

**InSigthec ExAblate 2000 Magnetic Resonance guided Focused
Ultrasound System (MRgFUS) for the Treatment of Uterine Fibroids**

Post-Approval Update

Obstetrics and Gynecology Devices Advisory Panel Meeting

December 14, 2007

Executive Summary

A. Background

The InSightec ExAblate 2000 MRgFUS system is a non-invasive thermal ablation device, fully integrated with a MR imaging system, used for the ablation of uterine fibroids. The device is indicated for use 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.

The device 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); and 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.

Alternate practices and procedures available to treat symptomatic uterine fibroids include: hysterectomy, abdominal myomectomy, laparoscopic and hysteroscopic myomectomy, hormone therapy, uterine artery embolization, and watchful waiting.

The ExAblate® 2000 System is marketed in Europe for uterine fibroids since October 2002. It is currently in commercial use in Israel, Canada, Mexico, Brazil, and Korea; and is limited to use in private clinics and hospitals in Japan.

In the United States, ExAblate® 2000 went through an expedited review in June 2004 and was approved with conditions October 2004. The post-approval commitments include:

1. Continue follow-up of the premarket cohorts for three years to collect data on long-term safety and effectiveness including: symptom severity (Symptom Severity Subscale (SSS) of the Uterine Fibroid Symptoms-Quality of Life Instrument (UFS-QoL)), fibroid re-growth, use of alternative procedures, pregnancies and serious adverse events.
2. Evaluation of safety and effectiveness on a subset of African American women who will undergo fibroid treatment with the ExAblate 2000 following commercial treatment guidelines. Data to be collected includes same safety and effectiveness endpoints as presented above. Additional data on the history of cesarean section are being collected for this cohort.

B. Treatment Guidelines

Each study cohort was treated under different treatment guidelines. In the Pivotal Study, treatment guidelines were limited to “prescribe volume”, defined as 33% of the fibroid volume. Similar treatment guidelines were initially used in the Continued Access Study. However, during the course of the Continued Access Study the protocol was amended to expand these treatment guidelines and to include a 2nd treatment within two weeks of the first

treatment if needed. The FDA approval also included the expansion of the treated volume from 33% of the fibroid volume to 50% of the fibroid volume. The first 96 patients in the Continued Access Study were treated under guidelines similar to Pivotal Study and the last 64 patients in the Continued Access Study were treated under expanded guidelines.

The New Post-Approval Cohort is being treated under commercial treatment guidelines.

The table below contrasts the treatment guidelines for each cohort.

Table 1 Treatment Guidelines for each Study Cohort.

	Pivotal	Continued Access-Initial Tx*	Continued Access-Extended Tx*	Commercial/Labeling Guidelines
Volume restriction as a percentage of fibroid	Prescribed volume limited to 33% of fibroid volume	Treated volume limited to 33% of fibroid volume	Treated volume limited to 50% of fibroid volume unless submucosal (33%)	Treated volume limited to 50% of fibroid volume
Volume restriction as a volume	100 cc per fibroid or 150 cc if more than 1 Fibroid	100 cc per fibroid or 150 cc if more than 1 Fibroid	150 cc regardless of number of treatments	None
Time restriction from first to last sonication	120 minutes	120 minutes	180 minutes	180 minutes
Restricted distance to the endometrium from the edge of sonication	1.5 cm	1.5 cm	None	None
Restricted distance to the serosa from the edge of sonication	1.5 cm	1.5 cm	1.5 cm	1.5 cm
Restricted distance to fibroid capsule	0.5 cm on side closest to serosa	0.5 cm on side closest to serosa	None	None
Second treatment session	No	No	Yes –limited to 2 within a 2 week period	Yes –limited to 2 within a 2 week period

*The expanded treatment guidelines were approved by FDA on Oct-2003, and were not approved by local IRB's until approximately April 2004.

C. Premarket Overview

1. Safety

Premarket Clinical data show the following potential adverse events, table 2.

Table 2 Incidence of Adverse Events in ExAblate ® 2000 in the Pivotal Clinical Study, N=109.

Adverse Event Description	Count	Incidence per 100 person-months*	95% Confidence Interval
Cardiovascular	3	0.5	0.1, 1.5
Pain/Discomfort	114	18.9	15.6, 22.8
Dermatological	21	3.5	2.2, 5.3
Gastrointestinal	32	5.3	3.6, 7.5
Gynecological	36	6.0	4.2, 8.2
Nervous System	8	1.3	0.6, 2.6
Urinary	33	5.5	3.8, 7.7
Systemic	23	3.8	2.4, 5.7
Other	1	0.2	0.004, 1.0
Total	271	44.9	39.9, 50.7

*Based on 603 patient-months contributed by 104 patients with 3-month assessment and 97 patients with 6-months follow-up. (3x104)+(3x97)

Source for patient-months UF002-Protocol V.5 112206 November 22, 2006

Source for adverse event count: Summary of Safety and Effectiveness, Table 9, page 19

2. Effectiveness

Table 3 shows the UFS-QOL Subscale Symptom Severity Score, from Table 11 in page 22 of Summary of Safety and Effectiveness.

Table 3 UFS-QOL Subscale Symptom Severity Scores

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 12 month Based on patients Participating in 12-month Visit	
≥ 10 Point Improvement: Baseline to > 12 months	42 (51.2%)
Unchanged or worsened Patients: Baseline to > 12 months	40 (48.8%)

Table 4 presents data on fibroid shrinkage, from table 7 in page 17 of Summary of Safety and Effectiveness.

Table 4 Fibroid Shrinkage data Six Months Post-Treatment

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%

D. Postmarket Update

This postmarket update is based on data included in the latest postmarket report (R006), submitted to the FDA June 26, 2007, which includes data as of March 31, 2007 for all three cohorts.

The next section presents information on the length of follow-up and follow-up status for each study cohort.

1. Follow-up Status

The premarket cohorts (Pivotal and Continued Access) were originally designed to only include follow-up through six months post-treatment. FDA later required re-consenting the patients for continuing follow-up through 36 months; the new Post-Approval Cohort includes follow-up through 36-months post-treatment.

Table 5 presents the follow-up status for each cohort. Enrollment is completed for the three cohorts. As of March 31, 2007 the follow-up phase of the Pivotal Cohort has been completed. Follow-up of the Continued Access Cohort and the New Post-Approval Cohort is ongoing. Long-term data (36-month assessment) on safety and effectiveness is available on 16.7% (57 out of 342) of all treated patients. This percent is expected to increase as the follow-up of the Continued Access Cohort and the new Post-Approval Cohort is completed.

Table 5 Follow-up status of study participants in the ExAblate Post-Approval Study as of March 31, 2007

Study Group	Initial Sample Size	Study Visits				
		3-months	6-months	12-months	24-months	36-months
Pivotal	109	104 ^a	97 ^a	62	42	29
Continued Access	160	149	145	107	78 ^b	28 ^b
New Postmarket Cohort	73	64	64	50 ^b	1 ^b	-
Total	342	317	306	219	121	57

^a PMA data; ^b Follow-up ongoing

Table 6 presents reasons for study exclusions. Most of the exclusions from follow-up are related to need for alternative treatments or second ExAblate treatments: 31.6 percent of the treated women needed alternative treatments and 6.7 percent had a second ExAblate treatment. Women that need additional treatment are dropped from follow-up at the time of the additional treatment. For estimates of the rate for the need of alternative treatment and second ExAblate treatment, see bullet “c.” in the “Effectiveness” section, below.

Table 6 Details on Subjects Exclusion in the ExAblate 2000 Post-Approval Study as of March 31, 2007

Type of Exclusion	Pivotal Study		Continued Access Study		New Postmarket Cohort	
	n	%	n	%	n	%
Lost to Follow-up ^a	28	25.7	18	11.3	11	15.1
Alternative Treatment	36	33.0	61	38.1	8	11.0
Second ExAblate	16	14.7	5	3.1	2	2.7
Became Pregnant	0	0	4	2.5	0	0
Ongoing Follow-up	0	0	44	27.5	52	71.2
Completed 36-month Assessment	29	26.7	28	17.5	0	0
Total	109	100.0	160	100	73	100.0

^a Lost to follow-up includes women that voluntarily withdrew study participation and women who sponsor was not able to contact.

2. Safety

a. Long-term follow-up of premarket cohorts

After product approval there were no adverse events to report during the extended follow-up of premarket cohorts.

b. Patients treated postmarket

This cohort only includes African American women. The table below presents the incidence estimates for non-significant anticipated adverse events in the postmarket cohort.

Table 7 Incidence rates for non-significant anticipated adverse events in New Postmarket Cohort.

Adverse Event Description	Count	Incidence per 100 person-months*	95% Confidence Interval
Cardiovascular	2	0.3	0.03, 1.0
Pain/Discomfort	13	1.9	1.0, 3.2
Dermatological	2	0.3	0.03, 1.0
Gastrointestinal	5	0.7	2.6, 1.7
Gynecological	2	0.3	0.03, 1.0
Nervous System	2	0.3	0.03, 1.0
Urinary	9	1.3	0.6, 2.4
Total	35	5.0	3.5, 7.0

*Based on 696 patient-months

Table 8 presents the severity of the adverse events observed in the New Post-Approval Cohort.

Table 8 Severity Data for Non-Significant Anticipated Adverse Events Observed in the New Post-Approval Cohort

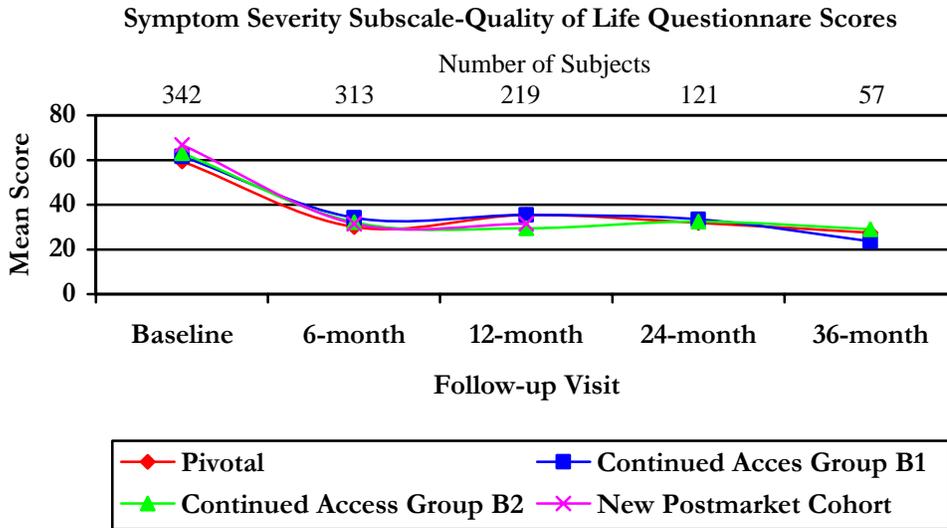
Adverse Event Description	n	Severity
<u>Cardiovascular (n=2)</u>		
Venous Infiltration	1	Mild
Hand Thrombophlebitis	1	Mild
<u>Pain Discomfort (n=13)</u>		
Abdominal Cramping	2	Moderate
Abdominal Pain	3	1 Mild, 2 Moderate
Abdominal Pain-Sonication Related	4	1 Mild, 3 Severe
Leg Pain-Position Worsening	1	Mild
Leg Pain-Sonication Related	2	1 Mild, 1 Severe
Pain-Other	1	Mild
<u>Dermatological (n=2)</u>		
Cellulitis	1	Moderate
Skin Burn	1	Mild
<u>Gastrointestinal (n=5)</u>		
Constipation	2	Mild
Nausea/Vomiting	3	Mild
<u>Gynecological (n=2)</u>		
Abnormal Vaginal Discharge	1	Mild
Vaginal Bleeding	1	Moderate
<u>Nervous (n=2)</u>		
Paresthesia	1	Moderate
Tremor	1	Mild
<u>Urinary (n=9)</u>		
Urinary Tract Infection	5	4 Mild, 1 Moderate
Urinary Retention	1	Moderate
Dysuria	3	2 Mid, 1 Moderate

3. Effectiveness

a. Scores for Symptom Severity Subscale¹ (SSS) from the Quality of Life Questionnaire Women that needed an alternative treatment or a second ExAblate treatment were excluded from follow-up at the time they had the additional treatment. Therefore, the data presented here only represent the results in women who remained in the study.

The chart below presents preliminary results on the mean scores for the SSS quality of life (QoL) questionnaire, by study cohort.

¹ 8 questions



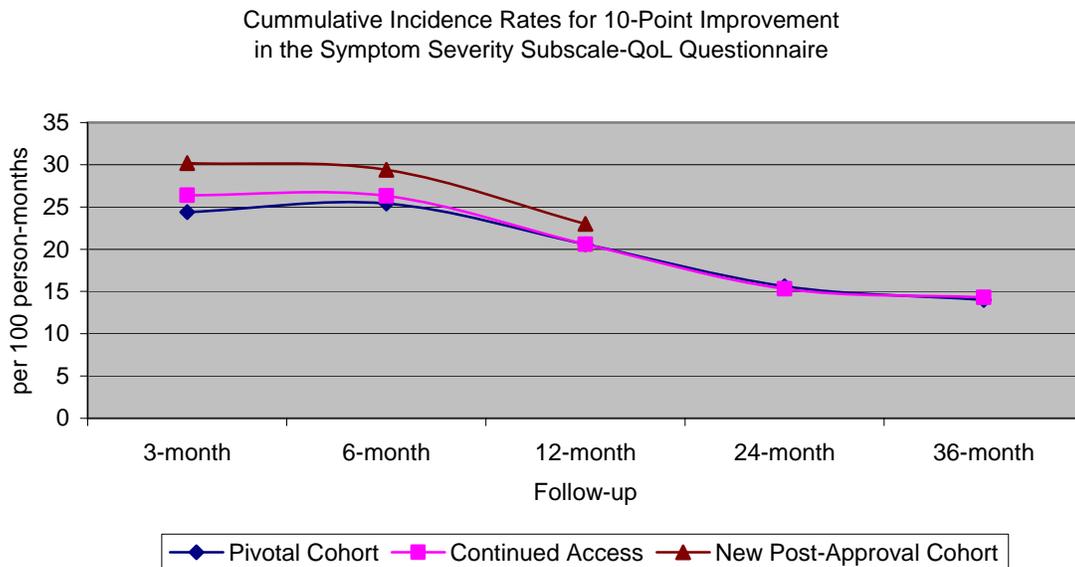
*Continued Access Group B1 includes women treated with limited treatment guidelines, Continued Access Group B2 includes women treated with extended treatment guidelines. See Table 1 in page 2

SSS QoL questionnaire mean scores seem to decrease shortly after procedure and remain below the baseline values. Long-term follow-up is available for 64.0%, 35.4% and 16.7% of patients at 1-year, 2-year and 3-year post-procedure, respectively (Table 5).

Continued Access study and New Postmarket Cohort are still under follow-up.

b. Ten-Points Score Improvement SSS-QoL questionnaire

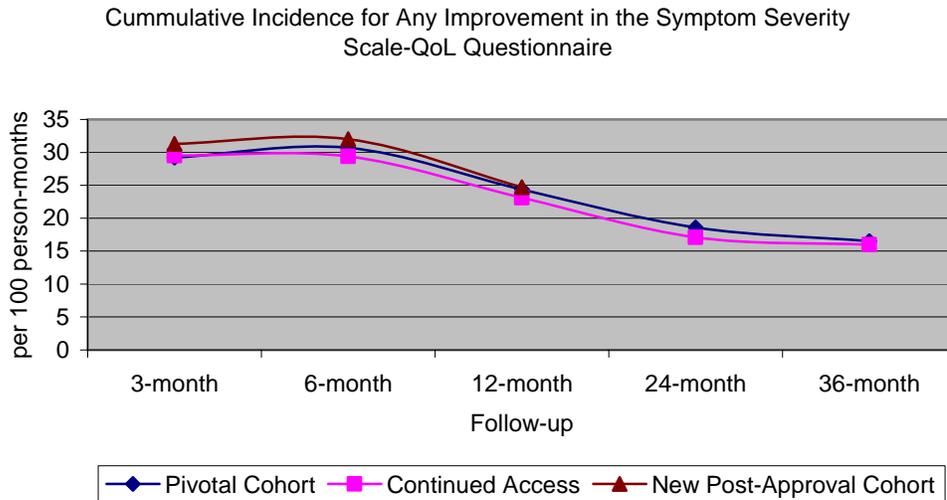
The chart below presents preliminary results on the incidence rate for 10-points improvement by study cohort.



Ten-point improvement in the QoL questionnaire score seem to be more frequent within

six months after treatment and then it decreases overtime.

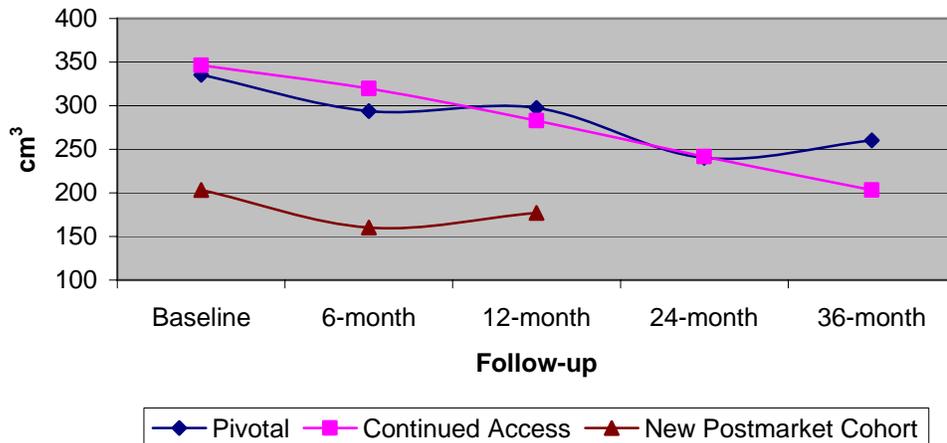
The chart below includes the rate for any improvement in the scores.



c. Fibroid re-growth

Preliminary data on the fibroid volume (fibroid size measured in cm^3) re-growth show fibroid size seem to decrease within the first 6-month post-treatment. The values at the 36-month visit for the Pivotal and Continued Access Cohorts are below baseline values. For the new postmarket cohort only 12-month data is available, and so far the results show similar trend, decreased volume size 6-month post-treatment. For the new postmarket cohort there is also an increase after 6-months, but this cohort is still being followed, and the trend could change after all patients complete follow-up assessments.

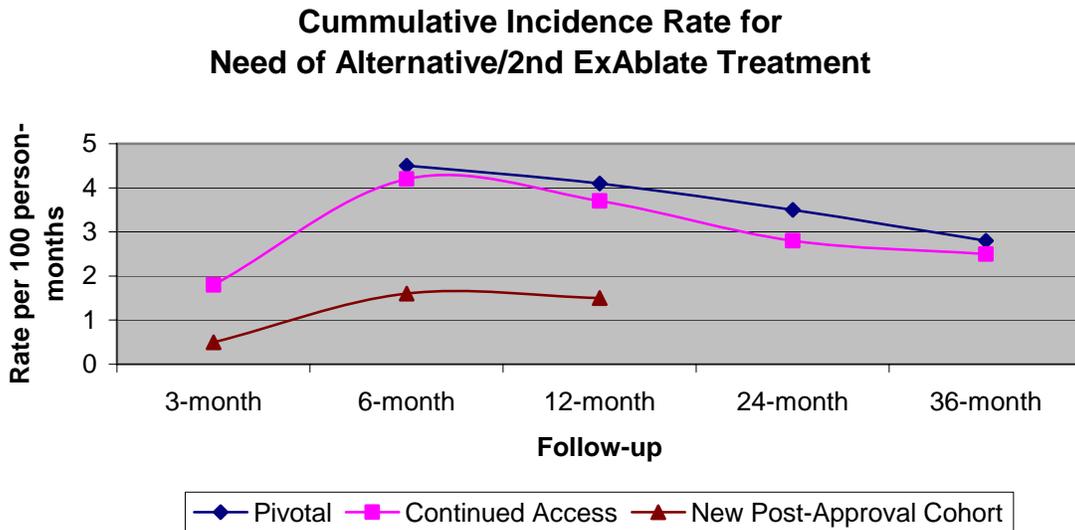
Fibroith Volume Regrowth by Study Cohort



d. Need for Alternative Treatments and Second ExAblate Treatment

The chart below presents the cumulative incidence rates per 100 person-months for the need of alternative/2nd ExAblate treatment.

Preliminary results show that the cumulative incidence rate for the need of alternative/2nd ExAblate treatment increases within the first 6-months after ExAblate treatment, and then decreases until the 36-month follow-up assessment. Data beyond 36-months is not available. The Continued Access Cohort and the New Post-Approval Cohort are still under follow-up.



3. Pregnancy Data and History of C-Section

a. Pregnancies

There were no pregnancies in the Pivotal Cohort.

For the two cohorts still ongoing:

There have been four pregnancies in the Continued Access Cohort. One baby spent several days in NICU due to collapsed lung. No other complications reported.

There have been no pregnancies in the New Post-Approval Cohort.

b. History of C-Section

This data is being collected only for the New Post-Approval Cohort. Out of 73 treated patients, 10 have history of c-section.

Out of 10 women with history of c-sections, 6 experienced adverse events. There were a total of 7 adverse events. Table 9 presents the description of the event and severity.

Table 9 Adverse Events Experienced by Women with History of C-Sections in the New Post-Approval Study

Adverse Event	Severity
Paresthesia	Moderate
Leg Pain-Sonication Related	Severe
Abdominal Pain and Abdominal Pain-Sonication Related	Both Severe
Abdominal Pain	Mild
Tremor	Mild
Urinary Tract Infection	Moderate

There were two mild, two moderate and three severe events. One woman experienced two severe events. The paresthesia case resolved in 8 months; for all other events the time to resolve ranges from the same day of treatment up to 15 days after treatment.

4. Discussion

a. Safety

Preliminary safety data shows device is performing at an acceptable postmarket safety level. However, the experience of study drop-outs may be different.

b. Effectiveness

Generalizability of long-term effectiveness data is limited to those that remain in study (16.7% of originally treated patients).

Results from each cohort must be interpreted separately due to different treatment guidelines. The original treatment guidelines restricted the treatment of uterine fibroids to 33% of the fibroid; and the extended guidelines allow for treatment of 50% of the fibroid.

c. Closing Remarks

- (1) ExAblate 2000 is a non-invasive procedure to treat uterine fibroids.
- (2) The long-term follow-up of premarket cohorts provides a good estimate for the need of alternative treatment or second ExAblate treatment, overtime.
- (3) The new postmarket cohort presents the opportunity to evaluate if the need for alternative treatments or second ExAblate treatments is decreased by the commercial treatment guidelines.
- (4) Final study results are awaited.