August 7, 2019 UPDATE: Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality

August 7, 2019

Earlier this year, we notified health care providers about a late mortality signal in patients treated for peripheral artery disease (PAD) in the femoropopliteal artery with paclitaxel-coated balloons and paclitaxel-eluting stents. We are issuing this update to provide the latest information on our analysis of long-term follow-up data from premarket trials and to provide summary information from our June 2019 advisory panel meeting. In addition, we are including recommendations to health care providers for assessing and treating patients with PAD using paclitaxel-coated devices.

This communication updates our January 17 (/medical-devices/letters-health-care-providers/treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting-stents) and March 15, 2019 (/medical-devices/letters-health-care-providers/update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting), notifications to health care providers.

Based on the conclusions of our analysis and recommendations of the advisory panel, the FDA is taking additional steps to address this signal, including working with manufacturers on updates to device labeling and clinical trial informed consent documents to incorporate information about the late mortality signal. The FDA is also continuing to actively work with the manufacturers and investigators on additional clinical evidence development for assessment of the long-term safety of paclitaxel-coated devices.

FDA Analysis and June 2019 Panel Meeting

On June 19-20, 2019, the FDA convened a public meeting (/advisory-committees/advisory-committee-calendar/june-19-20-2019-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting) of the Circulatory System Devices Panel of the Medical Devices Advisory Committee to discuss and make recommendations on the topic of a potential late mortality signal after treatment with paclitaxel-coated balloons and paclitaxel-eluting stents (collectively

called "paclitaxel-coated devices") to treat PAD in the femoropopliteal artery. The FDA's analysis of long-term follow-up data from the pivotal premarket randomized trials for paclitaxel-coated devices used to treat PAD was presented at the panel. Our meta-analysis of these trials identified a late mortality signal in study subjects treated with paclitaxel-coated devices compared to patients treated with uncoated devices. Specifically, in the three randomized trials which enrolled a total of 1090 patients, the crude mortality rate at 5 years 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. A meta-analysis performed by VIVA (Vascular InterVentional Advances) Physicians of patient-level data provided by manufacturers reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80).

The Panel concluded that a late mortality signal associated with the use of paclitaxel-coated devices to treat femoropopliteal PAD was present. The Panel and the FDA agreed that the magnitude of the signal 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. The Panel determined, and the FDA concurs, that additional clinical study data are needed to fully evaluate the late mortality signal.

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 Studies of Paclitaxel-Coated Devices

Because of the demonstrated short-term benefits of the devices, the limitations of the available data, and uncertainty regarding the long-term benefit-risk profile of paclitaxel-coated devices, the FDA believes clinical studies of these devices may continue and should collect long-term safety (including mortality) and effectiveness data. These studies require appropriate informed consent and close safety monitoring to protect enrolled patients.

RECOMMENDATIONS

Based on the FDA's review of available data and the Advisory Panel conclusions, we recommend that health care providers consider the following recommendations:

- Continue diligent monitoring of patients who have been treated with paclitaxel-coated balloons and paclitaxel-eluting stents.
- When making treatment recommendations, and as part of the informed consent process, consider that there may be an increased rate of long-term mortality in patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents.
- Discuss the risks and benefits of all available PAD treatment options with your patients. For many patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile based on currently available information.
- For individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.
- In discussing treatment options, physicians should explore their patients' expectations, concerns and treatment preferences.
- Ensure patients receive optimal medical therapy for PAD and other cardiovascular risk factors as well as guidance on healthy lifestyles including weight control, smoking cessation, and exercise.
- Report any adverse events or suspected adverse events experienced with the use of paclitaxel-coated balloons and paclitaxel-eluting stents. Voluntary reports can be submitted through MedWatch, the (http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)FDA Safety Information and Adverse Event Reporting program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda). Device manufacturers and user facilities must comply with the applicable Medical Device Reporting (MDR) regulations (/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities). Health care personnel employed by facilities that are subject to the FDA's user facility reporting requirements (/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities) should follow the reporting procedures established by their facilities. Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices.

FDA ACTIONS

- The FDA continues to work with the manufacturers and investigators on additional clinical evidence development to assess the long-term safety of paclitaxel-coated devices. Analyses of additional randomized trials and registry datasets are being planned to provide further insights into the magnitude and potential causes of the late mortality risk.
- The FDA is working with manufacturers on labeling updates for paclitaxel-coated devices to include information about the late mortality signal.
- For ongoing trials of paclitaxel-coated devices, the FDA is working with study investigators to modify informed consent documents to include information about the late mortality signal.

The FDA will keep the public informed as any new information or recommendations become available.

If you have questions about this letter, please contact the Division of Industry and Consumer Education (DICE) at DICE@FDA.HHS.GOV (mailto:DICE@FDA.HHS.GOV), 1-800-638-2041 or 301-796-7100.

Previous FDA Letters On This Topic

- (January 17, 2019) Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers (/medical-devices/letters-health-care-providers/treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting-stents)
- (March 15, 2019) UPDATE: Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers (/medical-devices/letters-health-care-providers/update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting)