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℞ Only

SIR-Spheres® Y-90 resin microspheres

(Yttrium-90 microspheres)

1 Description

SIR-Spheres microspheres consist of biocompatible microspheres containing yttrium-90 with a size between 20 and 60 microns in diameter. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission. The maximum energy of the beta particles is 2.27 MeV with a mean of 0.93 MeV. The maximum range of emissions in tissue is 11 mm with a mean of 2.5 mm. The half-life is 64.1 hours. In therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. The average number of particles implanted is 30 – 60 x 10^6. SIR-Spheres microspheres are a permanent implant.

SIR-Spheres microspheres are implanted into a hepatic tumor by injection into either the common hepatic artery or the right or left hepatic artery using a catheter or chemotherapy catheter port. The SIR-Spheres microspheres distribute non-uniformly in the liver, primarily due to the unique physiological characteristics of the hepatic arterial flow, the tumor to normal liver ratio of the tissue vascularity, and the size of the tumor. The tumor usually gets higher density per unit distribution of SIR-Spheres microspheres than the normal liver. The density of SIR-Spheres microspheres in the tumor can be as high as 5 to 6 times of the normal liver tissue. Once SIR-Spheres microspheres are implanted into the liver, they are not metabolized or excreted, and they stay permanently in the liver. Each device is for single patient use.

2 Indications for Use

SIR-Spheres microspheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

3 Contraindications

SIR-Spheres microspheres are contraindicated in patients who have:

- had previous external beam radiation therapy to the liver
- ascites or are in clinical liver failure
- markedly abnormal synthetic and excretory liver function tests (LFTs), such as total bilirubin > 2.0 mg/dL or albumin < 3.0 g/dL
- > 20% lung shunting of the hepatic artery blood flow, or > 30 Gy radiation absorbed dose to the lungs, as estimated by the ^{99m}Tc MAA scan
- pre assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel
- disseminated extra-hepatic malignant disease
- been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres microspheres
- portal vein thrombosis

4 Warnings

4.1 Non-Target Delivery of SIR-Spheres microspheres

Inadvertent delivery of SIR-Spheres microspheres to extra-hepatic structures such as the esophagus, stomach, duodenum, gallbladder or pancreas may result in radiation injury to these structures. Meticulous angiographic technique must be employed to prevent the non-target delivery of SIR-Spheres microspheres to any extra-hepatic structures.

4.2 Radioembolization Induced Liver Disease (REILD)

Delivery of excessive radiation to the normal liver parenchyma may result in REILD – see description in *Section 7*.

The risk of REILD may also be increased in patients with pre-existing liver disease. Consideration should be given to reducing the prescribed activity of SIR-Spheres microspheres in the following clinical settings[1]:

- Reduced liver functional reserve due to steatosis, steatohepatitis, hepatitis or cirrhosis
- Elevated baseline bilirubin level
- Small tumor burden (< 5% liver involvement)
- Small liver volume (< 1.5 L)
- Prior hepatic resection
- Prior liver directed therapy
- Extensive prior treatment with systemic chemotherapy and/or biologic therapies

4.3 Radiation Pneumonitis

High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis. The lung radiation dose must be limited to ≤ 30 Gy.

5 Precautions

- For determining the prescribed activity of SIR-Spheres microspheres to administer, the Body Surface Area (BSA) method is recommended. The Empirical method is not recommended. For some patients, the Empirical method may result in excessive activity being prescribed. For further information on the BSA method, refer to *Appendix III: Calculation of Individual Dose*.
- No studies have been done on the safety and effectiveness of this device in pregnant women, nursing mothers or children.
- Due to the radioactivity of this device and the significant consequences of misplacing the microspheres in situ, this product must be implanted by doctors with adequate training in the handling and implantation technique for this device.
- Sirtex recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres microspheres. The SPECT scan will detect the Bremsstrahlung radiation from the yttrium-90 to confirm placement of the microspheres in the liver.
- This product is radioactive. The use of this device is regulated under Title 10 of the Code of Federal Regulations Part 35. These regulations must be followed when handling this device.
- All persons handling, dispensing and implanting this device must be familiar with and abide by all Local, State and Federal regulatory requirements governing therapeutic radioactive materials. Accepted radiation protection techniques should be used to protect staff when handling both the isotope and the patient.
- Some patients may experience gastric problems following treatment, but H-2 blocking agents may be used the day before implantation of SIR-Spheres microspheres and continued as needed to reduce gastric complications.
- Many patients may experience abdominal pain immediately after administration of SIR-Spheres microspheres and pain relief may be required.
- SIR-Spheres microspheres demonstrated a mild sensitization potential when tested dermally in an animal model.

6 Clinical Trial Results

In a randomized, controlled clinical trial, a total of 70 patients were studied in two arms, 34 patients with FUDR chemotherapy (control group), and 36 patients with FUDR plus SIR-Spheres microspheres. The results are shown in the following tables.

Table 1 – Tumor Response by Volume

Response	CR	PR	NC	PD	Others
FUDR only (N = 34)	1	7	12	9	5
FUDR + SIR-Spheres microspheres (N = 36)*	2	16	10	5	3

*(P = 0.033)

Tumor response was measured by two consecutive CT scans in a 3-month interval period.

CR = Complete Response, PR = Partial Response, NC = No Change, PD = Progressive Disease, Others = No follow-up or unmeasurable

Table 1 indicates that there is a statistically significant improvement of the tumor response rates (CR+PR) in the group treated with FUDR plus SIR-Spheres microspheres, when compared with the group treated with FUDR only.

Table 2 – Time to First Progressive Disease in the Liver

	FUDR Only	FUDR + SIR-Spheres microspheres
Number of Patients	34	36
Mean Time in Days +/- SD*	312 Days +/- 330	510 Days +/- 516
Median Time in Days*	233 Days	366 Days

*(P = 0.05)

Progressive Disease was defined as more than 25% increase of tumor volume, or development of new lesion(s) in the follow up CT scan, when compared to the pre-treatment CT scan.

Table 2 indicates that there is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres microspheres, when compared with the group treated with FUDR only.

7 Adverse Events

When the patient is treated with proper technique, without excessive radiation to any organ, the common adverse events after receiving the SIR-Spheres microspheres are fever, transient decrease of hemoglobin, mild to moderate abnormality of liver function tests (mild increase in SGOT, alkaline phosphatase, bilirubin), abdominal pain, nausea, vomiting, and diarrhea.

In the Phase III randomized controlled clinical trial with 70 patients, there was a minimal increase of Grade 1 and 2 events, mostly transient abnormal LFTs and nausea and vomiting in the patients who

[1] Gil-Alzugaray et al. Hepatology, Vol 57, No. 3, 2013.

received SIR-Spheres microspheres. There was no difference in the number of patients who developed Grade 3 and 4 adverse events between the two groups. No patient died due to the adverse events directly related to SIR-Spheres microspheres.

Table 3 – Adverse Events

Events	Grade 1 and 2		Grade 3 and 4	
	FUDR	FUDR + SIR-Spheres microspheres	FUDR	FUDR + SIR-Spheres microspheres
Hemoglobin	4	5	1	0
Bilirubin	7	2	0	1
AST (SGOT)	110	109	14	7
Alk. Phos.	90	188	5	14
Nausea/ Vomiting	5	13	2	1
Diarrhea	6	3	1	0
TOTAL	**222**	**320**	**23**	**23**

The data are from a clinical trial with 34 patients on chemotherapy only, and 36 patients on chemotherapy plus SIR-Spheres microspheres.

Potential Serious Adverse Events Due to High Radiation

***Acute pancreatitis*:** causes immediate severe abdominal pain. Verify by SPECT imaging of the abdomen (Yttrium-90 Bremsstrahlung image) and test for serum amylase.

***Radiation Pneumonitis*:** causes excessive non-productive cough. Verify by X-ray evidence of pneumonitis.

***Acute Gastritis*:** causes abdominal pain. Verify by standard methods to diagnosis gastric ulceration.

***Acute cholecystitis*:** causes significant upper abdominal pain and may require cholecystectomy for resolution. Verify by appropriate imaging studies.

***Radioembolization induced liver disease (REILD)*:** REILD is a rare complication following SIRT. REILD is characterized by a well-defined constellation of temporal, clinical, biochemical and histopathologic findings. It typically manifests approximately 4 to 8 weeks post-SIRT and is characterized clinically by jaundice and ascites in the absence of tumor progression or bile duct obstruction.

The typical biochemical picture of REILD is an elevated bilirubin (> 3 mg/dL) in almost all cases, elevated alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) in most cases, accompanied by virtually no change in the transaminases (AST and ALT). In the event that a liver biopsy is performed, the typical histological appearance is of sinusoidal obstruction that may resemble veno-occlusive disease.

REILD may occur in both non-cirrhotic and cirrhotic patients.

Prophylactic treatment with methyl-prednisolone and ursodeoxycholic acid starting on the day of SIRT and continued for two months may reduce the incidence of REILD.

In the treatment of REILD, low molecular weight heparin may also be considered but both corticosteroids and heparin may only be useful if commenced very early in the course of the disease. See also *Section 4.2*.

8 Patient Selection and Pre-treatment Testing

Patients are indicated for treatment with SIR-Spheres microspheres when the metastatic colorectal cancer in the liver is considered non-resectable. In any of the following circumstances, patients would generally be considered non-resectable:

- Multiple liver metastases together with involvement of both lobes.
- Tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the metastases were resected.
- Tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken.
- Widespread metastases such that resection would require removal of more liver than is necessary to maintain life.

Resectability may be evaluated via imaging with a triple phase contrast angio-portal CAT scan or MRI.

Patient Tests Before Treatment with SIR-Spheres microspheres

The following tests are recommended before treatment:

- A hepatic angiogram should be performed to establish arterial anatomy of the liver.
- A nuclear medicine break through scan (Intrahepatic Technetium MAA Scan) to determine the percent lung shunting. If a port has been inserted, this test can be performed through the port.
- Serologic tests of liver function should be performed to determine the extent of liver function damage.

Appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

9 Radiation Safety

The preparation and implant procedure must be regarded as being a potentially serious radiation hazard to the staff and a serious contamination hazard. Regulatory and local radiation usage guidelines should be followed concerning implantation and post-implantation care.

The following are sample measured thermoluminescent dosimetry (TLD) exposures to personnel.

Table 4 – Exposure Dose per Patient for Implant Preparation (Technologist)

	Trunk mSv (mrem)	Lens of the Eye mSv (mrem)	Hands mSv (mrem)
Shallow Dose (0.07mm)	0.027 (2.7)	0.026 (2.6)	0.35 (35)
Deep Dose (10 mm)	0.003 (0.3)	0.004 (0.4)	

Assuming handling of a 3 GBq device and dose preparation time of 30 minutes. TLDs were worn near the pelvis, on the shirt's lapel, and on the working finger.

Table 5 – Exposure Dose per Patient for Implant Procedure (Physician)

	Trunk mSv (mrem)	Lens of the Eye mSv (mrem)	Hands mSv (mrem)
Shallow Dose (0.07mm)	0.038 (3.8)	0.12 (12)	0.32 (32)
Deep Dose (10 mm)	0.004 (0.4)	0.054 (5.4)	

Assuming average patient dose of approximately 2 GBq and dose injection time of 20 minutes.

Post-Implant Exposure

Exposure data from patients implanted with an average of 2.1 GBq at approximately 5-6 hours post implantation at the following distances from the patient's abdomen:

Distance	Exposure
0.25 m	18.8 μSv/hr
0.5 m	9.2 μSv/hr
1.0 m	1.5 μSv/hr
2.0 m	0.4 μSv/hr
4.0 m	<0.1 μSv/hr

(1 mSv = 100 mrem)

10 How Supplied

SIR-Spheres microspheres are provided in a vial with water for injection. Each vial contains 3 GBq of Y^{90} ± 10% (at the time of calibration) in a total of 5 cc water for injection. Each vial contains 40 – 80 million microspheres. The vial is shipped within a 6.4 mm minimum thickness lead pot. The package consists of a crimp-sealed SIR-Spheres microspheres glass vial within a lead pot, and a package insert within Type-A packing bucket.

The vial and its contents should be stored inside its transportation container at room temperature (15-25 °C, 59-77 °F).

The calibration date (for radioactive contents) and the expiration information are quoted on the vial label. The useful life of the SIR-Spheres microspheres ends 24 hours after the time of calibration. The particle size has been validated before shipment, as 32.5 μ ± 2.5 μ. Less than 10% will be < 30 μ and > 35 μ.

11 Appendices

I. General Information
II. Dose Preparation Procedure
III. Calculation of Individual Dose
IV. Radiation Dosimetry
V. Technique for Performing the Intra hepatic Technetium MAA Scan
VI. Correction for Decay
VII. Symbols Definition Glossary Table

Appendix I: General Information

Restricted to Accredited Facilities

SIR-Spheres microspheres may only be dispatched to a duly licensed or accredited facility capable of handling therapeutic medical isotopes.

Restricted to Trained and Licensed Physicians

This device is licensed by the Agency for distribution to persons licensed pursuant to 105 CMR 120.589 or under equivalent licenses of the Nuclear Regulatory Commission, an Agreement State, or a licensing State. Only doctors qualified and licensed under Title 10 Code of Federal Regulations Part 35 (Nuclear Regulatory Commission) and trained under the Sirtex TEC training program may order and implant SIR-Spheres microspheres.

Appendix II: Dose Preparation Procedure

Unpacking:

- Unpack SIR-Spheres microspheres, leaving shipping vial in lead pot.
- Place on the bench top in a lead or acrylic shielded box if available.
- Remove the center of aluminum seal from sterile Delivery vial with forceps and clean the septum with an alcohol swab.
- Place the Delivery vial in the acrylic holder or transport base for stability and shielding.

Vent Process:

- Insert a short 25-gauge needle through the septum of the Delivery vial until it just pierces the septum to create a vent

Priming:

- Consult the Class I SIROS Delivery System instructions for use for detailed priming information.

Drawing the Patient-Specific Activity Process

- Invert the lead pot and shake vigorously before opening to re-suspend the SIR-Spheres microspheres, which will have settled during shipping.
- Quickly open the lead pot and remove the shipping vial using forceps.
- Determine the total activity of SIR-Spheres microspheres in the shipping vial using an appropriate ion chamber (dose calibrator) and then return the shipping vial to the lead pot.
- Determine the volume of SIR-Spheres microspheres suspension that needs to be withdrawn from the shipping vial to provide the intended patient-specific activity of SIR-Spheres microspheres. Partially remove the aluminum seal

of the SIR-Spheres microspheres shipping vial, clean with alcohol swab.

- Insert a 25-gauge needle through the septum of the shipping vial to create a vent, ensuring the needle is well clear of the contents in the shipping vial.
- Use a shielded 5 ml syringe with a 21-gauge hypodermic needle at least 50 mm long to puncture the septum of the SIR-Spheres microspheres shipping vial, and quickly draw back and forth several times in order to mix the SIR-Spheres microspheres thoroughly.
- Quickly withdraw the pre calculated patient radiation dose, and transfer into the vented Delivery vial. Withdraw the required amount quickly before the contents of the shipping vial start to settle.
- Verify the patient dose in the Delivery vial by re-measuring the activity in the shipping vial with dose calibrator, and correct, if necessary.
- Add the pre-calculated additional volume of sterile water or D5W.

Secure top of the dedicated holder onto the Delivery vial.
The patient dose is now ready for transport to the SIR-Spheres microspheres implantation room.

Appendix III: Calculation of Individual Dose

The recommended method for calculating the individual patient dose is the Body Surface Area (BSA) method.

The safety profile of the prescribed activity equations that enable accurate lobar treatment with SIR-Spheres microspheres is well established. The BSA method can take into account the volume of a single treated lobe, as well as that of the entire liver.

In this respect, the approach of lobar treatment versus whole liver treatment with SIR-Spheres microspheres is based on the presence of visible tumors on pre-treatment CT or MR imaging. If liver tumors are only visible in one lobe, then SIR-Spheres microspheres should be administered to that lobe only, thus sparing the contralateral lobe from unnecessary internal radiation.

Use of dosimetry formulas
BSA must first be determined and is calculated from the following equation (Equation 1):

$$BSA\ (m^2) = 0.20247 \times height(m)^{0.725} \times weight(kg)^{0.425}$$

Prescribed activity calculation for whole liver / bilobar treatment

$$Prescribed\ activity\ of\ SIR\text{-}Spheres\ microspheres\ (GBq) = (BSA - 0.2) + \left(\frac{V_{tumor}}{V_{tumor} + V_{normal\ liver}}\right)$$

Where:
V_{tumor} is the total volume of tumor in the liver
$V_{normal\ liver}$ is the volume of the non-tumor liver tissue

Prescribed activity calculation for lobar or super-selective treatment
In patients who receive lobar or segmental treatment with SIR-Spheres microspheres the prescribed activity must be reduced in accordance with the size of the portion of the liver being treated.

$$Activity_L\ (GBq) = \left[BSA - 0.2 + \left\{\frac{Tumor\ volume_L}{Total\ volume_L}\right\}\right] \times \left[\frac{Total\ volume_L}{Total\ liver\ volume}\right]$$

Where:
$Activity_L$ is the prescribed activity for the lobe
$Tumor\ volume_L$ is the volume of tumor present in the lobe
$Total\ volume_L$ is the total volume of the lobe including the tumor in the lobe
$Total\ liver\ volume$ is the total volume of the liver including the tumor
BSA is the Body Surface Area as per Equation 1

Lung Shunt Calculation Procedure

- Inject 4 mCi (150 MBq) of ^{99m}Tc MAA into the hepatic artery via a catheter
- Use a large FOV gamma camera, and obtain anterior and posterior images of the chest and abdomen (with 700 k to 1 million counts on abdomen, and the same count on the chest)
- Take right lateral abdomen, using same count
- Draw ROI around the whole liver and the whole lung and get the total counts for the lung and the liver
- Calculate the % shunt using following formula:

$$\%\ Shunt = \left(\frac{Lung\ Counts}{Liver\ Counts + Lung\ Counts}\right) \times 100$$

In order to optimize the risk/benefit for patients receiving SIR-Spheres microspheres, limiting the radiation exposure to the lungs to ≤ 30 Gy is required. The calculation of estimated radiation exposure to the lungs is given by the following formulae:

Activity that may potentially reach the lung:

$$A_{lung}\ (GBq) = A_{total}\ \times L/100$$

Where:
A_{lung} = lung activity (GBq)
A_{total} = total prescribed activity (GBq)
L = lung shunt (%)

The resulting lung dose, given that a given amount of activity shunts from the liver to the lung:

$$D_{lung}\ (Gy) = \frac{49670 \times A_{lung}}{M_{lung}}$$

Where:
D_{lung} = lung dose (Gy)
A_{lung} = lung activity (GBq)
M_{lung} = mass of the lung (g)

Example of prescribed activity calculation for right lobe treatment
Total liver volume = 1,800 mL
Total right lobe volume including tumor = 1,200 mL
Tumor volume in the right lobe = 300 mL
BSA = 2.0 m^2
Liver-lung shunt = 20%
Lung Mass = 1000 g

$$Prescribed\ activity\ for\ the\ right\ lobe\ (GBq) = \left[2.0 - 0.2 + \left\{\frac{300}{1{,}200}\right\}\right] \times \left[\frac{1{,}200}{1{,}800}\right] = \mathbf{1.37\ GBq}$$

In this example, given the lung shunt = 20%, pulmonary radiation exposure is taken into consideration:

$$A_{lung}\ (GBq) = 1.37\ GBq\ \times 20/100\ = \mathbf{0.274\ GBq}$$

Given that 0.274 GBq shunts from the liver to the lung, the resulting lung dose is:

$$D_{lung}\ (Gy) = \frac{49670 \times 0.274}{1000\ g} = \mathbf{13.61\ Gy}$$

A pulmonary radiation exposure of 13.61 Gy is less than the 30 Gy established limit, therefore no reduction in prescribed activity would be required.

Note: SIR-Spheres microspheres are contraindicated in patients with greater than 20% lung shunting of the hepatic artery blood flow determined by Technetium MAA scan.

Appendix IV: Radiation Dosimetry

The radiation dosimetry of the SIR-Spheres microspheres can be a complex and difficult task due to the non-uniform distribution of the particles in the normal liver and the tumors. In general, 1 GBq (27 mCi) of yttrium-90/kg of tissue provides 50 Gy of radiation dose.[2] However, because of the non-uniform distribution of the dose between the tumor and the normal liver tissue, a proportionally larger amount of radiation will be delivered to the tumor tissue, and less amount to the liver.

For example, a patient has a liver weighing 1500 g, and has two tumor nodules, a 4 cm size tumor in the right lobe, and a 3 cm size nodule in the left lobe. The post-injection images suggest that there is 5:1 density ratio for unit volume between the tumor and the liver. The patient received 2 GBq of SIR-Spheres microspheres. In such a case, the calculated radiation dose to the tumor is 294 Gy and the dose to the liver tissue is 58.5 Gy.

The radiation dose for other organs would be minimal or negligible, except for the organs adjacent to the liver, such as the stomach, large intestine, gall bladder, and the lung. The radiation dose may increase significantly, when there is shunting of the arterial blood to the lung, stomach, or small intestine.

Appendix V: Technique for Performing the Intra-Hepatic Technetium MAA Scan

Purpose: To assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs.

Agent: Technetium-99 labeled MAA (Macro-Aggregated Albumin)

Dose: 150 MBq (4 mCi)

Equipment: Any large FOV gamma camera

Administration: The patient needs to have a surgically implanted port or trans-femoral catheter placed in the hepatic artery. The Technetium-99 labeled MAA is injected into the port or catheter.

Imaging: The patient is positioned supine under the gamma camera and the following images recorded:

- Anterior and posterior images of abdomen and thorax - collect 700k –1000k cts for abdomen and same time for thorax.
- Right lateral abdomen – same time acquisition as for anterior

Analysis: Draw ROI around whole of liver and whole of lung fields. Calculate G_{mean} for liver region and lung region. Calculate Lung/Liver ratio using the following formula:
% lung shunting = (counts of total lung / counts of total lung plus counts of liver) x 100

Appendix VI: Correction for Decay

The physical half-life of yttrium-90 is 64.1 hours. Radioactive decay factors should be applied at the time of patient dose preparation, in order to calculate the true value of radioactivity present.

Table 6 – Decay Factors of SIR-Spheres microspheres

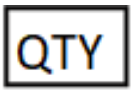
Hours	Decay Factor
0.5	0.995
1	0.989
2	0.979
3	0.968
4	0.956
5	0.947
6	0.937
7	0.927
8	0.917
9	0.907
10	0.898
11	0.888
12	0.878
24	0.772
36	0.678

[2] Russell, Carden, Herron: 'Dosimetry Calculations of Yttrium-90 used in the treatment of liver cancer.' Endocurietherapy/Hypertherm Oncol. 1988;4:171-186

48	0.595
72	0.459

Caution: The time of the initial calibration must be converted to the user's local time.

Appendix VII: Symbols Definition Glossary Table

SYMBOL	SYMBOL DEFINITION
	Manufacturer
	Date of manufacture
	Consult instructions for use
	Caution
	Use-by-date
	Lot or batch code
	Catalog number
	Serial number
	Quantity
	Sterilized using irradiation
	Sterilized using steam
	Ionizing radiation
	Single Use Only. Indicates a medical device that is intended for use on a single patient during a single procedure.

SYMBOL	SYMBOL DEFINITION
	Do not resterilize
	Product is not made with natural rubber latex
	Do not use if package is damaged
	Keep dry
	Temperature limit
	Caution: Federal law (USA) restricts this device to sale by or on the order of a physician or licensed healthcare practitioner.