UPDATE: Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers

March 15, 2019

Several weeks ago, we notified health care providers about the potential for increased long-term mortality after use of paclitaxel-coated balloons and paclitaxel-eluting stents (collectively "paclitaxel-coated products") to treat peripheral arterial disease (PAD) in the femoropopliteal artery, as identified in a recent **meta-analysis (https://www.ahajournals.org/doi/10.1161/JAHA.118.011245)** of randomized trials published in the Journal of the American Heart Association. In our **January 17, 2019 letter to health care providers (/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm629589.htm)**, we promised to communicate as new information became available.

We have now conducted a preliminary analysis of long-term follow-up data (up to five years in some studies) of the pivotal premarket randomized trials for paclitaxel-coated products indicated for PAD. While the analyses are ongoing, our preliminary review of this data has identified a potentially concerning signal of increased long-term mortality in study subjects treated with paclitaxel-coated products compared to patients treated with uncoated devices. Of the three trials with 5-year follow-up data, each showed higher mortality in subjects treated with paclitaxel-coated products than subjects treated with uncoated devices. In total, among the 975 subjects in these 3 trials, there was an approximately 50% increased risk of mortality in subjects treated with paclitaxel-coated devices versus those treated with control devices (20.1% versus 13.4% crude risk of death at 5 years).

These data 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, these studies 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.

Paclitaxel-coated balloons and stents are known to improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels. However, because of this concerning safety signal, we believe alternative treatment options should generally be used for most patients while we continue to further evaluate the increased long-term mortality signal and its impact on the overall benefit-risk profile of these devices. The FDA intends to conduct additional analyses to determine whether the benefits continue to outweigh the risks for approved paclitaxel-

coated balloons and paclitaxel-eluting stents when used in accordance with their indications for use. The FDA will also evaluate whether these analyses impact the safety of patients treated with these devices for other indications, such as treatment of arteriovenous access stenosis or critical limb ischemia.

Because of concerns regarding this issue, the FDA will convene an Advisory Committee meeting of the Circulatory System Devices Panel to:

- Facilitate a public, transparent, and unbiased discussion on the presence and magnitude of a long-term mortality signal;
- Discuss plausible reasons, including any potential biological mechanisms, for a long-term mortality signal;
- Re-examine the benefit-risk profile of this group of devices;
- Consider modifications to ongoing and future US clinical trials evaluating devices containing paclitaxel, including added surveillance, updated informed consent, and enhanced adjudication for drug-related adverse events and deaths; and
- Guide other regulatory actions, as needed.

Further details concerning the timing and location of the Advisory Committee meeting will be announced in the coming weeks.

RECOMMENDATIONS

Based on the FDA's preliminary review of available data, we recommend that health care providers consider the following until further information is available:

- 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 most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the safety signal has been performed.
- For some individual patients at particularly high risk for restenosis, clinicians may determine that the benefits of using a paclitaxel-coated product may outweigh the risks.
- 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.

The FDA continues to recommend that health care providers:

- 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 FDA Safety Information and Adverse Event Reporting program (/Safety/MedWatch/HowToReport/ucm2007306.htm)**. Device manufacturers and user facilities must

comply with the applicable **Medical Device Reporting (MDR) regulations (/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm)**. Health care personnel employed by facilities that are subject to the **FDA's user facility reporting requirements (/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm)** 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.

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

Previous Letter:

- (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 (/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm629589.htm)**

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