RE: InSightec ExAblate® 2000 (P040003)

Submitted testimony of Carla Dionne:

Members of the FDA Obstetrics and Gynecology Devices Panel Committee,

My name is Carla Dionne and I am the Executive Director of the National Uterine Fibroids Foundation. We are located in Colorado Springs, Colorado and represent the only national nonprofit patient education and advocacy group specifically representing women with uterine fibroids in the United States.

Thank you for the opportunity to submit my testimony today on a subject of tremendous importance to the health and welfare of women with uterine fibroids. Although I cannot attend today's meeting, I would like to present a few issues for the panel to consider when making a recommendation for potential approval of the Insightec ExAblate 2000 for the treatment of uterine fibroids.

Based on the limited information made publicly available June 2, 2004 regarding this study, the following areas are of great concern:

SAFETY AND EFFECTIVENESS

Typically, clinical trial recruitment of a motivated patient population can minimize loss to follow-up and provide more extensive information. This particular group of women who underwent focused ultrasound treatment for symptomatic fibroids should have been an incredibly low risk group for loss to follow-up. It is, therefore, quite surprising to see a nearly 30% loss rate within six months, a loss rate of 60% at 12 months, and an additional 20% of the final group (not lost to follow-up) who went on to a secondary alternative procedure.

The FDA has previously indicated that loss to follow-up of 15% or more make the determination of safety and effectiveness difficult to assess and, as such, the maximum calculated as 'acceptable' is generally 15%. It would seem loss to follow-up rates of 30% at 6 months and 60% by 12 months would completely negate the results of this study in terms of truly determining safety and effectiveness. Under the circumstances, and in consideration of the desperate attempts women make to avoid surgical intervention, it is extremely questionable as to why so many women would be lost to follow-up so soon after treatment. It is critical for the clinical investigators involved in this study to provide more information about follow-up for these women.

In an additional review of the initial phases of study (I/II) where women underwent hysterectomy after HIFUS, there were a seemingly inordinate number of patients who developed post-operative hematomas requiring surgical drainage. In addition, due to incisional bleeding, one patient required ligation of a single uterine artery. Given the current study under review, if HIFUS is non-durable for a great many women, what are the subsequent surgical risks? Has surgical or embolization risk increased due to treatment with HIFUS? If so, at what ratio and what would the severity of that potential risk truly be? Would undergoing HIFUS become a contraindication to myomectomy or embolization?

From the Agency for Healthcare Research and Quality (AHRQ):

> Based on the 1997 Healthcare Cost and Utilization Project (HCUP) State Inpatient Database for 19 States, the Postoperative Hemorrhage or Hematoma rate was 1.61 per 1,000 population at risk.

(Source: *Postoperative hemorrhage or hematoma: rate per 1,000 surgical discharges. AHRQ quality indicators. Guide to patient safety indicators [revision 1]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2003 May 28. 143 p. (AHRQ Pub; no. 03-R203).*
http://www.qualitymeasures.ahrq.gov/summary/summary.aspx?ss=1&doc_id=619)

It would seem the hysterectomy-after-HIFUS group had an incidence ratio significantly higher than the 'norm', per the above AHRQ study. However, given the small number of women studied post-HIFUS who subsequently underwent hysterectomy, only a larger study of women undergoing subsequent surgical treatment would potentially offer more conclusive information on this issue. Given this, an incredibly critical question remains unanswered: If HIFUS does NOT prove to be durable long-term (>1 year) for women, has undergoing the treatment compromised the potential for subsequently undergoing a more durable treatment safely, such as hysterectomy or myomectomy or even embolization?

In terms of efficacy, the 14% volume reduction at 6 months is disappointing, at best. Further, the decline in *Average % of fibroid shrinkage* at 12 months to 9.4% is abysmal.

Based on the data submitted regarding loss to follow-up, subsequent alternative procedures, potential for increased risk in subsequent procedures, and the overall decline in average volume reduction, the cost/benefit analysis must truly be in question here. Is this an appropriate treatment for women with symptomatic uterine fibroids? Will women desperate to avoid surgical intervention by any means possible truly understand the potential risks involved with undergoing this procedure?

LABELING & TRAINING

1. Exclusionary Considerations

Patient *exclusionary* criteria appears to be absent from public review but is absolutely essential to the very offering of HIFUS to women with fibroids.

The following *exclusionary* items should be reviewed for potential dissemination to the medical community treating women with fibroids **AND** to the general public of women with uterine fibroids who may be considering this treatment option for symptomatic fibroids:

- pedunculated submucosal or subserosal fibroids
- fibroids smaller than 4 cm or larger than 10 cm
- presence of more than 3-4 fibroids
- presence of abdominal/pelvic scars or keloids from prior treatment
- fibroid(s) located too close to bladder, bowel, or bone (w/in 4 cm?)
- hematocrit level <25%
- excessive fat and/or muscle in the abdomen
- presence of adenomyosis
- desired fertility/positive pregnancy test

In addition, the following *exclusionary* items related to ultrasound, contrast, and MRI should also be reviewed for dissemination:

- contrast allergies
- impaired renal function
- claustrophobia (~15% of the population has claustrophobia severe enough to NOT tolerate the enclosure of MRI)
- presence of any metallic substances or implanted materials (such as: heart pacemaker, surgical clips from prior surgery--sometimes applied during c-section or myomectomy to the uterine artery OR via tubal ligation, insulin pumps, cochlear implants, jewelry, etc.)
- presence of abdominal/pelvic tattoos -- depending on location they may contain enough trace elements of metal as to interfere with clarity of MRI
- weight/girth of no greater than 350 pounds (table limit) but abdominal GIRTH limit might place this at no greater than 250-300 pounds, depending on the individual

2. Training

What are the proposed plans for radiology and gynecology training and certification for the Insightec ExAblate 2000? Given exclusionary factors AND what appears to be a learning curve (based on the trials to date) on selecting appropriate patients and using this equipment in the treatment of symptomatic uterine fibroids, it is of tremendous concern that an appropriate training and certification plan be firmly in place prior to additional installation and use of this equipment.

POST-MARKET STUDY

Given the poor showing of data presented for this clinical trial in consideration of FDA approval of the Insightec ExAblate 2000, this device has simply failed to provide enough post-treatment patient information on it's safety and efficacy in the treatment of women with symptomatic uterine fibroids. In short, the Insightec ExAblate 2000 should NOT receive FDA approval at this time based on the data presented and with continued outstanding concerns over patient safety and efficacy.

It would be the recommendation of the National Uterine Fibroids Foundation that this device continue to be followed pre-market for an additional year prior to a subsequent review by the FDA. However, given the loss to follow-up rate currently identified, will there be any patients remaining from the pivotal study one year from now who are not also lost to follow-up? Will there be any additional effort to report on what, exactly, occurred to those patients lost to follow-up? Did they ultimately undergo an alternative procedure? Furthermore, if the average % of fibroid shrinkage declines any further, will there be a single patient left who was clinically (vs. technically) 'successfully' treated with HIFUS?

It would be our further recommendation that the members of this panel consider the absolute need for the design of a new study protocol with an increased awareness of the potential for loss to follow up, exclusionary factors, and risks to subsequent procedures required after the potential clinical treatment failure of HIFUS. Preferably this study would not be a comparative study to hysterectomy but, rather, comparative to other uterine sparing treatments and matched for appropriate patient controls.

The Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF) and the Society of Interventional Radiology (SIR), in cooperation with the Duke Clinical Research Institute (DCRI), have established the Uterine Artery Embolization (UAE) Fibroid Registry for Outcomes Data (FIBROID). The purpose of

the FIBROID Registry is to specifically assess the durability, impact on fertility and quality-of-life, and to obtain data which will allow researchers to compare UAE to other fibroid therapies. Due to the number of patients undergoing the non-surgical uterine sparing treatment of uterine fibroid embolization, there is an abundance of collected data for this treatment modality. This would distinctly set UFE apart from hysterectomy as a much more appropriate study group for comparison to HIFUS than hysterectomy and it would be our recommendation that this be reviewed for consideration.

Respectfully submitted,

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