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DISCLAIMER

This Molina clinical policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina clinical policy document and provide the directive for all Medicare members. [1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [2 24-25]

Essential tremor (ET) is a common movement disorder, the most common one in the adult population and prevalence is reported up to 9% in people older than 60 years. The etiology of ET is not clearly understood but many patients have a strong family history. Treatment for essential tremor includes medications such as beta

blockers, anti-epileptics, or sedatives. Surgery may be considered in people whose condition has not responded adequately to best medical therapy. Surgical treatments include deep brain stimulation and radiofrequency thalamotomy.

Magnetic resonance image guided high intensity focused ultrasound (MRgFUS) stereotactic intracranial lesion ablation utilizes multiple elemental arrays of ultrasound transducers to focus thermal ablation to the specific target area as small as millimeters in size. This disturbs the blood-brain barrier, but is noninvasive allowing for an alternative treatment to current open neurologic procedures. The system includes a helmet-like apparatus consisting of individual ultrasound transducers, which is attached to the head via a stereotactic frame. This procedure is carried out with the patient lying supine inside an MRI scanner. Continuous MRI and thermal mapping are used to identify the target area of the brain and monitor treatment. Low power ultrasound is delivered to confirm the chosen location. Then, high-power focused ultrasound pulses are administered to irreversibly ablate target tissue. Chilled water is circulated around the head during the treatment to prevent thermal damage to the scalp caused by the increase in bone temperature. The procedure takes approximately 2-3 hours, during which time the patient is awake and responsive and symptom relief should be immediate.

Food and Drug Administration (FDA): ExAblate 4000 Type 1.0 Neuro transcranial MRgFUS system (InSightec, Inc.) was FDA approved in July 2016 for transcranial unilateral thalamotomy in patients with idiopathic ET who have medication-refractory tremor. Patients must be at least 22 years of age. The designated area in the brain responsible for the movement disorder symptoms (VIM) must be identified and accessible for targeted thermal ablation by the ExAblate device. Contraindications to the procedure include those for MRI such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, allergies to MR contrast agent etc. Other main conditions excluded from MRgFUS include pregnancy, brain tumor, cerebrovascular disease, advanced kidney disease, dialysis, unstable cardiac status or severe hypertension, history of abnormal bleeding, hemorrhage, and/or coagulopathy, and those receiving anticoagulants. [2]

POSITION STATEMENT

Magnetic Resonance Guided Focused Ultrasound (MRgFUS) is considered experimental, investigational and unproven for the treatment of essential tremor (ET) due to insufficient evidence in the peer reviewed literature.

SUMMARY OF MEDICAL EVIDENCE [5-24]

The best available published evidence to date on ExAblate Neuro for transcranial thalamotomy in patients with medically refractory ET includes the U.S. pivotal randomized, sham-controlled trial (Elias et al., 2016) and the U.S. feasibility trial (Elias et al., 2013). Additional publications include a meta-analysis, a few very small case series as well as a retrospective registry study. Based on a paucity of data, there is currently insufficient evidence to support the use of MRgFUS for the treatment of ET. Studies published to date enrolled a small number of patients with limited follow-up and do not prove safety and efficacy of MRgFUS use in ET. A summary of the relevant studies are outlined below.

The Elias 2016 trial enrolled patients with moderate-to-severe essential tremor that had not responded to at least two trials of medical therapy and randomly assigned them in a 3:1 ratio to undergo unilateral focused ultrasound thalamotomy or a sham procedure. The Clinical Rating Scale for Tremor and the Quality of Life in Essential Tremor Questionnaire were administered at baseline and at 1, 3, 6, and 12 months. Tremor assessments were

videotaped and rated by an independent group of neurologists who were unaware of the treatment assignments. The primary outcome was the between-group difference in the change from baseline to 3 months in hand tremor, rated on a 32-point scale (with higher scores indicating more severe tremor). After 3 months, patients in the sham-procedure group could cross over to active treatment (the open-label extension cohort). The investigators included 67 patients in the analysis. Hand-tremor scores improved more after focused ultrasound thalamotomy (from 18.1 points at baseline to 9.6 at 3 months) than after the sham procedure (from 16.0 to 15.8 points); the between-group difference in the mean change was 8.3 points (95% confidence interval [CI], 5.9 to 10.7; P<0.001). The improvement in the thalamotomy group was maintained at 12 months (change from baseline, 7.2 points; 95% CI, 6.1 to 8.3). Secondary outcome measures assessing disability and quality of life also improved with active treatment (the blinded thalamotomy cohort) as compared with the sham procedure (P<0.001 for both comparisons). Adverse events in the thalamotomy group included gait disturbance in 36% of patients and paresthesias or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of patients, respectively. [11]

The Elias 2013 open-label, uncontrolled, pilot study, investigated the use of transcranial MRI-guided focused ultrasound thalamotomy for the treatment of essential tremor. From February 2011 through December 2011, these researchers used transcranial MRI-guided focused ultrasound to target the unilateral ventral intermediate nucleus of the thalamus in 15 patients with severe, medication-refractory essential tremor. They recorded all safety data and measured the effectiveness of tremor suppression using the Clinical Rating Scale for Tremor to calculate the total score (ranging from 0 to 160), hand subscore (primary outcome, ranging from 0 to 32), and disability subscore (ranging from 0 to 32), with higher scores indicating worse tremor. These investigators assessed the patients' perceptions of treatment efficacy with the Quality of Life in Essential Tremor Questionnaire (ranging from 0 to 100 %, with higher scores indicating greater perceived disability). Thermal ablation of the thalamic target occurred in all patients. Adverse effects of the procedure included transient sensory, cerebellar, motor, and speech abnormalities, with persistent paresthesia in 4 patients. Scores for hand tremor improved from 20.4 at baseline to 5.2 at 12 months (p = 0.001). Total tremor scores improved from 54.9 to 24.3 (p = 0.001). Disability scores improved from 18.2 to 2.8 (p = 0.001). Quality-of-life scores improved from 37 % to 11 % (p = 0.001). The authors concluded that in this pilot study, essential tremor improved in 15 patients treated with MRI-guided focused ultrasound thalamotomy. However, large, RCTs are needed to assess the procedure's safety and effectiveness. [10]

Zaaroor et al. (2018) examined 30 patients with severe medication-resistant tremor who underwent unilateral VIM thalamotomy using MRgFUS. Effects on tremor were evaluated using the Clinical Rating Scale for Tremor (CRST) in patients with ET and by the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) in patients with PD and ET-PD (defined as patients with ET who developed PD many years later). Quality of life in ET was measured by the Quality of Life in Essential Tremor (QUEST) questionnaire and in PD by the PD Questionnaire (PDQ-39). Thirty patients underwent MRgFUS, including 18 with ET, 9 with PD, and 3 with ET-PD. The mean age of the study population was 68.9 ± 8.3 years (range 46-87 years) with a mean disease duration of 12.1 ± 8.9 years (range 2-30 years). MRgFUS created a lesion at the planned target in all patients, resulting in cessation of tremor in the treated hand immediately following treatment. At 1 month posttreatment, the mean CRST score of the patients with ET decreased from 40.7 ± 11.6 to 9.3 ± 7.1 ($p < 0.001$) and was 8.2 ± 5.0 six months after treatment ($p < 0.001$, compared with baseline). Average QUEST scores decreased from 44.8 ± 12.9 to 13.1 ± 13.2 ($p < 0.001$) and was 12.3 ± 7.2 six months after treatment ($p < 0.001$).

In patients with PD, the mean score of the motor part of the UPDRS decreased from 24.9 ± 8.0 to 16.4 ± 11.1 (p = 0.042) at 1 month and was 13.4 ± 9.2 six months after treatment (p = 0.009, compared with baseline). The mean PDQ-39 score decreased from 38.6 ± 16.8 to 26.1 ± 7.2 (p = 0.036) and was 20.6 ± 8.8 six months after treatment (p = 0.008). During follow-up of 6-24 months (mean 11.5 ± 7.2 months, median 12.0 months), tremor reappeared in 6 of the patients (2 with ET, 2 with PD, and 2 with ET-PD), to a lesser degree than before the procedure in 5. Adverse events that transiently occurred during sonication included headache (n = 11), short-lasting vertigo (n = 14) and dizziness (n = 4), nausea (n = 3), burning scalp sensation (n = 3), vomiting (n = 2) and lip paresthesia (n = 2). Adverse events that lasted after the procedure included gait ataxia (n = 5), unsteady feeling (n = 4), taste disturbances (n = 4), asthenia (n = 4), and hand ataxia (n = 3). No adverse event lasted beyond 3 months. Patients underwent on average 21.0 ± 6.9 sonications (range 14-45 sonications) with an average maximal sonication time of 16.0 ± 3.0 seconds (range 13-24 seconds). The mean maximal energy reached was 12,500 ± 4274 J (range 5850-23,040 J) with a mean maximal temperature of 56.5° ± 2.2°C (range 55°-60°C). MRgFUS VIM thalamotomy to relieve medication-resistant tremor was safe and effective in patients with ET, PD, and ET-PD. Current results emphasize the superior adverse events profile of MRgFUS over other surgical approaches for treating tremor with similar efficacy. However, the study concluded that large randomized studies are needed to assess prolonged efficacy and safety. [24]

Mohammed et al. (2018) conducted a meta-analysis to analyze the overall outcomes and complications of MRgFUS in the treatment of essential tremor (ET). Patients with the diagnosis of ET who were treated with MRgFUS were included in the study. The change in the Clinical Rating Scale for Tremor (CRST) score after treatment was analyzed. The improvement in disability was assessed with the Quality of Life in Essential Tremor Questionnaire (QUEST) score. The pooled data were analyzed by the DerSimonian-Laird random-effects model. Tests for bias and heterogeneity were performed. Nine studies with 160 patients who had ET were included in the meta-analysis. The ventral intermediate nucleus was the target in 8 of the studies. The cerebellothalamic tract was targeted in 1 study. There was 1 randomized controlled trial, 6 studies were retrospective, and 2 were prospective. The mean number of sonications given in various studies ranged from 11 ± 3.2 to 22.5 ± 7.5 (mean ± SD). The maximum delivered energy ranged from 10,320 ± 4537 to 14,497 ± 6695 Joules. The mean of peak temperature reached ranged from 53°C ± 2.3°C to 62.0°C ± 2.5°C. On meta-analysis with the random-effects model, the pooled percentage improvements in the CRST Total, CRST Part A, CRST Part C, and QUEST scores were 62.2%, 62.4%, 69.1%, and 46.5%, respectively. Dizziness was the most common in-procedure complication, occurring in 45.5%, followed by nausea and vomiting in 26.85% (pooled percentage). At 3 months, ataxia was the most common complication, occurring in 32.8%, followed by paresthesias in 25.1% of the patients. At 12 months posttreatment, the ataxia had significantly recovered and paresthesias became the most common persisting complication, at 15.3%. In conclusion, the MRgFUS therapy for ET significantly improves the CRST scores and improves the quality of life in patients with ET, with an acceptable complication rate. Therapy with MRgFUS is a promising frontier in functional neurosurgery. [19]

PROFESSIONAL SOCIETY GUIDELINES: [3-6]

The American Academy of Neurology guideline for treatment of ET states that thalamotomy is possibly effective; there are no recommendations regarding MRgFUS for treatment of ET. [3]

National Institute for Health and Care Excellence (NICE) has developed a draft guidance (2018) entitled Unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor. This guidance

indicates that the evidence on the safety of unilateral MRI-guided focused ultrasound unilateral thalamotomy for treatment-resistant essential tremor raises no major safety concerns. However, current evidence on its efficacy is limited in quantity. Therefore, this procedure should not be used unless there are special arrangements for clinical governance, consent, and audit or research. [4]

CMS

Centers for Medicare & Medicaid (CMS)

According to LCD L37421 (effective 4/1/2018): MRgFUS is a promising new treatment approach that has attributes, positive and negative, distinct from both traditional thalamotomy and DBS. However, long-term effectiveness and safety remain uncertain and warrant a direct comparison with DBS, the current surgical standard. Widespread non-coverage by both Medicare and commercial payers supports this interpretation. However, given the support for traditional thalamotomy, generally, as an alternative "if DBS is not available or practical", and the support for MRgFUS thalamotomy, specifically, as an alternative in patients "who are not a candidate for DBS" by the American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS) and the American Association of Stereotactic and Functional Neurosurgery (ASSFN), NGS considers MRgFUS reasonable and necessary in that context. Patient selection criteria will largely mirror those used in the pivotal study. [1]

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed
HCPCS	**Description**
	N/A

ICD-10	Description: [For dates of service on or after 10/01/2015]
G25.0 & G25.2	Essential and other specified forms of tremor

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REVIEW/REVISION HISTORY

7/10/18: New Policy
9/18/19 & 4/23/20: Policy reviewed, no changes.
2/8/21: Policy reviewed, no changes to criteria. Two new guidelines found at reference #5-6: American Society for Stereotactic and Functional Neurosurgeons (ASSFN) & Health Quality Ontario (HQO).