

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

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I. GENERAL INFORMATION

Device Generic Name: Magnetic Resonance Guided Focused
Ultrasound Surgery System

Device Trade Name: ExAblate[®] 2000 System

Applicant's Name and Address: InSightec, Ltd.
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Premarket Approval Application
(PMA) Number: P040003

Date of Notice of Approval to Applicant: October 22, 2004

II. INDICATIONS FOR USE

The **ExAblate[®] 2000 System** is intended for ablation of uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure. Patients must have a uterine size of less than 24 weeks and have completed child bearing.

III. CONTRAINDICATIONS

- The ExAblate[®] 2000 treatment is contraindicated for use in women who should not undergo magnetic resonance imaging (MRI) (e.g., women who have metallic implants that are incompatible with MRI or sensitivity to MRI contrast agents).
- The ExAblate[®] 2000 treatment is contraindicated if the clinician is unable to avoid having important structures [e.g., scar, skin fold or irregularity, bowel, pubic bone, IUD (intrauterine device), surgical clips, or any hard implants] in the path of the ultrasound beam.

IV. WARNINGS AND PRECAUTIONS

The WARNINGS and PRECAUTIONS can be found in the ExAblate[®] 2000 System labeling.

V. DEVICE DESCRIPTION

InSightec's ExAblate[®] 2000 System integrates a phased array high intensity focused ultrasound system with MR imaging (both conventional and thermographic) and a mechanical transducer positioning system to map and deliver ultrasound energy and thermally ablate uterine fibroids. The ultrasound energy is focused through the abdomen to target tissue in the uterus, with a maximum focal volume of 12 x 12 x 30 mm. The energy raises the temperature of the target tissue to approximately 65-85° C, sufficient to cause protein denaturation in the tissue and resultant thermal ablation. There is a 90-second refractory period for tissue to cool before the next sonication.

Conventional MR images are used to plan and guide these sonications; more newly developed MR-thermography – based on phase information to calculate changes in tissue temperature – is used to monitor and calibrate the ablation process.

The ExAblate[®] 2000 System integrates with a commercially available GE Signa 1.5T MR imaging system. This application of the Signa device uses a special MR coil that is suitable for use with the ExAblate[®] 2000 System. That is, the GE device obtains MR images the same way it always has, but the way the images are presented to and used by the user is based on the InSightec software.

Hardware

The ExAblate[®] 2000 System hardware is composed of a patient table, an equipment cabinet housing the electronics and amplifiers required to power the system, and an operator workstation to control the treatment.

The patient table, on which the patient lies during treatment, houses the focused ultrasound transducer and its positioning system in a water bath, as well as the power modules that activate elements of the transducer. The patient table docks onto an existing, compatible MR system.

The equipment cabinet, usually located in an equipment room nearby, houses additional electronics, amplifiers and power supplies. It includes an imbedded computer that communicates with the physician workstation by receiving instructions, processing and executing instructions, and translating the instructions into physical system operations (e.g., begin sonication, end sonication, move transducer, execute safety stop).

The workstation is a Windows-based PC that has the ExAblate[®] 2000 software installed. The workstation has a monitor, a mouse and a stop sonication button that immediately stops the programmed sonication in case of emergency. During treatment, the workstation retrieves planning images and phase images from the MR computer. The workstation's graphical user interface overlays icons and colors on the

MR images for treatment planning and evaluation. The workstation is where the physician sets treatment parameters (such as power, duration, and spot size) and monitors acoustic reflection and cavitation during sonication. The information on treatment parameters and the next spot to be sonicated is communicated to the equipment cabinet computer, when then implements the instructions. The workstation also communicates with the MR system.

Software

The ExAblate[®] 2000 software performs the following principal functions:

- Graphical User Interface (GUI) for treatment planning and system operation;
- MR communication and remote operation of the MR;
- ExAblate[®] 2000 hardware system operation and control;
- MR image acquisition and viewing;
- Graphical planning tools; and
- Calculations of thermal dose, and graphical monitoring of treatment (reflection and spectrum).

The GUI display and associated displayed “tool tips” assist the user through the treatment planning and execution process.

Accessories

The following accessories are needed for operation of the ExAblate[®] 2000:

- Treatment Kit: each kit contains all the necessary disposable items involved in a patient treatment (degassed water, scraper, patient drape, ultrasound gel, acoustic coupling gel pad);
- Pelvic Coil: a pelvic coil (cleared in K033753) for use with the GE Signa 1.5T MR imaging system designed to fit onto the ExAblate[®] 2000 patient table; this coil is used to acquire the planning and post-treatment images; and
- DQA (daily quality assurance) phantom: a tissue-mimicking phantom for testing the functionality of the ExAblate[®] 2000.

Principles of Operation

The system combines MR technology with high intensity focused ultrasound. The MR is used to map leiomyomata uteri (uterine fibroids) and monitor the treatment temperatures. The high focused ultrasound allows the physician to create thermal energy to heat and destroy fibroid tissue. The treatment is monitored using MR thermometry to decrease the risk of injury to tissues outside the uterus. The entire procedure can be performed without an incision.

The patient undergoes an MR for treatment planning prior to the day of the procedure.

On the day of the procedure, the patient is placed prone on a patient table that fits into a standard MR scanner. A MR scan will be performed with T2 weighted sequences in 2 axes to localize and measure the fibroid lesions to be treated. The operator draws the treatment volume using the MR images. This volume must

maintain a minimum boundary, in all dimensions, of 15 mm of tissue from the treatment volume to the uterine serosa.

Using information from MR images, the ExAblate[®] 2000 System therapy planning software is used to calculate the type and number of sonications required. This is typically 20-50 individual sonications, each of which lasts 10-30 seconds followed by a 90-second cooling period. During each sonication, a small volume of focused ultrasound energy is directed to the target tissues. Absorption of the ultrasound energy by the target causes tissue heating to temperatures from approximately 65° C to 95° C to achieve coagulation.

The ExAblate[®] 2000 System can produce MR thermography images (thermal mapping) to permit visualization of the patient anatomy for treatment planning and quantitative information on the change in tissue temperature to monitor and control the treatment. This enables the physician to confirm that thermal energy is delivered to target tissue and that upper limits on temperature to target tissue are not being exceeded.

The ExAblate[®] 2000 System also allows for the placement of fiducial markers by the physician on the MR planning images. These markers appear on the thermal images produced for each sonication. They serve as a precaution to help the physician detect unanticipated movement of the target tissue if the patient moves during treatment. There is also an independent safety monitoring loop that compares physical position of the ultrasound transducer to the target in order to detect motion. If unintended motion is detected, the system immediately stops delivery of energy to the patient.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternate practices and procedures that are currently available to treat symptomatic uterine fibroids include

- Hysterectomy;
- Abdominal myomectomy;
- Laparoscopic and hysteroscopic myomectomy;
- Hormone therapy;
- Uterine artery embolization; and
- Watchful waiting.

VII. MARKETING HISTORY

The ExAblate[®] 2000 System received the CE mark in Europe for uterine fibroids in October 2002. It is currently in commercial use in Israel and is limited to use in private clinics and hospitals in Japan.

The ExAblate[®] 2000 System has not been withdrawn from the market in any country for any reason relating to the safety or the effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Summary of Adverse Effects Observed in Clinical Study

Adverse events that were observed during the trial are summarized in Table 1.

Table 1. Incidence of Adverse Events in ExAblate® 2000 Patients in the Pivotal Clinical Study (N=109)

Body System	Adverse Event	n (%)
Pain/Discomfort	Abdominal pain	42 (38.5%)
	Other pain *	14 (12.8%)
	Back pain - positional	11 (10.1%)
	Abdominal tenderness	10 (9.2%)
	Leg pain – sonication related **	8 (7.3%)
	Abdominal cramping	4 (3.7%)
	Back pain – sonication related **	4 (3.7%)
	Discomfort	2 (1.8%)
Gynecological	Abnormal vaginal discharge	10 (9.2%)
	Heavy menses	8 (7.3%)
	Vaginal bleeding	1 (0.9%)
	Abdominal cramping	5 (4.6%)
	Vaginal discharge	1 (0.9%)
Urinary	Urethral pain	8 (7.3%)
	Bladder symptoms	6 (5.5%)
	Increased urinary frequency	6 (5.5%)
	Urinary tract infection	4 (3.7%)
Gastrointestinal	Nausea/vomiting	14 (12.8%)
	Diarrhea	4 (3.7%)
	Constipation	3 (2.8%)
	Flatulence	1 (0.9%)
	Bowel distention	1 (0.9%)
	Bowel symptoms	2 (1.8%)
Systemic	Fatigue	8 (7.3%)
	Discomfort	7 (6.4%)
	Fever	2 (1.8%)
Dermatologic	Skin burn	5 (4.6%)
	Skin redness	4 (3.7%)
	Edema	4 (3.7%)
	Skin irritation	2 (1.8%)
	Firmness	1 (0.9%)
	Scarring	1 (0.9%)

* This is patient reported pain related to position or other causes.

** This is patient reported pain that was directly related to the sonication.

Potential Risks

The following adverse effects might be expected (potential), but have not yet been observed in the clinical study of ExAblate[®] 2000:

- Hemorrhage
- Pulmonary embolism
- Complications of pregnancy
- Damage to organs outside of the uterus
- Sepsis
- Complications leading to serious injury or death

Additional adverse event information is presented in Section X (Summary of Clinical Studies).

IX. SUMMARY OF PRECLINICAL STUDIES

The ExAblate[®] 2000 has undergone comprehensive non-clinical testing to demonstrate that its performance properties are appropriate for clinical use.

Electrical Safety and Electromagnetic Compatibility (EMC)

The objective of the testing was to ensure electrical safety and electromagnetic compatibility of the device.

Electrical safety testing was conducted in accordance with IEC 60601-1:1998 and Amendment 1:1991 and Amendment 2:1995. The device was tested on and passed all applicable sections.

EMC testing was conducted in two parts. The first set of tests was conducted in accordance with EN 60601-1-2:1993. The testing covered the following: conducted emission, radiated emission, immunity from electrostatic discharge, and immunity from radiated electromagnetic fields. The test results were acceptable.

The second set of EMC testing was conducted in accordance with EN 60601-1-2:2001. This testing covered immunity from: radiated electromagnetic fields; electrical fast transient, conducted disturbances induced by radio-frequency fields; power frequency magnetic field; and voltage dips, short interruptions, and voltage variations. The test results were acceptable.

Focusing of the Transducer

The objective of the test was to ensure the appropriate ability to focus on the target tissue *in vivo*. Testing of the transducer was performed in water, in a gel phantom, and in a fatty material. The results of these tests demonstrated the ability of the transducer to focus correctly on all media tested.

Transducer Power Measurements

The objective of this test was to characterize the acoustic power output of the transducer relative to the electrical power input and to verify that it could be calibrated to deliver a requested level of acoustic power. A characteristic plot was generated, which demonstrated a relatively constant efficiency over an appropriate range of electrical power levels.

Generation of Larger Focal Regions via Spot Types

The objective of this test was to verify that the ExAblate[®] 2000 could steer the focal sonication points to predetermined locations. By cycling the focus with different steering dimensions, the focal size could be “spread out” to create a larger effective focus size. The results demonstrated that the device could achieve a larger spot size by this means.

Cavitation Detection

The objective of this test was to verify that the ExAblate[®] 2000 was capable of spectral detection of cavitation signals from the receiving transducer. Cavitation was detectable at sub-harmonics of the sonication signal, manifested as broadband noise around the $\frac{1}{2} f_0$ frequency. The results demonstrated that cavitation could be detected.

Detection of Acoustic Coupling

The objective of this test was to demonstrate the ExAblate[®] 2000's ability to detect poor acoustic coupling at the interface. A gel pad was placed in contact with a Mylar film both with and without water at the interface to mimic good coupling and poor coupling, respectively. The results demonstrated that the poor coupling did generate reflection above the specified threshold and, therefore, was detected.

MR Thermometry Testing

The sponsor submitted a number of pre-clinical studies relating to the calibration of the MR thermal mapping feature. Calibration translates the observed change in proton resonant frequency with temperature into the temperature change. In the ExAblate[®] 2000, the calibration factor relating frequency change to temperature change is assumed to be 0.009 ppm/°C, independent of temperature rise, tissue type or thermally induced changes in the tissue. The calibration studies submitted by the sponsor included *in vitro* studies in samples of a variety of tissues, and *in vivo* studies, principally in rabbit muscle. A calibration was not performed in human uterine fibroid. The most definitive study, the *in vitro* study in rabbit muscle, suggested that the error increases with temperature, and is approximately +/- 20%.

comparing scores between women with normal menstrual cycles and women with symptomatic fibroids (*Ob Gyn*; 99(2):290-300, 2002). In addition to the Symptom Severity Score, the UFS-QOL includes a number of other health-related quality of life subscales, including level of concern regarding symptoms, impact of symptoms on activities, energy/mood, control over one's life, feeling self-conscious, and sexual function. For the pivotal study, success for an individual study subject was defined as a minimum 10-point improvement in her SSS subscale, the difference between baseline (pre-treatment) and 6-month post-treatment scores. To demonstrate that ExAblate[®] 2000 is an effective treatment for symptomatic uterine fibroids, the sponsor was required to show success for a minimum of 50% of the study subjects,

Secondary Outcome Measures

- (1) Significant clinical complications (SCC) for patients in both the ExAblate[®] 2000 group and the hysterectomy group;
- (2) QOL scores on the SF-36 subscales (physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) for both the ExAblate[®] 2000 group and the hysterectomy group;
- (3) Overall treatment effect and patient satisfaction; and
- (4) Post-treatment fibroid size (ExAblate[®] 2000 patients only)

Study Methodology

This study was a multi-center, international concurrent non-randomized control design whereby patients were enrolled into one of two parallel treatment arms (ExAblate[®] 2000 or hysterectomy). Separate sites were used for ExAblate[®] 2000 and hysterectomy arms. Study subjects were enrolled in a 3:2 ratio (ExAblate[®] 2000: hysterectomy). A total of 192 study subjects were enrolled in the study (109 ExAblate[®] 2000; 83 hysterectomy). The study was initially designed to provide follow-up at 3 and 6 months post-treatment. A longer follow-up period with visits at 12, 24, and 36 months was subsequently added.

Inclusion Criteria

- Women age 18 years and older who presented with symptomatic uterine fibroids and who had completed their families;
- Patients using hormone replacement therapy acceptable (not required);
- Clinically normal Pap smear within timing of national guidelines in the country of the clinical site;
- Able and willing to give consent and able to attend all study visits;
- Ability to read in English, French, German, or Hebrew;
- Transformed score of 41 or greater on the UFS-QOL Symptom Severity Score;
- Patient was pre- or peri-menopausal (within 12 months of last menstrual period);
- Able to communicate sensations during the ExAblate[®] 2000 procedure;
- Uterine fibroids which were device accessible (i.e., positioned in the uterus such that they could be accessed without being shielded by bowel, bladder, or bone).

- Tumor(s) clearly visible on non-contrast MRI; or
- Use or non-use of hormonal contraception maintained uniformly from 3 months pre-study through the 6-month follow-up period.

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

- Uterine size >24 weeks as evaluated by ultrasound or MR;
- Patients on dialysis;
- Hematocrit < 25%;
- Hemolytic anemia;
- Previously on GnRH agonist therapy within the 6 months prior to the start of the study;
- Unstable cardiac status including:
 - Unstable angina pectoris on medication;
 - Documented myocardial infarction within 6 months of protocol entry;
 - Congestive heart failure that required medication (other than diuretic);
 - Anti-arrhythmic drugs;
 - Severe hypertension (diastolic BP > 100 on medication); or
 - Cardiac pacemakers
- Severe cerebrovascular disease [multiple CVA (cerebrovascular accident) or CVA within the 6 months prior to the start of the study];
- Anticoagulation therapy, underlying bleeding disorder;
- Active pelvic infection or history of pelvic inflammatory disease;
- Pelvic mass outside the uterus suggesting other disease processes;
- Weight > 250 pounds;
- Severe hematological, neurological, or other uncontrolled disease;
- Pregnant, as confirmed by serum at time of screening, or urine pregnancy on the day of treatment;
- Patients with standard contraindications for MR imaging such as MR-incompatible implanted metallic devices, or sensitivity to MR contrast agent (e.g., Gadolinium or Magnevist);
- Patients who were not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 hours);
- Patients who had an intrauterine contraceptive device anywhere in the treatment beam path;
- Extensive abdominal scarring in an area of the abdomen directly anterior to the treatment area;
- Patients who were breast-feeding.

Study Results

Demographics

The demographic characteristics of the study population are displayed in Table 2.

Table 2. Summary of Patient Demographic Data

Characteristic	Number (%) of Treated Patients		P-value between groups
	ExAblate 2000 Group (N=109)	Hysterectomy Group (N=83)	
Age (years)			
Mean±SD	44.8±4.9	44.3±5.6	0.597
Range	30.0 – 58.0	29.0 – 55.0	
BMI (kg/m²)			
Mean±SD	25.8±5.2	29.9±6.0	<0.001
Range	18.6 – 43.9	17.4 – 44.2	
Race, n (%)			0.001
Am Indian or Alaska Native	0 (0%)	3 (4%)	
Asian (incl. South Asian)	3 (3%)	2 (2%)	
Black or African American	12 (11%)	28 (34%)	
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	
White (European origin or Arab/Middle Eastern)	87 (80%)	45 (54%)	
Hispanic or Latino	1 (1%)	2 (2%)	
Other	6 (6%)	3 (4%)	
Missing data	0 (0%)	0 (0%)	
Hormonal status			0.530
Premenopausal	102 (94%)	80 (96%)	
Perimenopausal	6 (6%)	3 (4%)	
Postmenopausal	0 (0%)	0 (0%)	
Missing data	1 (1%)	0 (0%)	

Demographic and Other Baseline Characteristics

The mean age of the patient population in both groups was approximately 44 years, which is consistent with a uterine fibroid patient population. There were no statistically significant differences between the groups with regard to age or hormonal status. There were significant differences between the ExAblate[®] 2000 and hysterectomy groups with regard to the variables BMI and race. The women in the hysterectomy group had a higher BMI, and while 11% of the ExAblate[®] 2000 patients were African-American, 34% of the hysterectomy patients were African-American.

Other co-morbid conditions were compared between the treatment and the control groups. Out of the 18 recorded conditions, the following were higher in the hysterectomy control vs the treatment group: diabetes mellitus (10% vs 3%); hypertension (24% vs 4%); anemia (11% vs 2%); and affective disorder (12% vs 0%). Of the remaining 14 conditions (including gynecological conditions), the groups were well matched.

Baseline/Procedure Information for ExAblate[®] 2000 Group:

For patients in the ExAblate[®] 2000 group, MR information was available to characterize the location, type(s), number, and size(s) of the fibroids (see Table 3).

Table 3. Summary of Fibroid Information and Characteristics for Patients in the ExAblate[®] 2000 Group of the Study	
Variable	(mean±SD)
Uterine volume (cm ³) ^a	595.0±362.5
Number of visible fibroids/patient ^b	2.3±2.0
Number of treated fibroids/patient ^c	1.3±0.6
Total # of Treated fibroids	(N=137)^g
Location	
Submucosal (n)	28
Intramural (n)	81
Subserosal (n)	24
Undetermined (n)	4
Total (n)	137
Total Fibroid Load, at baseline (cm ³) ^c	372±235
Volume of sum of slices (cm ³) ^d	284.7±225.4
Region of treatment (cm ³) ^e	25.6±18.4
Thermal dose volume (cm ³) ^e	25.5±18.2
Nonperfused volume (cm ³) ^f	62.4±70.4

a: 106 patients b: 99 patients c: 102 patients
d: 98 patients e: 100 patients f: 101 patients
g: Number of fibroids with Core Lab data

Seventy-one patients (69%) had one fibroid treated while 32 patients (31%) had multiple (up to four) fibroids treated.

Endpoint Evaluation

The data were analyzed for both the intent-to-treat and the evaluable patient populations. Table 10 presents the patient accountability data.

Primary Study Hypothesis (Effectiveness Evaluation)

The primary hypothesis was evaluated using the primary effectiveness endpoint of the study, the Symptom Severity Score (SSS) subscale of the Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire. The SSS includes a series of questions related to the predominant uterine fibroid symptoms of bulk and bleeding. In the UFS-QOL instrument, and henceforth in this document, raw SSS scores are converted to “transformed” scores where 100 is the worst possible score. Reduction in SSS score constitutes an improvement in patient symptoms. A 10-point improvement in the SSS at 6-months post-treatment was defined as

Figure 1a is a bar graph showing the distribution of the SSS subscale for ExAblate[®] 2000 study subjects, taken on both the day of the screening visit and the day of treatment (“baseline”). Fig 1b is a bar graph showing the distribution of the *difference* in the SSS subscale between the screening day and the baseline day. There were typically about 30 days between screening and treatment (baseline) when the ExAblate[®] 2000 procedure was performed. SSS scores fluctuated somewhat during this time interval. For most of the study subjects (82/109, 75%), the change in the SSS subscale between screen and baseline for any individual was less than 12 points, with an overall correlation between the two scores of 0.69. Fluctuation was fairly evenly distributed between improving and worsening scores.

Figure 1a. Distribution of Screening and Baseline Pre-treatment Symptom Severity Scores among ExAblate[®] 2000 Subjects

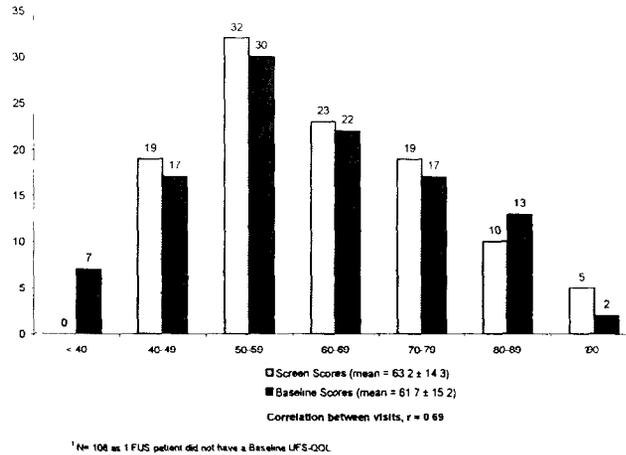


Figure 1b. Distribution of the Difference between Pre-treatment Screening and Baseline Scores among ExAblate[®] 2000 Subjects

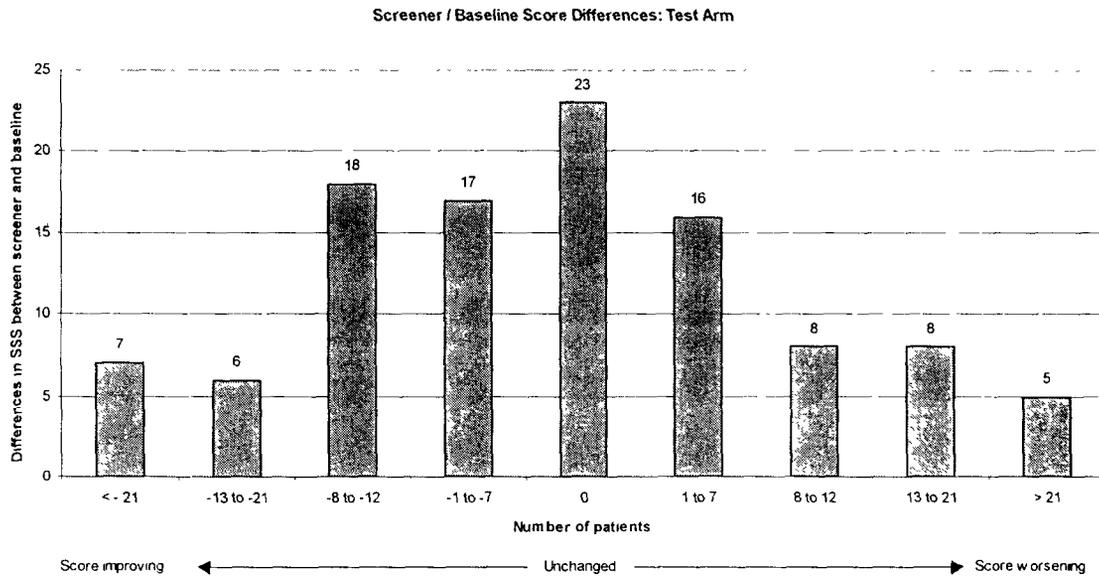


Figure 2 is a bar graph showing the distribution of changes in the SSS subscale for study subjects 6 months after treatment with the ExAblate[®] 2000 study subjects. On a *per protocol* intent-to-treat basis, 77 of the 109 subjects (70.6%) treated with the ExAblate[®] 2000 procedure had a reduction of at least 10 points in their SSS subscale.

Figure 2. Intent-to-Treat Distribution in Reduction in Symptom Severity Scores for ExAblate Treated Patients at 6 Months (higher score indicates greater reduction in symptoms)

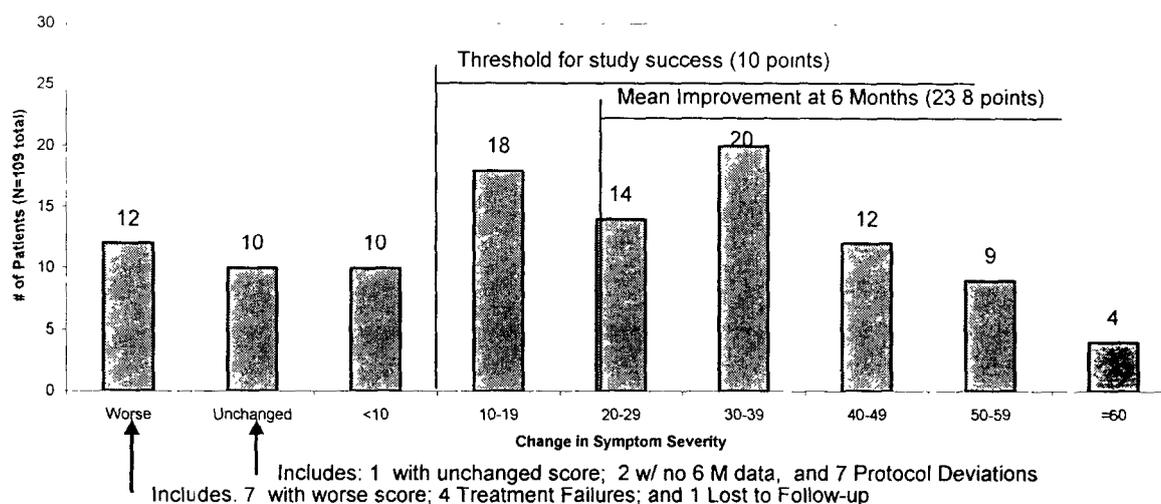


Table 4 presents these overall findings both for the intent-to-treat (ITT) population and for the subgroup of “evaluable” study subjects, which excludes patients who withdrew, were lost to follow-up, or who were treated outside of the protocol limitations, all of whom were counted as ITT failures. The 95 evaluable subjects were all treated within all specifications of the study protocol. Study subjects in the hysterectomy arm did not report an SSS subscale, because these patients were no longer considered to have fibroid-related symptoms once their uterus was removed.

Table 4. Success Rate for Month 6, Intent-to-Treat Population	N=109
≥ 10 Point Improvement: Baseline → 6M	77 (70.6%)
Unchanged or Worsened patients: Baseline → 6M – All Patients	32 (29.4%)
Success Rate For Month 6, “Evaluable” Patient Population	N=95
≥ 10 Point Improvement: Baseline → 6M	67 (70.5%)
Unchanged or Worsened patients: Baseline → 6M – All Patients	28 (29.5%)

Table 5. Overall Mean Changes in the SSS Subscale Across the Entire Study Population

Symptom Severity Score	Baseline Mean (SD)	Month 6 Mean (SD)	Mean Change Score (SD)	Change Range	P-value
ITT (N=109)	61.0 (16.3)	37.3 (21.4)	-23.8 (21.2)	-81.3 to 18.8	<0.0001
Evaluable† (N=95)	61.6 (14.9)	37.9 (21.2)	-23.7 (21.4)	-81.3 to 18.8	<0.0001

Note: A higher Symptom Severity Score indicates a higher level of symptom severity.

† The “evaluable” cohort represents ITT minus off-protocol, withdrawals, and lost-to-follow-up.

The *per protocol* definition of study success was that at least 50% of the ExAblate® 2000 subjects must achieve a minimum of a 10-point improvement on their SSS subscales at 6 months. Study results showed that 70.6% of subjects achieved the minimum improvement on the SSS subscale, thus exceeding the study target. The majority of the symptom improvement was observed at 3 months post-treatment; however, there was continued evidence of slight improvement over the next three months.

Secondary Effectiveness Endpoints

SF-36 Quality of Life Results

At one month, ExAblate® subjects scored statistically significantly better in all categories except general health and mental health (neither of which differed between the two groups.) At three months, the two study groups only differed significantly in the categories bodily pain and mental health, both of which favored hysterectomy. By six months, the hysterectomy group showed significant advantage in the following categories: role physical; bodily pain; general health; vitality and mental health.

Overall Treatment Effect and Patient Satisfaction

At the 6-month visit, patients were asked for their general impression of the treatment. The results from 102 patients who responded are shown in Table 6.

Table 6. ExAblate[®] 2000 Patient Satisfaction Results at 6-Months

	N = 102
Were you satisfied with your treatment?	76% Satisfied
How effective was this treatment in eliminating your symptoms?	72% Effective
Would you recommend this to a friend with same health problem?	84% Would Recommend

Fibroid Shrinkage

MR images prior to treatment and at 6 months were compared to determine fibroid shrinkage. This is shown in Table 7. MR images were available for review on 102 patients.

Table 7. Fibroid Shrinkage

Parameter	N = 102
Mean Baseline Volume of Treated Fibroids (cm ³)	334.4 ± 240.4
Mean 6 month Volume of Treated Fibroids (cm ³)	295.4 ± 256.4
Mean 6 month % Shrinkage of Treated Fibroids	15.3 % ± 30.4%

Safety Evaluation

Significant Clinical Complications (SCCs)

To allow comparison of the relative risks of the ExAblate[®] 2000 arm versus the control arm of the study, a common set of “Significant Clinical Complications” (SCC) was prospectively defined based on the literature and compared for both groups (see Table 8). The primary statistical comparison between treatment groups was with respect to the incidence of such complications. However, it is problematic to draw conclusions regarding the relative safety of the two procedures based on these SCCs because of the significant differences in baseline health of the two study arms as noted earlier.

**Table 8. Incidence of Significant Complications in the Pivotal Clinical Study:
ExAblate® 2000 Group and Hysterectomy Group**

	ExAblate® 2000 (N=109)	Hysterectomy (N=83)
Number of patients with at least 1 Significant Clinical Complication	13 (12%)	38 (46%)
Re-hospitalization duration > 24 hours	8	8
Fever > 38°C on any 2 post-treatment days (excluding first 24 hours)	3	12
Antibiotic use starting > 24 hours post-treatment	3	30
Transfusion	3	6
Unintended surgical procedure related to treatment	0	4
Referral to a rehabilitation facility	0	0
Discharge with appliance	0	1
Life-threatening event	0	0
Interventional treatment	0	2
Death	0	0
Total number of occurrences	17	63

Trajectory of Recovery

Data with respect to disability days demonstrated the recovery pattern of the ExAblate® 2000 patients. At the Month 1 visit, patients in the ExAblate group reported an average of 1.2 disability days, compared to 19.2 days in the hysterectomy group.

Patients who were treated by ExAblate® required 84% fewer provider encounters, and 66% fewer additional procedures compared to the hysterectomy group.

Anesthesia Regimen and Dosage

All ExAblate® 2000 patients were managed with conscious sedation. Medication dosage was adjusted based on patient feedback.

Adverse Events

ExAblate® 2000 was compared to a control group treated with total abdominal hysterectomy. A total of 271 AEs was observed over the 6-months of the Pivotal Study in the ExAblate® 2000 patients (see Table 9). The majority of these events, 79% (214) occurred during the first 10 days post ExAblate® 2000 treatment,

days post-treatment, only 5 events (1.8% of the 271 total number of events) were reported to be severe: 1 event of urinary tract infection and 4 events of menses-like symptoms.

**Table 9. Summary of Adverse Events by Body System:
0 – 10 days, 11 days – 6 Months post-treatment with ExAblate® 2000**

	Test Arm: N=109	
	0 – 10 days	11 days – 6 months
Total Number of Adverse Events	271	
Body System	n (%)	n (%)
Pain/discomfort	97(45.3%)	17(29.8%)
Gynecological	21 (9.8%)	15(26.3%)
Urinary	28 (13.1%)	5 (8.8%)
Gastrointestinal	28(13.1%)	4 (7.0%)
Systemic	15 (7.0%)	8(14.0%)
Dermatological	16 (7.5%)	5 (8.8%)
Nervous	6 (2.8%)	2 (3.5%)
Cardiovascular	3 (1.4%)	0 (0.0%)
Dental	0 (0.0%)	1 (1.8%)
Other	0 (0.0%)	0 (0.0%)
Total	214 (79%)	57 (21%)

In addition to the general adverse event information reported above, there are two specific risks of ExAblate® 2000 treatment that are described in greater detail below: (1) sacral nerve stimulation or injury; and (2) skin burns.

Nerve Stimulation or Injury

A number of patients treated with the ExAblate® 2000 experienced leg pain or sensations of nerve “tingling” or activation during the treatment process. In most cases, the patient noticed the sensation of lower extremity pain during one or more sonications, and the pain had completely subsided by the day after treatment. However, in a few cases, pain or possible sacral nerve injury persisted beyond this period. This pain was attributed to the heating of the sacral nerves in the far field, which may have resulted from improper beam angulation or failure to maintain the 4 cm minimum distance between the treatment focus and the bone. As discussed in the Information for Prescribers (physician labeling), during treatment planning, these key structures must be identified to minimize/avoid any heating where it may be a potential risk to the patient, e.g., the sacral bundle in the far field of the beam.

Fourteen instances of leg pain were reported among the 109 ExAblate® 2000 patients, of which 8 were determined to be sonication-related. Of these 3 were

transient, and did not persist after the treatment, and 1 patient had pain that lasted 2 days. In all but 4 Pivotal Study patients the pain resolved completely by 3 days post-treatment. One patient had long lasting clinically significant effects. This patient was 39 years old at the time of her treatment. Immediately after the treatment she reported pain in her left leg and left buttock. At the initial follow-up visit three days later, she reported that the pain had increased, and her left leg was weak. At one month she returned for a scheduled visit and reported significant sciatic pain. A neurological workup indicated damage to the sacral nerve on the left side. Over the next several months, she showed progressive improvement and returned to near-baseline status at 11 months post-treatment with full mobility and was pain free.

If pain occurs during a given sonication, the patient herself can instantly terminate the delivery of energy with the Stop Sonication Button. As discussed in the physician labeling, the treatment plan for the succeeding sonication should be reviewed, and if appropriate, the treatment location and/or treatment angle immediately adjusted before the treatment continues. If sonication-related leg pain persists, the treatment should be terminated. Continuing interaction between the patient and the physician is important to ensure that any patient sensations of nerve activation are communicated to permit adjustment of the treatment plan as necessary to avoid injury. In addition to leg pain that may be indicative of potential nerve injury, “tingling” of the nerves or similar sensations were sometimes reported in the clinical study for individual sonications. Such sensations may also be indicative of heating of the nerves. Therefore, the labeling directs the physician to investigate any report of pain or tingling in the back or leg before proceeding to the next sonication. The treatment plan should be modified as appropriate to reduce this risk (e.g., evaluate the far field beam path to identify nerve location, move or delete sonications in this area, change the tilt of the transducer to move the far field off the nerve, or change the tilt of the transducer to increase the incidence with the sacrum or other bony structures).

Skin Burns

Improper acoustic coupling between the skin and the gel pad can result in undesired heating of the skin due to increased reflection of the ultrasound energy. Examples are air bubbles present in the skin folds and around the hair, or oil between the skin and the gel pad. There were 5 cases of first or second degree skin burns during the Pivotal Study. In all the cases of skin burns, the patients had hair in the sonication pathway. One patient also moved and decoupled from the acoustic gel, resulting in a first degree skin burn.

The following actions are recommended in the physician labeling to minimize the occurrence of skin burns:

- Shave all hair from the lower abdomen to two centimeters below the crest of the pubic bone;
- Clean the skin on the abdomen with alcohol to remove oil on the skin;
- Limit patient movement by using restraints; and
- Examine the MR planning images for air bubbles at the skin-gel interface and for skin folds prior to sonication.

12-MONTH LONG-TERM FOLLOW-UP STUDY

Study subjects from the pivotal study were re-assessed at one-year after treatment (Table 10).

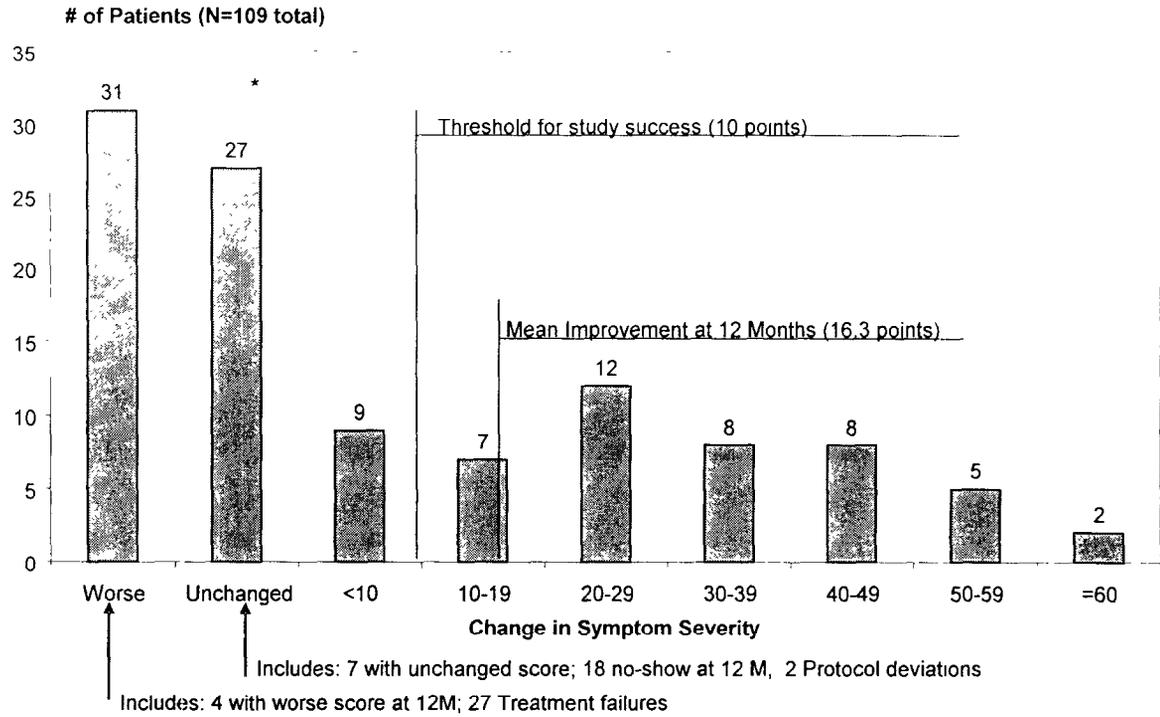
	<u>Treated</u>		<u>0-6 Months</u>		<u>6-12 Months</u>	
	ExAblate	Hysterectomy	ExAblate	Hysterectomy	ExAblate	Hysterectomy
Participating	109	83	106 (97.3%)	68 (81.9%)	91 (83.5%)	N/A
Withdrew			3	2	0	
Lost to Follow-Up			0	13	6	
Declined Participation*			0	0	9	
Evaluable			95	63	82	
Non-Evaluable **			11	5	9	
Treatment Failures (Alternative Treatment)			4	0	23	

*These patients were contacted but declined to return for follow-up at 12 months. The study and the patients' consent had initially been limited to 6 months.
 **Patients were non-evaluable due to diagnosis of adenomyosis, baseline UFS-QOL score taken >45 days prior to treatment, no symptom severity score (SSS), or too few sonications. These patients are considered to have had a change in SSS of 0.

Evaluation of Effectiveness for Patients in the 12-Month Long Term Follow-Up Study

Figure 3 and Table 11 show the score changes on the SSS scale for the 109 subjects in the ExAblate® 2000 group; this includes patients who withdrew, were lost to follow-up, or who were treated outside of the protocol limitations, all of whom were counted as failures.

Figure 3 – ITT Distribution in Reduction in SSS subscale at Month 12 for subjects treated with ExAblate® 2000



Success Rate For Month 12 Based on Original Intent to Treat Population	(N= 109)
≥ 10 Point Improvement: Baseline to > 12 months	42 (38.5%)
Unchanged or Worsened patients: Baseline to > 12 months	67 (61.1%)
Success Rate For Month 12 Based on Patients Participating in 12-Month Visit	(N=82)
≥ 10 Point Improvement: Baseline to > 12 months	42 (51.2%)
Unchanged or Worsened patients: Baseline to > 12-months 12M	40 (48.8%)

Table 11 shows the success rate at Month 12 based on both the original treatment population (N=109) and the participating patients (N=82). Of the original treatment population of 109 patients, 38.5% of these patients had ≥ 10 points improvement from baseline. There were 51.2% participating patients that had ≥10 points improvement from baseline. At the 12 month point, 21% (23) of the original ExAblate® 2000 patients had chosen to go on to additional surgical treatments; 4 had undergone a second ExAblate® 2000 treatment.

12-Month Safety

There were no occurrences of other adverse events between 6 and 12 months post-treatment by ExAblate® 2000. For patients in the ExAblate® 2000 group, throughout the 12 month post-treatment period, there was no device-related death, life-threatening injury or permanent injury, acute hospitalization, or device-related emergency interventional procedure.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The results of the studies demonstrate that ExAblate® 2000 is safe and effective for non-incisional treatment for patients with symptomatic fibroids. Further, under the treatment guidelines employed during the study, ExAblate® 2000 has a low incidence of device-related or treatment-related side effects.

Therefore, it is reasonable to conclude that the treatment benefits of the device for the target population outweigh the risks of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

At an advisory meeting on June 3, 2004, the Obstetrics and Gynecology Devices Panel met to discuss the InSightec, Inc. PMA (P040003) for the ExAblate® 2000 intended for use in pre- or peri-menopausal women with symptomatic uterine fibroids. At the conclusion of the deliberations, the Panel recommended that FDA approve the ExAblate® 2000 for the treatment of symptomatic uterine fibroids, subject to the following conditions:

1. Applicant provide analysis of data on uterine volumes and possible correlation with treatment failure;
2. Applicant and FDA develop a strategy for assessing the impact of this procedure on future pregnancy;
3. Applicant conduct a post-approval study to gather additional data to evaluate the safety and long-term effectiveness of ExAblate® 2000, including a larger cohort of African-American patients;
4. Applicant provide the following information in the physician labeling:
 - a. explicit information regarding the possibility of nerve damage;
 - b. specific information on how to minimize the risk of nerve injury;
 - c. an adequate description of training, including classroom time and phantom laboratory practice;
 - d. a discussion of the primary endpoint of the pivotal study and up-to-date references on the UFS-QOL;
 - e. information on scars in the treatment area and the possible impact of previous Cesarean section;

- f. a discussion of the importance of the level of patient sedation and the need to maintain continuous communication with the patient to reduce the risk of nerve injury.

5. Patient labeling should explicitly indicate the possibility of nerve damage.

XIII. CDRH DECISION

On August 5, 2003 (prior to the PMA submission), the applicant submitted a Request for Expedited Review for the ExAblate® 2000 System. On October 2, 2003, the Agency issued a letter to the applicant informing that its application would receive expedited processing because the device potentially offered significant advantages over existing approved alternatives.

CDRH agreed with the June 3, 2004 Panel recommendation that the ExAblate® 2000, when used as indicated, is safe and effective for the treatment of symptomatic uterine fibroids. Subsequent to the Panel meeting, the applicant provided the requested analysis which failed to show a relationship between uterine volume and treatment failure. The applicant made all of the changes to the physician and patient labeling requested by the Panel and CDRH. The labeling includes treatment guidelines to ensure the procedure is performed as safely as possible. The applicant agreed to conduct a post-approval study to address the other conditions of approval identified by the Panel, as outlined below.

In making this assessment, CDRH reviewed the treatment guidelines used in the Pivotal Study. These guidelines were developed to ensure that the ExAblate® 2000 procedure was performed as safely as possible and considerably restricted the area of treatment. The treatment guidelines used in the Pivotal Study were as follows:

- The prescribed area intended for treatment could not exceed 33% of the total volume of each fibroid to be treated.
- The treatment plan must maintain a 15 mm margin between the prescribed treatment volume and the serosa or endometrium.
- The prescribed volume could not be closer than 5 mm from the inner portion of the capsule of the fibroid on the side of the fibroid adjacent to the uterine serosa. On the side of the fibroid adjacent to the endometrial cavity, treatment may include the fibroid capsule.
- Up to a total of 4 fibroids could be treated.
- The maximum prescribed volume could not exceed 100 cc for a single fibroid, and 150cc in the case of 2 or more fibroids. Only a single treatment was allowed.

Uterine fibroids that are incompletely infarcted have the potential for re-growth. This re-growth may lead to recurrence of the fibroid symptoms. Furthermore, during the course of the Pivotal Study, there was no safety issue related to heating of the endometrium and serosa, or thermal injury to bowel or bladder. Consequently, for patients treated following marketing of the ExAblate® 2000 System, the treatment guidelines have been changed as follows:

- The maximum volume of an individual fibroid to be sonicated should not

exceed 50%.

- When targeting a volume of fibroid, ensure that no portion of the targeted volume is within 15 mm of uterine serosa.
- A second ExAblate® 2000 treatment session may be performed within 2 weeks of the first treatment.

These treatment guidelines, which are now described in the current physician labeling, ensure patient safety, while at the same time providing the ExAblate® 2000 as an alternative for treatment of uterine fibroids.

The duration of treatment relief may vary from patient to patient. The applicant will continue to evaluate the duration of symptom relief in the post-approval study of the ExAblate® 2000 described below. The applicant agreed to will conduct a three-year post-approval study on the ExAblate® 2000 patients to collect additional long-term key safety and effectiveness data, including but not limited to:

1. UFS-QOL SSS score
2. Fibroid re-growth
3. Alternative procedures
4. Serious adverse events
5. Pregnancies
6. C-Section history
7. African-American women

The applicant's manufacturing facility was inspected and found to be in compliance with the Quality System Regulation (21 CFR 820). CDRH issued an approval order to the applicant on October 22, 2004.

XIV. APPROVAL SPECIFICATIONS

Patient information: See the patient labeling.

Directions for use: See the physician labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-Approval Requirements and Restrictions: See approval order.