verify recovery from the procedure and general condition of the treatment site.

The animal is cleared to return home after clearance by the Radiation Safety Officer or Authorized User. The external dose rate from the animal must be below the pre-set limit as specified in the license or in regulatory guidelines for radiation dose rate at 1 meter and/or 1 foot from the treatment site. A dose rate should also be measured at, or as close to the surface of the treatment site as practical.

The owner must be given written instructions for minimizing radiation exposure to themselves and family members.

Attachment A

Methods for Determining Amount of Product Administered

Activity of Product Administered:

This method is based on the assumption that the Y-90 particles/activity are uniformly distributed throughout the product volume. The product is supplied in two vials that are combined and mixed just prior to administration. The vial containing the radioactive Y-90PO₄ microparticles is supplied with a magnetic stir bar placed within the vial. A magnetic stir plate commonly available from a laboratory supply vendor can be used to agitate the solution and keep the particles uniformly suspended. The individual YPO₄ particles are very small (approximately 1 micron in diameter) and will remain suspended in the hydrogel for several minutes without agitation.

NOTE: If particle settling is observed or suspected at any point during the administration procedure stop, return any unused product to the product vial, and re-establish mixing/agitation of the product before proceeding.

Prior to performing the procedure measure the activity supplied in the product vial using a calibrated instrument such as a dose calibrator (well-type ion chamber). Verify that the instrument is calibrated for the isotope and vial configuration being measured. Record the instrument reading, date and time of measurement. The manufacturer can provide recommendations for instrument calibration including measurements for linearity and constancy.

NOTE: All activity measurements must be decay-corrected to a single calibration date and time, typically noon on the day of treatment in the local time zone. For Y-90 (half-life = 64.1 hr.) use the following calculation where T_{cal} and T_{meas} are in units of hours.

$$A_{cal} = A_{meas} \times \exp((T_{cal}-T_{meas}) \times 0.69315/64.1)$$

After the procedure measure the residual activity remaining in the product vial. Also measure any significant amount of residual activity remaining in syringes used during the procedure to assure as much of the supplied activity is accounted for as possible. Place the syringes and swabs in a clean plastic bag or

secondary container to avoid depositing contamination inside the instrument chamber.

The activity of product administered is determined by taking the activity prior to administration and subtracting the final activity as well as the residual activity remaining in the syringes/swabs. All activities must be decay corrected to a single calibration date and time.

Volumetric Method:

This method is less precise than the method using the activity or mass of product administered but may be adequate depending on the level of accuracy desired. Individual volume measurements can be determined within 1-2% uncertainty which may be acceptable for most brachytherapy procedures.

As with the activity method, an underlying assumption with this method is that the Y-90PO₄ particles are uniformly distributed in the final product. Observe the same precautions as noted above if any particle settling is observed or suspected.

Record the initial and final volume of product for each syringe used to administer the product. The volume administered per syringe is the difference between these measurements. Sum the values for all syringes used to administer the product.

At the end of the procedure use additional syringe(s) to remove as much residual material as possible from the product vial. Record the volume of residual material recovered.

The fraction of total product administered will be the volume administered divided by the volume administered plus residual from the product vial.

Mass of Product Administered:

This method is based on the assumption that the Y-90 particles/activity are uniformly distributed throughout the product volume. The product is supplied in two vials that are combined and mixed just prior to administration. The vial containing the radioactive Y-90PO₄ microparticles is supplied with a magnetic stir bar placed within the vial. A magnetic stir plate commonly available from a laboratory supply vendor can be used to agitate the solution and keep the particles uniformly suspended. The individual YPO₄ particles are very small

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(approximately 1 micron in diameter) and will remain suspended in the hydrogel for several minutes without agitation.

NOTE: If particle settling is observed or suspected at any point during the administration procedure stop, return any unused product to the product vial, and re-establish mixing/agitation of the product before proceeding.

Prior to performing the procedure weigh and record the mass of the component vials and the syringes to be used for administering the product. If all syringes are the same size and configuration, they may be weighed together placed within a suitable container such as a kidney tray.

Administer the product according to the recommended procedure. Collect all used and unused syringes to be weighed at the end of the procedure. Replace the needle covers that were present when the syringes were weighed prior to the procedure. Use the same tray for holding the syringes that was used to weigh them prior to the procedure. Subtract the pre-administration mass from the final mass to obtain the mass of residual product remaining in the syringes.

After the procedure re-weigh the product vials. The mass of product administered is determined by taking the mass prior to administration and subtracting the final mass as well as the residual mass remaining in the syringes.

To calculate the fraction of total supplied activity that was administered it is necessary to determine the mass of the product prior to administration. To calculate the mass prior to administration it is necessary to weigh the product vials separately before and after the procedure and to obtain the tare or empty weight of the combined product vial. The latter may be provided by the manufacturer from known or measured masses of the product vial and the magnetic stir bar provided. If the tare weight is not available the user may estimate the value by removing as much residual material as possible then weighing the product vial. The pre-administration mass is determined by subtracting the tare, or empty mass of the product vial from the mass of the product vial containing the mixed product.

Determination of Source Shelf-Life

Y-90 IsoPet has a half-life of 64.1 hours and must be corrected for decay in order to properly calculate the activity present at the time of implantation. Decay factors are provided in the Table below.

Decay Factors of Yttrium-90 IsoPet[®]

Hours	Decay Factor
0.5	0.995
1	0.989
2	0.979
3	0.968
4	0.956
5	0.947
6	0.937
7	0.927
8	0.917
9	0.907
10	0.898
11	0.888
12	0.878
24	0.772
36	0.678
48	0.595
72	0.459

Attachment B

Method for Removing IsoPet[®] Adhered to Surfaces

IsoPet[®] administration procedures and techniques are designed to minimize the potential for backflow of the product from the treatment site. The hydrogel component of IsoPet is thermally sensitive and solidifies as the material warms to internal body temperature. This process is rapid but does not occur instantly as a finite period of time is required for heat to transfer from warm body tissue to freshly injected product.

If backflow does occur it poses the hazard of acute localized radiation dose to the animal's skin. This situation is to be avoided as much as possible. The user administering IsoPet should be prepared to take the following actions to mitigate the potential for IsoPet[®] adhering to the skin surface:

- Keep sterile gauze and/or swabs on hand as the injections are being administered. If backflow of liquid is observed from an injection site immediately absorb with a swab or gauze and dispose in the radioactive waste receptacle.
- If the product warms and solidifies protruding from the surface it may be removed manually using normal surgical instruments such as tweezers or clamps. Assume any instruments used will be contaminated and isolate for decontamination, or hold for decay.
- If the product forms a thin layer or film on the surface, it may be readily removed by swabbing with alcohol. The polymer component of the hydrogel is soluble in alcohol but may require sufficient contact time with a moist swab to achieve complete removal.
- If the product forms a larger mass or pools and solidifies on the surface it is possible to convert the material back to liquid state by applying a small ice-pack to the surface long enough to soften the material and revert to near-liquid state. The material can then be absorbed with a swab or gauze or wiped off with alcohol.