June, 2020

Field Safety Notice
Paclitaxel-coated Balloons and Paclitaxel-Eluting Stents

Addition of a warning and a clinical summary section in the instructions for use (IFU) of paclitaxel-coated balloons and paclitaxel-eluting stents used in the treatment of peripheral arterial disease of the lower limbs.

List of affected Medical Devices:
BioPath™
ELUVIA™
IN.PACT Admiral™
IN.PACT Pacific™
LEGFLOW OTW
LEGFLOW RX
Luminor
Lutonix®
Passeo-18 Lux
Ranger™
Ranger™ SL
SeQuent® Please OTW
Stellarex
Zilver® PTX®

Dear Healthcare Professional,

In December 2018, Katsanos et al published a meta-analysis on the "Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg"[1]. After the publication of this meta-analysis, Agence Nationale de Sécurité du Medicament et des produits de santé (ANSM), French competent authority, has requested of all manufacturers the addition of a warning and clinical summary related to the Katsanos Paclitaxel meta-analysis to European Instructions for Use (IFU)s. The meta-analysis authors describe an increased risk of death at 2 and 5 years following the application of paclitaxel-coated balloons and stents in the femoropopliteal artery in the studies analyzed.

The purpose of this communication is now to draw your attention to updates that will be made to the IFUs for these devices throughout Europe. These updates will include a warning and a summary of the Katsanos publication, provided in Appendix One and supplemented with the clinical data specific to each device concerned. Please note that the indications and contraindications of the concerned devices remain unchanged.

No product batch/lot is being recalled in relation to this field safety notice. As noted in Appendix One, "the benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality)". Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. It is also important to remember that health professionals should inform patients and their follow- up physicians of the nature of the devices used during the procedure.

Please read this notice carefully and provide it to any relevant person in your organization.

If you have any questions or would like assistance regarding the content of this letter, please contact your usual representative of the company that supplies you with the devices concerned in your institution.

Yours sincerely,

B. Braun Melsungen AG
Biosensors Europe SA
Biotronik AG
Boston Scientific International S.A.
CARDIONOVUM GmbH
Cook Ireland LTD
Lutonix, Inc
LVD Biotech SL
Medtronic, Inc
Spectranetics Corporation

Appendix one: Wording for EU IFUs of the paclitaxel medical devices

Warning

A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment 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.

Summary of the meta-analysis

A meta-analysis of randomized controlled trials published in December 2018 by Katsanos et. al. identified an increased risk of late mortality at 2 years and beyond for paclitaxel-coated balloons and paclitaxel-eluting stents used to treat femoropopliteal arterial disease. In response to these data, the United States Food and Drug Administration (FDA) performed a patient level meta-analysis of long-term follow-up data from the pivotal premarket randomized trials of paclitaxel-coated devices used to treat femoropopliteal disease using available clinical data through May 2019. The meta-analysis also showed a late mortality signal in study subjects treated with paclitaxel-coated devices compared to patients treated with uncoated devices. Specifically, in the 3 randomized trials with a total of 1090 patients and available 5-year data, the crude mortality rate was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 - 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. As presented at the June 2019 FDA Advisory Committee Meeting, an independent meta-analysis of similar patient-level data provided by VIVA Physicians, a vascular medicine organization, reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80). Additional analyses have been conducted and are underway that are specifically designed to assess the relationship of mortality to paclitaxel-coated devices.

The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

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 benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).

Additional information regarding clinical data on LEGFLOW OTW/ RX

In the RAPID trial (ISRCTN47846578), Kaplan Meier estimates freedom from all-cause mortality at 12 months was 98.0% (95% CI 94.1% to 100%) in the Legflow + bare metal stent group alone versus 96.1% (95% CI 90.8% to 100%; p=0.483) in the bare metal stent group alone as reported by Katsanos et al. Similar results confirming safety of Legflow at 2 years follow up in the RAPID trial have been published: de Boer SW, de Vries JP, Werson DA, Fioole B, Vroegindeweij D, Vos JA, van den Heuvel D; RAPID trial investigators. Drug coated balloon supported Supera stent versus Supera stent in intermediate and long-segment lesions of the superficial femoral artery: 2-year results of the RAPID trial. J Cardiovasc Surg (Torino). 2019 Oct 9. doi: 10.23736/S0021-9509.19.11109-3.