DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

October 29, 2015

Dear Global Endometrial Ablation Manufacturer:

Since 1997, the FDA has approved five global endometrial ablation (GEA) devices based on the results of randomized controlled trials (RCTs) that compared the safety and effectiveness of the GEA device to the same control – hysteroscopic rollerball ablation. Rollerball ablation is an older, well-known surgical technique used to treat heavy menstrual bleeding from benign causes. After analyzing the results of these five RCTs, the FDA identified an optional Objective Performance Criteria (OPC) for future GEA clinical trials.

The study designs that supported the approval of the five GEA devices were very similar. They enrolled between 250 and 350 subjects using either a 1:1 or 2:1 (device:control) randomization scheme and had comparable patient populations. The primary endpoint for all five studies was the reduction in menstrual blood loss measured by the Pictorial Blood Loss Assessment Chart (PBLAC), a validated menstrual blood loss scoring system. One of the inclusion criteria required a baseline PBLAC score of at least 150 or 185, and the individual patient success criteria for effectiveness was defined as a PBLAC score of less than or equal to 75 at one year following the ablation procedure. For all subjects, pretreatment evaluation was performed to confirm the study eligibility criteria were satisfied (e.g. absence of cavity distortions, lesions that might interfere with the GEA therapy). The analysis population consisted of all subjects who presented for their scheduled treatment, having satisfied the study eligibility criteria (intent-to-treat). This analysis population included women who presented for treatment, but did not receive the planned therapy due to reasons such as identification of exclusionary pathology immediately prior to ablation, withdrawal of consent, etc. Patients with missing PBLAC scores at one year following the ablation procedures were considered treatment failures. A study was considered a success if the proportion of successes in the GEA group met a pre-specified non-inferiority margin compared to the proportion of successes in the rollerball ablation control group.

The FDA saw that the effectiveness of the rollerball ablation control was consistent across all five RCTs. This prompted the FDA to reassess whether a control group was needed for future premarket approval applications for GEA devices. To evaluate this possibility, the FDA analyzed the data from the five available clinical trials with input from industry and members of the Obstetrics and Gynecology Devices Advisory Panel.

Using a generalized linear mixed model with study as a random effect, the FDA determined that the average success rate across the five GEA devices was 75.6% (65.6%, 83.5%) and 77.2% (66.5%, 85.2%) for the rollerball ablation control. The FDA performed additional analyses to evaluate the effect of baseline covariates on the primary endpoint, including age (above and below 40), baseline PBLAC score (over 150), uterine sound (6 to 12 centimeters), and presence

of fibroids (< 3 cm). Using analysis of covariance methods, the FDA found that none of these baseline covariates had a significant impact on the study results. Based on this analysis, the FDA identified an objective performance criterion (OPC) for the minimum success rate for effectiveness . The OPC is 66% based on the lower bound of the 95% confidence interval of the average success rate for the five approved GEA devices.

The OPC provides an option for manufacturers to conduct a single-arm study to support approval of future GEA devices. The effectiveness of a new GEA device can be compared to the OPC, rather than a concurrent control group, if other aspects of the single-arm study are comparable to the five completed RCTs, e.g., patient population, individual patient success criteria, and the analysis population for determining study success. Given that a control group is not necessary when using an OPC, the overall study size will be reduced.

Manufacturers who use the OPC can complete their studies with fewer subjects, lower cost, and in less time compared to a RCT but should keep in mind that in order to provide a clinically meaningful assessment of the safety of the new GEA device, the study sample size (usually based on the number of subjects necessary to test the primary effectiveness hypothesis) must be sufficient. Patients may prefer enrolling in a single arm study rather than an RCT, because they know the treatment they will receive. By leveraging the clinical data from the five previously approved GEA devices, the OPC provides the option for a less burdensome path to market for future GEA devices.

Sincerely,

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