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Horizon Scanning Technology Prioritising Summary Update

MRI-guided high intensity ultrasound for the non-invasive treatment of uterine fibroids

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PRIORITISING SUMMARY UPDATE 2008

REGISTER ID: 000301

NAME OF TECHNOLOGY: MRI GUIDED HIGH INTENSITY FOCUSED
ULTRASOUND

PURPOSE AND TARGET GROUP: NON-INVASIVE TREATMENT OF SYMPTOMATIC
UTERINE FIBROIDS

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes ARTG number 128137
- No
- Not applicable

TGA approval was granted in 2006. Sponsor Name: GE Healthcare Australia Pty Ltd
ADG: Class: Class IIb Product Id: 212416 Product Name: Hyperthermia system,
ultrasound. In addition MRgFUS has been approved in the following countries:
United States, UK, Germany, France, Canada, Mexico, Brazil, Russia, Korea, Taiwan
and Singapore.

2008 DIFFUSION

The Royal Woman's Hospital, Melbourne, Australia, has purchased a 3T MRI and ExAblate 2000 with uterine fibroids application. The MRI will be installed at the beginning of September 2008 and the ExAblate will be installed late September 2008. The Head of Radiology Department at the RWH, Dr. Andrew Dobrotwir and Dr. Healy (gynaecologist), will be in charge of using the ExAblate 2000 (personal communication CPR Communications on behalf of InSightec Ltd).

2008 SAFETY AND EFFECTIVENESS ISSUES

Since the original prioritising summary, there have been four case series studies published which investigated the safety and effectiveness of magnetic resonance imaging guided high intensity focused ultrasound (MRgFUS) for the treatment of uterine fibroids.

Stewart et al (2007) reported 24-month follow-up data on 359 pre-menopausal women completing four sponsored studies of MRgFUS surgery with ExAblate[®] 2000 system (level IV intervention evidence). Three of the four trials were part of the phase III evaluation of the MRgFUS technology; the fourth one was a post-marketing study. Immediately after treatment, the intravenous magnetic resonance contrast agent gadolinium was injected and used to assess the efficacy of tissue devascularisation. The non-perfused volume (NPV), which indicates the volume of tissue where blood flow is cut off after treatment, was used as a surrogate measure of treatment success. In order to control for the heterogeneity of the size and the number of both treated and

untreated uterine fibroids, the relationship between outcomes and treatment was standardised by using the NPV ratio (calculated as the ratio of the sum of the NPV of all treated fibroids divided by the NPV of all uterine fibroids, both treated and untreated) after MRgFUS treatment. The study examined the relationship between the NPV ratio and the following long-term outcomes: 1) quality of life outcomes, measured by the symptom severity score (SSS) of the Uterine Fibroid Symptoms Quality of Life Questionnaire (UFS-QOL) 24 months after treatment; 2) clinical endpoints, including uterine shrinkage, the need for additional fibroid treatment, the time to additional fibroid treatment (using survival analysis), and the change in haematocrit level after treatment.

Patients were stratified into two groups according to their NPV ratio (median level attained during treatment): those with a NPV of 20 per cent or less (n=204, mean NPV = $8.9 \pm 6\%$) and those with a NPV greater than 20 per cent (n=155, mean NPV = $38 \pm 15.3\%$). For both of these groups the SSS 3-months after MRgFUS treatment was significantly reduced from baseline. The NPV ratio had a clinically meaningful effect on the SSS, both at and beyond 3-months post MRgFUS treatment. Patients in the high NPV ratio group (>20%) reported a significantly greater improvement on the SSS than patients in the low NPV ratio group ($p < 0.001$). The survival analysis indicated that there was evidence that an increased NPV ratio reduced the risk of undergoing additional fibroid treatment ($p < 0.001$). The mean shrinkage and the mean residual NPV ratio varied inversely over all treatment NPV ratios at six and 12-months, suggesting that the volume of tissue coagulated at time of treatment is broken down and absorbed over time. For the high NPV ratio group, the mean shrinkage and the mean residual NPV ratio were both significantly above zero at six months ($p < 0.001$). With treatment NPV ratios of 10% or less, no shrinkage was observed, and a trend towards growth was observed. From a safety perspective, the incidence of adverse events was low and a learning curve effect was noted. No serious adverse events were observed amongst the participants in this study.

Fennessy et al (2007) carried out a prospective multicentre clinical trial, investigating patient response within 12 months after MRgFUS treatment for uterine fibroids with the ExAblate[®] 2000 system (level IV intervention evidence). A total of 160 premenopausal women were enrolled and treated, according to original MRgFUS treatment protocol (n=96) or a slightly modified MRgFUS treatment protocol¹ (n=64). In the original protocol group, at 12-months post-MRgFUS treatment, nine patients were lost to follow-up and 23 patients sought an alternative treatment, indicating a total of 32/96 (33.3%) who could be considered as treatment failures. At 12-months post-MRgFUS, in the modified treatment protocol, one patient was lost to follow-up and seven patients sought an alternative treatment for relief of symptoms. A total of 8/64 (12.5%) could then be considered treatment failures in this patient group. The

¹ Increased maximum treatment time (180 vs 120 mins), increased treatment volume of fibroid, second treatment allowed

mean UFS-QOL SSS of the overall study population was 62.1 ± 16.3 at baseline, which decreased to 35.5 ± 19.5 at 3-months ($p < 0.001$), 32.3 ± 19.8 at 6-months ($p < 0.001$), and 32.7 ± 21.0 at 12-months ($p < 0.001$). Patients in the modified protocol group had a significantly greater SSS decrease at 3-months ($p = 0.037$) than those in the original protocol group. By 6- and 12-months after treatment, this rate of response was no longer significantly different between the two groups. At 12-months after treatment, 73 per cent of the patients in the original protocol group and 91 per cent of those in the modified protocol group reported a significant 10-point decrease in SSS. After MRgFUS treatment, the NPV ratios, as a percentage of the total fibroid load, were significantly increased in the modified protocol group ($25.8 \pm 21.8\%$) compared to the original protocol group ($16.7 \pm 16.6\%$) ($p < 0.001$). The authors suggest that treatment with MRgFUS should aim to treat as much tissue as possible as higher NPV ratios correlated with a greater reduction in symptoms. At 12-months after MRgFUS treatment, the odds of a 10-point improvement in SSS in the modified protocol group was 2.8 in those with an NPV ratio of ≥ 30 per cent compared with those with an NPV ratio of less than 30 per cent ($p < 0.038$). Although no serious adverse events were reported in this study, 13 per cent of patients in the original protocol group reported minor adverse events. The most serious adverse events were reported by one patient who complained of paraesthesia at the site of the intravenous cannula, which resolved within six weeks; and another patient reported mild sonication-related leg pain that resolved within two days. All other adverse events were insignificant, the most common being pain or discomfort related either to position within the magnet or uterine discomfort due to sonication. Fewer minor adverse events were reported in the modified protocol group than in the original protocol group (47% vs. 54%).

A study by Hindley et al (2004) assessed the MRgFUS surgery outcomes of 109 women presenting with symptomatic uterine fibroids (level IV intervention evidence). It was reported that 79.3 per cent of the patients achieved a greater than 10-point reduction in the UFS-QOL SSS ($p < 0.0001$). The mean reduction in SSS was 27.3 points and most of this improvement occurred in the first three months after treatment. The mean reduction in fibroid volume at six months was small at 13.5 ± 32 per cent, however MRI images at the same time showed a mean NPV of 51.2 cm^3 remaining within the treated fibroid which may represent nonviable fibroid tissue and potential future shrinkage. Although a total of nine serious adverse events were reported, only one was considered to be related to the MRgFUS treatment. This patient was readmitted to the hospital after MRgFUS treatment due to nausea, however recovery occurred overnight and the patient was discharged the next day.

A smaller MRgFUS case series was conducted by Funaki et al (2007) on 69 patients with symptomatic uterine fibroids (level IV intervention evidence). Fibroids were classified into three types according to the signal intensity on magnetic resonance imaging (low, intermediate and high intensity). Seven patients (10.1%) required alternative treatment after MRgFUS surgery and five of these patients had high

intensity fibroids, which are regarded as more difficult to treat, requiring higher power. The mean SSSs were reduced after MRgFUS surgery in all three intensity types. No severe adverse event was reported and symptoms such as frequent urination and heavy menstrual bleeding resolved over time post-MRgFUS for the majority of patients. Follow-up was almost complete at three months (n=61), however follow-up at 12 months was poor with only 19 patients completing the symptom improvement follow-up. Of those patients follow-up at three months, 11 (18%) reported no change in symptoms, compared to five who were symptom free (8.2%), 28 (45.9%) improved a great deal and 17 (27.9%) who were somewhat improved.

COST IMPACT

Zowall et al (2008) conducted the first cost-effectiveness analysis of MRgFUS in the treatment of symptomatic uterine fibroids using Markov modelling comparing it to uterine artery embolisation (UAE), myomectomy and hysterectomy. MRgFUS was reported to be only slightly more effective but less costly than other treatments. Treatment with MRgFUS resulted in a cost saving of £295² but with only a gain of one-hundredth of a QALY per woman. The probabilistic simulations demonstrated the range of outcomes that might be expected in practice, given the underlying uncertainty in available data. It was indicated that MRgFUS treatment was cost-effective in approximately 86 per cent of simulations. In addition, the authors pointed out that the cost per QALY gained was sensitive to the cost of MRgFUS relative to other treatment options, the age of the woman and the NPV ratios. However, it needs to be stressed that this cost-effectiveness analysis was not based on a randomised controlled trial (RCT), which involves head-to-head comparison between MRgFUS and other treatment options. In this study, the Markov model of the treatment of uterine fibroids developed in a hypothetical cohort of symptomatic women who are treated by MRgFUS, hysterectomy, myomectomy or UAE. Thus the model, by necessity, depended on inferred comparisons in the absence of data from RCTs; comparisons that are subject to bias and confounding. Therefore, the authors emphasised that the results should be treated with caution recognising the availability and quality of the underlying data.

The cost of the complete ExAblate system varies between AUD\$2-4 million depending on the configuration of the MRI (1.5 or 3 tesla) (personal communication CPR Communications on behalf of InSightec Ltd).

2008 OTHER ISSUES

InSightec are planning to conduct research in Australia on the use of ExAblate and its effect on fertility. This research will be conducted in conjunction with Dr. Andrew Dobrotwir from the Royal Woman's Hospital, Melbourne, Australia (personal communication CPR Communications on behalf of InSightec Ltd).

² As of 14th July 2008, £295 = A\$605

PRIORITISING SUMMARY 2007

REGISTER ID: 000301

NAME OF TECHNOLOGY: MRI GUIDED HIGH INTENSITY FOCUSED ULTRASOUND

PURPOSE AND TARGET GROUP: NON-INVASIVE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input checked="" type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|---|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input checked="" type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States		✓	
Germany	✓		
United Kingdom	✓		

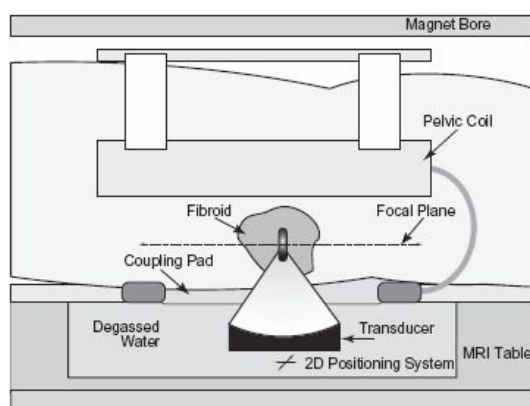
IMPACT SUMMARY:

Several systems are available for use in high intensity focused ultrasound (HIFU). ASERNIP-S has previously reported on the Sonablate[®] 500 system for the treatment of localised prostate cancer, without the use of MR guidance (ANZHSN 2006). InSightec Ltd (Haifa, Israel) provides the ExAblate[®] 2000 system, an MRI guided focussed ultrasound system (MRgFUS) with the aim of targeting and ablating uterine fibroids. The technology does not have TGA approval but was approved by the FDA in October 2004 and received CE marking in 2002. ExAblate[®] would be made available through specialist hospitals with interventional radiology facilities for pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure.

BACKGROUND

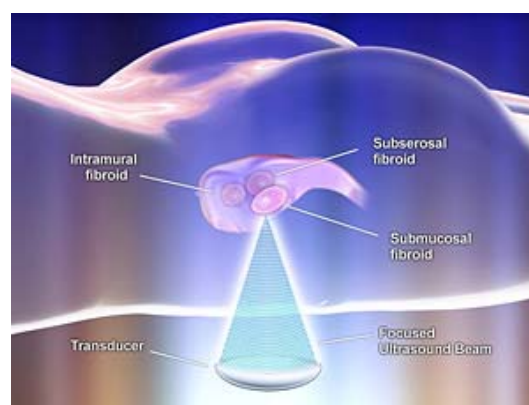
Uterine fibroids³ are benign tumours composed of smooth muscle cells and collagenous fibrous tissue that develop within or near the wall of the uterus. Although the majority of fibroids are asymptomatic, approximately 25 per cent are associated with severe symptoms including pelvic pain, menorrhagia, dysmenorrhagia, dyspareunia, pelvic fullness, urinary frequency and infertility (Fennessy & Tempny 2005; Hesley et al 2006).

HIFU is essentially a thermal ablation technique which utilises sound waves focussed at a point to deliver heat (65-95°C) to tissue, resulting in tissue necrosis, apoptosis and cell death (Fennessy & Tempny 2005). MRgFUS combines MRI and high intensity focussed ultrasound. A specialised table is required that is capable of docking into conventional MRI units. The patient lies in a prone position on the table which houses the focussed ultrasound phased array transducer and its positioning system, held in a cooling water bath (Figure 1a). The patient's abdominal wall is positioned over the water tank, protected by a plastic membrane which allows the ultrasound beam to penetrate within the pelvic area. The transducer array controls the location of the ultrasound focal spot and ultrasound waves are focussed through the abdominal wall, causing high temperature deposition at the focal point for a few seconds, resulting in the thermal ablation of the fibroid (Figure 1b) (FDA 2005; Fennessy & Tempny 2005).



1a

Figure 1a MRgFUS set up of specialised table in MRI unit (Hynynen & MacDannold 2004)



1b

Figure 2b The focussed ultrasound beam on the uterine fibroid (printed with permission SightLine Houston)

MRgFUS is conducted as a day surgery procedure. Patients undergo MRI treatment planning the day before the MRgFUS procedure, to identify and confirm the location of the fibroids (FDA 2005; Fennessy & Tempny 2005). As ultrasound interacts with gases, patient preparation prior to the procedure is important. All hair needs to be removed from the pelvic area to prevent the formation of gas bubbles which may cause burns. In addition, any skin lotions must be removed with alcohol as these may reduce the acoustic coupling (Hynynen & MacDannold 2004). To reduce motion and discomfort, patients are consciously sedated, allowing the patient to provide feedback on pain experienced during the procedure. The ExAblate[®] 2000 System software uses the pre-treatment MRI images to calculate the number and type of sonications required. Treatment typically consists of 20-50 separate sonications, lasting between

³ Also known as leiomyomas, leiomyofibromas, fibromyomas and myomas –

10-30 seconds each, followed by a 90 second cooling period. Post-treatment imaging, before and after administration of contrast agent, is conducted immediately to calculate the necrotic volume (FDA 2005; Fennessy & Tempny 2005).

The ExAblate[®] 2000 system is contraindicated for use in women who have:

- obstructions in the treatment beam path such as a scar, skin fold, bowel, intrauterine device or any hard implants;
- fibroids that are close to sensitive organs such as the bowel or bladder; and
- MRI related issues such as an allergy to contrast agent or metallic implants (FDA 2004).

CLINICAL NEED AND BURDEN OF DISEASE

Uterine fibroids are one of the most common disorders of the uterus and the most prevalent tumour in women (one in four women are affected). However, uterine fibroids are predominantly asymptomatic and do not require treatment in approximately 60-90 per cent of the women affected. Ethnicity may have an impact on the incidence of fibroids, with a higher incidence documented in African American women (Broder 1999; Technology Evaluation Center 2002; Topfer 2002).

The number of public hospital separations relating to uterine leiomyoma for Australian women in 2004–05 was 13,140, which represents a total of 41,654 patient days. Many of these women may wish to have their fibroids treated whilst at the same time sparing their uterus, especially those of a child bearing age. Of the total number of women with the principle diagnosis of leiomyoma of the uterus, 5,329 (40.6%) were women under the age of 44 years (AIHW 2007). These figures may underestimate the true burden of disease because only severe symptomatic uterine fibroids are treated with hospital procedures (usually hysterectomy or myomectomy), whereas less severe symptoms would be treated in an outpatient setting.

DIFFUSION

MR guided HIFU for the treatment of uterine fibroids is currently not practiced in Australia. There is, however, considerable interest in this technology but the high capital outlay required may be hindering the establishment of this technique in Australia (personal communication, Vascular and Interventional Radiology, Alfred Hospital).

COMPARATORS

There are two categories of treatment for symptomatic uterine fibroids – uterine-removing and uterine-conserving. If there is no desire for future childbearing, the standard treatment for symptomatic uterine fibroids is hysterectomy. Abdominal or vaginal hysterectomy involves the surgical removal of the uterus and is the most certain cure of fibroids as there is no possibility of fibroid recurrence. Hysterectomy is the most common invasive treatment for symptomatic uterine fibroids (Broder 1999).

A large range of uterine-conserving, but *not necessarily* fertility-preserving, treatments are also available. The type of treatment may depend on the location, size and number of uterine fibroids and whether the treatment is aimed at the fibroid itself or the control of symptoms associated with the fibroid (Smith 2000).

In younger women, myomectomy⁴ is a common alternative to hysterectomy and involves the surgical removal of uterine fibroids. Myomectomy may be indicated for women with symptomatic uterine fibroids who have experienced infertility or repeated miscarriage, or have a desire for future childbearing (Braunwald et al 2001; Pugh 2000).

A recent MSAC report assessed the safety and effectiveness of uterine artery embolisation (UAE), a uterine-conserving, minimally invasive technique that treats symptomatic uterine fibroids. UAE achieves its aim by blocking blood supply to the dominant fibroid via the injection of embolic material into the uterine arteries. The dominant fibroid undergoes cell death and necrosis due to a lack of blood supply, resulting in a reduction in size of the fibroid and relief in the primary patient-relevant symptoms of menorrhagia, pelvic pain and pelvic bulk. The MSAC recommended that UAE received interim funding on the Medicare Benefits Schedule for 5-years (MSAC 2006).

Fibroids can also be treated medically through the administration of progesterone or progesterone-like drugs or gonadotropin releasing hormone (GnRH) antagonists which cause fibroid shrinkage. Hormone therapy may produce menopausal symptoms, increase the risk of osteoporosis and may result in a rapid return of symptoms once treatment has ceased (InSightec Ltd 2007; MSAC 2006).

EFFECTIVENESS AND SAFETY ISSUES

Safety and effectiveness data were reported in the original submission (the pivotal study) to the FDA from a multi-centre trial on women with symptomatic fibroids enrolled in two separate (non-randomised) treatment arms: MRgFUS with ExAblate[®] (n=109) and hysterectomy (n=83) (level III-2 intervention evidence). There was no difference in the demographic and baseline characteristics of the two groups (FDA 2005).

The primary endpoint for the women enrolled in the MRgFUS arm was a symptom severity score (SSS) relating to quality of life questions, in particular symptoms of bulk and bleeding. At 6-months follow-up, a 10-point improvement in the SSS was reported in 77/109 (70.6%) women, which was defined as a clinically significant improvement, with the remaining patients reporting unchanged or worsened symptoms. The mean baseline SSS value of all women was reported to be 61.0 ± 16.3 , and at 6-months the mean was significantly reduced at 37.3 ± 21.4 , $p < 0.0001$. At 6-month follow-up, 102 women were available for MRI to evaluate fibroid shrinkage.

⁴ Also known as fibroidectomy, leiomyomectomy, fibromectomy or hysteromyomectomy

Baseline volume of fibroids was 334.4 ± 240.4 compared to the volume at 6-months of 295.4 ± 256.4 , a reduction of 15.3 ± 30.4 per cent (not reported to be a significant reduction). It should be noted that the standard deviations for all measurements were large. These results were not reported for the hysterectomy group as they were considered to no longer have fibroid related symptoms once their uterus was removed. By 6-months the hysterectomy group reported significant improvements in the following SF-36 quality of life categories compared to the ExAblate[®] treated women: role physical, bodily pain, general health, vitality and mental health.

A total of 17 (15.6%) women in the ExAblate[®] group reported clinically significant complications compared to 63 (75.9%) in the hysterectomy group. For the ExAblate[®] and hysterectomy groups, respectively, rehospitalisation rates were 7.3 vs 9.6%, fever $>38^{\circ}\text{C}$ for two consecutive days 2.8 vs 14.5%, transfusion rates were 2.8 vs 7.2%, unintended surgical procedure related to treatment 0 vs 4.8%, and interventional treatment 0 vs 2.4%. Antibiotic use was high in the hysterectomy group compared to the ExAblate[®] group 24-hours post-treatment (36.1 vs 2.8%). In addition, 14 (12.8%) patients treated with ExAblate[®] experienced leg pain or nerve tingling, eight of which were deemed to be sonication-related. Symptoms resolved after 3-days in all but one patient, who reported severe sciatic pain which did not resolve until 11-months post-treatment. There were five cases of first or second degree skin burns in the ExAblate[®] group, the majority resulted from hair being present in the sonication pathway and one case resulted from patient movement (FDA 2005).

Stewart et al (2006) reported 12-month follow-up data on 82/109 (75.2%) of the same ExAblate[®] treatment group. Of the initial 109 women, 23 (21%) sought an alternative treatment for their fibroids ie hysterectomy, myomectomy or UAE. At 12-months 42/82 (51.2%) women met the targeted 10-point improvement in SSS, however if considered on an intention-to-treat basis then this proportion is reduced markedly to 38.5 per cent (42/109). The mean SSS score at 12-months was still significantly below that observed at baseline (38.8 vs 61.1) (Stewart et al 2006).

A small MRgFUS study was conducted on 42 women (mean age 46 years, range 38-54) with symptomatic fibroids by the Mayo Clinic (level IV intervention evidence). One patient (2.4%) with large fibroids was treated on two consecutive days, two patients (4.7%) received less than one third the required number of sonications due to discomfort and three patients (7.1%) required re-treatment 12-18 months after initial treatment to further reduce symptoms. One patient (2.4%) who underwent additional MRgFUS treatment was diagnosed with deep vein thrombosis and remains on anticoagulation therapy. One patient (2.4%) reported sciatic pain which resolved over the 12-months post-treatment. No skin burns were reported. Before treatment 29/42 (69%) women reported excessive menstrual bleeding. This number was reduced to 13/42 (30.9%) at 6-months follow-up. Of the 37 (88%) patients experiencing pressure symptoms before treatment, only one (2.7%) reported no improvement after treatment, with 18 (48.6%) reporting improvement and 18 (48.6%) reporting complete

relief from pressure symptoms. Nocturia⁵ was reported in 25 women pre-treatment and was completely resolved in 17 (68%) women with the remaining women reporting some (24%) or no (8%) improvement. Of the 42 women enrolled, 17 (40.5%) sought either re-treatment with MRgFUS (n=6) or an alternative fibroid treatment: hysterectomy (n=6), myomectomy (n=2), UAE (n=1), or endometrial ablation (n=2) (Hesley et al 2006).

Other studies have reported on that the administration of gonadotrophin releasing hormone agonist potentiates the thermal effects of MRgFUS (Smart et al 2006) and that phase of the menstrual cycle does not influence MRgFUS treatment outcome (So et al 2006).

In summary, although MRgFUS is a non-invasive treatment option for women with symptomatic fibroids who wish to maintain their fertility, it appears to have a high failure rate with 21 and 26 per cent of women seeking an alternative treatment for their fibroids. However, this may be a reflection on the severity of symptoms before treatment. In addition, adverse events such as deep vein thrombosis and transfusion, although not common, are considered severe.

COST IMPACT

No cost information was available at the time of writing this summary, however costs would include the purchase of the specialised MR table and the image interpreting software.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

A non-invasive procedure to treat uterine fibroids may be an attractive option for women with symptomatic fibroids who may wish to retain their uterus for future child bearing.

OTHER ISSUES

The FDA approved the ExAblate[®] 2000 system in 2004 under the proviso that InSightec provide three year follow-up data on the women enrolled in their pivotal study (n=109) and the continued access study (n=250) which were the basis of the company's successful application to the FDA (FDA 2004).

RECOMMENDATION:

A number of treatment options, including uterine conserving, are currently available for the treatment of symptomatic uterine fibroids. MRgFUS may be attractive option for many women due to the non-invasive nature of the procedure, however, it appears that this technology is still in the "learning curve" phase of introduction, with the number of adverse events reported and a large proportion of women seeking treatment alternatives. Therefore it is recommended that this technology be monitored.

⁵ Excessive urination at night

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