| Subject: Deep Brain Stimulation for Epilepsy with the Activa® PC Neurostimulator | | Original Effective Date: 3/11/2019 |
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| **Policy Number: MCP-335** | **Revision Date(s):** | |
| **MCPC Approval Date:** 3/11/2019, 4/23/2020, 2/8/2021 | **Review Date:** 4/23/2020, 2/8/2021 | |

# Contents



## 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

Epilepsy is a chronic neurological disorder characterized by recurrent and unprovoked seizures that can severely diminish health and quality of life. Epilepsy is further defined by the Epilepsy Foundation as a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. A seizure is an event and epilepsy is the disease involving recurrent unprovoked seizures. At the current time there are three standard treatment modalities for which there is evidence of effectiveness in the treatment of refractory epilepsy: Pharmacotherapy with

antiepileptic drugs (AEDs), resective surgery, and device-based therapy including vagus nerve stimulation (VNS). [3]

The Medtronic Deep Brain Stimulation (DBS) System for Epilepsy (Activa® PC neurostimulator) is bilateral stimulation of the anterior nucleus of the thalamus (ANT) which is used as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures (seizures originating from one cerebral hemisphere), with or without secondary generalization (spreading to the other hemisphere), that are refractory to three or more antiepileptic medications. Each lead is connected to an extension and the extensions are connected to a single neurostimulator, implanted in a subcutaneous pocket. The neurostimulator provides mild electrical stimulation to the targeted area in the brain which is thought to override neuronal activity thereby reducing seizure frequency. The patient will also receive a hand-held Intercept™ patient therapy programmer, which is an external device that allows the patient control over the therapy delivered within physician-prescribed parameters. The stimulation may be programmed, and adjusted, non-invasively by the clinician to help maximize symptom control and minimize side effects. [2]

The Medtronic DBS system has been FDA approved as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications and for patients who average six or more seizures per month over the three most recent months prior to system implant (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures. [2]

Contraindications to DBS for epilepsy include patients exposed to diathermy (i.e. shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy); certain types of MRI imaging, and transcranial magnetic stimulation (TMS). [2]

## POSITION STATEMENT [6-25]

The Medtronic Deep Brain Stimulation (DBS) System for Epilepsy (Activa® PC neurostimulator) is considered experimental, investigational and unproven for the treatment of epilepsy due to insufficient evidence in the peer reviewed literature.

## SUMMARY OF MEDICAL EVIDENCE [3-5 6-25]

The peer reviewed published literature includes randomized clinical trials, Cochrane and systematic reviews, retrospective reviews, case studies and review articles which are insufficient to provide evidence that supports the efficacy and safety of deep brain stimulation for epilepsy. Results of clinical trials show promising outcomes, however, larger, longer-term randomized controlled studies are needed to better define safety, efficacy and the subset of patients who would benefit most from this potential treatment for epilepsy. Professional society guidelines have not endorsed or mention deep brain stimulation as a treatment for epilepsy. [3-4-5]

The most relevant and applicable studies are outlined below.

Fisher et al (2010) reported a multi-center, double-blind, randomized trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy (SANTE Trial). Subjects were adults with medically refractory partial seizures, including secondarily generalized seizures. Half received stimulation and half no

stimulation during a 3-month blinded phase; then all received unblinded stimulation. A total of 110 subjects were randomized. Baseline monthly median seizure frequency was 19.5. In the last month of the blinded phase the stimulated group had a 29 % greater reduction in seizures compared with the control group, as estimated by a generalized estimating equations (GEE) model (p = 0.002). Unadjusted median declines at the end of the blinded phase were 14.5 % in the control group and 40.4 % in the stimulated group. Complex partial and "most severe" seizures were significantly reduced by stimulation. By 2 years, there was a 56 % median percent reduction in seizure frequency; 54 % of patients had a seizure reduction of at least 50 %, and 14 patients were seizure-free for at least 6 months. Five deaths occurred and none was from implantation or stimulation. No subject had symptomatic hemorrhage or brain infection. Two subjects had acute, transient stimulation-associated seizures. Cognition and mood showed no group differences, but subjects in the stimulated group were more likely to report depression or memory problems as adverse events. The authors concluded that bilateral stimulation of the anterior nuclei of the thalamus reduces seizures. Benefit persisted for 2 years of study. Complication rates were modest. The authors stated that DBS of the anterior thalamus is useful for some people with medically refractory partial and secondarily generalized seizures but more studies are needed to determine whether this approach can result in long-term benefits. [9]

Salanova et al (2015) reported Long-term outcomes of the SANTE trial, described above. The uncontrolled open-label portion of the trial began after three months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the three-year follow-up, and 83 (75%) completed five years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at one year and 69% at five years ($p<0.001$ for both). During the study, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first several months after implantation. The most frequently reported serious adverse events were implant site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the study and none were considered to be device-related. Depression was reported in 41 (37%) patients over the study; in three cases, this was considered device related. Memory impairment (non-serious) was reported in 30 (27%) patients during the study, half of which had a history of the condition. Although some patients appear to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was overall modest. [20]

Fountas et al (2010) reviewed the pertinent literature to outline the role of cerebellar stimulation (CS) in the management of medically refractory epilepsy. The PubMed medical database was systematically searched for the following terms: "cerebellar," "epilepsy," "stimulation," and "treatment," and all their combinations. Case reports were excluded from this study. The pertinent articles were categorized into 2 large groups: animal experimental and human clinical studies. Particular emphasis on the following aspects was given when reviewing the human clinical studies: their methodological characteristics, the number of participants, their seizure types, the implantation technique and its associated complications, the exact stimulation target, the stimulation technique, the seizure outcome, and the patients' psychological and social post-stimulation status. Three clinical double-blind studies were found, with similar implantation surgical technique, stimulation target, and stimulation parameters, but quite contradictory results. Two of these studies failed to demonstrate any significant seizure reduction, whereas the third one showed a significant post-stimulation decrease in seizure frequency. All possible factors responsible for these differences in the findings are analyzed in the present

study. The authors concluded that CS seems to remain a stimulation target worth exploring for defining its potential in the treatment of medically intractable epilepsy, although the data from the double-blind clinical studies that were performed failed to establish a clear benefit in regard to seizure frequency. Large-scale, double-blind clinical studies are needed for accurately defining the efficacy of CS in epilepsy treatment. [10]

Cochrane: Sprengers et al (2014 updated in 2017), assessed the safety, efficacy and tolerability of DBS and cortical stimulation in patients with refractory epilepsy. The reviews included RCTs comparing DPS to sham stimulation, resective surgery or further treatment with antiepileptic drugs. Of the 10 RCTs identified for inclusion in the 2014 review, three trials were specific to DBS (1 anterior thalamic DBS trial, n=109 treatment periods; two centromedian thalamic DBS trials, n=20, 40 treatment periods). The studies added in the 2017 update were a cross-over RCT of bilateral anterior thalamic stimulation (n=4) and a double blind RCT of hippocampal stimulation (n=6) that was not included in the meta-analysis due to missing detailed methodology. The primary outcome measures included the proportion of patients who were disease free and a 50% or greater reduction in seizure frequency after 1-3 months. The evidence was rated as moderate quality and no statistical or clinically significant differences were reported based upon the primary outcome measures. Authors concluded that there is insufficient evidence upon which to draw conclusions regarding the efficacy and safety of hippocampal DBS or centromedian DBS as a treatment for epilepsy. [22-23]

Cukiert et al (2017) conducted a double-blind, placebo-controlled randomized trial evaluating 16 patients with refractory temporal lobe epilepsy. Prior to treatment, all patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). All patients underwent DBS device implantation, and were followed for six months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. There was a significant difference in FIAS frequency from the first month of full stimulation until the end of the blinded phase ($p<0.001$) and FAS frequency for the same period except for the third month of the blinded phase. [8]

Troster et al (2017) assessed neuropsychological adverse events from the SANTE trial during the three-month blinded phase, and at seven-year follow-up during the open-label noncomparative phase. At baseline, there were no differences in depression history between groups. During the three-month blinded phase of the trial, depression was reported in eight (15%) patients from the stimulation group and in one (2%) patient from the no stimulation group ($p=0.02$). Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (seven in the active group, one in the control group; $p=0.03$). At seven-year follow-up, after the treatment groups had been combined, there was no SUR84 | 10 statistically significant difference in Profile of Mood State depression score compared with baseline and most cognitive function tests did not improve over baseline measurements. [24]

Li et al (2018) preformed a systematic review that identified 10 RCTs and 48 uncontrolled studies. Summaries of the studies were discussed by area of the brain targeted by DBS. A review of the studies showed that DBS might be effective in reducing seizures when DBS targets the anterior nucleus of the thalamus or the hippocampus. Across studies, more than 70% of patients experienced a reduction in seizures by 50% or more. However, there were very few RCTs and the observational studies had small sample sizes. Individual responses

varied, depending on seizure syndrome, presence or absence of structural abnormalities, and electrode position. Results were inconclusive when DBS targeted the centromedian nucleus of the thalamus, the cerebellum, and the subthalamic nuclei. Safety data on DBS was limited due to the small population sizes. Additional limitations of this review include that the literature search date was not reported and Meta-analyses were not performed. [17]

**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 |
|---|---|
| 61863 | Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array |
| + 61864 | each additional array (List separately in addition to primary procedure) |
| 61867 | Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array |
| + 61868 | each additional array (List separately in addition to primary procedure) |
| 61880 | Revision or removal of intracranial neurostimulator electrodes |
| 61885 | Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array |
| 61886 | with connection to 2 or more electrode arrays |
| 95970 | Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without programming |

| HCPCS | Description |
|---|---|
| L8680 | Implantable neurostimulator electrode, each |
| L8681 | Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only |
| L8682 | Implantable neurostimulator radiofrequency receiver |
| L8683 | Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver |
| L8685 | Implantable neurostimulator pulse generator, single array, rechargeable, includes extension |
| L8686 | Implantable neurostimulator pulse generator, single array, rechargeable, includes extension |
| L8687 | Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension |
| L8688 | Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension |
| L8689 | External recharging system for battery (internal) for use with implantable neurostimulator, replacement only |
| L8695 | External recharging system for battery (external) for use with implantable neurostimulator, replacement only |

| ICD-10 | Description: [For dates of service on or after 10/01/2015] |
|---|---|
| G40.00-G40.89 | Epilepsy and recurrent seizures |

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## REVIEW/REVISION HISTORY

3/11/2019: New Policy
4/23/2020: Policy reviewed, no changes.