

Seventy-Third Meeting of the  
**Obstetrics and Gynecology Devices Panel**

Friday, December 14, 2007  
Hilton Washington DC North, Gaithersburg, MD

**General Topic Discussion – Clinical Trial Design Issues for Endometrial  
Ablation Devices for Women Seeking Elective Cessation of Menses**

**Draft Discussion Questions**

*Study Design*

1. FDA recognizes the importance of a well controlled-study for addressing issues such as bias. However, for a ‘lifestyle’ indication such as cessation of bleeding, there is no obvious control procedure for comparison. A single-arm trial design will require careful consideration of the benchmark for study success, both in terms of the individual as well as the overall study. An objective performance criterion (OPC) for menstrual bleeding could be established, based on the many previous studies of endometrial ablation that FDA has reviewed in the past. With this approach, a study hypothesis could be established around a “target” success rate. Alternatively, a simple single-arm study of the appropriate population could be used to estimate the amenorrhea rate (with sufficient precision), and this information would be used to consent an endometrial ablation candidate who would have to weigh that benefit against the known procedural risks. We are interested in the panel’s opinions regarding these two approaches and how they may be successfully implemented in a new clinical investigation.

*Study inclusion/exclusion criteria*

2. We are interested in the panel’s input on the following issues related to study entry:
  - a. To date all endometrial ablation device manufacturers have used the Pictorial Blood Loss Assessment Chart (PBLAC) to quantify blood loss for the purposes of enrolling patients with menorrhagia (PBLAC  $\geq 150$ ) and defining success, i.e., “normal” bleeding (PBLAC  $\leq 75$ ). Does the panel agree that study entry for this indication should include a comparable assessment, i.e., some PBLAC defined number representing “normal” bleeding, e.g.,  $\leq 75$ ? Or is some alternative measure acceptable for including women with “normal” bleeding? In addition, should there be stratification of results based on PBLAC score at study entry?
  - b. The approved labeling for endometrial ablation devices intended for use in women with menorrhagia includes a contraindication for women who want to become pregnant in the future. The labeling also includes a warning that the use of the device does not achieve sterilization and therefore patients should be advised of appropriate birth control methods. Does the panel think that such an

- advisory is appropriate in this patient population or should entry into the study require that the patient have a history of permanent sterilization? If the panel believes that permanent sterilization should be a requirement, please discuss the potential for an increased risk of post-ablation tubal sterilization syndrome (PATSS).
- c. Given that this procedure is a permanent, irreversible treatment, there is concern regarding patient regret. In light of this concern, we are interested in the panel's thoughts regarding patient age for study entry.
3. The labeling for all approved endometrial ablation devices contraindicates the device for use in patients:
- Who are pregnant or want to become pregnant in the future.
  - With known or suspected endometrial carcinoma (uterine cancer) or premalignant change of the endometrium, such as unresolved adenomatous hyperplasia.
  - With any anatomic condition (e.g., history of previous classical cesarean sections or transmural myomectomy) or pathologic condition (e.g., chronic immunosuppressive therapy) that could lead to weakening of the myometrium.
  - With active genital or urinary tract infection at the time of procedure (e.g., cervicitis, vaginitis, endometritis, salpingitis, or cystitis) or with active pelvic inflammatory disease (PID).
  - A patient with an intrauterine device (IUD) currently in place.
- Are there any other contraindications/study exclusions that are warranted based on this new intended use?

#### *Study Outcome*

4. In this population should the definition of success be limited to amenorrhea (PBLAC = 0) or might it include spotting? Should there be differentiation between predictable and unpredictable spotting and the use of a pantiliner versus no protection?
5. Endometrial ablation devices approved for use in women with menorrhagia were based on 12-month follow-up pre-market. (An additional 24-month follow-up was required in the post-market setting.) What does the panel think is the appropriate time frame for evaluating safety and effectiveness in the pre-market setting for this new indication?
6. As a secondary outcome measure, we would expect sponsors to gather information on quality of life issues. This would typically include a questionnaire that assesses patient satisfaction with the procedure and its outcome. Does the panel think that a more comprehensive questionnaire is necessary for this type of study? Is it necessary for such a questionnaire to be validated in this patient population?

### *Risk/Benefit*

7. The known serious adverse events associated with endometrial ablation in women with menorrhagia include: uterine perforation; hysterectomy; thermal injury to bowel; bowel resection; post ablation tubal sterilization syndrome; endometritis; hematometra; thermal injury to vagina and perineum; infection and sepsis. We are interested in the panel's opinion regarding how we should evaluate the adverse events in the context of the risk/benefit ratio for this new patient population. Does the panel think the overall complication rate from the original study should be set as the target for the "elective use" study?
8. As with all endometrial ablation procedures, there is the theoretical possibility for a uterine cancer to be masked or the diagnosis made more difficult as a result of the procedure. Please comment on the known versus theoretical risk of delayed diagnosis of uterine cancer as a result of endometrial ablation and how and to what extent this should be considered in light of the new patient population.
9. An endometrium of normal thickness may provide less of a buffer during the ablation when compared to the endometrium of women with menorrhagia. If so, the target population may be at an increased risk of thermal injury. Does the panel agree that this population may be at increased risk? If so, what are the recommendations for minimizing the risk?

### *Follow-up*

10. As a follow-up to question #5 above regarding the necessary pre-market follow-up, what does the panel think is an appropriate post-market follow-up period for patients enrolled in this type of study?