Medtronic's Activa® Neurostimulator for Dystonia Treatment

Humanitarian Device Exemption (HDE) H020007

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Device Description

Source: Adapted from Medgadget.com

Dystonia 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 older.

Annual Distribution Number (ADN)

- The humanitarian Device Exemption (HDE) was approved with an ADN = 4,000
- Number of dystonia devices sold in the US in 2015: 24
- Number of devices implanted in the US in 2015: 887 implants (159 in pediatric patients)
- Number of active implants in the US during CY 2015: 3365 active implants (601 in pediatric patients)

Medical Device Reports (MDRs)

Limitations of MDRs

- Under-reporting
- Data quality issues
- Biased information
- Inability to determine rate
- Cannot definitively determine causality/relationship to device

Methods

FDA Medical Device Adverse Event Database

MDR Search Inclusion Criterion:

- *Date Entered*: September 28, 2014 – September 27, 2015
- Any of the following criterion:
  - *Brand Name*: Activa
  - *Product Codes*: MRU (dystonia), MHY (Parkinsonian tremor)
  - *Premarket Submission Number*: H020007

Search Results: 333 pertinent MDRs

Overview of MDRs Entered September 28, 2014 – September 27, 2015

Event Type	Pediatric	Adult	Unknown	Total
Malfunction	22	101	22	145
Injury	34	122	29	185
Death	0	0	3*	3
Total	56	223	54	333

* The three MDRs reporting patient death were associated with two unique events

Overview of MDRs for the 2014, 2015 and 2016 PAC Reporting Periods

	PAC 2014			PAC 2015			PAC 2016		
Event Type	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**
Malfunction	14	46	11	19	91	26	22	101	22
Injury	35	101	65	22	84	38	34	122	29
Death	0	2	0	1	1	0	0	0	3
Total	49	149	76	42	176	64	56	223	54

PAC reporting period date ranges:

- 2014 PAC: date report entered prior to 9/27/13
- 2015 PAC: date report entered 9/28/13-9/27/14
- 2016 PAC: date report entered 9/28/14-9/27/15

Overview of MDRs Entered September 28, 2014 – September 27, 2015

Reporting Country	Pediatric	Adult	Unknown	Total
US*	48	198	17	263
OUS**	6	25	36	67
Unknown	2	0	1	3

Patient Gender	Pediatric	Adult	Unknown	Total
Female	21	130	11	162
Male	35	93	17	145
Unknown	0	0	26	26

*United States (US), **Outside the United States (OUS)

Reported Patient Deaths: Patient Ages Unknown

- The patient died secondary to comorbid conditions (Batten's disease, Dystonia and seizure disorder) and post-operative complications (fever, respiratory distress, hypoxia and infection).

- The patient experienced post-surgical hemorrhage at the site of the lead tip. The patient went into a coma and required life support as a result of the "unrecoverable brain damage". The patient was subsequently taken off of life support and died.

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Adverse Event	Number of MDRs *
Device explanted	32
Device replaced	24
Return or worsening of symptoms	24
Infection	10
Battery/charging issue	9
Growth related issues	6
Electromagnetic Interference (EMI)	6
Lead break/fracture	5
Stroke	3
Cognitive Issues	3

* A single MDR may be associated with more than one event.

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Device Explanted and Replaced (N=24)

- Impedance issues (age range 11-18 years)
- Lead fracture (age range 8-17 years)
- Infection (age range 2-16 years)
- Encapsulation of device into bone/connective tissue (age 17 years)
- Normal battery depletion (age 21 years)
- Neurological deficit (age 16 years)
- Behavioral changes (age 16 years)
- Patient growth (age 17 years)
- Battery failure (age 15 years)

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Device Explanted without replacement (N=8)

- Infection (age range 12-21 years)
- “Mild Stroke” (age 15 years)

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Worsening or Return of Dystonia Symptoms (N=24)

- Battery/charging issues (ages range 3-21 years)
- Impedance issues of unknown cause (ages range 15-18 years)
- Unknown causes (age range 10-18 years)
- Lead breaks (age range 15-17 years)
- Device reset due to potential EMI (age 16 years)
- Impedance issues potentially due to patient growth (age 17 years)
- Lead enclosed in bone or connective tissue (age 17 years)
- Intermittent device shut off (age 18 years)

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Infection (N=10)

- The organisms associated with the patient infections included:
  - Staphylococcus aureus (age range 16-21 years)
  - "fungus" (age 21 years)
  - Group A Streptococci (age 12 years)

- The infections were treated with antibiotics (oral and intravenous), debridement and device explant.
- All of the infections resulted in full or partial device explant

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Battery/charging issues (N=9)

- Premature battery depletion (age range 13-21 years)
- Issues with recharging remote (age range 17-21 years)
- Difficulty recharging due to coupling problems (age range 17-18 years)
- “Flipped implantable neurostimulator” (age 15 years)
- Intermittent continuity (age 21 years)

These battery/charging related issues resulted in a return of patient symptoms (N=5), pocket revision (N=1), loss of therapy (N=1), device replaced (N=1) and no known impact on patient (N=1).

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Potential Patient Growth Related Issues (N=6)

- "Mechanical issues" (age 17 years)
- Multiple system revisions due to patient growth (age 17 years)
- Possible "tension on extension" due to growth (age 16 years)

Electromagnetic Interference (N=6)

- Unknown sources (age range 10-21 years)
- Exposure to a "standing x-ray" (age 16 years)

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Lead break/fracture (N=5)

- Intraoperative lead fracture (age 8 years)
- Electrode fracture of unknown cause (age 15 years)
- Conductor on the proximal end of the lead was broken due to possible patient growth (age 17 years)

Clinically Significant Pediatric MDRs Entered September 28, 2014 – September 27, 2015

Stroke (N=3)

- "Mild stroke after implant". No patient outcome was reported (age 15 years)
- Left brain stroke at the time of implant (age 10 years)

Cognitive issues (N=3)

- Altered mental status, potentially due to device related infection. (age 21 years)
- Mood changes due to GPi stimulation. (age 16 years)

PAC 2016: Summary of MDRs

There were 56 MDRs reporting 39 unique events associated with use of the Activa neurostimulator in pediatric patients.

A return or worsening of dystonia symptoms (loss of therapeutic effect) was the most frequently reported pediatric patient problem.

The most frequently reported device problem was impedance issues.

No new device or patient problems were identified.

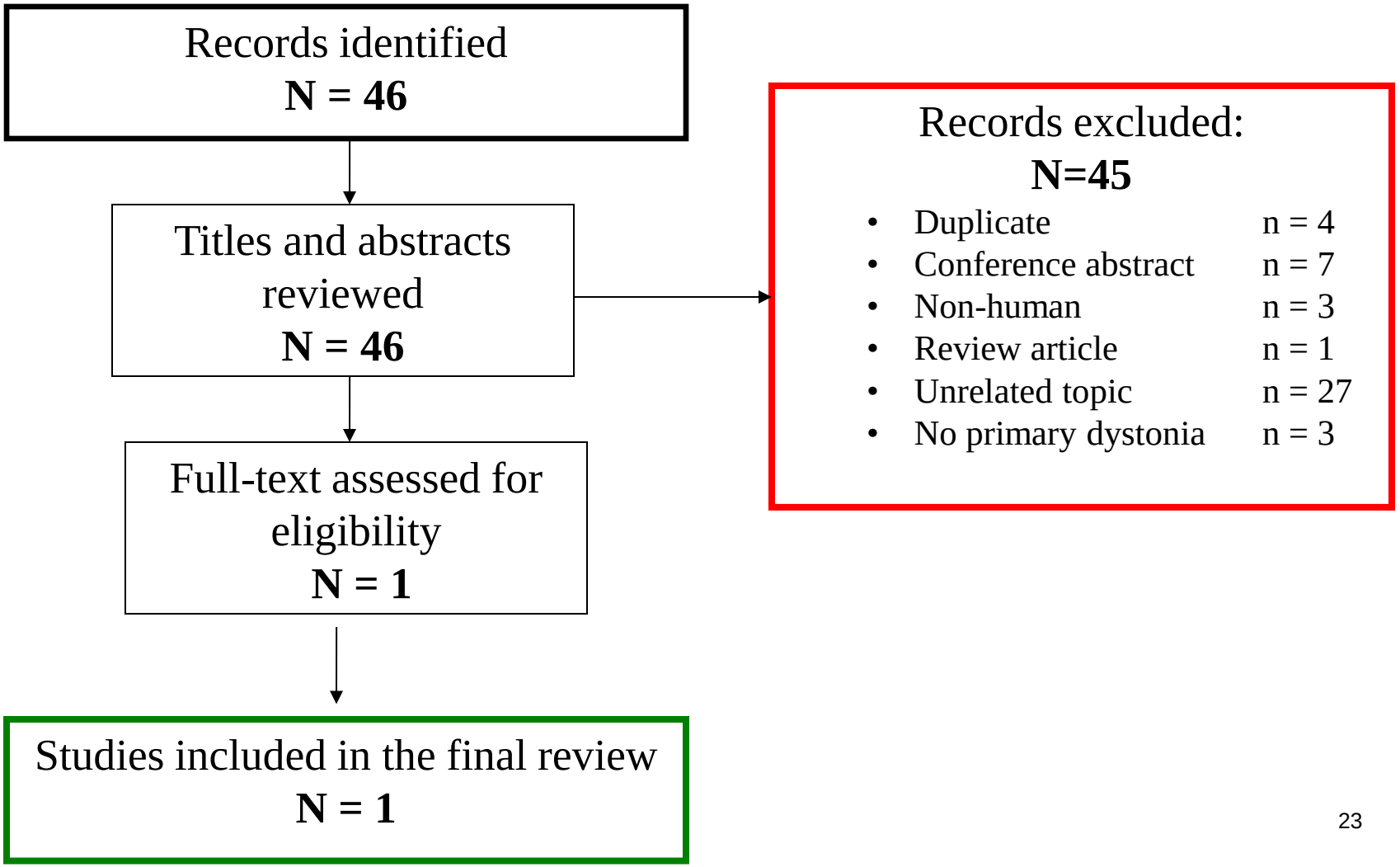
PAC 2016: Literature Review

A systematic review to evaluate the adverse events following the use of the device for primary dystonia in pediatric patients.

2016 PAC: Literature Review Methods

Search Terms	(medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR activa OR (dbs AND pediatric AND Dystonia).
Database	PubMed and EMBASE
Date of Search	November 5th, 2015.
Time Limit	November 11, 2014 to November 5, 2015; Papers published since the last search

2016 PAC: Literature Review Results



2016 PAC: Literature Review Results

Article	Rizzi et al
N	11
Study Type	Observational
Age (mean; range)	13.5 y (8 – 21 y)
Follow up duration	7.6 y (1-15 y)
Adverse events (AE)	Mortality from causes other than DBS: 9.1% AEs after DBS* and before 1st replacement: 0 Total complications: 22.7%; 18% of complications ascribable to IPG** replacement. Individual complications not listed.

*Deep Brain Stimulator (DBS), **Internal Pulse Generator (IPG)

2016 PAC: Literature Review Conclusions

- No novel safety event detected in literature published since the last PAC.
  - Rizzi et al: Adverse events not listed.

- These findings are consistent with the conclusions from the systematic review conducted for the previous PAC meetings.

FDA Recommendations and FDA Question to the PAC

- FDA recommends continued surveillance and will report the following to the PAC in 2017:
- Annual distribution number
- PAS follow-up results
- Literature review
- MDR review

Question: Does the Committee agree with the FDA's conclusions and recommendations?