FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Circulatory System Devices Panel
Advisory Committee Meeting on
Paclitaxel-Coated DCB and DES Late Mortality

June 19 & 20, 2019

FDA Panel Questions (cont.)-Day 2

Question 6: Paclitaxel Dose/Mortality Relationship

FDA conducted statistical analyses to determine a potential relationship between paclitaxel dose delivered and mortality. From these analyses, there was no consistent dose trend across the four pivotal RCTs that had a non-paclitaxel-coated device control group. One study suggested increased mortality with increased dose (LEVANT 2 RCT) and three studies did not show a relationship (IN.PACT SFA I & II, ZILVER PTX RCT, and ILLUMENATE RCT). Please discuss the relationship between paclitaxel dose and mortality.

Question 7: Pre-clinical Studies

Pre-clinical animal safety studies of paclitaxel-coated devices showed trends in the available clinical pathology results. For example, the average absolute leukocyte count trended lower at the time of sacrifice (30, 90 or 180 days post-treatment) in animals treated with paclitaxel-coated devices compared to baseline or to treatment with uncoated devices, especially in the safety margin studies. Nevertheless, all values fell within reference range for the animal model. It is challenging to draw conclusions from the available animal studies, and FDA's pre-clinical safety and pharmacology/toxicology reviewers were unable to identify likely biological mechanisms for mortality observed in clinical trial patients. Please comment on whether the non-clinical animal data provide mechanistic insights into the late mortality signal and discuss and describe what new animal studies (if any) may be helpful.

Question 8: Benefit-Risk Profile

Paclitaxel-coated products have been shown to demonstrate sustained benefits with increased patency rates and reduced clinically-driven target lesion revascularization (CDTLR) rates. Prior to FDA approval, no concerning or unexpected safety trends were noted for these devices. However, an increase in late mortality has been identified. Given the totality of the data, please discuss benefit-risk considerations related to paclitaxel-coated DCB and DES for the treatment of symptomatic femoropopliteal (SFA/PPA) disease. In your discussions please comment on the continued marketing of paclitaxel-coated devices for patients with symptomatic SFA/PPA disease.

Question 9: Post Market Studies/Surveillance

If you conclude that the totality of the available data shows that the benefits outweigh the risks for paclitaxel-coated devices, but the potential late mortality signal is not fully understood, please discuss whether post-approval studies or post-market surveillance assessments are recommended. Please discuss the objectives of new post-market data collections, what information should be collected, study endpoints, and study design. In addition, please comment on the feasibility of conducting new studies of paclitaxel-coated devices in patients with symptomatic SFA/PPA disease.

Question 10: Labeling

Based on your conclusions regarding the presence and potential cause of a late mortality signal, please discuss modifications, if any, should be made to the labeling of all approved paclitaxel-coated devices, as well as devices being studied in clinical trials, in order to convey appropriate safety information.

Question 11: Changes to Study Design

Given the limitations in the available studies of paclitaxel-coated devices (e.g., small sample size, missing data, and missing covariates), please discuss any study design recommendations to better evaluate these devices. For example:

a. Please comment on whether an assessment of the primary safety endpoint at 12-month is sufficient to ensure the safety of these devices to support PMA approval. If you believe that a longer-term endpoint would be more appropriate, please discuss your recommended primary analysis timepoint and its feasibility. In addition to mortality, please discuss other clinical events that should be included in primary or secondary safety endpoints.
b. Please comment on how the death adjudication process can be improved to help determine potential causes for late mortality.
c. For ongoing and future IDE studies, please identify what information, if any, should be included in the informed consent document related to the late mortality signal.
d. Please provide recommendations for future clinical IDE studies of paclitaxel-coated devices regarding study design, control population, statistical analysis plan, and efforts to minimize missing data.

Question 12: Other Indications

The data discussed above are relevant to paclitaxel-coated coated devices used to treat symptomatic SFA/PPA disease. However, there are some paclitaxel-coated devices approved for other indications (e.g., for treatment of stenoses in arteriovenous dialysis fistulae), and there are ongoing studies for other indications (e.g., for treatment of critical limb ischemia). Based on the available data, please comment on whether you believe any of your above recommendations are applicable to paclitaxel-coated devices with other indications for use. Please also discuss whether you believe benefit-risk considerations for these indications (e.g., AVF, CLI) are likely to be different than for SFA/PPA disease.