ISOAID ADVANTAGE-LOAD ™ 1-125 WITH C4 MRI MARKERS ADVANTAGE BRACHYTHERAPY DEVICE SYSTEM

⚠ Instructions for Use – This leaflet contains important product use and safety information. Please read carefully,and retain these instructions for future

PRODUCT NAME:

ISOAID ADVANTAGE-LOAD ™ 1-125 WITH C4 MRI MARKERS ADVANTAGE BRACHYTHERAPY DEVICE SYSTEM

Description:

The IsoAid Advantage-Load ® Advantage Brachytherapy Device System (ABDS), utilizing Advantage I-125 Brachytherapy Seeds is provided preloaded in 18-gauge needles with or without spacers or and C4 MRI Marker(s)™in a pre-sterilized device system. The Advantage I-125 sources consist of a laser welded Titanium capsule, containing Iodine-125 chemically affixed (adsorbed), as silver iodide, onto a silver rod which acts as an x-ray detectable marker. The needle tips are occluded with bone wax and the iodine seeds are loaded loose or with a trailing spacer. The stainless-steel needles are provided in 20 cm length. A maximum total of 20 seeds and spacers can be loaded into a needle. The spacers are made from the same material as sutures and stranding material. Bone Wax is used at the tip of the needle to keep the implants from falling out of the needle.

The Advantage-Load I-125 Product may be configured with or without a spacer and with or without C4 MRI Markers; and may be supplied in a 20-cm stainless-steel needle. The C4 MRI Marker is a sealed polyether ether ketone (PEEK) polymer capsule containing a cobalt chloride: N-Acetylcysteine solution. The following configurations are loaded into the Advantage Load I-125 needle:

- Advantage 1-125 Seeds
  and/or:
- with or without a spacer
  and/or:
- with or without C4 MRI Marker

⚠ ***Note: A spacer and C4 MRI Marker cannot be loaded (encapsulated) within the same suture sleeve strand.***

During the implantation procedure, utilizing the Advantage Load I-125, the seeds, spacers and C4 MRI Markers provide radiation therapy and aid in the location of the tumor for verification of placement of the brachytherapy seeds. The verification of the placement is achieved by the healthcare team's use of the Advantage seeds at the time of implantation and after implantation, by the use of a gamma probe, or similar instrument.

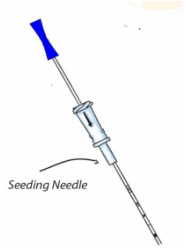
The C4 MRI Marker within the Advantage-Load configuration facilitates MRI identification of implanted radioactive seeds and delineation of surrounding anatomy. The implanted radioactive seeds can be located by proximity to the C4 MRI Marker and in relation to surrounding anatomy during a single imaging

procedure. The C4 MRI Marker reduces inter-observer variability in the assessment of implant quality. The C4 MRI Markers may also be implanted in the place of a spacer and perform the seed spacing function during a routine brachytherapy procedure

Indications for Use:

Refer to the Advantage I-125 Instructions for Use (IFU)

The Advantage-Load is intended to be used on individuals with tumors that are localized, unresectable, or have low to moderate radiosensitivity. The IsoAid Advantage-Load ® Brachytherapy Device System, accessories and components is intended for the treatment of selected localized tumors. The devices are implanted as a source of nuclear radiation for therapy.



The radioactive seeds are intended to be a permanent **implant.**

⚠ **Contraindications:**

Note: Do not use non-sterile needles to implant sources.

Physical Characteristics:

Iodine-125 has a half-life of 59.41 days and decays by electron capture with the emission of characteristic photons and electrons. The principal photon emissions are 27.2 KeV, 27.5 KeV, 31.0 KeV and 35.5 KeV with an average energy of 28.5 KeV. Table 1. shows the decay of I-125 seeds

Calibration:

ADVANTAGE™ I-125 sources are calibrated by direct comparison against a standard source of the same model that has been calibrated by the National Institute of Standards and Technology for Air Kerma Strength. The resulting calibration is reported in Air Kerma Strength (μGy m^2/h) as well as Apparent Activity (mCi).

ADVANTAGE™ I-125 sources are calibrated to the NIST SK99std WAFAC standards for I-125 seeds.

Sterilization:

The Advantage Load Brachytherapy Device System is sterilized with a Sterility Assurance Level of 10^{-6} by Ethylene Oxide gas. The sterile packaging has a thirty-one (31) day shelf-life. If the products expiration date has been exceeded the product is considered not sterile and therefore cannot be used. Do not re-sterilize the product. The product is intended to be used on the day of implant specified by the physician. However, should the implant be delayed it may not exceed the expiration date marked on the sterile pack label.

Table 1. Iodine-125 Decay

Day	Decay Factor	Day	Decay Factor	Day	Decay Factor	Day	Decay Factor
0	1.00	20	0.79	40	0.63	60	0.50
1	0.99	21	0.78	41	0.62	61	0.49
2	0.98	22	0.77	42	0.61	62	0.49
3	0.97	23	0.76	43	0.61	63	0.48
4	0.95	24	0.76	44	0.60	64	0.47
5	0.94	25	0.75	45	0.59	65	0.47
6	0.93	26	0.74	46	0.58	66	0.46
7	0.92	27	0.73	47	0.58	67	0.46
8	0.91	28	0.72	48	0.57	68	0.45
9	0.90	29	0.71	49	0.56	69	0.45
10	0.89	30	0.70	50	0.56	70	0.44
11	0.88	31	0.70	51	0.55	71	0.44
12	0.87	32	0.69	52	0.55	72	0.43
13	0.86	33	0.68	53	0.54	73	0.43
14	0.85	34	0.67	54	0.53	74	0.42
15	0.84	35	0.66	55	0.53	75	0.42
16	0.83	36	0.66	56	0.52	76	0.41
17	0.82	37	0.65	57	0.51	77	0.41
18	0.81	38	0.64	58	0.51	78	0.40
19	0.80	39	0.63	59	0.50	79	0.40

In Vivo Characteristics:

During implantation procedure, the I-125 seeds and spacers provide radioactive localization point of the lesion and aid in the identification of implanted radioactive seeds and delineation of surrounding anatomy and verification of placement of the Advantage Load Brachytherapy Device System. Verify the placement of the seeds at time of implantation and after implantation using a gamma probe, or similar instrument.

Instructions for Safe Use:

The radioactive seeds are introduced via an 18-gauge needle using standard ultrasound or radiography guidance. Once guided to the desired location of the tumor, the seeds are deployed through the bone wax with the aid of the needle stylet. Ultrasound or radiography confirms the appropriate placement of the seeds.

Radiation Protection & Handling:

The 27- 35.5 KeV photons of the Secure Seed ® I-125 are substantially absorbed by any high Z material but exhibit desirable penetration in tissue.

Half Value Layer Lead = 0.025 mm
Half Value Layer Tissue = 20.0 mm

Exposure can be reduced by 99.9% with a thin sheet of lead (0.25 mm or 0.01 inch). The shielding of the I-125seed results in a reduction of exposure to attending medical personnel and visitors. Advantage I-125 sources should be handled only by those individuals trained by an authorizing governmental agency in the safe use & handling of radioisotopes.

- Direct contact with I-125 sources should be avoided. The use of vacuum or reverse action tweezers is recommended. Proper precautions must be taken when handling the sources.
- Personnel monitoring is required. Dosimetry monitors, such as TLD devices, should be used to monitor hand and whole-body exposure. During preparation and source implantation procedures, all practical steps should be taken to keep exposure as low as reasonably achievable. Limited exposure time, increasing distance, careful planning of the administration procedure and use of shielded barriers should be considered in meeting this goal.

Accidental Damage:
Do not use the product if there is suspicion that the product is damaged or if the sterile barrier has been breached. It is possible through rough handling (abrasion, incision, etc.), high temperatures or crushing that a seed could rupture and leak. The internal components of the seed are non-toxic, but the area should be closed off immediately and personnel limited to avoid radioactive contamination. The damaged seeds should be placed in a sealed container and the area should be decontaminated. In accordance with radiation regulations only authorized, specialized staff trained in handling radioactive substances may handle the I-125 seeds.

Accountability & Disposal:
Records of receipt, storage and disposal of I-125 sources should be maintained in accordance with government regulatory policies. I-125 sources should be strictly controlled and stored in a secured area.

When disposal is indicated, the I-125 sources should be transferred to an authorized radioactive waste disposal agency or returned to IsoAid for disposal. I-125 sources should not be disposed of in normal waste. Any discrepancies must be reported immediately to IsoAid Customer Service.

Licensing:
The Florida Department of Health (FDOH), Bureau of Radiation Control has approved this sealed source for distribution to persons licensed pursuant to Florida Administrative Code Chapter 64E-5, "Control of Radiation Hazard Regulations," Part VI or under equivalent licenses of the USNRC or issued by an Agreement State. IsoAid requires proof of USNRC radioactive materials license or respective government license as well as agreement state and licensing state information. Orders cannot be processed without license verification. Compliance with the applicable local, state, country, and/or government regulations concerning procurement, possession, use and disposal of radioactive materials is the responsibility of the customer.

Canada- Canadian Nuclear Safety Commission

Application of REGDOC-2.12.3, Security of Nuclear Substances: Sealed Sources for typical uses of sealed sources, Brachytherapy - low dose rate is a category 4 source. Category 4 Sources that are very unlikely to permanently injure anyone. However, this amount of unshielded radioactive material, if not safely managed or securely protected, could possibly – although it is unlikely – temporarily injure someone who handled it or was otherwise in contact with it, or who was close to it for a period of many weeks. This Code of Conduct on the Safety and Security of Radioactive Sources was approved by the Board of Governors of the International Atomic Energy Agency (IAEA) on 8 September 2003. It replaces the version published (with the symbol IAEA/CODEOC/2001) by the IAEA in March 2001. It reflects the important findings produced by the International Conference on Security of Radioactive Sources held in Vienna in March 2003 (the Hofburg Conference). Member States to be encouraged to join and effectively implement these Conventions. Canada is already a signatory to these conventions, together with codes of conduct on nonproliferation, research reactors and the safety and security of radioactive sealed sources, along with the Comprehensive Nuclear Test-Ban Treaty.

Canadian Nuclear Safety Commission

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Web site: nuclearsafety.gc.ca

Australia- Australian Radiation Protection and Nuclear Safety Agency

The establishment of a NRWMF is governed by the National Radioactive Waste Management Act 2012. A NRWMF also needs to adhere to the Environment Protection and Biodiversity Conservation Act 1999, the Nuclear Non-Proliferation (Safeguards) Act 1987 and the Australian Radiation Protection and Nuclear Safety Act 1998.

The proposed National Radioactive Waste Management Facility would be a controlled facility under the Australian Radiation Protection and Nuclear Safety Act 1998 (the Act). Under the Act, licences are required to prepare a site for, construct, or operate a controlled facility. The decision to submit a licence application is a matter for the applicant. Before an application is made to the CEO of ARPANSA for a licence to prepare a site for the National Radioactive Waste Management Facility, the applicant will have to obtain approval from the Minister for the Environment under the Environment Protection and Biodiversity Conservation Act 1999. Before any radioactive material is allowed to be transported it must be packed, shielded, labelled and marked as set out in the ARPANSA Code: Safe Transport of Radioactive Materials. This code is based on the International Atomic Energy Agency's (IAEA) Regulations for Safe Transport of Radioactive Material. nrwmfsupport@arpansa.gov.au; www.arpansa.gov.au

A radioisotope is considered to be for medical use when it is intended to be:

1. administered to humans or used for any therapeutic procedure or purpose in any planned exposure of humans to ionising radiation
2. used in any in vitro medical diagnosis or test
3. used in research which is either directly or indirectly related towards medical diagnosis or therapy in humans.

Note: Sealed and unsealed radioactive sources that are used to calibrate instruments in medical practices and pathology laboratories are also included as medical radioisotopes for permit purposes. The applicant/"end user" declares that he/she holds an appropriate licence issued by the relevant Commonwealth, State or Territory radiation regulatory authority to deal with the above radioisotopes. The applicant/"end user" also undertakes not to supply any of the above radioisotopes to an unapproved user. The applicant/ "end user" should contact the relevant Commonwealth, State or Territory radiation regulatory authority for advice on legislative requirements. medicalpermits@arpansa.gov.au

; www.arpansa.gov.au

ARPANSA, like other regulatory bodies in Australia and abroad, has been working on developing capability in holistic safety. Charged with the function of protecting the health and safety of people under the Australian Radiation Protection and Nuclear Safety Act 1998 (the Act), ARPANSA proposes to use a holistic approach to assess and monitor the safety of licence holders and applicants. These guidelines outline ARPANSA's vision and expectations for holistic safety.

Leak Testing:

I-125 Brachytherapy sources are 100% leak tested prior to shipment and have passed a leak test showing less than 185 Bq (5 nCi) of removable I-125 surface contamination as required by ISO 9978 "Radiation protection – Sealed radioactive sources." Secure Seed ® I-125 seeds do not require any additional leak testing provided the seeds are used within the use-by-date.

ISOAID ADVANTAGE-LOAD ™ 1-125 WITH C4 MRI MARKERS

ADVANTAGE BRACHYTHERAPY DEVICE SYSTEM

⚠ **Adverse Reactions:**

- Any adverse reaction associated with tissue radiation damage may be associated with use of I-125 sources. Proper precautions must be taken when handling the sources.
- As with any surgical procedure, complications may occur including: bruising, discomfort, prolonged bleeding, inflammation or infection near the implant site.
- Although the risk of source migration is minimal it can be significantly reduced through the use of stranding that links the seed and spacer together prior to implantation.
- As brachytherapy sources achieve therapeutic results through radiation, any adverse event associated with tissue radiation damage may be associated with use of I-125.
- Adverse reactions associated with implant usage in the prostate. Bladder, uterus, anal and colon implant usage have been reported to include irritative uropathy symptoms including increased urinary frequency, urgency, incontinence, and obstruction.
- Complications have also included cystitis, urethritis, superficial urethral necrosis, hematuria, stricture/contracture, incontinence, proctitis, and impotence, bleeding and discharge, fibrosis and necrosis.
- Seed migration to other parts of the body is possible.
- Allergic reaction to Iodine.

⚠ **Precautions:**

- ⚠ Use caution when patients are diagnosed with non-cancerous tumors/lesions.
- ⚠ Product should remain in leaded pouch until ready for use. Handle lead pouch and contents with care to prevent damage to product.

⚠ **Contraindications:**

- ⚠ Do not use Advantage Brachytherapy Device System in neurological or cardiovascular tissues.
- ⚠ The ABDS is sold sterile. Use of a non-sterile device may compromise patient care. Do not re-sterilize.
- ⚠ Caution should be taken when using an MRI to aid in delivery of the seeds. The needles used to deliver the seeds are stainless steel and may affect the quality of the diagnostic information.
- ⚠ No not use needle in an MRI Environment.
- ⚠ Do not use a damaged seed or a seed that may have become damaged when using the device.
- ⚠ Do not use bent or broken needle.
- ⚠ Do not come in direct contact with the I-125 sources. Use vacuum or reverse action tweezers to handle the I-125 sources.

⚠ **Warnings:**

- ⚠ Dispose of radioactive material per nuclear regulatory guidelines (for USA, 10 CFR 35.1000; for EU per EURATOM 1493/93)
- ⚠ Loss of a radioactive seed must be avoided. Protocols must be in place to ensure tracking of the seed throughout the process.
- ⚠ Any attempt to cut or segment stranded product may adversely result in radioactive contamination. Use product as intended.
- ⚠ Do not use if damaged. Discard if damaged during use or after use in accordance with waste disposal procedures.
- ⚠ Do not use when patients are pregnant or breastfeeding. An alternative non-radioactive device should be used to avoid radiation exposure.

MR-Conditional:

The I-125 seeds have been evaluated for safety in the MRI environment. It is MRI-conditional and has been tested for heating, migration, and image artifact in the MRI environment. IsoAid seeds are made with titanium shell with non-magnetic internal materials. Patients with the seeds may safely undergo MRI under the following conditions: 1) Static field of 3 T or less 2)Whole body SAR of 4 W/kg or less and head SAR of 3.2 W/kg or less 3) Normal or first level controlled mode of the MRI system for both RF and gradients 4) Maximum spatial gradient in the static field of 30 T/m (3000 Gauss/cm) 5) Maximum slew rate of the time-varying magnetic gradient for the seed is 200 [T/m/s], which is the high-end gradient slew rate and is worst-case for the seed that does not have any magnetic or transistors in the seed components, no conceivable negative impact. However, the stainless-steel needle may produce image artifact if an MRI is performed during the Advantage-Load ABDS procedure.

⚠ **CAUTION: No not use needle in an MRI Environment.**

⚠ **CAUTION: Federal (USA) and State law(s) restrict this device to sale by or on the order of a physician.**

⚠ **CAUTION: Use and Distribution in the EU is governed by EURATOM 2013/59 and 1493/93.**

⚠ **CAUTION: Canadian National and Regional/State law(s) restrict this device to sale by or on the order of a physician.**

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Seeds that have become separated from their host are considered biohazardous and must be contained and disposed of in accordance with standard precautions.

The Advantage-Load ABDS Product may be configured with or without a Spacer; and may be supplied in a 20cm stainless-steel needles.

⚠ The stainless-steel needle may produce image artifact and may affect the quality of the image, it is recommended that the needle is not used during the MRI procedure performed during the Brachytherapy procedure.

MR-Conditional:

The Advantage C4 MRI Markers were developed specifically so that patients can be scanned safely under the following conditions: 1) Static magnetic field of 1.5-Tesla (1.5T) or 3.0-Tesla (3.0T). 2) Maximum spatial gradient field less than or equal to 10 T/m (1,000 G/cm). First Level Controlled Mode. 3) Maximum whole—body specific absorption rate (SAR) of' 4.0 W/kg for 15 minutes of scanning in First Level Controlled Mode at 1.5T. 4) 4.0 W/kg f or 15 minutes of scanning in First Level Controlled Mode at 3.0T. 5) 3.0TRF heating in non—clinical testing with body coil excitation, the device produced a maximal differential temperature rise of less than 1. 0°C when exposed to a maximum specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning in a 3.0—Tesla MR system Scaling of the SAR and observed heating indicates that SAR of 4.0 W/kg would be expected to yield a localized temperature rise of less than 0 degrees C. 6) 1. 5 TRF heating in non—clinical testing with body coil excitation, the device produced a maximal differential temperature rise of less than 1. 0 degrees C when exposed to a maximum specific absorption rate (SAR) of 1.5 W/kg for 15 minutes of scanning in a 1.5—Tesla MR system. Scaling of the SAR and observed heating indicates that SAR of 4.0 W//cg would be expected to yield a localized temperature rise of less than 2.0 degrees C.

⚠ Caution: The RF heating behavior does not scale with static field strength.

⚠ Devices which do not exhibit detectable heating at one field strength may exhibit high values of localized heating at another field strength.

MRI Imaging

MR-Conditional:

⚠ MRI Safety Information: Non-clinical testing has demonstrated that the Advantage C4 MRI Marker is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 or 3.0 T only
- Maximum spatial gradient magnetic field of 3,640 gauss/cm (36.40 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Mode)

⚠ Warnings:

⚠ The Advantage C4 MRI Marker is intended to be used in conjunction with brachytherapy seeds. In order to safely scan a patient, you must follow the MRI Safety information for all of the treatment components.

⚠ Under the scan conditions defined above the Advantage C4 MRI Marker is expected to produce a maximum temperature rise of less than 2°C after 15 minutes of continuous scanning.

⚠ In non-clinical testing, the image artifact caused by the Advantage C4 MRI Marker extends less than 2 mm for the Advantage C4 MRI Marker when imaged with a gradient echo pulse sequence and a 1.5 or 3.0 T MRI system.

⚠ RF Heating
The radio frequency (RF) induced heating results are summarized in Tables 1 and 2. At 1.5T and 3.0T, the results indicated that under the conditions of this testing but with the application of a limitation to a SAR of 4.0 W/kg, the largest expected differential temperature rise is 1.3°C and 0.4°C, respectively. This level of heating is not expected to be associated with any adverse physiological effect.

Table 1 – Summary of 1.5T field strength RF induced heating results

Test Sample	Probe	Probe Location	ΔT [°C]	ΔT Scaled to Control SAR	ΔT – Control ΔT
Control*	1,2	Control	0.9	—	—
	3	Contralateral	0.3	—	—
Device	1	Head	1.4	1.4	0.5
	2	Foot	1.2	1.2	0.3
	3	Contralateral	0.9	0.9	0.6

Table 2 – Summary of 3.0T field strength RF induced heating results

Test Sample	Probe	Probe Location	ΔT [°C]	ΔT Scaled to Control SAR	ΔT – Control ΔT
Control*	1,2	Control	1.5	—	—
	3	Contralateral	0.7	—	—
Device	1	Head	1.6	1.6	0.1
	2	Foot	1.8	1.8	0.3
	3	Contralateral	1.0	1.0	0.3

*Control represents the average of probes 1 and 2

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Maximum whole-body SAR of 4.0 W/kg

Table 1. Summary of MRI compatibility test results.

Evaluation	Field Strength	Device
Displacement Force (ASTM criteria)	3.0T	Pass
Torque	3.0T	None
Artifact (maximum ASTM)	1.5T	0.2 cm
	3.0T	0.2 cm
Heating † (maximum)	1.5T	1.3°C
	3.0T	0.4°C

† Maximum whole-body SAR of 4.0 W/kg.

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Seeds that have become separated from their host are considered biohazardous and must be contained and disposed of in accordance with standard precautions.

Part Number	Description
# 2034	Advantage-Load seeds and spacers or C4 Markers loaded into needles

	Caution: Consult Accompanying Documents
	Do Not Reuse
	Consult Instructions for Use
STERILE EO	Ethylene Oxide Sterilization
	Use by Date
REF	Catalog Number
	Do not Resterilize
	Date of Manufacture
	Biohazard
	Radioactive
MR	MR Conditional
	Do not use if package is damaged

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