BIO PROTECT

INSTRUCTIONS FOR USE

BioProtect Balloon Implant™ System

OPL-10365 Rev.01

INSTRUCTIONS FOR USE
BioProtect Balloon Implant™ System

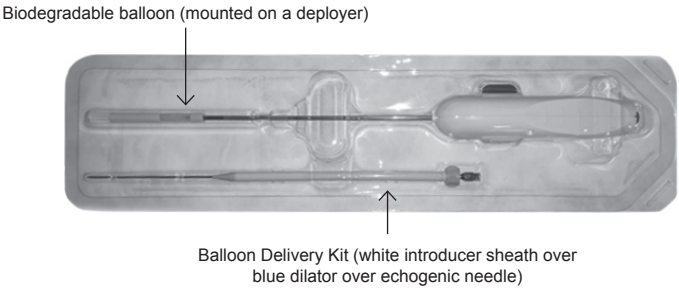
The Instructions for Use provides instructions for use and recommended guidelines specifically dedicated to the BioProtect Balloon Implant™ System. Read carefully and entirely before using the system.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed health care professional.

DEVICE DESCRIPTION

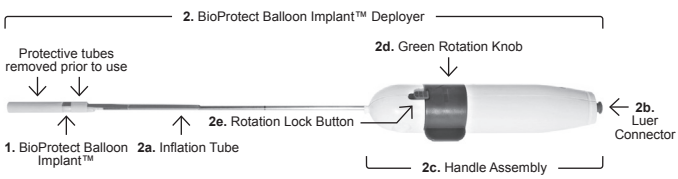
The BioProtect Balloon Implant™ System is a single use, biodegradable, inflatable balloon implant, designed to act as a spacer between the prostate and the rectum. The BioProtect Balloon Implant System is supplied sterile (sterilized by EO). When removed from the sterile package, the system is ready to use.

The BioProtect Balloon Implant System is packed in a sterile blister and Tyvek and comprised of:



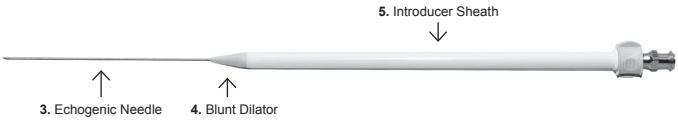
› Biodegradable, inflatable balloon (mounted on a deployer) that includes

	Component	Material
1	BioProtect Balloon Implant	Poly L-Lactide-co-e-Caprolactone
2	BioProtect Balloon Implant Deployer	See below
A	Inflation Tube assembly	Stainless steel + PET
B	Luer Connector	Polyoxymethylene (POM) – Acetal
C	Handle Assembly	Polycarbonate
D	Green Rotation Knob	
E	Rotation Lock Button	



› Balloon Delivery Kit (echogenic needle, blunt dilator and introducer sheath)

	Component	Material
3	Echogenic Needle	Stainless steel
4	Blunt Dilator	HDPE tubing compound
5	Introducer Sheath	



The Balloon (implant) is Biodegradable, inflatable balloon made of Poly L-Lactide-co-e Caprolactone.

PACKAGE CONTENTS:

› BioProtect Balloon Implant™ System
› Instructions for Use
› Quick Guide
› 4 Patient Labels
› Humidity Indicator
› Desiccant

In addition to the devices listed in the package contents section, the following items (not provided) are required for the procedure and should be readily available prior to commencing the procedure:

› Saline solution (0.9%)
› 20 ml Sterile, disposable luer-lock syringe
› Scalpel
› 10 ml tapered/slip tip syringe (for hydrodissection)
› Suturing kit

INDICATIONS FOR USE

The BioProtect Balloon Implant™ System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of the BioProtect Balloon Implant System to reduce the radiation dose delivered to the anterior rectum.

The BioProtect Balloon Implant System is composed of a balloon made of a biodegradable material that maintains the space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

CONTRAINDICATIONS

› The BioProtect Balloon Implant System should not be implanted into areas with active or latent infection or signs of tissue necrosis.
› The BioProtect Balloon Implant System should not be used if the patient has any disorder which would create an unacceptable risk of post-operative complications such as an uncontrolled bleeding tendency, immuno-suppression or severe chronic diseases.
› Do not use if the patient has a known allergy to any of the device components.

IMPLANT MAGNETIC RESONANCE IMAGING (MRI) SAFETY INFORMATION

The BioProtect Balloon Implant System is MR safe and poses no known hazards resulting from exposure to any MR environment.

All other BioProtect Balloon Implant System delivery components are MR unsafe.

WARNINGS AND PRECAUTIONS

BEFORE USE

- BioProtect Balloon Implant System should be used by physicians experienced with performing trans-perineal procedures under transrectal ultrasound guidance.
- User should be trained by a BioProtect representative.
- Do not use the BioProtect Balloon Implant System if the package was opened, broken or damaged, as sterility may have been compromised.
- Do not inflate prior to insertion.
- Do not use the BioProtect Balloon Implant System if the humidity indicator inside the package shows 40% or above (the 40% indicator is lavender color).
- Do not re-sterilize or reuse the BioProtect Balloon Implant System or any of its components.
- Do not use any part of the BioProtect Balloon Implant System after the indicated expiration date.
- The US pivotal trial did not include patients with prior radical prostatectomy, cryosurgery, or other local therapy for prostate cancer; prior radiotherapy to the pelvis; active inflammatory bowel disease or known/suspected rectal carcinoma; history of prior surgery involving the rectum or anus or peri-rectal/ prostatic area; acute or chronic prostatitis.
- If placing fiducials, do so with a transperineal approach prior to BioProtect Balloon Implant placement. Do not use the BioProtect Balloon Implant System if fiducials that were implanted with transrectal approach are in place.
- The US pivotal trial included prostate cancer patients with clinical stage T1-T3 disease, median age of 71 years, for a median follow up period of 12 months. Additional details regarding the pivotal trial are provided below:
  - **Tables 1-4** below provide further data on BioProtect Balloon Implant implantation during the US pivotal trial regarding hydrodissection during implantation, balloon inflation volume, balloon height, and rectal wall thickness.
  - **Tables 5-6** below list the overall number of gastrointestinal and genitourinary adverse events in the pivotal study regardless of their attribution to the device, procedure, radiation treatment, or the clinical study for both arms.
  - With respect to bladder volume, the pre-implantation mean of 194.3cc (±128.51cc) and post-implantation mean of 231.5cc (±134.56cc) show a modest increase. (see Table 7 below).
  - Regarding treatment constraint combinations from the study, no plan in the balloon group failed to meet all constraints. As illustrated in Table 8 below, there was a significantly higher likelihood in achieving PTV and all rectal constraints (83.5% vs 57.7%) favoring the balloon arm, as well as all PTV and bladder constraints (70.5% vs 60.3%).

Table 1. Hydrodissection During Implantation

Summary	Hydrodissection	No Hydrodissection	All Balloons
Hydrodissection, n (%)			
Yes	60 (42.0%)		60 (42.0%)
No		83 (58.0%)	83 (58.0%)
Method of Marking, n/N (%)			
Fiducial Markers	45/60 (75.0%)	82/83 (98.8%)	127/143 (88.8%)
Radio Beacon	15/60 (25.0%)	1/83 (1.2%)	16/143 (11.2%)
Ease of Marking, n/N (%)			
Easy	59/60 (98.3%)	82/83 (98.8%)	141/143 (98.6%)
Moderately Difficult	1/60 (1.7%)	1/83 (1.2%)	2/143 (1.4%)
Difficult	0/60 (0.0%)	0/83 (0.0%)	0/143 (0.0%)
Ease of Instrumentation Use, n/N (%)			
Easy	55/60 (91.7%)	79/83 (95.2%)	134/143 (93.7%)
Moderately Difficult	5/60 (8.3%)	4/83 (4.8%)	9/143 (6.3%)
Difficult	0/60 (0.0%)	0/83 (0.0%)	0/143 (0.0%)
Ease of Balloon Implantation, n/N (%)			
Easy	50/58 (86.2%)	64/75 (85.3%)	114/133 (85.7%)
Moderately Difficult	7/58 (12.1%)	11/75 (14.7%)	18/133 (13.5%)
Difficult	1/58 (1.7%)	0/75 (0.0%)	1/133 (0.8%)
Not Available	2	8	10
Problems During DRE, n/N (%)			
Yes	0/60 (0.0%)	0/83 (0.0%)	0/143 (0.0%)
No	60/60 (100.0%)	83/83 (100.0%)	143/143 (100.0%)

Table 2. Balloon Inflation Volume

Volume of Balloon Inflation Volume (cc)	
n	142
Mean (SD)	14.43 (2.477)
Median	14.94
Min, Max	5.20, 19.67

Table 3. Balloon Height*

Post-Implantation (cm)	
n	142
Mean (SD)	1.93 (0.374)
Median	1.94
Min, Max	0.60, 3.58

**See Balloon Insertion section.*

Table 4. Rectal Wall Thickness*

Rectal Wall Thickness (mm)	
n	142
Mean (SD)	3.17 (0.640)
Median	3.1
Min, Max	1.6, 5.2

**See Balloon Insertion section.*

Table 5. Gastrointestinal (GI) Adverse Events, Per-Protocol Population

	Balloon (N=143)		Control (N=79)	
	≤183 Days	> 183 Days	≤ 183 Days	> 183 Days
Subjects Included in Window, n	143	125	79	66
Subjects with One or More Gastrointestinal Adverse Events, n (%)	**38** (26.6%)	**11** (8.8%)	**22** (27.8%)	**7** (10.6%)
Total Number of Gastrointestinal Adverse Events, n	55	14	30	8
Gastrointestinal Adverse Events by Term, n				
Abdominal pain	2	3	0	0
Abdominal tenderness	1	0	0	0
Bowel incontinence	0	0	1	0
Bowel urgency	5	0	4	0
Diarrhea	9	4	11	1
Gas	2	0	1	0
Hematochezia (blood in stool)	2	1	2	0
Ileus	0	0	1	0
Loose stools	1	0	3	0
Pain (narcotic given)	2	0	0	0
Rectal bleeding	4	3	1	0
Rectal wall puncture	1	0	0	0
Rectal-anal mucositis (irritation and ulceration)	2	0	0	0
Straining (newly developed)	1	0	0	0
Tenesmus (feeling of incomplete defecation)	6	0	1	0
Other	17	3	5	7
Other Gastrointestinal Adverse Events (Specify Text), n				
Abnormal bowel habit	0	0	0	1
Abscess of right gluteal area/ perianal area	0	0	0	1
Bleeding hemorrhoids - prior condition got worse	0	0	1	0
Cancer - newly diagnosed	0	1	0	0
Constipation	8	1	2	2
Defecation reflex when urinating	1	0	0	0
Difficulty controlling bowel function	0	0	0	1
Epigastric pain	1	0	0	0
Flatulence	2	0	0	1
Gastric cancer	0	0	0	1
Irregular bowel movements	1	0	0	0
Mucus in stool	1	0	0	0
Nausea	1	0	0	0
Nausea and vomiting	1	0	0	0
Perianal discomfort	1	0	0	0
Proctitis	0	0	2	0
Sigmoid cancer	0	1	0	0

Table 6. Genitourinary (GU) Adverse Events, Per-Protocol Population

	Balloon (N=143)		Control (N=79)	
	≤ 183 Days	> 183 Days	≤ 183 Days	> 183 Days
Subjects Included in Window, n	143	125	79	66
Subjects with One or More Genitourinary Adverse Events, n (%)	**79** (55.2%)	**17** (13.6%)	**46** (58.2%)	**14** (21.2%)
Total Number of Genitourinary Adverse Events, n	157	28	88	24
Genitourinary Adverse Events by Term, n				
Acute urinary retention	2	0	1	0
Bladder spasms	1	1	1	0
Burning with urination	14	2	12	2
Dysuria (difficulty emptying bladder)	38	0	19	1
Erectile dysfunction	4	5	3	5
Hematuria	3	2	1	1
Hemospermia (blood in sperm)	1	0	0	1
Impotence	1	0	0	0
Infection - Urinary Tract	1	2	1	0
Nocturia (newly developed)	21	5	7	4
Pain (no narcotic given)	7	1	3	0
Pruritis	1	0	0	0
Urgent, frequent urination	48	4	26	6
Urinary incontinence	3	3	3	0
Other	12	3	11	4
Other Genitourinary Adverse Events (Specify Text), n				
Anejaculation	0	1	0	0
Cystitis	1	0	2	0
Drip after urination	1	0	0	0
Dysuria	1	0	0	0
E coli in urine culture	0	0	1	0
Hesitation of flow during urination	1	0	0	0
Induced cystitis, minor UTI	1	0	0	0
Itching penis	0	0	1	0
No ejaculation	0	0	1	0
Nocturia	0	1	0	0
Nocturia - prior condition got worse	0	0	1	0
Pelvic pain	0	1	0	0
Penile contraction	1	0	0	0
Radiation cystitis near bladder neck	0	0	0	1
Right flank pain	0	0	0	1
Slowing of urinary stream	0	0	0	1
Swelling and pain- epididymitis	0	0	1	0
Transurethral resection of prostate	0	0	1	0
Ureteral stones	0	0	1	0
Urethral stricture	0	0	0	1
Urinary hesitancy	1	0	0	0
Urinary retention	3	0	0	0
Weak current urination	1	0	0	0
Weak urinary flow	0	0	2	0
Weak urine stream	1	0	0	0

Table 7. Pre- and Post-Implantation Bladder Volume

Summary	Pre-Implantation (N=143)	Post-Implantation (N=142)	Change from Pre-Implantation	% Change from Pre-Implantation
Volume of Bladder (cc)				
n	143	142	142	142
Mean (SD)	194.3 (128.51)	231.5 (134.56)	37.2 (155.28)	46.3 (103.56)
Median	158.8	202.4	27.0	14.3
Min, Max	38.4, 729.0	34.6, 662.8	-418.9, 485.4	-81.4, 456.2
Median 95% CI			9.1, 50.8	5.8, 32.2
P-Value			0.007	0.007

Table 8. Summary of Treatment Constraint Combinations from Site Assessments, Per-Protocol Population

Constraint	Balloon (N=139)[1]	Control (N=78)[1]
Prostate PTV and Rectum Constraints, n (%)		
PTV Met and All Rectum Constraints Met	116 (83.5%)	45 (57.7%)
PTV Met and One or More Rectum Constraints Not Met	7 (5.0%)	16 (20.5%)
PTV Not Met and All Rectum Constraints Met	15 (10.8%)	11 (14.1%)
PTV Not Met and One or More Rectum Constraints Not Met	1 (0.7%)	6 (7.7%)
Prostate PTV and Bladder Constraints, n (%)		
PTV Met and All Bladder Constraints Met	98 (70.5%)	47 (60.3%)
PTV Met and One or More Bladder Constraints Not Met	25 (18.0%)	14 (17.9%)
PTV Not Met and All Bladder Constraints Met	15 (10.8%)	10 (12.8%)
PTV Not Met and One or More Bladder Constraints Not Met	1 (0.7%)	7 (9.0%)
Rectum and Bladder Constraints, n (%)		
All Rectum Constraints Met and All Bladder Constraints Met	106 (76.3%)	51 (65.4%)
All Rectum Constraints Met and One or More Bladder Constraints Not Met	25 (18.0%)	5 (6.4%)
One or More Rectum Constraints Not Met and All Bladder Constraints Met	7 (5.0%)	6 (7.7%)
One or More Rectum Constraints Not Met and One or More Bladder Constraints Not Met	1 (0.7%)	16 (20.5%)
Prostate PTV, Rectum, and Bladder Constraints, n (%)		
PTV Met, Rectum Met, Bladder Met	92 (66.2%)	42 (53.8%)
PTV Met, Rectum Met, Bladder Not Met	24 (17.3%)	3 (3.8%)
PTV Met, Rectum Not Met, Bladder Met	6 (4.3%)	5 (6.4%)
PTV Met, Rectum Not Met, Bladder Not Met	1 (0.7%)	11 (14.1%)
PTV Not Met, Rectum Met, Bladder Met	14 (10.1%)	9 (11.5%)
PTV Not Met, Rectum Met, Bladder Not Met	1 (0.7%)	2 (2.6%)
PTV Not Met, Rectum Not Met, Bladder Met	1 (0.7%)	1 (1.3%)
PTV Not Met, Rectum Not Met, Bladder Not Met	0 (0.0%)	5 (6.4%)

[1] Per-Protocol subjects in the primary safety analysis.
For all PTV volumes, more than 95% of the PTV was to receive at least 100% of the prescribed dose. For standard fractionation (1.8 – 2.0 GY fraction) dose constraints for rectum were V75< 15%, V70< 25%, V65< 35%, V60< 50%, and for bladder V80< 15%, V75< 25%, V70< 35%, and V65< 50%. For 20 fractions regimen, dose constraints for rectum were V60< 15%, V56< 25%, V52< 35%, V48< 50%, and for bladder V60< 25%, V56< 35%, and V52< 50%. For 28 fractions regimen, dose constraints for rectum were V70< 10 cm3, V65< 10%, V40< 35%, and for bladder V70< 10 cm3, V65< 15%, and V40< 35%. For 29-30 fraction regimen, dose constraints for rectum were V70< 10cc, V72< 5%, V66< 20%, V54< 30%, and V36< 50%. For bladder V72< 3%, V64< 25%, and V50< 50%.

DURING PROCEDURE

› Special care must be taken during dissection and balloon insertion to avoid perforation of adjacent organs and vessels or nerve damage. Pay attention to the UltraSound (US) monitor during insertion of the needle and dilator.

› Do not fill the balloon before it is located at the desired position.

› The saline solution should be 35-40°C (95-104°F) when filling the balloon.

› Do not overfill the balloon - the maximal amount of saline solution required to fill the balloon is 17ml.

› If you encounter difficulty filling the balloon in the proper space, remove the balloon or leave it in place empty.

POST PROCEDURE

› If subsequent infection, signs or symptoms of damage to adjacent organs is detected, the patient should be inspected and treated accordingly using modalities such as: patient reassurance, antibiotics, rectal examination, balloon needle aspiration or removal of the device.

› Ensure safe disposal of needle and any used components and packaging materials utilizing standard hospital safety regulations and procedures and universal precautions for bio-hazard waste.

DIRECTIONS FOR USE

Note: For detailed implantation steps use BioProtect Balloon Implant™ System Implantation Quick Guide MKD-10534.

PATIENT PREPARATION

› Prior to the procedure the patient may receive medication to relieve anxiety. Various anesthesia methods may be used (local, epidural, general) with or without sedation.

› The patient should receive broad spectrum antibiotics for a total of 5 days, starting two (2) days before the procedure and for two (2) consecutive days after, or per treating institution's standard practice.

› Make sure that the patient had bowel preparation per the treating institution's standard practice.

› Position the patient in lithotomy position per local practice.

› Introduction of a urethral catheter at the beginning of the session is optional and may aid in visualization of the urethra. At the end of the procedure (or per standard practice) the catheter should be removed.

› Position the US probe in the patient's rectum and ensure optimal visibility.

› If placing fiducials, do so with a transperineal approach prior to the implantation of the balloon.

OPENING THE STERILE PACK

› Check the carton pack for expiration date to ensure that the pack is not damaged.

› Open the carton pack and remove the foil pack.

› ⚠ The outer surface of the sterile blister pack is non-sterile.

› Inspect the humidity indicator, make sure there is no change in color, then discard. At 40% humidity the indicator should show blue. If colored pink, the device should be discarded.

› Holding the blister pack in one hand, and working from the end with the straight edge, peel back the cover to expose the inner sterile blister pack.

› Present the external blister pack for aseptic removal of the inner sterile blister pack.

› Remove the lid from the inner blister pack, by pulling upwards (where indicated by Pull mark).

BLUNT DISSECTION

› Insert the needle approximately 1-2 cm anterior to the anal opening, using a finger's width as guide.

› Push the echogenic needle forward on the midline under US vision towards the top of the rectourethralis muscle (visible mound proximal to the prostate).

› Perform a 6mm deep and 6mm long incision at the point of entry and advance the beveled tip dilator over the echogenic needle up to the rectourethralis muscle, and remove the echogenic needle.

› Once below prostate apex, ensure dilator is at midline.

› Slowly advance the dilator, gliding between the prostate and the rectal wall towards the prostate base at the seminal vesicles level. If tissue resistance is noticed, hydrodissection is optional using a slim tip syringe.

› Using axial view, raise and gently wiggle the dilator to ensure that there is no rectal wall involvement. Upon reaching the prostate base, maintain the dilator in place.

› Once the desired location at midline is confirmed, withdraw the blue dilator while holding the white introducer sheath in place.

BALLOON INSERTION

› Remove (push away) the upper (blue) protecting tube from the balloon while holding the balloon base to prevent balloon movement.

› Remove (pull it toward the handle) the lower (blue) protecting tube.

› Ensure that the balloon deployer's red knob is facing up and introduce the balloon through the white introducer sheath.

› Advance the deployer through the white introducer sheath up to the designated mark on the deployer and hold the deployer in place.

› Fill a 20 ml luer lock syringe with 17ml of warm, bubble-free saline solution and connect it to the balloon deployer.

› Fully uncover the folded balloon by pulling the white introducer sheath all the way back until it reaches the deployer handle.

› Under sagittal view, slowly fill the balloon, ensuring optimal prostate-apex through to base separation. Halfway through inflation volume, stop filling and check the balloon's position using sagittal and axial views.

  › If balloon repositioning is desired, ensure full deflation of the balloon before repositioning. Once the balloon is repositioned, follow the instructions above to fill the balloon again.

  › Once desired balloon position is confirmed, lower the US probe slightly while maintaining sufficient visibility, and slowly deflate the balloon until you reach a balloon height of ~18 mm and rectal wall thickness is >1mm.

  › Release (push forward) the red safety lock button and rotate the green knob on the balloon deployer 180º to the right. This will seal the balloon, detach the deployer from the balloon and leave the balloon sealed in situ.

› Pull out the introducer sheath and deployer.

› Verify the balloon is in correct location and is intact.

CLOSING OF INCISION

› Suture the incision.

› Perform digital rectal examination to confirm rectal mucosa integrity.

RISKS RELATED TO BIOPROTECT BALLOON IMPLANT™ SYSTEM PROCEDURE:

Risks associated with the fiducial marker and/or balloon implantation procedure include, but are not limited to:

› Fever greater than 100°F/37.7°C;

› Site bleeding - mild to moderate;

› Site hematoma - temporary, self-terminated;

› Site infection and related symptoms - Infection along the trajectory of the insertion of surgical tools, including the site of implantation;

› Rectal wall puncture / perforation;

› Abdominal tenderness;

› Burning with urination;

› Dysuria;

› Hematuria;

› Hemospermia;

› Fatigue;

› Pain;

› Nausea and vomiting;

› Constipation.

Risks specifically associated with the BioProtect Balloon Implant System include:

- Erosion through a hollow organ wall such as bowels, urinary bladder, etc.;
- Local inflammatory reaction;
- Migration of the device from the desired location;
- Needle penetration into bloodstream, bladder, prostate, rectal wall, rectum or urethra;
- Premature balloon deflation;
- Urinary retention;
- Rectal urgency, tenesmus;
- Tissue necrosis;
- Abdominal tenderness;
- Burning with urination;
- Dysuria;
- Constipation;
- Defecation reflex while urinating.

The risks and benefits of implanting the BioProtect Balloon Implant System in patients with blood coagulation disorders, compromised immune systems or any other conditions that would compromise healing should be carefully considered.

Note: adverse events related to radiation are not discussed here.

STORAGE

- Until use, the BioProtect Balloon Implant System should be stored in a clean and dry area, out of direct sunlight. Maintain a temperature between 0-29˚C (32-84˚F).

SHELF LIFE

- The expiry date is indicated on the package.

USE OF ORIGINAL PRODUCTS

The components of the BioProtect Balloon Implant System are designed for a specific use and complement each other. No system components may be replaced by a product from another manufacturer even if the other product or part is comparable or identical to the original product in appearance and dimensions. Any material used from other manufacturers, any structural alterations resulting from use of products from another source and/or impurities of the material as well as minor adjustments of the BioProtect Balloon Implant System or any of its components, might introduce unforeseen risks to both patient and user.

COMPANY CONTACT INFORMATION

BioProtect Ltd.
8 Tsor St., Tzur Yigal
4486200, Israel

Mail: info@bioprotect.com

SYMBOLS ON THE PACKAGING

	Catalog Number
	Serial Number
	Date of Manufacture
	Use-by Date
	Volume
	Caution
	Consult Instructions for Use
	Sterilized using Ethylene Oxide
	Do Not Re-sterilize
	Do Not Re-use
	Fragile, Handle with Care

	Keep Dry
	Keep away from sunlight
	Do not use if package is damaged and consult instruction for use
	Manufacturer
	Temperature limit
	Single sterile barrier system with protective packaging outside
UDI	Unique Device Identifier
MD	Medical Device
MR	MR Safe
Rx only	“Caution: Federal law restricts this device to sale by or on the order of a physician”

NOTES