24 Hour Summary of the Circulatory System Devices Panel Meeting Paclitaxel-Coated DCB and DES Late Mortality General Issues Panel June 19-20, 2019

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on June 19-20, 2019 to discuss and make recommendations on the late mortality safety signal associated with paclitaxel-coated products (i.e., paclitaxel-coated balloons and paclitaxel-eluting stents) used to treat peripheral arterial disease in the femoropopliteal arteries. FDA requested the panel to review the available information and provide feedback on: (1) the presence and magnitude of a late mortality safety signal; (2) whether all paclitaxel-coated vascular products (regardless of device platform or dose) are associated with the signal; (3) the impact of missing data and covariates on the signal; (4) potential mechanism of death (causality) considering drug dose exposure and pre-clinical data; (5) reconsideration of the benefit-risk profile related to the use of these products; (6) the need for the collection of additional data and/or device labeling changes; and (7) the impact of the signal on ongoing femoropopliteal disease clinical trials as well as on paclitaxel-coated products marketed or under clinical evaluation for other indications (e.g., treatment of stenoses in arteriovenous dialysis fistulae, critical limb ischemia).

Panel Deliberations/FDA Questions-Day 1:

Question 1. Presence and Magnitude of Late Mortality Signal Associated with Treatment of Paclitaxel-Coated Devices

The panel unanimously agreed that the aggregate data showed a mortality signal. However, there was uncertainty regarding the signal magnitude, primarily due to the small number of trials with 5-years follow-up and high levels of missing data.

Question 2. Class Effect Among FDA-Approved Paclitaxel-Coated Balloons and Stents

Given limitations in the data, the panel could not conclude that the late mortality signal represented a class effect among the devices. However, the panel believed that the available data would not *a priori* exclude any individual device from the group. The panel

agreed that any future regulatory actions related to the late mortality signal should pertain to all marketed devices until additional clinical data demonstrates otherwise.

Question 3. Impact of Missing Data

The panel appreciated industry efforts to collect additional data, but they indicated that the amount of missing data (notably vital status, repeat interventional treatments and additional paclitaxel exposure) was disappointingly high and hindered the interpretation of the analyses. The panel recommended that future trials include mechanisms to reduce missing data to the greatest degree possible.

Question 4. Subgroup Analyses

Due to the limited data available, the panel could not identify patient subgroups that might be at particularly high (or low) mortality risk following treatment with paclitaxel-coated devices. The panel recommended that future studies include a heterogeneous population to help enhance the value of subgroup analyses.

Question 5. Cause of Death Analysis

The panel agreed that the observed rates of both cardiovascular and non-cardiovascular death were higher in patients treated with paclitaxel-coated devices vs. uncoated devices. However, the panel noted the challenges with attributing a single cause of death to patients with numerous co-morbidities. Based on the limited available data and the lack of consistent cause of death definitions, the panel could not identify a particular cause of death to explain the late mortality signal in patients treated with paclitaxel-coated devices.

Panel Deliberations/FDA Questions-Day 2:

Question 6. Paclitaxel Dose/Mortality Relationship

The panel indicated that dose analyses were limited and precluded determination of a relationship between paclitaxel dose and mortality. Panel members noted that there was uncertainty in some dose estimates and that dose can be correlated with lesion length and more extensive disease, which could add complexity to the analysis. Multiple panelists recommended further work on this issue including collecting clinical data on all paclitaxel exposures in on-going and future studies and conducting a patient-level meta-analysis of paclitaxel dose and mortality.

Question 7. Preclinical Studies

The panel agreed that the available preclinical animal data do not indicate a potential biological mechanism for the late mortality signal. One panelist expressed concern with the high paclitaxel concentrations in the lungs. Several panelists suggested additional research in animal models may be valuable to determine specific drug-drug interactions, assess potential cellular and physiological pathways, and consider disease animal models. However, several panelists disagreed, noting the additional preclinical data may not be as informative as human clinical data.

Question 8. Benefit-Risk Profile

The panel unanimously agreed that the short-term benefits of paclitaxel-coated devices continue to outweigh the risks, and that these devices should not be removed from the market. Several panelists noted that patients highly value the improved quality of life and reduced reinterventions. All panelist agreed that risks should be communicated to the patient to support an informed choice. Numerous panelists noted that treatment decisions should be left up to the patient and treating physician. The panel also discussed the importance of risk stratification, since some patients at high risk and/or with multiple co-morbidities may opt for treatment with paclitaxel-coated devices despite risks.

Question 9. Post-market Study/Surveillance

The panel recognized the challenges associated with enrolling a new large randomized controlled trial. Some panelists suggested conducting further analysis of currently-available clinical data from randomized controlled trials; modifying ongoing trials to collect additional information to evaluate this signal (e.g., extend follow-up to beyond 5 years, capturing detailed information for repeat interventions); and initiating a randomized study that could be embedded in high-quality registries. Two panelists acknowledged the limitations associated with observational non-randomized registry data, because statistical methods (such as propensity matching) may not adequate to address confounding. The panel strongly recommended that the industry collaborate and with FDA on future study design efforts to evaluate the late mortality signal.

Question 10. Labeling

The panel recommended adding language to the labeling (e.g., instructions for use) for vascular paclitaxel-coated devices to indicate the presence of a potential late morality risk, and this language should be balanced with potential benefits, including reduced reinterventions and improved quality of life.

Question 11. Changes to Study Design

The panel agreed that FDA should continue to approve devices with 12-month clinical data that demonstrated an assurance of safety and effectiveness, but FDA should strengthen post-approval conditions to ensure adequate data collection for potential signal detection. The panel stressed the importance to minimize missing data in future studies and collect post-procedural information regarding additional reinterventions. The panel stated that informed consent forms for paclitaxel-coated device studies should include a discussion of potential mortality risks to allow the patient to make an informed choice. Additionally, the panel indicated that studies and registries would benefit from a uniform set of data elements and event definitions.

Question 12. Other Indications

The panel indicated that the recommendations for paclitaxel-coated devices for the SFA should also apply to clinical studies, informed consent, and labeling for paclitaxel-coated devices used in other indications (e.g., AVF and CLI). The panel noted that the benefit-risk profile for these patients may be different given the high mortality rates for these patients within 2-3 years.