English

Instructions for Use:

Bio*divYsio*™ AS

PC (phosphorylcholine) Coated Stent Delivery System

STERILE
SINGLE USE ONLY
NON-PYROGENIC

Sterilized by ethylene oxide
Do not use if the package is opened or damaged.

DESCRIPTION

Bio*divYsio*™ AS PC (phosphorylcholine) Coated Stent Delivery System (Bio*divYsio*™ AS PC)

The Bio*divYsio*™ AS is a flexible, balloon-expandable PC-coated stent 15 mm in length composed of laser-cut 316L implant grade stainless steel metal tubing mounted on a semi-compliant balloon catheter between two radiopaque marker bands. The stent is coated with a sub-micron thickness of a cross-linked phosphorylcholine ("PC") polymer. The Bio*divYsio*™ AS stent delivery system is used to carry the stent through the coronary vasculature to the target lesion where the stent is deployed as the balloon is inflated. The Bio*divYsio*™ AS is available in nominal diameters of 3.0, 3.5 and 4.0 mm. The Bio*divYsio*™ AS coated stent delivery system is compatible with PTCA guide wires $\leq$ 0.014"/0.356 mm and PTCA guide catheters ≥6F (I.D. 0.062"/1.57 mm).

INDICATIONS FOR USE

The Bio*divYsio*™ AS is intended for use in subjects with symptomatic ischemic heart disease due to *de novo* native coronary artery lesions (length ≤25 mm) with a reference vessel diameter ranging from ≥3.0 mm to ≤4.0 mm and intended to improve coronary luminal diameter. Long term outcome (beyond six months) for this permanent implant is unknown at present.

CONTRAINDICATIONS

The Bio*divYsio*™ AS is contraindicated for use in:

- Patients with intolerance or contraindication to antiplatelet or anticoagulant therapy
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.

WARNINGS/PRECAUTIONS

Warnings

Judicious selection of patients is necessary since the use of this device carries the associated risk of (sub)acute thrombosis, vascular complications and/or bleeding events.

Do not expand the stent beyond 4.25mm in diameter.

Persons allergic to 316L stainless steel may suffer an allergic reaction to this implant.

Use prior to the "Use Before" date shown on the label and preceded by the symbol:

The stent must not be deployed until it is in the appropriate position within the treatment vessel. Once deployment begins the stent cannot be repositioned.

Precautions

- The implantation of the stent must be performed only by physicians who have received adequate training in stent placement.
- A cardiac surgical team should be available while stent implantation is being performed.
- Subsequent restenosis may require repeat dilation of the arterial segment containing the stent. The long-term outcome following repeat dilation of endothelialized BiodivYsio™ AS is unknown at present.
- When multiple stents are required, stent materials should be of similar composition.
- The target lesion must be adequately pre-dilated to ensure placement of the Bio*divYsio*™ AS.
- High-quality fluoroscopic equipment must be used to determine the position of the Bio*divYsio*™ AS.

Stent Handling – Precautions

- **For single use only.** Do not resterilize or reuse.
- **Do not remove stent from its delivery balloon** as removal may damage the stent and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important during catheter removal from packaging, placement over guide wire and advancement through hemostasis valve adapter and guiding catheter hub.
- Do not "roll" the mounted stent with your fingers as this action may loosen the stent from the delivery balloon.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

Stent Placement – Precautions

- Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use balloon purging technique described in the Instructions for Use.
- Balloon pressures should be monitored during inflation. Do not exceed Balloon Rated Burst Pressure (RPB) as indicated on product label. Use of pressures higher than specified on product label may result in a ruptured balloon with possible intimal damage and dissection.
- Do not expand the stent if it is not properly positioned in the vessel. (See Stent/System Removal – Precautions).

- Do not attempt to pull an unexpanded stent back through the guiding catheter, dislodgement of the stent from the balloon may occur. (See Stent/System Removal – Precautions).
- Implanting a stent may lead to dissection of the vessel distal and /or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (CABG, further dilation, placement of additional stents, or other).
- Placement of a stent has the potential to compromise side branch patency.
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order removes the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma or pseudoaneurysm.

Stent/System Removal – Precautions
If any **abnormal resistance** is met during advancement of the Bio*divYsio*™ AS the entire system **must be removed as a whole**. Excessive force could result in damage to the delivery system or loss of the stent.

When removing the system as a single unit:
DO NOT retract the delivery system into the guiding catheter.
Position the proximal balloon marker just distal to the tip of the guiding catheter.
Advance the guide wire into the coronary anatomy as far distally as safely possible.
Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter; then remove the guiding catheter and delivery system as a **single unit.**

- Failure to follow these steps and/or applying excessive force to the delivery system can potentially result in loss or damage to the stent and/or delivery system components.

- If it is necessary to retain guide wire position for subsequent artery/lesion access, leave the guide wire in place and remove all other system components.

Post Implant – Precautions
- Great care must be exercised when crossing a **newly deployed stent** with a coronary guide wire or balloon catheter to avoid disrupting the stent.

- A magnetic resonance imaging scan should not be performed until the implanted stent has been completely endothelialized (approximately eight weeks) in order to minimize the risk of the stent migration under the strong magnetic field.

ADVERSE EVENTS

A total of 686 patients were enrolled in the Bio*divYsio*™ Stent in Randomized Control Trial (DISTINCT) multicenter trial to evaluate the safety and effectiveness of the Bio*divYsio*™ AS for the treatment of symptomatic coronary artery disease. Of these, 377 received the Bio*divYsio*™ AS and 309 received the ACS Multi-Link Duet stent. The randomized patients form the basis for the observed events reported.

Table 1: Summary of Clinical Study Patient Enrolment (N=686)

	Bio*divYsio*™ AS	ACS Multi-Link™ Duet	Patients Total
Randomized Clinical Study	313	309	622
Roll in Phase	64	0	64
Patients Total	377	309	686

Observed Adverse Events

Three patients who were implanted with the Bio*divYsio* AS Stent died during the trial. The deaths occurred between 157 and 197 days post stenting and were due to cerebral vascular accident, pneumonia and ventricular fibrillation (cardiac arrest). In addition, three patients experienced out-of-hospital Q wave myocardial infarctions (MI's) and ten patients required coronary artery bypass graft (CABG) surgery.

The incidence of vascular (local) complications in the clinical study was 0.32% (1/312) and the rate for bleeding requiring transfusion was 0.32% (1/312).

Initial delivery failure occurred in 2.88%(9/312), one was a failure to deliver a second stent and eight were failures to deliver the first stent only. In the study there were four occasions (1.28%, 4/312) when the assigned stent was not delivered, one event of each of the following, wrong stent given to investigator, guidewire caused abrupt closure, predilation balloon did not cross lesion and stent size was not available. There were eleven (3.5%) mixed stent implantations, 10 were due to dissection or intimal flap and one due to lesion length.

Of the 64 patients enrolled in the roll-in phase of the trial, one patient died at 213 days post stenting due to colon cancer. In addition, one patient underwent CABG surgery and three patients underwent repeat PTCA.

Table 2: Major Adverse Events (Event Based) – In-Hospital vs. Out-of-Hospital Complications

Complication	Bio*divYsio*™ AS Stent n=312	ACS Multi-Link Duet n=309
Death Total		
Early (In-Hospital)	0.0% (0.0, 1.2) 0/312	0.0% (0.0, 1.2) 0/309
30-Days	0.0% (0.0, 1.2) 0/312	0.0% (0.0, 1.2) 0/309
Out-of-Hospital	1.0% (0.2, 2.8) 3/312	1.0% (0.2, 2.8) 3/309
Q-Wave MI Total		
Early (In-Hospital)	0.0% (0.0, 1.2) 0/312	0.3% (0.0, 1.8) 1/309
Out-of-Hospital	1.0% (0.2, 2.8) 3/312	0.0% (0.0, 1.2) 0/309
Non Q-Wave MI Total		
Early (In-Hospital)	0.6% (0.1, 2.3) 2/312	0.6% (0.1, 2.3) 2/309
Out-of-Hospital	0.6% (0.1, 2.3) 2/312	1.0% (0.2, 2.8) 3/309
CABG Total		
Early (In-Hospital)	0.3% (0.0, 1.8) 1/312	0.0% (0.0, 1.2) 0/309
Out-of-Hospital	2.9% (1.3, 5.4) 9/312	1.3% (0.3, 3.3) 4/309
SubAcute Occlusion Total		
Early (In-Hospital)	0.0% (0.0, 1.2) 0/312	0.6% (0.1, 2.3) 2/309
Out-of-Hospital	0.0% (0.0, 1.2) 0/312	0.0% (0.0, 1.2) 0/309
Bleeding Complications	0.3% (0.0, 1.8) 1/312	0.6% (0.1, 2.3) 2/309
Vascular Complications	0.3% (0.0, 1.8) 1/312	1.3% (0.3, 3.3) 4/309
Stent Delivery Failure	2.9% (1.3, 5.4) 9/312	1.3% (0.3, 3.3) 4/309

Note: One patient was removed from the Bio*divYsio*™ AS analysis because two lesions were treated. Data on 312 patients in randomized phase reported.

Potential Adverse Events

The following complications relating to PTCA and stenting have been reported and may occur:

- Dissection of coronary artery
- Injury, rupture or other damage to the coronary artery
- Sudden total occlusion of the coronary artery
- Thrombosis of the coronary artery
- Unstable angina
- Arterial spasm
- Myocardial infarct
- Ventricular fibrillation
- Disturbance of cardiac conductibility
- Pseudo aneurysm
- Embolism
- Restenosis of the dilated artery
- Stent migration
- Death
- Drug reaction to antiplatelet agents
- Stent embolism
- Ischemia

CLINICAL STUDIES

A multicenter, prospective trial was conducted at 35 centers in North America (21 in US, 14 in Canada). A total of 686 subjects were enrolled between November 27, 1998 and May 10, 1999 in two phases: 64 subjects in the roll-in phase and 622 in the randomized phase. In the randomized phase, 622 were randomly assigned to either

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Bio*divYsio*™ AS group (313) or ACS Multi-Link Duet control group (309). One Bio*divYsio*™ AS patient was removed from the analysis because two lesions were treated. Data on 312 Bio*divYsio*™ AS patients in randomized phase are reported. Clinical follow-up at 6 months was obtained in 90.6% of the Bio*divYsio*™ AS group and 97.1% in the ACS Multi-Link Duet group. The first two thirds of the randomized subjects (410) were required to undergo angiographic follow-up at 6-months post-procedure (Bio*divYsio*™ AS Stent 206 and ACS Multi-Link Duet Stent 204). Angiographic follow-up was obtained in 72.3% of the Bio*divYsio*™ AS group and 74.0% in the ACS Multi-Link Duet group. Mean age of the subjects was 60 years, with 71% subjects being males. All other clinical characteristics were similar between the two groups. There was a statistically significant difference in the number of patients with the target lesion located in the left anterior descending (LAD) artery between the Bio*divYsio*™ AS group and the ACS Multi-Link Duet Stent group (46.1% vs. 37.7%).

Computer assisted **Quantitative Coronary Angiography** (QCA) was performed at a central core laboratory at baseline, immediately after the procedure in all subjects and again at 6 months on a subset (two thirds), as well as any subjects returning for angiographic evaluation due to signs or symptoms of ischemia. Clinical and angiographic data were analyzed based on an intent-to-treat data set. An independent Clinical Events Committee (CEC) evaluated all MACE, (sub)acute occlusions and bleeding and vascular complications and an independent Data and Safety Monitoring Board (DSMB) evaluated the study progress at predetermined points during the trial.

The anticoagulation regime was acetylsalicylic acid (325 mg / day) prescribed for a minimum of 6 months, ticlopidine, prescribe 250 mg b.i.d. for 2-4 weeks or clopidogrel, prescribed 75 mg q.d. for 28 days.

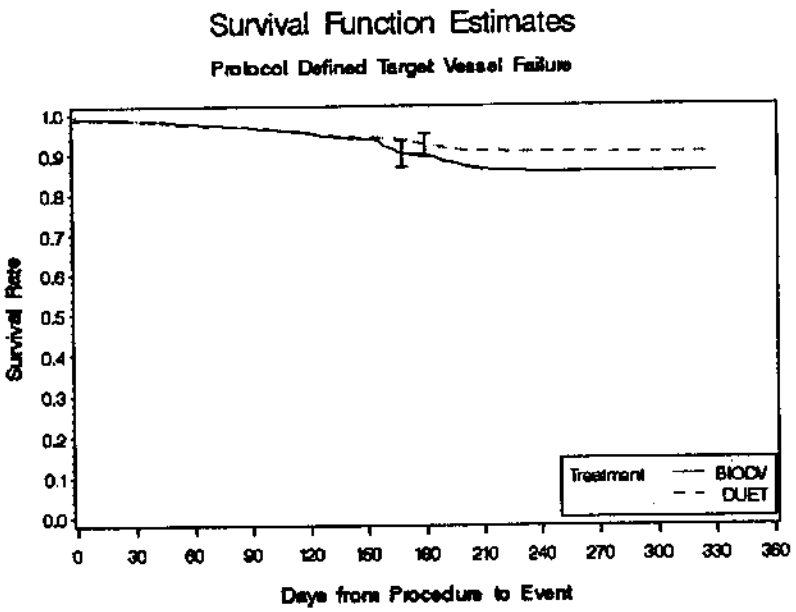
Follow up intervals were 2, 4 weeks, 6 and 12 months post procedure.

Table 3: Principal Effectiveness and Safety Results, All Patients Treated (N=621)

	Bio*divYsio* AS Group n=312	ACS Duet Group n=309	Difference (CI)
Effectiveness Measures:			
Technical Device Success	95.5% (296/310)	97.7% (301/308)	-2.2% (-5.1%, 0.6%)
Clinical Device Success	94.8% (294/310)	96.4% (297/308)	-1.6% (-4.8%, 1.6%)
Procedure Success	91.9% (285/310)	96.7% (298/308)	-4.8% (-8.4%, 1.2%)
TVF-Free (protocol) at 6 months*	90.1%	92.2%	-2.1% (-6.6%, 2.3%)
TVF-Free (revised) at 6 months*	92.0%	92.9%	-0.9% (-5.0%, 3.3%)
TVR-Free at 6 Months*	91.3%	94.2%	-2.8% (-6.9%, 1.3%)
TLR-Free at 6 Months*	91.3%	94.8%	-3.5% (-7.4%, 5.1%)
%DS at 6 Months by QCA	33.3%	29.3%	4.0 (-0.9, 8.8)
Restenosis Rate	19.9% (29/146)	20.1% (30/149)	-0.3 (-9.4%, 8.9%)
Restenosis Rate for Procedural Success	17.7% (24/135)	18.7% (27/144)	-1.0 (-10.0%, 8.1%)
Safety Measures:			
In-Hospital Clin Events	1.6% (5/312)	3.2% (10/309)	-1.6 (-6.2, 1.8)
Out-Hospital Clin Events	15.4% (48/312)	11.0% (34/309)	4.4 (-1.5, 11.4)
(Sub)Acute Occlusions	0.0% (0/312)	0.6% (2/309)	-0.6 (3.8, 1.5)
Vascular Complications	0.3% (1/312)	1.3% (4/309)	-1.0 (-4.7, 1.5)
Bleeding Complications	0.3% (1/312)	0.6% (2/309)	-0.3 (-3.8, 2.0)

*Survival analysis is based on Kaplan Meier survival methods.
Numbers are % (numerator/denominator), mean, 1 SD, CI = 95% confidence interval.
Odds ratio = Bio*divYsio*™ AS/Duet group
Difference = Bio*divYsio*™ AS – Duet
KM Difference = S_{Biodiv}/S_{Duet} SE_{diff}= sqrt($SE_{Biodiv}^2 + SE_{Duet}^2$) and CI = diff $\pm$ 1.96SE_{diff}
Technical Device Success—Intended stent successfully implanted as first stent with a ≥ 20% reduction in percent diameter stenosis of the target lesion and a ≤ 50% final diameter stenosis.
Clinical Device Success—Technical device success and no MACE events through discharge
Procedural Success—≥20% reduction in percent stenosis of the target lesion and a ≤50% final diameter stenosis using the assigned treatment stent alone.
TVF (per protocol) - target vessel failure is a composite of death, MI, and ischemia-driven revascularization (PTCA or CABG) to the target vessel.
TVF (revised)—target vessel failure as revised is a composite of death, recurrent MI, emergent CABG, and ischemia driven revascularization (PTCA or CABG) to the target vessel.
Clinical Events—MACE (death, non-fatal MI, and CABG or PTCA at the target vessel or target lesion), (sub)acute occlusions or bleeding and vascular complications as determined by the Clinical Events Committee.
DS—diameter stenosis compared to the reference vessel diameter
Restenosis Rate—percent diameter stenosis > 50% at 6 months follow-up by QCA when compared to the reference vessel lumen diameter.
Restenosis Rate for Procedural Success—restenosis rate in the angiographic cohort who achieved procedural success.
QCA—quantitative coronary angiography
Bleeding Complications—bleeding requiring transfusion or prolonged hospitalization
Vascular Complications—events requiring surgery
CABG—Coronary Artery Bypass Graft
PTCA—Percutaneous Transluminal Coronary Angioplasty

Figure 1: Kaplan Meier Estimate for Freedom from TVF*



	Days after Procedure							
	0	7	14	30	90	180	248	273
Bio*divYsio* AS								
# At risk	313	310	310	310	309	301	279	263
# Events	3	3	3	4	11	31	45	45
% Survived	99.0%	99.0%	99.0%	98.7%	96.5%	90.1%	85.5%	85.5%
SE	0.006	0.006	0.006	0.006	0.010	0.017	0.020	0.020
ACS Duet								
# At risk	309	305	305	305	305	299	284	278
# Events	4	4	4	4	9	24	29	30
% Survived	98.7%	98.7%	98.7%	98.7%	97.1%	92.2%	90.6%	90.3%
SE	0.006	0.006	0.006	0.006	0.010	0.015	0.017	0.017

Tests Between Groups

Test	Chi-Square	DF	P-value
Log-Rank	3.0923	1	0.0787
Wilcoxon	2.9263	1	0.0871

Patient Selection and Treatment

Individualization of Treatment

The risks and benefits described above should be carefully considered for each patient before use of the Bio*divYsio*™ AS. Patient selection factors to be assessed should include a judgement regarding risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease; see Contraindications).

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure and severe

obesity) should be reviewed. The relation of baseline and procedural variables to Target Vessel Failure (TVF) was examined. The only significant predictor of TVF was stent placement in the LAD artery and patients with prior CABG.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3.0 mm, vessel thrombosis, poor distal flow, and/or dissection following stent implantation. In patients that have undergone coronary stenting, the persistence of a thrombus or dissection in considered a marker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation because stent thrombosis may occur during this period.

Specific Patient Populations

The safety and effectiveness of the Bio*divYsio*™ AS has not been established for patients with any of the following characteristics:

- Patients with intended angioplasty of more than one lesion within 30 days of the procedure or any other location in the same vessel during the 12-month study period.
- Patients with prior angioplasty of the same target lesion or of a coronary bypass graft.
- Patients with lesion in a vessel supplied by a patent venous or arterial graft.
- Patients with intended angioplasty of a lesion with a large side branch (≥2.0 mm).
- Patients with lesion longer than 25 mm.
- Patients with aorto-ostial lesions (left main or right ostial).
- Patients with lesion with angiographic evidence of thrombus.
- Patients with severe calcification or proximal tortuosity that may impair stent deliverability in the opinion of the physician.
- Patients with total occlusions.

PREPARATION OF THE Bio*divYsio*™ AS PC (phosphorylcholine) COATED STENT DELIVERY SYSTEM

1. Remove the product from the protective hoop and carefully inspect the entire product for any damage. Care must be taken during preparation and placement with the delivery system as any damage could make the product unsafe. Particular care must be taken to avoid handling the stent or disrupting the stent's accurate placement on the balloon.
2. Care must be taken to ensure that the other products used in the procedure are not damaged.
3. Remove the protective sheath and mandrel from the mounted stent and inspect the stent to ensure it has not been damaged or moved from its original position on the balloon, centrally between the distal and proximal markers on the balloon. If the stent has any damage or has been moved do not use the product.
4. Moisten the mounted stent with sterile saline.
5. Using heparinized saline to flush the guidewire lumen of the delivery system.
6. Prepare the balloon lumen of the delivery system using 50/50 contrast-saline mixture in the following manner:
   (a) Attach a 3-way stopcock to the delivery system hub and flush through the stopcock.

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(b) Attach a 20cc syringe with 5cc of contrast-saline mixture to the 3-way stopcock and apply negative pressure for 30 seconds allowing air removal from the balloon.
(c) Slowly release negative pressure to zero pressure in order to allow the contrast-saline mixture to fill the balloon lumen.
(d) Do not introduce air. Repeat steps (a) and (b) until no air bubbles come from the balloon lumen and then leave a meniscus of contrast-saline mixture on the 3-way stopcock.
(e) Attach an inflation device to the 3-way stopcock. (Prepare the inflation device according to the manufacturer's instructions)
(f) **DO NOT APPLY POSITIVE OR NEGATIVE PRESSURE WITH THE INFLATION DEVICE. LEAVE AT ZERO.**

7. The Bio*divYsio*™ AS is now ready to be advanced to the target lesion on the guide wire using conventional angioplasty technique.

DELIVERY AND DEPLOYMENT OF THE Bio*divYsio*™ AS

Warning: The target lesion must be pre-dilated before deployment of the BiodivYsio™ AS

1. Ensure the guiding catheter and guidewire will provide adequate stability for safe advancement of the delivery system and deployment of the Bio*divYsio*™ AS
2. Advance the delivery system to the target lesion using high-quality-fluoroscopic equipment ensuring the stent is not damaged and has not lost its position on the delivery system's balloon.

Warning: Once the stent is in the artery it is NOT recommended to pull an unexpanded stent back into the guiding catheter if it cannot be delivered to the target site. It is recommended to slightly inflate the balloon catheter to approximately 0.5 atm/50 kPa and to pull back the entire Bio*divYsio*™ AS and guiding catheter in the introducer sheath as a single unit. Do not try to pull back the stent in the guiding catheter as it could lead to loss of the stent and distal embolism.

3. Use the distal and proximal markers on the delivery system's balloon to accurately position the stent across the lesion. **The stent is positioned between the balloon's markers.**
4. Before deployment of the stent, check its position with angiography.
5. Inflate the balloon to the required pressure to ensure desired stent diameter (minimum deployment pressure of 8 atm/800 kPa). Maintain inflation pressure for at least 20 seconds to fully deploy the stent.

Warning: Do not exceed the Rated Burst Pressure as indicated on the label.

6. The entire stent must be in full contact with the arterial wall for the stent to be fully deployed.

Warning: Over expansion of the stent could result in dissection of the vessel.

7. Deflate the balloon by applying negative pressure on the inflation device and allow time for the balloon to fully deflate.
8. Carefully remove the deflated balloon.
9. Angiographic evaluation of the treated lesion is required after deployment of the stent to ensure the stent has been adequately deployed and the lesion adequately treated.
10. If the stent has not been adequately deployed, further inflations may be necessary.
11. If the target lesion has not been adequately treated with the single stent, the use of additional stents may be necessary.

Table 5: Balloon Diameters and Inflation Pressures

Inflation (atm)	2.0 mm	2.5mm	3.0mm	3.5mm	4.0mm
6	2.0	2.5	3.0	3.5	4.0
8*	2.06	2.56	3.06	3.56	4.06
10	2.12	2.62	3.12	3.62	4.12
12	2.18	2.68	3.18	3.68	4.18
14**	2.25	2.75	3.25	3.75	4.25
16	2.28	2.78	3.28	3.78	4.28
18	2.31	2.81	3.31	3.81	4.31

* Nominal Inflation Pressure

**Balloon Rated Burst Pressure – Do not exceed.

Explanation of symbols used on the package labels:


Single use only


See instructions for use before use

REF Catalogue number

Lot number

Sterilized by ethylene oxide


Use before


Store below 40° Celsius


Store in a dry place


Keep away from light

The Bio*divYsio*™ AS are manufactured on behalf of
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Manufactured under one of more of the following US patents;
US 5705583, US 5755771. Other US and foreign patents pending