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Coverage Policy

Cigna does not cover high-intensity focused ultrasound (HIFU), including magnetic resonance (MR)-guided focused ultrasound (MRgFUS), for ANY indication because it is considered experimental, investigational or unproven.

General Background

High Intensity focused Ultrasound (HIFU)
High intensity focused ultrasound (HIFU) is a minimally-invasive surgical technique for the thermal ablation of both malignant and benign tumors and cessation of internal bleeding in injured vessels and organs with little damage to the surrounding tissue. HIFU has also been proposed as an alternative to surgery for treatment of cancer and other tumor types, including but not limited to prostate, breast, brain, and renal cancer. It is also being studied for palliation of pain (e.g., tumors metastasis to bone). Currently, the primary area of study is for use in the treatment of prostate cancer.

U.S. Food and Drug Administration (FDA): The Sonablate® 500 is manufactured by SonaCare Medical, Inc. (Charlotte, NC) and Misonix, Inc. (Farmingdale, NY) and is approved by the FDA as an investigational device for clinical trials in the United States. The Ablatherm® HIFU device is manufactured by EDAP TMS S.A. (Vaulx-en-Velin, France). At this time, neither device has received pre-market approval or 510(k) clearance.
**Prostate Cancer:** Methods to manage localized prostate cancer include watchful waiting and active surveillance. Treatment options for localized prostate cancer include radical prostatectomy, radiotherapy, brachytherapy, cryotherapy, and intensity-modulated radiation therapy. Transrectal high intensity focused ultrasound (HIFU) involves the use of a probe to image the prostate and deliver timed bursts of heat to create coagulation necrosis in a targeted area. HIFU remains unique compared with other modalities for localized prostate cancer in that it has been proposed to result in much less adjacent tissue damage. This makes it a repeatable technology and thus potentially more salvageable by other techniques when it fails. Without harming adjacent healthy tissue. A cooling balloon surrounding the probe protects the rectal mucosa from the high temperature. HIFU treatment can be repeated if necessary. This procedure is typically carried out in an outpatient setting and is performed under a spinal or general anesthesia. Prolonged urinary retention secondary to edema and urethral sloughing have been the most common reported complications following primary HIFU treatment. Therefore, many of the current HIFU techniques include a pre-procedural TURP. Reported long-term complications following salvage HIFU include rectourethral fistulas, incontinence, rectal or perineal pain, and bladder neck contractures or urethral strictures (Koch, 2011; Chaussy, et al., 2011; Catalona, et al., 2011; National Institute for Clinical Excellence [NICE], 2008; Rebillard, et al., 2008; Zelefsky, et al., 2008; Prostate Cancer Research Institute [PCRI], 2011; Uchida, et al., 2006; NICE, 2005).

**Literature Review/Prostate:** The peer-reviewed published literature consists of non-randomized studies and case series studies. The long-term efficacy, safety and long-term health outcomes of HIFU prostate cancer treatment has not been established in controlled clinical trials. Overall, there is insufficient information to recommend HIFU as standard therapy (Ahmed, et al., 2012; Wu, et al., 2011; Asimakopoulos, et al., 2011; Boutier, et al., 2011; Chaussy, et al., 2011; El Fegoun, et al., 2011; Fujisue, et al., 2011; Ganzer, et al., 2011; Grimm, et al., 2011; Inoue, et al., 2011; Koch, et al., 2011; Netsch, et al., 2011; Ripert, et al., 2011; Uchida, et al., 2011; Wu, et al., 2011; Catalona, et al., 2011; Crouzet, et al., 2010; Shoji, et al., 2010; NICE, 2008; Wilt, et al., 2008; Muto, et al., 2008; Zacharakis, et al., 2008; Misrai, et al., 2008; Blana, et al., 2007; Uchida, et al., 2005; Blana, et al., 2004; Hummel, et al., 2003).

Lukka et al. (2011) conducted a systematic review of the literature to evaluate the evidence comparing HIFU with standard treatment in patients with localized prostate cancer. No randomized controlled trials or meta-analyses were identified. Seven systematic reviews and two practice guidelines were identified; neither contained randomized controlled trials. Adjusting the selection criteria to include case series found 34 clinical studies of HIFU. Twenty-nine evaluated HIFU as the primary treatment and five examined HIFU as salvage treatment for recurrence after radiotherapy. In most studies the outcomes used to determine efficacy were negative biopsy rates or prostate-specific antigen (PSA) levels. The authors reported that the current evidence on HIFU use in prostate cancer patients is of low quality, rendering it difficult to draw conclusions about its efficacy. Until results from case series are confirmed in prospective studies, the widespread use of HIFU is not supported.

Rebillard et al. (2008) conducted a systematic review of the literature. The authors reported that published clinical studies on HIFU are limited to case series; neither randomized studies comparing HIFU with another technique or active surveillance, nor studies with matched controls were found. Most papers originated in a few centers and it appears that several articles related to the same study with different numbers of patients and/or different times of follow-up. Most reports were of single-center studies. The authors reported that long-term follow-up studies are needed to further evaluate cancer-specific and overall survival rates. In addition, the efficacy and safety of HIFU as a primary therapy should be further evaluated in randomized controlled trials comparing it with other (minimally invasive) therapies. These are the same conclusions reported in a systematic review of the literature by Warmuth et al. (2010).

In an Agency for HealthCare Review and Quality (AHRQ) systematic review on comparative effectiveness and harms of treatments for clinically localized prostate cancer, HIFU is not discussed as a treatment option. The authors reported that assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence (Wilt, et al., 2008).

**Benign Prostatic Hypertrophy (BPH):** BPH is a noncancerous enlargement of the prostate gland. Symptoms of BPH include frequent urination, urgency, and excessive urination at night. Drug therapy may benefit patients with mild symptoms. Transurethral resection of the prostate has been established as the standard treatment for moderate to severe BPH. The procedure is done through a resectoscope and involves use of an electrocautery loop to remove a substantial portion of the prostate. HIFU is one of several less invasive alternatives to surgical
resection of the prostate that are currently under clinical study. HIFU delivers targeted high-intensity ultrasound that rapidly elevates the temperature in a precise focal zone, thereby ablating excess prostate tissue (ECRI, 2011).

**Literature Review/BPH:** Evidence in the published peer-reviewed medical literature evaluating HIFU for BPH consists primarily of few case series. Ohigashi et al. (2007) evaluated the efficacy and durability of three different minimally invasive therapies for BPH in a five-year prospective cohort study (n=103). Interventions were: transurethral microwave thermotherapy (n=34); transurethral needle ablation (n = 29); and transrectal HIFU (n = 40). There were no statistical differences found in efficacy or in the durability among the three interventions.

A case series (n=150) by Lu et al. (2007) safety and efficacy of transrectal HIFU for BPH. Outcomes included international prostate symptom score (IPSS), quality of life (QOL), uroflowmetric findings and transrectal ultrasound, and incidence of complications. At 12-month follow-up, maximum urine flow rate (p<0.01), post void residual (p<0.01) and prostatic volume (p<0.05) were significantly improved 12 months after the operation. However limitations of this study include its nonrandomized, uncontrolled design and short follow-up period.

There is insufficient evidence in the peer-review medical literature from which to draw conclusions regarding safety and efficacy of HIFU for BPH.

**Liver Cancer:** Hepatocellular carcinoma (HCC) is relatively uncommon in the United States, but it is the most common primary malignancy of the liver. The only potentially curative treatments are surgical resection and liver transplantation. The majority of patients with primary or metastatic liver cancers are not suitable candidates for surgical resection at the time of diagnosis. In addition, chemotherapy and radiotherapy rarely produce a complete or sustained response in patients with advanced disease. HIFU is under investigation for the ablation of unresectable HCC.

**Literature Review/Liver Cancer:** HIFU for liver cancer has been evaluated primarily in case series. Li et al., (2007) compared HIFU plus supportive care (n=151) to supportive treatment alone (n=30). Tumor imaging parameters, serum AFP levels and symptom scores improved significantly in the HIFU group compared with the control group (all p< 0.05). The one- and two-year survival rates were 50.0% and 30.9%, respectively, in the HIFU group, which were significantly greater than those (3.4% and 0%, respectively) in the control group (both p< 0.01). No severe complications occurred during and after HIFU. Although study results suggest improved outcomes with HIFU, there are limitations which include lack of randomization and short-term follow-up.

Additional well-designed studies with larger patient populations are needed to support the safety and effectiveness of HIFU for the treatment of unresectable liver cancer.

**Renal Cancer:** Renal cell carcinoma (RCC), also referred to as kidney cancer, is a disease in which cancer cells are found in the lining of tubules in the kidney. Approximately 90% of renal tumors are RCCs. Symptoms of RCC may include: blood in the urine, loss of appetite, pain in the side that doesn’t subside, weight loss, and anemia. Standard treatment available for patients with RCC includes surgery, chemotherapy, external or internal radiation therapy, and immunotherapy. Surgical excision in the form of a simple or radical nephrectomy is the accepted, often curative, treatment for stages I, II and III of RCC. The estimated five-year survival rate is 96% for patients presenting with stage I disease, 82% for stage II disease, 64% for those with stage III disease (NCCN, 2013). HIFU has been proposed as an intervention for small renal masses as well as advanced stage renal malignancy.

**Literature Review/Renal Cancer:** There is a paucity of studies in the published peer-reviewed scientific literature evaluating the safety and effectiveness of HIFU for renal cancer. Case series with small patient populations (n=13-17) provide preliminary, but insufficient data from which to draw conclusions (Ritchie, et al., 2011; Ritchie, et al., 2010; Wu, et al., 2003). The role of HIFU has not been established for this indication.

**Magnetic Resonance (MR)-Guided Focused Ultrasound (MRgFUS)**

MRgFUS technology combines a high intensity focused ultrasound beam that heats and destroys targeted tissue non-invasively and magnetic resonance imaging (MRI) which visualizes anatomy, and continuously monitors the tissue effect. HIFU therapy using MR- guidance has been proposed for the treatment of uterine
fibroids (leiomyomatia), cancer, and other tumor types, however to date the primary clinical application of MRgFUS has been treatment of uterine fibroids (leiomyomata).

**U.S. Food and Drug Administration (FDA):** In November 2004, the FDA granted premarket approval (PMA) for an MRgFUS system for the proposed targeting and destruction of symptomatic fibroids. The ExAblate® 2000 System (InSightec—North America, Dallas, TX) is indicated for the ablation of symptomatic fibroids in women who have completed childbearing, do not intend to become pregnant, and have a uterine gestational size of less than 24 weeks. The ExAblate 2000 is contraindicated for use in women who have:

- MRI-related issues, such as metallic implants or sensitivity to MRI contrast agents
- obstructions in the treatment beam path, such as a scar, skin folds or irregularity, bowel, pubic bone, intrauterine device (IUD), surgical clips, or any hard implants
- fibroids that are close to sensitive organs, such as the bowel or bladder, or are outside the image area

In October 2012, the FDA granted premarket approval (PMA) for the ExAblate® System, Model 2000/2100/2100 (InSightec—North America, Dallas, TX) is. The device is indicated for pain palliation of metastatic bone cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy. The bone tumor to be treated must be visible on non-contrast MR and device accessible. The device was evaluated through an expedited review process. In addition to the unpublished randomized controlled trial upon which PMA approval was based, the manufacturer is required to conduct two post-approval studies to evaluate device performance under actual conditions of use and to further evaluate device safety (FDA, 2012).

**Uterine Fibroids:** Uterine leiomyomata, or fibroids, are benign tumors of the uterus that are made up of smooth muscle and the extracellular matrix proteins, collagen and elastin. Fibroids can lead to abnormal uterine bleeding, dysmenorrhea and noncyclic pelvic pain. They can also cause constipation, urinary frequency, and infertility, depending on their size and location. The current standards of care for the treatment of symptomatic fibroids include:

- nonsteroidal anti-inflammatory agents
- oral contraceptives
- pharmacological agents (gonadotropin-releasing hormone [GnRH]) for short-term therapy
- myomectomy (laparoscopic or open)
- uterine artery embolization
- hysterectomy

Myomectomy and uterine artery embolization are surgical options for patients who wish to preserve their fertility, since a hysterectomy would render these individuals permanently infertile.

MRgFUS has been proposed as a non-invasive technique used to ablate uterine fibroids in women who do not intend to become pregnant in the future. Although early studies showed that some fibroid symptoms decreased (n=71%) following the procedure, a high percentage of patients (n=21%) needed alternative surgical treatment for their fibroids within one year of having the procedure because their previous symptoms returned. Reported adverse effects of MRgFUS have included paresthesia, burns on the abdomen, excessive postoperative bleeding, and reactions to medication.

**Literature Review/Uterine Fibroids:** Studies in the published peer-reviewed scientific literature evaluating the safety and effectiveness of MRgFUS ablation of uterine fibroids consists primarily of case series with few comparative trials.

ECRI issued an Emerging Technology Evidence Report on the effectiveness of MRgFUS for uterine fibroids. The evaluation was based on non-randomized controlled trials (n=2 studies) and case series (n=7 studies/702 subjects). Limitations of the evidence base included the lack of randomized controlled trials comparing the technology to other minimally invasive procedures intended to treat uterine fibroids, inconsistent reporting of adverse events, and short-term follow-up in available studies. Results of three of four small studies suggested that MRgFUS resulted in clinically significant symptom reduction for at least 50% of patients at 12-month follow-up. About 13% of study patients in the 4 studies required additional treatments for fibroids during 12–24-month
follow-up. According to the ECRI report, questions on the efficacy of MRgFUS using the ExAblate 2000 system could not be answered because the evidence was of small quantity and low quality (ECRI, 2011).

A comparative uncontrolled study (n=192) by Taran et al. (2009) reported a lower number of complications and adverse events for women who underwent MRgFUS (n=109). However, at six months of follow-up, most of the SF-36 subscale scores were significantly better for women in the hysterectomy group (n=83).

The results of a number of prospective and retrospective case series (n=35–359 subjects) suggest that MRgFUS may reduce fibroid volume and improve symptoms over the short term (Gorny, et al., 2011; Funaki, et al., 2009; Morita, et al., 2008; Fennessy, et al., 2007; Rabinovici, et al., 2007; Stewart, et al., 2007; Stewart, et al., 2006; Hindley, et al., 2004). However, limitations of these studies include short follow-up, and for some trials, very small sample sizes.

The Agency for Healthcare Research and Quality (AHRQ) published an updated evidence report on the management of uterine fibroids. The report evaluated two studies (Stewart, et al., 2006; Hindley, et al., 2004), and concluded that although the data demonstrated safety and preliminary efficacy of the procedure for improving symptoms, comparative trials and longer-term follow-up are needed for this fibroid treatment modality (AHRQ, 2007).

Although some the available data suggest that MRgFUS holds promise, the role of this procedure in the management of patients with fibroids has not been established at this time.

Bone Cancer: Metastatic bone disease is one of the most common causes of cancer pain. Existing treatments include supportive measures, pharmacologic agents and radiation therapy. For treating pain associated with bone metastases, the aim of MRgFUS treatment is to destroy nerves in the bone surface surrounding the tumor and achieve local palliation of the metastatic lesion.

Literature Review/Bone Cancer: Few case series with small patient populations (n=7-80) and follow-up periods from one-five years have evaluated the safety and effectiveness of imaging-guided HIFU for primary and metastatic bone tumors (Chen, et al., 2010; Li, et al., 2010; Li, et al., 2009). Overall survival rates of 89.8%, 72.3%, 60.5%, 50.5%, and 50.5%, at one, two, three, four, and five years, respectively have been reported (Chen, et al., 2010). However, conclusions regarding safety and effectiveness cannot be drawn from this limited data.

Well-designed clinical trials with larger sample sizes are needed to determine the role of HIFU for bone cancer.

Miscellaneous: Isolated case series have been published for HIFU/ MRgFUS used to treat indications such as brain, breast and pancreatic cancers. This evidence is inadequate to make determinations regarding safety and effectiveness.

Professional Societies/Organizations
National Comprehensive Cancer Network ® (NCCN®): The 2013 NCCN Clinical Practice Guidelines in Oncology Prostate Cancer states that emerging focal therapy like HIFU warrant further study. Other NCCN guidelines do not specifically refer to HIFU.

National Cancer Institute (NCI): HIFU is not discussed in the 2013 Prostate Cancer Treatment health professional version Physician Data Query (PDQ). In the 2013 Prostate Cancer Treatment patient version Physician Data Query (PDQ) HIFU is listed as a new type of treatment being tested in clinical trials.

American Cancer Society (ACS): HIFU is mentioned as a newer treatment for early stage prostate cancer. The ACS states that new treatments could be used either as the first type of treatment or after radiation therapy in cases where it was not successful. HIFU treatment has been used more in Europe, but it is not available outside of clinical trials in the United States at this time. Studies are now under way to determine its safety and effectiveness (ACS, 2013).

American Urological Association (AUA): The AUA Guideline for the Management of Clinically Localized Prostate Cancer reports that standard options for the management of clinically localized prostate cancer include watchful waiting and active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, radical prostatectomy, as well as primary hormonal therapy. HIFU is listed under other treatment options in this
The panel did not include other treatment options in the analysis and recommendations due to a combination of factors, including limited published experience and short-term follow-up as well as the similar issues that affected evaluations of other treatment options (Thompson, et al., 2007). This guideline was reviewed and the validity confirmed in 2011.

**American College of Radiology (ACR) Appropriateness Criteria**: The 2011 American College of Radiology Expert Panel on Radiation Oncology-Prostate Work Group’s guideline on locally advanced (high-risk) prostate cancer does not mention the use of HIFU in the list of treatment options. The summary states that HIFU is currently an experimental therapy.

**American College of Obstetricians and Gynecologists (ACOG)**: ACOG states that “whereas short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRI-guided focused ultrasound surgery will lead to durable results beyond 24 months” (ACOG, 2008).

**Use Outside of the US**

**European Association of Urology (EAU)**: The 2013 updated European Association of Urology Guideline on Prostate Cancer summary of experimental therapeutic options to treat clinically localized prostate cancer concludes that “all other minimally invasive treatment options, such as HIFU microwave and electrosurgery, are still experimental or investigational. For all of these procedures, a longer follow-up is mandatory to assess their true role in the management of prostate cancer.” The recommendations for the management of PSA relapse after radiotherapy states, “HIFU may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality, due to the short follow-up periods reported” (Heidenreich, et al., 2013).

The 2011 EAU Guidelines on Prostate Cancer: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer Diagnosis discusses HIFU in the section on treatment of relapse after curative therapies stating that HIFU may be discussed as a treatment option in carefully selected patients. In the section on management of prostate-specific antigen failures after radiation therapy HIFU is discussed as an alternative treatment option. In the section on salvage cryosurgical ablation of the prostate for radiation failures the authors report that HIFU still cannot be recommended as a standard care procedure in patients with relapsing prostate cancer. HIFU is not mentioned as a treatment in the recommendations under the guidelines on treatment options for prostate-specific antigen relapse following local treatment (Mottet, et al., 2011).

**Canadian Urology Association**: The 2010 high-intensity focused ultrasound treatment for prostate cancer practice guideline concluded that HIFU is currently not recommended as an alternative to accepted curative treatment approaches for localized prostate cancer (Lukka, et al., 2010). The National Institute for Clinical Excellence (NICE) guidance for MRI-guided transcutaneous focused ultrasound for uterine fibroids states that the current evidence on the efficacy is adequate, although further treatment may be required and the effect on subsequent pregnancy is uncertain. There are well-recognized complications but the evidence on safety is adequate support the use of the procedure providing that normal arrangements are in place for clinical governance and audit. According to the NICE, further research studies should report long-term outcomes including the need for further treatment (NICE, 2011).

**Summary**

In general, the long-term efficacy and safety of high-intensity focused ultrasound (HIFU) compared to established interventions for various conditions, such as prostate liver and renal cancer has not been proven in controlled clinical trials. Presently, there are no U.S. Food and Drug Administration (FDA)-approved HIFU devices.

Magnetic resonance (MR)-guided, focused ultrasound system (MRgFUS) treatment with the ExAblate® systems remains unproven for all indications due to the lack of well-designed, randomized, controlled clinical trials with adequate follow-up. Published data are limited, and the long-term safety and efficacy of this procedure has not yet been demonstrated. Study population numbers have been low, and it is unknown what impact this treatment will have on patients’ safety or what adverse effects might occur during long-term follow-up. The role of HIFU/MRgFUS has not been established for any indication.
Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered:

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<td>0072T</td>
<td>Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume greater or equal to 200 cc of tissue</td>
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<td>C9734</td>
<td>Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance</td>
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References


