SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. General Information

Device Generic Name: Implantable multi-programmable quadripolar deep brain stimulation system

Device Trade Name: Medtronic Activa® Dystonia Therapy, consisting of:

Model 3307 Activa® Dystonia Therapy Kit:
Model 7426 Soletra Neurostimulator
Model 7482 Extension
Model 3387 DBS™ Lead
Model 7452 Control Magnet

Model 3309 Activa® Dystonia Therapy Kit:
Model 7426 Soletra Neurostimulator
Model 7482 Extension
Model 3389 DBS™ Lead
Model 7452 Control Magnet

Associated Products:
Model 7432 Clinician Programmer
Model 7460 MemoryMod Software Cartridge
Model 8840 N'Vision Clinician Programmer
Model 8870 Application Card
Model 3353/3354 Lead Frame Kit
Model 3625 Test Stimulator
Model 7438 Therapy Controller
Burr Ring Hole and Cap

Applicant's Name and Address: Medtronic Neurological
710 Medtronic Parkway NE
Minneapolis, MN 55432-5604

Humanitarian Device Exemption (HDE) Number: H020007

Date of Humanitarian Use Device Designation: November 27, 2001

Date of Panel Recommendation: Not applicable.

Date of Good Manufacturing Practices (GMP) Inspection: December 26, 2002

Date of notice of Approval to the Applicant: April 15, 2003

II. Indications for Use

The Medtronic Activa® Dystonia Therapy is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid

in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.

For purposes of this document, the Medtronic Activa® Dystonia Therapy will be referred to as the Activa® System.

III. Contraindications

Implantation of an Activa® System is contraindicated for:

- Patients exposed to diathermy. Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

  Diathermy is further prohibited because it can also damage the neurostimulation system components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. Injury or damage can occur during diathermy treatment whether the neurostimulation system is turned "on" or "off". Patients should inform all their health care professionals that they should not be exposed to diathermy treatment.

- Patients who will be exposed to Magnetic Resonance Imaging (MRI) using a full body radio-frequency (RF) coil or a head transmit coil that extends over the chest area. Refer to the product labeling for comprehensive safety information on the use of MRI in patients with implanted Activa systems.

- Patients who are unable to properly operate the stimulator.

IV. Warnings and Precautions

Please refer to the device labeling for a complete list of warnings and precautions.

Special Considerations for Pediatric Patients:

Warnings:

- Patient growth and lead/extension length – Evaluate the patient's implanted lead/extension assembly for sufficient strain relief (e.g., consider patient comfort, range of motion, x-ray visualization of the extension) at regular post-implant follow-up sessions, especially for patients whose growth is not complete at implant. Consideration should be given to replacement of the extension with one of greater length during other elective surgery procedures, such as during the regular change out of neurostimulators that must occur because of battery depletion.

- Patient brain growth and lead migration – Medtronic recommends the use of Activa Therapy for individuals with dystonia in whom brain growth is approximately 90% complete. In cases where growth of the brain and/or skull is not complete at time of

implant, the distance from the lead anchor point (burr hole) to the target site increases with time and growth of the individual. As a result, lead migration relative to the target site may occur. If significant patient growth and potential resultant lead migration are anticipated, this should be considered at the time of initial lead placement. The need for frequent programming or the inability to control dystonic symptoms may indicate lead migration. Consider assessing system performance and potential modifications to the therapeutic settings (neurostimulator settings and/or electrode configurations). These factors should be considered in the establishment of long-term care and follow-up schedules for individuals who receive an Activa System at an early age.

- Children are often engaged in active play and sports activities that could damage components of the implanted system. While some degree of rough play may be unavoidable, children should be advised to avoid games, sports and other pastimes where a strain to the lead/connector assembly or a percussive injury to system components may be likely to occur (e.g., soccer, football/rugby).

Precaution:

- Dual System Implant - If two neurostimulators are implanted, they must be implanted at least 8 inches apart to minimize interference. In smaller patients consider placing one neurostimulator in the abdomen and one in the chest region. In this case, route both lead/extension assemblies and implant both neurostimulators on the same side of the body to minimize potential electromagnetic interference. A 95-cm extension is recommended to connect the lead to the abdominal neurostimulator. Verify final programmed parameters by reviewing both devices at the conclusion of any programming session.

V. Device Description

The Medtronic Activa® Dystonia Therapy uses an implantable neurostimulator to deliver electrical stimulation to the internal globus pallidus (GPi) or subthalamic nucleus (STN) of the brain. The device consists of a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. The Medtronic Activa® Dystonia Therapy consists of two "kits" comprised of the individual medical device components that are required by an implanting physician. The two kits are the Model 3307 and the Model 3309 Activa Dystonia Therapy kits. Their contents differ only by the model of DBS lead contained within each kit. The Activa® Dystonia Therapy kits include a Soletra Model 7426 Neurostimulator, a Model 7482 Extension, a Model 7452 Control Magnet, and either a Model 3387 (Model 3307 kit only) or Model 3389 (Model 3309 kit only) lead. Several associated products (listed below) are used in conjunction with the Activa® Dystonia Therapy kits but are not included in the kit. All contents of the model 3307 and 3309 Activa Dystonia Therapy kits and associated products have been approved by the FDA within prior Pre-Market Approval (PMA) submissions. A description of each of the system components follows.

Activa® Dystonia Therapy Kits

Model 7426 Soletra Neurostimulator:

The neurostimulator is implanted subcutaneously in the subclavicular or upper abdominal region. It is comprised of a battery and integrated circuits that are hermetically sealed within an oval-shaped titanium enclosure. The neurostimulator delivers electrical stimulation pulses with a variety of parameters, modes, and polarities. A connector assembly on the neurostimulator allows connection to the extension. The electrical pulses are carried from the neurostimulator to an implanted intracerebral lead by means of a lead extension. Four setscrews provide electrical contact between the lead/extension and the neurostimulator. The stimulation parameters can be non-invasively adjusted to optimize control of the symptoms of Dystonia and minimize side effects. The adjustments are made via radio-frequency communication using the Model 7432 Physician Programmer with the Model 8840 N'Vision Programmer. The neurostimulator is battery powered, and when the battery is depleted, it can be replaced surgically. The frequency of replacement is dependent upon the amount of time the neurostimulator is used each day and the stimulation parameters used. The neurostimulator case shields are manufactured of titanium with a Parylene coating. The connector assembly is manufactured of polyurethane with titanium setscrews. Material characterizations and toxicity testing have been previously performed on all materials in accordance with applicable standards.

Model 7482 Extension:

The extension is a set of wires within silicone tubing that connects the lead to the neurostimulator, providing an electrical path that allows stimulation to be delivered to the target site. The extension is subcutaneously passed from the scalp area, where it connects to the lead, through to the subclavicular area or upper abdominal region, where it connects to the neurostimulator.

Model 3387/Model 3389 DBS™ Leads :

The DBS leads consist of a polyurethane protective sheath with four 1.5 mm platinum/iridium electrodes near the tip of each lead that deliver stimulation to the target site. Lead models include Model 3387, in which the 4 electrodes are spaced 1.5 mm apart and Model 3389, in which the electrodes are spaced 0.5 mm apart. The leads are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring.

Model 7452 Control Magnet:

The control magnet allows the patient to turn stimulation on and off.

Activa® Dystonia Therapy Associated Products

Model 7432 Clinician Programmer:

The Model 7432 Physician Programmer consists of a printer, programmer, and programming head that communicates via telemetry to the neurostimulator. Clinicians use the programmer to adjust the neurostimulator stimulation parameters and to verify current settings.

Model 7460 MemoryMod Software Cartridge:

The Model 7460 MemoryMod Software Cartridge is a plug-in cartridge designed to control the specific functions of the Model 7432 Clinician Programmer. It contains the necessary software to program the Soletra Neurostimulator.

Model 8840 N'Vision Clinician Programmer:

The Model 8840 N'Vision Programmer is used with the Model 7432 Physician Programmer to program the neurostimulator.

Model 8870 Application Card:

The Model 8870 Application Card is a plug-in card designed to control the specific functions of the Model 8840 N'Vision Clinician Programmer. It contains the necessary software to program the Soletra Neurostimulator.

Model 3353/3354 Lead Frame Kits:

The lead frame kits (which are designed to fit Electa/Leksell and Radionics or Radionics-like stereotactic frames) are used to stabilize the lead in the insertion cannula during implantation.

Model 3625 Test Stimulator:

The test stimulator is used for perioperative testing. Parameters that can be adjusted include amplitude, pulse width, rate, and electrode selection. The test stimulator enables the physician to evaluate the efficacy of neurostimulation for the patient, particularly in relation to lead position, during intraoperative testing.

Model 7438 Therapy Controller:

The therapy controller is designed for use by a patient or caregiver. Using the therapy controller, the patient or caregiver can turn therapy on or off, check whether the therapy is on or off, and check the condition of the neurostimulator's battery.

Burr Hole Ring and Cap:

The burr hole ring is constructed of nylon and the cap is made of silicone. The ring has ridges that hold it in place within the burr hole in the skull. Troughs are machined into the ring, and when the leads are inserted, the burr hole cap secures the lead in one of the troughs.

VI. Alternative Practices or Procedures

According to Brin (1998), treatment of primary dystonia includes oral medications, injections of therapeutic agents directly into nerve or muscle tissue, and surgery. Medical therapy is largely determined by the specific diagnosis, based on the clinical categorization and etiology, and includes use of anticholinergics, muscle relaxants, antiepileptics, and dopamine replacement therapy. Alternative treatments include the injection of therapeutic agents leading to chemodenervation and neuromuscular blockade.

Surgical treatment, only recommended for patients who fail to improve with either medication or injections, may include lesioning. Physical therapy also plays a supplementary role for some patients. Supportive therapy (e.g., counseling, etc.) can help some individuals' psychosocial adjustment to the disorder.

VII. Marketing History

Deep brain stimulation (DBS) therapy for dystonia has not been commercialized to date. The Medtronic Activa® Tremor Control System has been commercially available in Europe, Canada and Australia since March 1995 and in the United States (PMA P960009) since August 1997. Medtronic Activa Parkinson's Control Therapy has been commercially available in Europe since April 1998 and in the United States (P960009/S7) since January 2002. Medtronic's Activa System has not been withdrawn from the market in any country for reasons related to its safety and/or effectiveness.

VIII. Potential Adverse Effects of the Device on Health

Reported Adverse Effects
Thirty-four manuscripts on published studies to date were reviewed. The studies described consist of non-randomized, non-blinded trials involving a total of 201 patients. Literature described the following adverse events:

- Hemiplegia/Hemiparesis
- Worsening of Motor Impairment
  - Dysphagia
- Sensory Impairment
- Speech/Language
- Subcutaneous Hemorrhage/Seroma
- Cerebral Spinal Fluid Abnormality
- General*
  - Infection
  - Erosion
  - Lead fractures
  - Hardware Breakage
  - IPG Failure
- Déjà vu corrected by surgically revised lead placement
- Irritating cough with stimulation ON

* *Includes adverse events related to the system components*

Potential Adverse Effects
Additionally, one may reasonably expect the risks associated with the use of the Activa system for the approved indications of Parkinson 's disease (PD) and Essential Tremor (ET) to be similar in treating dystonia. As described in the summary of safety and effectiveness data for a supplemental premarket approval application for bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic Activa ?Parkinson's Control Therapy indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication (P960009S007), a description of adverse events that may also be applicable for use with dystonia is provided from a prospective open label design study (Table 1).

Over the entire study duration, 12/160 patients (7.5%) had intracranial hemorrhage; 17/160 patients (10.6%) had device-related infection; 16 patients (10.0%) had paresis/asthenia; and 13/160 patients (8.1%) had hemiplegia/hemiparesis. The rate of stimulation-related adverse events was 51.9% (83/160 patients) and the rate of ongoing stimulation-related events was 22.5% (36/160 patients). The rate of serious stimulation-related adverse events was 9.4% (15/160) and the rate of ongoing serious stimulation related adverse events was 3.1% (5/160) patients. Ongoing serious stimulation-related adverse events included: worsening of motor impairment/PD symptoms (dyskinesia), sensory impairment (pain); and speech/language (dysarthria, hypophonia, and speech disorder). Other stimulation related adverse events included: worsening of motor impairment/PD symptoms (worse motor fluctuations, incoordination, abnormal gait, akinesia/bradykinesia, tremor, rigidity, myoclonus and dysphagia); sensory impairment (paresthesia, sensory disturbance, hypesthesia, hearing [tinnitus] and headache); speech/language (voice alteration); eye (visual disturbances [diplopia, abnormal vision and visual field defect] and eye disorders [twitching]); cognitive (thinking abnormal, confusion, alteration of mentation [dizziness]); general (respiratory [laryngismus], musculo-skeletal [abnormal posture], gastrointestinal [vomiting], urogenital [urinary incontinence], metabolic/nutritional [weight loss], skin and appendages [sweating] and systemic [accidental injury]; sleep [somnolence and insomnia]; neuropsychological (psychiatric disturbances [manic reaction and neurosis]); general paresis/asthenia; internal system events (shock/jolt, positioning difficulties); cardiovascular (cerebrovascular accident); hemiplegia/hemiparesis (asthenia) and depression.

The rate of device-related adverse events was 36.9% (59/160 patients) and the rate of ongoing device-related events was 10.0% (16/160 patients). The rate of serious device-related adverse events was 17.5% (28/160 patients) and the rate of ongoing serious device-related adverse events was 6.3% (10/160 patients). Ongoing, serious device-related adverse events included: internal DBS system events (intermittent continuity, electromagnetic interference, and lead breakage); infection, worsening of motor impairment/PD symptoms (worse motor fluctuations, and incoordination) due to loss of effect; and skin and appendages (erosion). Other device-related adverse events included: internal DBS system events (shock/jolt, dislodged, migration, normal battery failure, malfunction, current leak, wire breakage, kinked electrode, electrode problem, positioning difficulties, impedance low); external system events (difficult to program, printer problem); sensory impairment (pain, sensory disturbance, paresthesia and headache); speech/language (hypophonia); skin and appendages (skin disorder); subcutaneous hemorrhage/seroma (seroma); paresis/asthenia; metabolic/nutritional (edema); and cerebral spinal fluid abnormality (pneumocephalus).

One patient experienced manic symptoms (manic reaction) and attention and cognitive deficits (thinking abnormal) concurrent with exposure to an electronic article surveillance (electromagnetic interference) device.

Table 1. Summary of Adverse Events Reported in the Parkinson's Disease Clinical Trial

Adverse Event All Patients (n=160)				
Major Category	**# of Events (known serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Intracranial Hemorrhage*	13 (8)	13	12 (7.5)	3.4, 11.6

Adverse Event All Patients (n=160)				
Major Category	**# of Events (known serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Device-Related Infection*	32 (23)	31	17 (10.6)	5.9, 15.4
Infection with Explant*	15 (15)	15	9 (5.6)	2.1, 9.2
Infection without Explant*	17 (8)	16	12 (7.5)	3.4, 11.6
Paresis/Asthenia*	16 (1)	6	16 (10)	5.4, 14.7
Hemiplegia/Hemiparesis*	15 (8)	10	13 (8.1)	3.9, 12.4
Worsening of Motor Impairment/ PD Symptom*	357 (48)	130	110 (68.8)	61.6, 75.9
Dyskinesia*	131 (22)	64	60 (37.5)	30.0, 45.0
Worse Motor Fluctuations*	85 (15)	23	56 (35)	27.6, 42.4
Abnormal gait*	38 (4)	10	30 (18.8)	12.7, 24.8
Incoordination*	33 (3)	14	29 (18.1)	12.2, 24.1
Tremor*	22 (0)	4	18 (11.3)	6.4, 16.2
Akinesia/Bradykinesia*	20 (0)	9	19 (11.9)	6.9, 16.9
Dysphagia*	13 (3)	2	12 (7.5)	3.4, 11.6
Rigidity*	13 (1)	3	12 (7.5)	3.4, 11.6
Myoclonus	1 (0)	1	1 (0.6)	0, 1.9
Therapeutic Response, decreased	1 (0)	0	1 (0.6)	0, 1.9
Sensory Impairment*	148 (14)	59	79 (49.4)	41.6, 57.1
Pain*	71 (5)	15	50 (31.3)	24.1, 38.4
Paresthesia*	37 (1)	23	29 (18.1)	12.2, 24.1
Sensory Disturbance*	18 (2)	11	16 (10)	5.4, 14.7
Headache*	16 (4)	8	14 (8.8)	4.4, 13.1
Neuralgia	3 (2)	0	3 (1.9)	0, 4.0
Hearing*	2 (0)	1	2 (1.3)	0, 3.0
Neuropathy	1 (0)	1	1 (0.6)	0, 1.9
Cognitive*	142 (21)	61	72 (45)	37.3, 52.7
Confusion*	56 (5)	27	44 (27.5)	20.6, 34.4
Thinking abnormal*	39 (3)	16	33 (20.6)	14.4, 26.9
Hallucinations	15 (2)	1	11 (6.9)	3.0, 10.8
Alteration of Mentation*	16 (5)	9	14 (8.8)	4.4, 13.1
Amnesia*	9 (2)	6	8 (5.0)	1.6, 8.4
Delusions*	5 (4)	0	4 (2.5)	0, 4.9
Dementia	2 (0)	2	2 (1.3)	0, 3.0
DBS System*	93 (33)	80	57 (35.6)	28.2, 43.1
Internal*	86 (33)	74	55 (34.4)	27.0, 41.7
External*	7 (0)	6	6 (3.8)	0.8, 6.7
Speech/Language*	77 (15)	48	59 (36.9)	29.4, 44.4
Dysarthria*	47 (6)	32	42 (26.3)	19.4, 33.1
Speech/Language*	30 (9)	16	23 (14.4)	8.9, 19.8
Neuropsychological*	55 (18)	6	31 (19.4)	13.3, 26.0
Psychiatric Disturbances*	25 (8)	4	14 (8.8)	4.4, 13.1
Personality Disorder	12 (4)	1	9 (5.6)	2.1, 9.2
Hostility	6 (2)	0	5 (3.1)	0.4, 5.8
Manic Reaction*	5 (2)	2	3 (1.9)	0, 4.0

Adverse Event All Patients (n=160)				
Major Category	**# of Events (known serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Neurosis*	1 (0)	1	1 (0.6)	0, 1.9
Paranoid Reaction	1 (0)	0	1 (0.6)	0, 1.9
Anxiety*	25 (7)	2	20 (12.5)	7.4, 17.6
Apathy	4 (2)	0	4 (2.5)	0, 4.9
Suicide Attempt	1 (1)	0	1 (0.6)	0, 1.9
Depression*	41 (10)	4	35 (21.9)	15.5, 28.3
Sleep*	45 (1)	8	37 (23.1)	16.6, 29.7
Eye*	48 (6)	25	39 (24.4)	17.7, 31.0
Visual Disturbance*	33 (6)	20	30 (18.8)	12.7, 24.8
Eye Disorder*	10 (0)	5	9 (5.6)	2.1, 9.2
Eye Infection	5 (0)	0	4 (2.5)	0, 4.9
Subcutaneous Hemorrhage/Seroma*	15 (6)	10	14 (8.8)	4.4, 13.1
Convulsions	7 (6)	5	7 (4.4)	1.2, 7.5
Death	3 (3)	0	3 (1.9)	0, 4.0
Cerebral Spinal Fluid Abnormality	5 (1)	5	5 (3.1)	0.4, 5.8
General*	312 (52)	40	110 (68.8)	61.6, 75.9
Systemic*	75 (14)	7	49 (30.6)	23.5, 37.8
Gastrointestinal*	55 (5)	9	41 (25.6)	18.9, 32.4
Urogenital*	53 (7)	3	43 (26.9)	20.0, 33.7
Respiratory	43 (10)	8	30 (18.8)	12.7, 24.8
Metabolic/Nutritional*	36 (4)	6	29 (18.1)	12.2, 24.1
Musculo-Skeletal*	21 (7)	2	19 (11.9)	6.9, 16.9
Skin and Appendages*	25 (5)	5	22 (13.8)	8.4, 19.1
Ecchymosis	1 (0)	0	1 (0.6)	0, 1.9
Erosion*	3 (3)	2	3 (1.9)	0, 4.0
Infection, fungal	2 (0)	0	2 (1.3)	0, 3.0
Lymphedema	1 (0)	0	1 (0.6)	0, 1.9
Petechia	1 (0)	0	1 (0.6)	0, 1.9
Psoriasis	1 (1)	0	1 (0.6)	0, 1.9
Rash	7 (0)	0	7 (4.4)	1.2, 7.5
Skin Disorder	6 (1)	2	6 (3.8)	0.8, 6.7
Sweating*	3 (0)	1	3 (1.9)	0, 4.0
Ear	4 (0)	0	4 (2.5)	0, 4.9
Cardiovascular*	64 (14)	24	32 (20)	13.8, 26.2

* *Includes adverse events related to the system components.*

** *Note: Exact 95% confidence intervals were used when the # (%) of patients was 0 (0%) because the normal approximation to the binomial does not provide a confidence interval. In every other case, the normal approximation to the binomial was used to calculate confidence intervals.*

IX. Summary of Preclinical Studies

All components of the Medtronic Activa ® Dystonia Therapy have been commercially approved for the Medtronic Activa ® Tremor Control System (PMA P960009, PMA P960009/S3, PMA P960009/S9, and PMA P960009/S10) and Medtronic Activa ® Parkinson's Control Therapy (P960009/S7). Therefore, the preclinical testing of these components provided in Medtronic Activa® Tremor Control System PMAs and the Medtronic Activa® Parkinson's Control Therapy PMA are also applicable to the Medtronic Activa ® Dystonia Therapy. No additional bench testing was required to qualify the devices for the treatment of dystonia.

X. Summary of Clinical Information

The Medtronic Activa® Dystonia Therapy uses an implantable neurostimulator to deliver electrical stimulation to the internal globus pallidus (GPi), or subthalamic nucleus (STN). Neurologists and neurosurgeons have used electrical stimulation for more than 35 years as a way to locate and distinguish specific sites within the brain. Literature available has shown its use in patients with dystonia, and consists of retrospective, single institution, unblinded case series that employed a variety of classification and rating scales to select patients and evaluate outcomes.

Patient Data Available

There were 201 patients represented in 34 manuscripts discussing specific case studies and outcomes. Patient gender for known cases included 83 females (83/201, 41%), 57 males (57/201, 28%), and 61 of unknown gender (61/201. 30%). In select case studies where age was reported at the time of first surgery, the mean age was 27.7 years (range: 5 to 78 years, N=91). Patient age classification at the time of first surgery included 21 children, 18 adolescents, 53 adults, and 109 of unknown age as shown in Table 2. Eighty-one percent (81%) of the pediatric patient population studied (N=21) was above age 7.

Table 2. Age Classification at Surgery in Literature (n=201)

Age Classification	N	Average Age (yrs.)
Pediatric (0-12 yrs.)	21	8.6
Adolescent (13-17 yrs.)	18	14.8
Adult (>18 yrs.)	53	39.9
Unknown	109	-

The majority type of dystonia experienced in these patients was generalized dystonia (65.2%) as shown in Table 3. There were 34 patients where the type of dystonia was unspecified.

Table 3. Type of Dystonia in Literature (n=201)

Type of Dystonia	N	% (n=201)
Generalized	131	65.2
Cervical	17	8.5
Hemidystonia	5	2.5
Multifocal	3	1.5
Segmental	8	4
Cervical (and truncal)	1	0.5

Focal	1	0.5
Dystonic Tremor	1	0.5
Unspecified	34	16.9

The follow-up experience in this literature ranged from 0.7 months to 132 months (Average: 12.1 months). Follow-up experience data was available on 191 of 201 patients. More than 50% of dystonic patients treated with deep brain stimulation participated in greater than 3 months of follow-up. The stimulation target was primarily the globus pallidus internus (bilateral GPi 71.2%, unilateral GPi 6.8%) as shown in Table 4.

Table 4. Stimulation Target in Literature (n=201)

Stimulation Target	**N**	**Percent (n=205)***
GPi, bilateral	146	71.2
GPi, unilateral	14	6.8
GPi, unspecified	8	3.9
Pallidal, bilateral	1	0.5
Pallidal, unspecified	5	2.4
STN, bilateral	15	7.3
VLp, bilateral posterior	7	3.4
VLp, unilateral posterior	6	2.9
Vim, unilateral	1	0.5
Internal capsule, thalamic interphases, bilateral	1	0.5
VPL thalamic nucleus, unilateral	1	0.5

* *There were 201 patients represented in the 34 manuscripts discussing specific case studies and outcomes. Four patients experienced multiple surgeries.*

Patient Outcome

Assessment of probable benefit from 3 publications describing more than 10 patients shows the following: Coubes et al.(2002a) reported 19 patients with generalized dystonia positive for the DYT1 mutation, with a clinical score improvement of 71% and functional score improvement of 63% following one year of therapy; improvement defined as the percent decrease between pre- and post-implant motor assessment scores (Burke-Fahn-Marsden Dystonia Rating Scale (BFM)). Vidaihet et al. (2002) reported 14 primary generalized dystonia patients (with at least 6 months follow up) treated with bilateral stimulation. Clinical scores were 56 $\pm$ 21 pre-operatively and 26 $\pm$ 16 postoperatively (BFM). Broggi et al. (2002) reported 10 primary dystonia patients. Eight of the 10 patients observed clinical improvement evaluated by BFM, ranging between 27 and 88% (up to 6 months follow up); improvement defined as the percent decrease between pre- and post-implant motor assessment scores.

Deep Brain Stimulation Therapy in Children & Adolescents

Eight manuscripts discuss specific outcomes in pediatric populations. In the largest series, Coubes et al. (2002a,b) treated dystonic children ($\leq$12 years, N=20) and adolescents (13 to 17 years, N=14) with deep brain stimulation therapy. Clinical scores (BFM) in patients with generalized dystonia positive for the DYT1 mutation were 61 $\pm$

23 pre-operatively and 21 ± 21 postoperatively (at 3 months), 11 ± 11 postoperatively (at 6 months), and 14 ± 17 postoperatively (at 12 months).

XI. Risk Probable Benefit Analysis

Limited treatment strategies exist for chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis). The three main approaches to the treatment of primary dystonia include systemic pharmacological agents (oral medications), local pharmacological agents (injected directly into affected muscles or their nerve supply), and destructive surgical or neurosurgical intervention. When local injection therapy is impractical or unsafe, and when systemic medications are not effective or produce unacceptable side effects, surgery may be considered. Surgical treatments of dystonia, including ablative therapies such as thalamotomies and pallidotomies, are irreversible, destructive procedures that can be associated with disabling complications. The patient group characterized in the Humanitarian Use Device application may also be candidates for deep brain stimulation therapy. Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and in some cases, progress to a life-threatening stage or constitute a major fixed handicap. When the age of dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychosocial development (due to ostracization and/or prevention of normal peer relationships), but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses which may cause permanent disfigurement.

Risks associated with DBS therapy for dystonia appear to be similar to the risks associated with the performance of stereotactic surgery and the implantation of DBS systems for currently approved indications (Parkinson's Disease and Essential Tremor), except for when used in either child or adolescent patient groups. These additional risks include the use of general anesthetic instead of local anesthesia during implantation, potential lead strains or fractures related to elongation of the trunk of the patient (due to normal growth) while the length of implanted conductor (from the neurostimulator to the burr hole) remains fixed, the risk of lead migration due to patient head growth resulting in ineffective stimulation and the added risk of children being engaged in active play and sports activities that could damage components of the implanted system. The risks of lead strain, fracture and migration can be minimized by evaluating the patient's implanted lead/extension assembly for sufficient strain relief at regular post-implant follow-up sessions and by considering the replacement of the extension with one of greater length during other elective surgery procedures, such as during the regular change out of neurostimulators that must occur because of battery depletion. In cases where lead tip displacement may occur due to cranial growth the lead tip migration may be accommodated through reprogramming due to the number and spacing of the electrode contacts.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XII. Panel Recommendation

This HDE was not reviewed by an FDA advisory panel. The panel has previously reviewed the device that is the subject of this HDE for the treatment of Parkinson's disease. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIII. CDRH Decision

CDRH has determined that, based on the data submitted in the HDE, that the Medtronic Activa® Dystonia Therapy will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on April 15, 2003.

XIV. Approval Specifications

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

XV. References

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