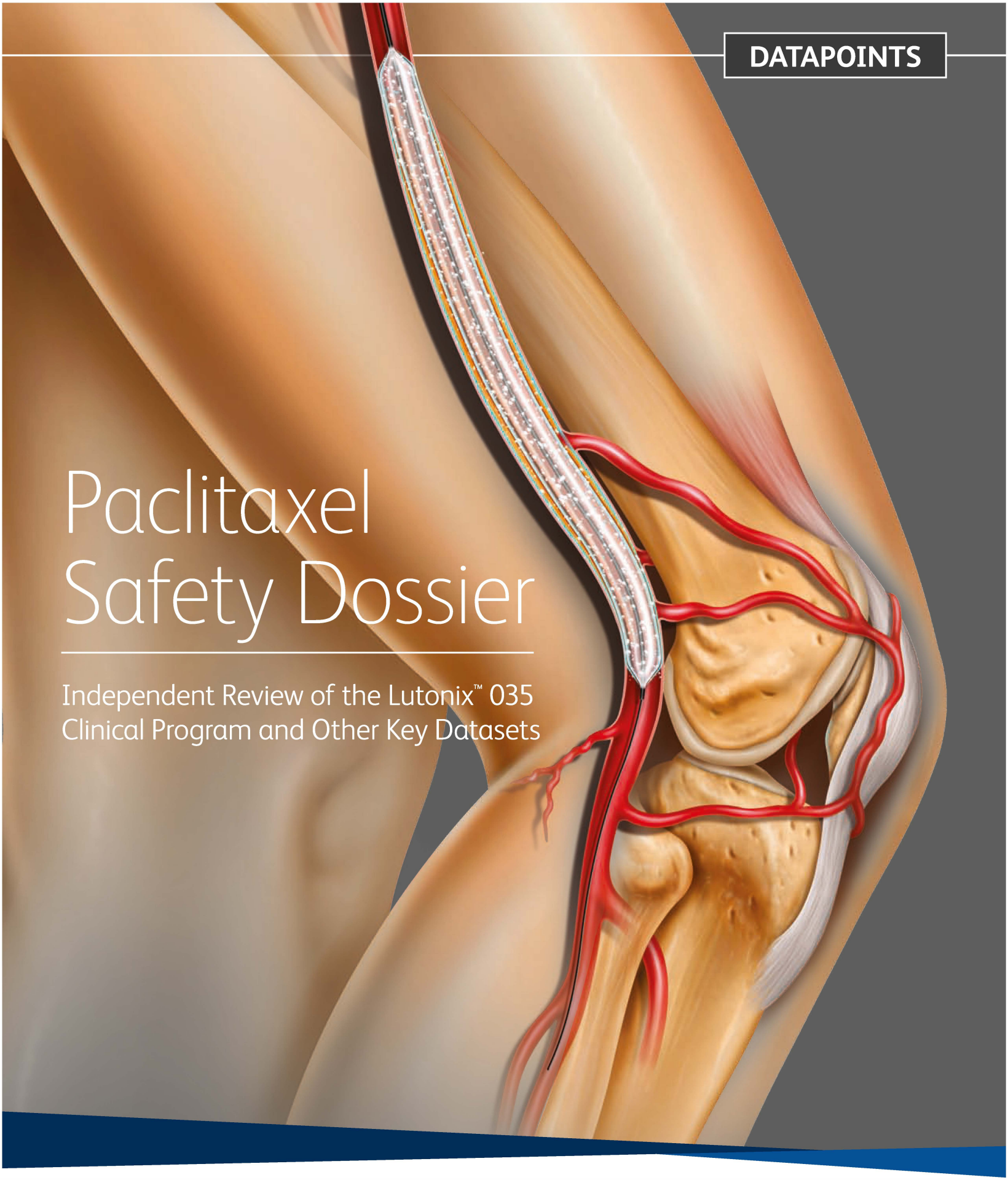
DATAPOINTS



Paclitaxel Safety Dossier

Independent Review of the Lutonix™ 035 Clinical Program and Other Key Datasets

BD

BARD
has joined BD

FDA Updates Prior & Post-Panel Meeting

The FDA has issued several letters to healthcare providers since the release of the Katsanos paper in December 2018.

DEC
- SWEDEPAD & BASIL 3 halt enrollment
- Katsanos et al. published

JAN
- LINC
- 1st FDA Letter

FEB
- ISET
- Secemsky Medicare Analysis published in JAMA

MAR
- VIVA VLF Forum & CRT
- 2nd FDA Letter
- Secemsky Medicare Analysis published in JACC

APR
- SWEDEPAD resumes enrollment
- Charing Cross

MAY
- NCVH
- FDA approves Lutonix™ 018 line extension

JUN
- BASIL 3 resumes enrollment
- FDA Panel Committee

JUL

AUG
- 3rd FDA Letter

SEP
- Syntactx Analysis published in JACC

March 15, 2019 - FDA Letter to HCPs[1]

- Preliminary review identified a potentially concerning signal of increased long-term mortality
- Approximately 50% increased risk of mortality in subjects treated with paclitaxel-coated devices versus control devices (20.1% vs. 13.4% crude risk of death at 5 years)
- For most patients, alternative treatment options to paclitaxel coated devices should generally be used

August 7, 2019 - FDA Letter to HCPs[2]

- Applies to all paclitaxel coated devices
- Risk: Includes hazard ratios derived from the **FDA and VIVA meta-analysis** presented at the FDA Panel
- Risk Caution Statement: Data should be interpreted with caution due to limitations:
  - Wide confidence intervals due to a **small sample size**
  - **Pooling** of studies of different devices
  - Substantial amounts of **missing study data**
  - **No clear evidence of a paclitaxel dose effect on mortality**
  - **No identified pathophysiologic mechanism** for the late deaths
- Risk-Benefit: Benefits outweigh risks in **patients at high risk for restenosis and repeat femoropopliteal interventions**
  - Paclitaxel-coated balloons and stents improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels compared to uncoated devices. **The Panel concluded that the benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).**
- Clinical trials: Studies of these devices may continue and should collect long-term safety (including mortality) and effectiveness data

Independent Review of the LEVANT Clinical Program[3]

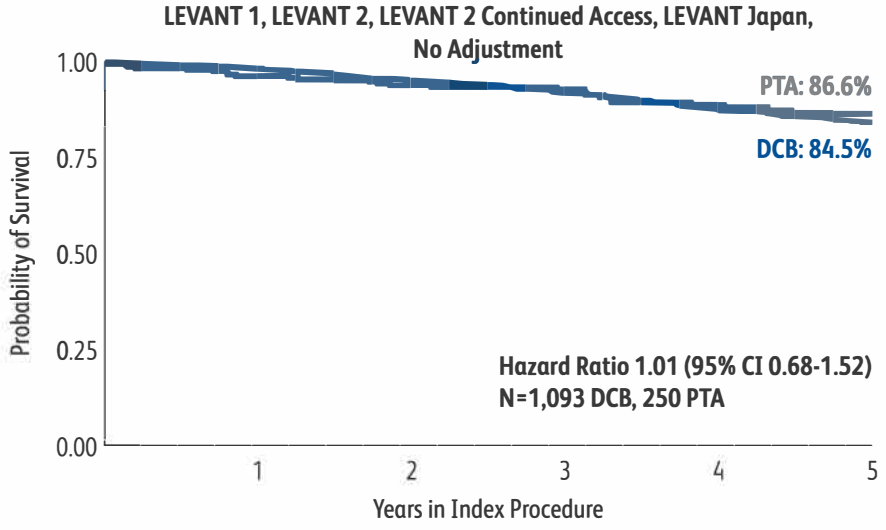
Lutonix SFA clinical data including LEVANT 1, LEVANT 2 including the Continued Access cohort, and LEVANT Japan were analyzed.

Study	Study Design	Subjects (DCB:PTA)	Geography	Follow-Up
LEVANT 1	RCT	101 (49:52)	Europe	24 Months
LEVANT 2	RCT with Roll-Ins	532 (316:160) randomized 56 DCB Roll-In	US, Europe	60 Months
	Continued Access	657	US, Europe	60 Months
LEVANT Japan	RCT	109 (71:38)	Japan	24 Months

Exclusive Statistical Techniques Included in the Review of the LEVANT 2 Program[3]

	Katsanos	FDA	VIVA	BD Lutonix
Analysis population (denominator)				
Total enrollment	✓	✓	✓	✓
Subjects who completed follow-up				✓
Addition of lost to follow-up subjects		✓	✓	✓
Patient-level data		✓	✓	✓
Study populations				
LEVANT 2 RCT	✓	✓	✓	✓
LEVANT 2 Continued Access		✓		✓
LEVANT 2 Combined				✓
Propensity adjustment				✓
Time dependent analyses, including subsequent intervention				✓
Multivariate analyses				✓

The aggregated hazard ratio for the LEVANT program is 1.01 at 5 years.[3]

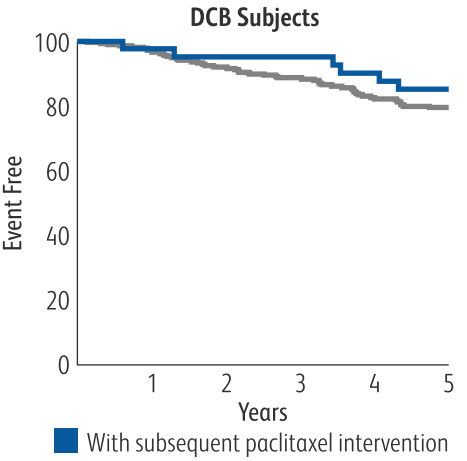


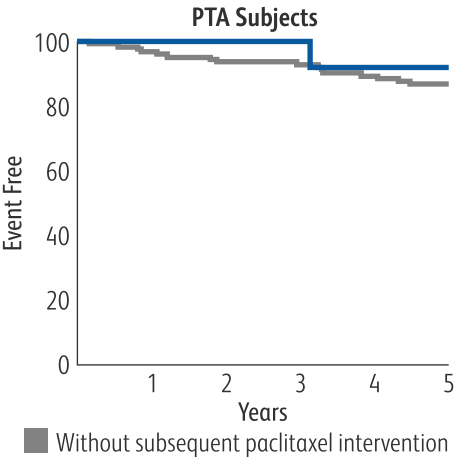
Subsequent Interventions with Paclitaxel Devices[3]

The effect of subsequent interventions with paclitaxel devices, which increases drug exposure, was analyzed.

Subjects in both groups, DCB and PTA, who subsequently underwent an intervention with a paclitaxel device had higher 5-year survival rates than those who did not.

These findings are counter-intuitive if additional paclitaxel exposure is harmful in the long-term.





	DCB (n=1,078)	PTA (n=212)
All Cause Death	151	22
Total Deaths	173	
Deaths adjudicated as related to paclitaxel	0	

Independent Adjudication

LEVANT 1 and LEVANT 2, including Continued Access, deaths were re-adjudicated by a medical advisory committee consisting of an interventionalist and oncologist. If in disagreement, another oncologist was introduced to break the tie.

Approximately **50%** of patients who were previously lost to follow-up were recovered for this analysis.

Criteria	LEVANT Review Findings	Criteria Met
Consistency: Were paclitaxel concerns identified in the animal studies?	No safety issues identified in animal studies[4]	No
Strength: Was the effect shown for all studies?	Effect not shown in all studies No significant difference between groups and no clustering of cause of death	No
Specificity: Was the mortality paclitaxel related?	Treatment not a significant predictor of mortality or adverse events	No
Plausibility: Was there a mechanism of action?		No
Coherence: Do other findings support the mortality concern?		No
Biological Gradient: Is there a dose response?	No increase in mortality with increased dose, subsequent interventions with paclitaxel-coated device was protective	No
Experiment: Does disease risk decline with cessation of exposure?		No
Temporality: Does mortality increase following index procedure?	Temporality is present	Yes
Analogy: Could the effects be due to immunogenic particulates?	Particulates have been implicated in other situations	Yes

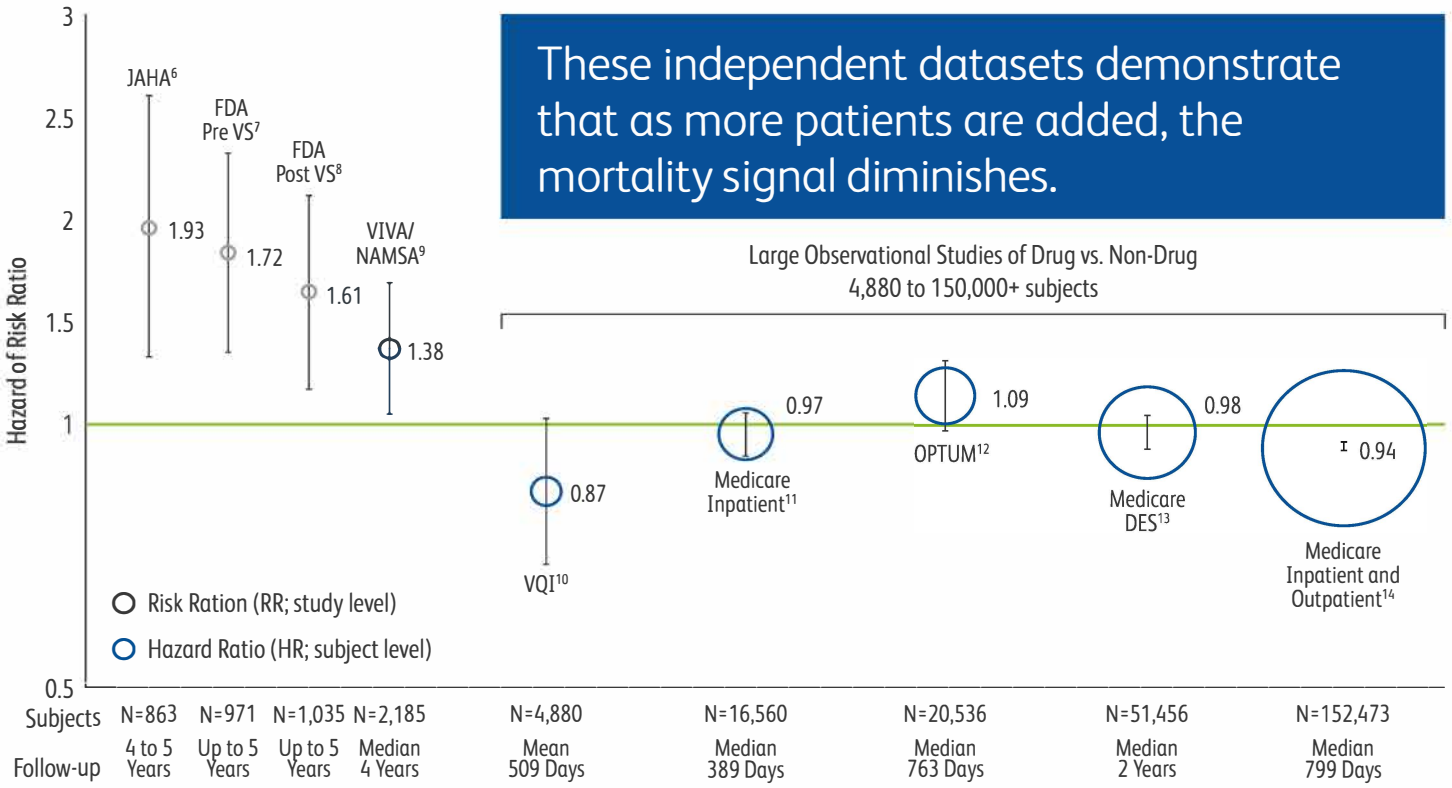
Association vs Causality[3]

The Bradford Hill criteria, a set of nine principles, was used to determine the relationship between paclitaxel and long-term mortality. All nine principles must be present to prove causality.

Concerning the LEVANT clinical program, 7 of 9 criteria could be ruled out completely.

The absence of 7 of the 9 criteria is consistent with association but not causation between paclitaxel and mortality.

Large Observational Studies Suggest No Mortality Signal Related to Paclitaxel Coated Devices[5]



Title	Association of Survival with Fempop Revascularization with Drug-Coated Devices[15]	Drug-Eluting Stent Implantation and Long-Term Survival Following Peripheral Artery Revascularization[16]	Mortality After Use of Paclitaxel-Based Devices in Peripheral Arteries: A Real-World Safety Analysis[17]
Author	Secemsky et al	Secemsky et al	Freisinger et al
Data Source	Medicare	Medicare	German health insurance data
Description	Large observational study of patients treated with drug vs non-drug	Large observational study of patients treated with drug-eluting stents vs non-drug bare metal devices	Large real-world analysis of patients who underwent interventions between 2007 and 2015
Sample Size	16,560	51,456	64,771
Follow-Up	389 days (median) 600 days (longest)	720 days (median) 1,440 days (longest)	Up to 11 years
Adjusted Hazard Ratio	0.97 (95% CI 0.91-1.04, p=0.43)	0.98 (95% CI 0.93-1.03, p=0.53)	0.64 – 1.10; all P>0.057 after DES application
Conclusions	No evidence of increased all-cause mortality following fempop revascularization for drug-coated devices compared with non-drug devices	There was no association between stent type and mortality after multivariable adjustment. No difference in mortality between DES and BMS through the end of the follow-up period.	Analysis found the use of paclitaxel-coated devices to be safe for endovascular therapy of the lower limbs

Relationship Between Paclitaxel & Mortality

Several studies have examined patient data, for both US and international government agencies, to assess the relationship between paclitaxel and long-term mortality.

Each analysis concluded there was no evidence of increased mortality between drug coated devices and non-drug coated devices.

DATAPOINTS

[1] FDA Letter to Health Care Providers released on 3/15/2019.

[2] FDA Letter to Health Care Providers released on 8/7/2019.

[3] Analysis conducted by an independent clinical research organization, Syntactx LLC for which it was compensated by BD. 173 deaths in LEVANT 1 and LEVANT 2 (including patients from Continued Access arm of LEVANT 2), with 151 occurring in Lutonix™ 035 DCB patients (14.0%) and 22 in PTA patients (10.4%). Data on file. Bard Peripheral Vascular, Inc. Tempe, AZ.

[4] Vermani et al.

[5] For specific adjustments and methodologies, see the cited publications as shown at FDA Panel, June 20, 2019, https://www.fda.gov/media/128326/download

[6] Katsanos. K. JAHA 2018; 7:e011245.

[7] FDA Analysis, pre vital status.

[8] FDA Analysis, post vital status.

[9] VIVA-NAMSA Analysis. June 3, 2019.

[10] Bertges DJ, SVS Abstract 2019.

[11] Secemsky EA et al. JAMA Cardiol 2019.

[12] Yeh RW, FDA Presentation, June 19-20, 2019.

[13] Secemsky EA et al. J Am Coll Cardiol 2019;73:2636-2638.

[14] Secemsky EA, FDA Presentation, June 19-20, 2019.

[15] Secemsky, Eric A., et al. "Association of survival with femoropopliteal artery revascularization with drug-coated devices." JAMA cardiology 4.4 (2019): 332-340.

[16] Secemsky, Eric A., et al. "Drug-eluting stent implantation and long-term survival following peripheral artery revascularization." Journal of the American College of Cardiology 73.20 (2019): 2636-2638.

[17] Freisinger, Eva, et al. "Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis." European heart journal (2019).

In August 2019, the U.S. Food and Drug Administration (FDA) issued an updated letter to health care providers noting an increased risk in late mortality (2-3 years post-treatment) with paclitaxel-coated devices when used to treat peripheral arterial disease in the femoropopliteal artery as compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. BD will continue to work collaboratively with FDA and industry for additional safety data collection and inform labeling as appropriate. These communications as well as information about the FDA Panel meeting can be found at: https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel

Lutonix™ 035 Drug Coated Balloon PTA Catheter

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: **1)** Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy. **2)** Women who are breast-feeding, 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. 3) Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

Warnings: 1) Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use. **2)** Do not use if product damage is evident. **3)** The Lutonix™ Catheter is for use in one patient only; do not reuse in another patient, reprocess or resterilize. Risks of reuse in another patient, reprocessing, or resterilization include: Compromising the structural integrity of the device and/or device failure which, in turn, may result in patient injury, illness or death. Creating a risk of device contamination and/or patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to patient injury, illness or death. **4)** Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended. **5)** Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon. **6)** This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds. **7)** The safety and effectiveness of the Lutonix™ Catheter have not been established for treatment in cerebral, carotid, coronary, or renal vasculature. 8) The safety and effectiveness of using more than four Lutonix™ drug coated balloons (i.e., a maximum drug coating quantity of approximately 15.1 mg paclitaxel) in a patient has not been clinically evaluated.

Precautions: General Precautions: 1) The Lutonix™ Catheter should only be used by physicians trained in percutaneous interventional procedures. **2)** Consideration should be given to the risks and benefits of use in patients with a history of non-controllable allergies to contrast agents.

Potential Adverse Events: Potential adverse events which may be associated with a peripheral balloon dilatation procedure include: Additional intervention · Allergic reaction to drugs, excipients, or contrast medium · Amputation/loss of limb · Aneurysm or pseudoaneurysm · Arrhythmias · Embolization · Hematoma · Hemorrhage, including bleeding at the puncture site · Hypotension/ hypertension · Inflammation · Occlusion · Pain or tenderness · Pneumothorax or hemothorax · Sepsis/infection · Shock · Stroke · Thrombosis · Vessel dissection, perforation, rupture, or spasm

Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

CE
2797

BD Switzerland Sarl, Route de Crassier 17, Business Park Terre-Bonne, Batiment A4,
1262 Eysins Switzerland, Tel: +41 21 556 30 00. Fax: +41 44 722 5370

crbard.com/peripheral-vascular | bd.com

BD, Tempe, AZ, USA, 1 800 321 4254

BD

BARD
has joined BD