BD Peripheral Intervention
Becton, Dickinson and Company
1415 West 3rd Street
Tempe, AZ 85281

Tel: (800) 321-4254
(480) 894-9515
Fax: (800) 440-5376

March 16, 2019

Dear Colleague,

Patient safety and product quality are the top priorities at BD. On March 15, the FDA issued a letter to Health Care Providers[1] containing information related to a potential increase in mortality associated with the use of paclitaxel-coated balloons and paclitaxel-eluting stents in patients with Peripheral Arterial Disease (PAD) in the femoropopliteal artery. BD has completed an extensive, comprehensive review of all available LUTONIX® DCB clinical data and is sending this letter to confirm the safety and efficacy of the LUTONIX® DCB and to share with you a summary of supporting data. These data are included in the appendix for your review.

In their communication the FDA acknowledged the data in the letter should be interpreted with caution for several reasons. First, there is large variability in the risk estimate of mortality due to the limited amount of long-term data. Second, the studies referenced by FDA in the letter were not originally designed to be pooled, introducing greater uncertainty in the results. Third, the specific cause and mechanism of the increased mortality is unknown.

We agree that paclitaxel-coated devices are not all the same and analyzing stents, balloons, various doses, formulations and coating technologies together as a class may result in significant confounding of results. To summarize some of the pre-clinical and clinical results specific to LUTONIX®:

- BD evaluated more than 250 formulations and performed 45 pre-clinical studies before selecting the formulation that could deliver an effective therapeutic dose while minimizing plasma half-life (6.88 hours) and systemic paclitaxel exposure.
- The low-dose formulation of the LUTONIX® DCB was designed to balance efficacy and safety.
- The LUTONIX® DCB was the **only** DCB that underwent a rigorous advisory panel review by the FDA, requiring over 1,000 patients to be treated with the LUTONIX® DCB under the LEVANT 2 IDE protocol (1,029 LUTONIX® DCB patients, 160 PTA), ultimately leading to a unanimous 9-0 vote in favor of the LUTONIX® DCB's approval.
- LEVANT 2 enrolled 1,189 patients for the FDA panel's safety evaluation; this Intent To Treat (ITT) population was reevaluated at five years and we do not see a signal of increased long-term mortality in this large patient cohort (p=.198). While subset analysis of the randomized portion (476 patients) of the LEVANT 2 trial did cross the line to significance (p=.046) at 5 years, the broader data set confirms the safety of this product and is larger than the pooled dataset referenced in the FDA letter.
- A further analysis of the RCT portion of the LEVANT 2 study was undertaken to better understand the specific cause and mechanism of death as outlined in the FDA notice. Three physicians, acting independently, reviewed patient-level narratives of mortality events and potential/plausible links to paclitaxel exposure. After adjudicating the deaths and removing those that could not reasonably be attributed to paclitaxel (e.g. homicide, known pre-existing conditions, etc.), the results of each of these analyses found no statistically significant difference in mortality between DCB and PTA at any timeframe.

As with any treatment plan, we support/recommend discussing the risks and benefits of all available PAD treatment options with your patients. We are confident that our DCB, with our coating formulation, provides a safe option for the treatment of PAD. We look forward to collaborating with global regulators, academic societies and other thought leaders in the analysis of long-term, patient-level data and further investigating the important issue of safety and DCBs.

Sincerely,

JD Meler, MD
Vice President, Medical and Clinical Affairs
BD Peripheral Intervention

BD Peripheral Intervention
Becton, Dickinson and Company
1415 West 3rd Street
Tempe, AZ 85281

Tel: (800) 321-4254
(480) 894-9515
Fax: (800) 440-5376

Below you will find a summary of all-cause death by LUTONIX® DCB study, a pooled data analysis, and a summary of all peer-reviewed LUTONIX® DCB clinical and pre-clinical publications with their respective safety outcomes.

All-Cause Death by Study*

Study	Time Point	DCB	PTA	P-value
Levant I	24 Months	8.2% (4/49)	9.6% (5/52)	0.798
LEVANT 2 All Patients	60 Months	14.3% (147/1029)	10.6% (17/160)	0.198
LEVANT 2 RCT Only	60 Months	17.4% (55/316)		0.046
LEVANT 2 Roll in and Continued Access Patients	60 Months	12.9% (92/713)	NA	NA
Levant Japan	24 Months	2.8% (2/71)	7.9% (3/38)	0.241
ISR	36 Months	11.3% (6/53)	10.3% (3/29)	0.892
Long Lesion	36 Months	7.6% (9/118)	NA	NA
Global Registry	24 Months	5.2% (36/691)	NA	NA

*Analyzed based on the ITT population

All-Cause Death Pooled Data Analysis[2]

Study	DCB	PTA	P-value
Pooled Lutonix Data	10.1% (204/2011)	10.0% (28/279)	0.955

All-Cause Mortality by Time*

Time Point	General PAD Population[3] (n=487)	LEVANT 2 All Patients		
		DCB Subjects (n=1029)	PTA Subjects (n=160)	P-value
1 Yr	6.6% (32/487)	1.7% (18/1029)	2.5% (4/160)	0.530
2 Yrs	10.9% (53/487)	4.5% (46/1029)	5.0% (8/160)	0.768
3 Yrs	16.0% (78/487)	8.0% (82/1029)	6.3% (10/160)	0.437
4 Yrs	20.3% (99/487)	11.8% (121/1029)	8.8% (14/160)	0.250
5 Yrs	23.4% (114/487)	14.3% (147/1029)	10.6% (17/160)	0.198

*Analyzed based on the ITT population

RCT Adjudicated All-Cause Mortality by Time

Levant 2 Randomized – Adjudicated Subjects[4]			
Time Point	DCB Subjects (n=316)	PTA Subjects (n=160)	P-value
1 Yr	1.3% (4/316)	1.3% (2/160)	0.988
2 Yrs	2.8% (9/316)	1.3% (2/160)	0.249
3 Yrs	3.2% (10/316)	2.5% (4/160)	0.681
4 Yrs	4.7% (15/316)	2.5% (4/160)	0.219
5 Yrs	5.7% (18/316)	3.1% (5/160)	0.200

*Analyzed based on the ITT population

BD Peripheral Intervention
Becton, Dickinson and Company
1415 West 3rd Street
Tempe, AZ 85281

Tel: (800) 321-4254
(480) 894-9515
Fax: (800) 440-5376

Lutonix Publications & Safety Outcomes

Study	Author	Journal	Year	Study Design	Safety Outcomes
LEVANT I	D. Scheinert et al.	Journal of American College of Cardiology	2014	Prospective, Multi-Center (9 sites), Randomized 1:1, single blinded (patient), controlled clinical trial; N=101	- Composite 24 month MAEs were 39% for DCB vs. 46% for PTA All-cause death: - 12 month: 4.1% DCB vs. 7.7% PTA - 24 month: 8.2% DCB vs. 9.6% PTA
LEVANT 2	K. Rosenfield et al.	New England Journal of Medicine	2015	Prospective, Multi-Center (54 global sites), Randomized 2:1, single blinded, controlled clinical trial; N=476	- Freedom from primary composite safety events was 83.9% for DCB vs. 79.0% for PTA (p=0.005) All-cause death: - 12 month: 2.4% DCB vs. 2.8% PTA
German Subanalysis (LEVANT 2)	D. Scheinert et al.	Journal of Endovascular Therapy	2016	LEVANT 2 Design N=126; German patients at 8 sites	- Freedom from primary composite safety event was 94% DCB vs. 72% PTA (p=0.001) All-cause death: - 12 month: 1.3% DCB vs. 0% PTA
Lutonix Global Registry (24mo)	M. Thieme et al.	Journal of American College of Cardiology	2017	Prospective, Multi-Center (38 global sites) Registry; N=691	Freedom from composite safety events: - 12 month: 92.1% - 24 month: 86.7% All-cause death: - 12 month: 2.8% DCB - 24 month: 5.9% DCB
Pre-Clinical Lutonix Pharmaco-kinteic Analysis[5]	S. Yazdani et al.	Catheterization and Cardiovascular Interventions	2014	Femoral arteries of 45 swine were treated with 1x and 4x dose of Lutonix DCB. Treated arteries, downstream vascular beds, and organs were assessed histologically at 28, 90, & 180d.	- No detectable plasma paclitaxel levels at 1 day - Medial SMC loss peaked at 90 days - Healing of treated arteries peaked at 180 days - No evidence of ischemia from downstream emboli or systemic toxicity observed at 4x dose
Pre-Clinical Particulate Analysis (Lutonix vs. In.Pact DCB)[5]	FD. Kolodgie et al.	Journal of Vascular Interventional Radiology	2016	Single and overlapping 80mm In.Pact and Lutonix 035 DCBs assessed in femoral arteries of 21 swine with 28d and 90d follow-up, with a POBA control. Histologic analysis of arterial wall and downstream skeletal muscle and coronary band.	- Downstream necrosis at 90d: In.Pact=46.2% vs. Lutonix=0.0% (p=0.01) - Downstream embolic crystalline material at 90d: In.Pact=5% vs. Lutonix=0% - Downstream skeletal muscle PTX concentrations at 28d: In.Pact=170.9ng/g vs. Lutonix=3.7ng/g - Downstream coronary band (hoof of swine) PTX concentrations at 28d: In.Pact=871.0ng/g vs. Lutonix=31.5ng/g
Lutonix AV IDE 6-month Results	S. Trerotola et al.	Clinical Journal of American Society of Nephrology	2018	Prospective, Global, Multicenter, Randomized (1:1), Core Lab Blinded; N=285	- Freedom from primary safety event: 95% DCB vs. 96% PTA (p=0.002)

Footnotes:

[1] Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm633614.htm

[2] Pooled data analysis is reflective of an aggregate of all LUTONIX® DCB femoropopliteal data from various patient populations and time points.

[3] Mueller T et al, 'Mortality Rates and Mortality Predictors in Patients with Symptomatic Peripheral Artery Disease Stratified According to Age and Diabetes', J Vasc Surg 2014; 59:1291-9.

[4] Adjudicated (censored) analysis was based on the removal of any death certain to not be related to the device or procedure. Any death that was undefined or did not have enough information to rule out was kept in the analysis.

[5] Pre-clinical animal test results may not be indicative of clinical performance. Different test methods may yield different results.

LUTONIX® DCB pre-clinical and clinical data on file. Bard Peripheral Vascular, Inc., Tempe, AZ.

Indications for Use: The LUTONIX® 035 Drug Coated Balloon PTA catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions up to 300 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm. **Contraindications:** The LUTONIX® Catheter is contraindicated for use in: Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure. Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

Please consult product labels and instructions for use for indications, contraindications, hazards, warnings and precautions. Rx Only.