Medtronic’s
Activa® Neurostimulator for Dystonia
Treatment
Humanitarian Device Exemption (HDE) H020007

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Food and Drug Administration

Pediatric Advisory Committee (PAC) Meeting
March 24, 2015
Presentation Outline

Device Description:
Amber Ballard, Ph.D.

Postmarket Medical Device Reporting:
Amber Ballard, Ph.D.

Systematic Literature Review:
Nathan S. Ivey, Ph.D.
Device Description

- Lead
- Targeted Area of the Brain
- Electrode
- Extension
- Neurostimulator
Indication 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.
Annual Distribution Number (ADN)

• The humanitarian use designation (HUD) was approved with an ADN = 4,000

• Number of dystonia devices sold in the US in 2014: 13

• Number of devices implanted in the US in 2014: 776 implants (148 in pediatric patients)

• Number of active implants in the US during CY 2014: 2,350 active implants (484 in pediatric patients)
Medical Device Reports (MDRs)

Limitations of MDRs

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

MAUDE (Manufacturer And User Facility Device Experience) Database

MDR Search Criteria

- Brand Name: Activa
- Product Codes: MRU (dystonia), MHY (Parkinsonian tremor)
- Premarket Submission Number: H020007
- Date received: September 28, 2013 – September 27, 2014

Search Results: 176 unique MDRs
Overview of MDRs Received
September 28, 2013 – September 27, 2014

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Pediatric</th>
<th>Adult</th>
<th>Unknown</th>
<th>Total</th>
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<tr>
<td>Malfunction</td>
<td>10</td>
<td>58</td>
<td>22</td>
<td>90</td>
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<tr>
<td>Injury</td>
<td>12</td>
<td>57</td>
<td>16</td>
<td>85</td>
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<tr>
<td>Death</td>
<td>1</td>
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<tr>
<td>Total</td>
<td>23</td>
<td>115</td>
<td>38</td>
<td>176</td>
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# Overview of MDRs Received

September 28, 2013 – September 27, 2014

<table>
<thead>
<tr>
<th>Reporting Country</th>
<th>Pediatric</th>
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<tr>
<td>US</td>
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<td>10</td>
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<td>OUS</td>
<td>1</td>
<td>9</td>
<td>26</td>
<td>36</td>
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<table>
<thead>
<tr>
<th>Patient Gender</th>
<th>Pediatric</th>
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<tr>
<td>Female</td>
<td>15</td>
<td>57</td>
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<td>Male</td>
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<td>56</td>
<td>7</td>
<td>71</td>
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<tr>
<td>Unknown</td>
<td>0</td>
<td>2</td>
<td>24</td>
<td>26</td>
</tr>
</tbody>
</table>
Clinically Significant Pediatric MDRs Received September 28, 2013 – September 27, 2014

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total MDRs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device replaced</td>
<td>9</td>
</tr>
<tr>
<td>Return or worsening of symptoms</td>
<td>9</td>
</tr>
<tr>
<td>Lead break/fracture</td>
<td>5</td>
</tr>
<tr>
<td>Battery/charging issue</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
</tr>
<tr>
<td>Device explanted</td>
<td>1</td>
</tr>
</tbody>
</table>

* A single MDR may be associated with more than one event.
Clinically Significant Pediatric MDRs Received September 28, 2013 – September 27, 2014

Device Replaced (n = 9)

- Battery/charging issues (ages 14, 17, 17, 21)
- Impedance issue (age 21)
- Lead break/fracture (age 18)
- Electric shocks/pain (age 10)
- Open circuit (age 17)
- Adaptor too large (age 11)
Clinically Significant Pediatric MDRs Received September 28, 2013 – September 27, 2014

Return or Worsening of Symptoms (n = 9)

– Intermittent shut off (ages 13, 14*, 15)
– Lead break/fracture (ages 12, 12*)
– Unknown reason for loss of stimulation (ages 16, 19)
– Open circuit (age 17*)
– Overstimulation (age 19)

*Neurological deficit or dysfunction
Clinically Significant Pediatric MDRs Received
September 28, 2013 – September 27, 2014

Lead break/fracture (n = 5)
– Short circuit and loss of stimulation (age 14)
– Device replaced (age 18)
– Return or worsening of symptoms (ages 12, 12)
– Unknown outcome (age 13)

Battery/charging issue (n = 4)
– Premature battery depletion (ages 17, 17)
– Normal battery depletion (age 21)
– Extended recharge time (age 14)
Clinically Significant Pediatric MDRs Received September 28, 2013 – September 27, 2014

Infection (n = 2)
- Death unrelated to device itself (age 15)
- Device explanted (age 9)

Device Explanted (n = 1)
- Infection (age 9)
Summary of MDRs

Pediatric Death Report (n = 1)
  – Unrelated to the device itself

Patient Problems
  – Top patient problem: Return or Worsening of Symptoms
    • Occurred in 39.13% of all pediatric patient MDRs (n = 23)
    • Typically resolvable issues (2 device replacements; 1 device reprogrammed)
    • Addressed in labeling
  – No new patient problems occurring
  – No cerebrovascular accidents (CVAs)
Summary of MDRs

Device Problems

- **Top device problem: Impedance Issues**
  - Occurred in 47.83% of all pediatric patient MDRs (n = 23)
  - Generally associated with battery/charging issues and lead breaks
  - Surgical intervention often required (6 device replacements)
  - Addressed in labeling
- **No new device problems occurring**
- **No confirmed device revisions due to patient growth**
2015 PAC Panel Meeting

Medtronic’s
Activa® Neurostimulator for Dystonia Treatment
H020007

Nathan S. Ivey, PhD
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Center for Devices & Radiological Health
Food and Drug Administration

March 24, 2015
Purpose

This systematic literature review evaluates the adverse events associated with the use of the device for dystonia in pediatric patients in the assessed literature published since the 2014 PAC.
Article Retrieval and Selection

Records identified in Pubmed and Embase (n=172)

Number after duplicates removed (n=172)

Titles and abstracts reviewed (n=172)

Full-text articles reviewed (n=27)

Articles included in qualitative synthesis (n=13)

Articles excluded (n=145)

Articles excluded (n=14)
Pediatrics with 1º Dystonia Diagnosis

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Age Range</th>
<th>Sample Size</th>
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</thead>
<tbody>
<tr>
<td>Bhanpuri, 2014</td>
<td>Cohort</td>
<td>9-21</td>
<td>11</td>
</tr>
<tr>
<td>Lumsden, 2013</td>
<td>Cohort</td>
<td>3-20</td>
<td>42</td>
</tr>
<tr>
<td>Petrossian, 2013*</td>
<td>Cohort</td>
<td>9-25</td>
<td>14</td>
</tr>
<tr>
<td>Starr, 2014</td>
<td>Cohort</td>
<td>8-14</td>
<td>6</td>
</tr>
</tbody>
</table>

*Study had one adult, age 25.

- 4 articles
  - 4 observational cohort studies
- Sample sizes 6-42
- Age range 3-25
- Patient diagnosis: Primary dystonia
Pediatric – Only Articles

• **Bhanpuri** and **Lumsden**: Reported no AE and no device malfunctions through 4.7 yrs mean follow-up (range: 0.5-8) and 1 yr post-op, respectively.

• **Petrossian**: Mean follow-up: 50.8 months (range: 16-84). 7 hardware related AEs in 5 patients (4 lead fractures in 2 patients, 2 infections, and 1 lead migration.) A complex partial seizure in one patient occurred due to lead migration to bilateral temporal lobes 7 years postop.

• **Starr**: Through 1-yr post-op, the only device malfunction was an open circuit on 1 contact of a lead. 5 AEs noted were single episodes of transient slurred speech, transient dyskinesia, unexplained nausea and dizziness, right knee pain, and left shoulder pain.
Mixed Age Cohort with ‘Other Movement Disorder’ Studies

- 9 articles
  - 4 case reports
  - 4 cohort study
  - 1 retrospective study
- Sample sizes 1-368
- Age range 3-76
- Patient diagnosis: Secondary dystonia, cerebral palsy, post-traumatic tremor, cerebral palsy, Tourette syndrome
- Follow-up ranged from none to 10 years

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Age Range (mean)</th>
<th>Number of pediatrics/Sample Size</th>
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</thead>
<tbody>
<tr>
<td>Aydin, 2013</td>
<td>Case Report</td>
<td>5</td>
<td>1/1</td>
</tr>
<tr>
<td>Bjerknes, 2014</td>
<td>Retrospective</td>
<td>60 (3-84)</td>
<td>NR/368</td>
</tr>
<tr>
<td>Bob, 2013</td>
<td>Case Report</td>
<td>13</td>
<td>1/1</td>
</tr>
<tr>
<td>Cao, 2013</td>
<td>Cohort</td>
<td>31 (7-76)</td>
<td>NR/27</td>
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<tr>
<td>Carvalho, 2014</td>
<td>Case Report</td>
<td>18</td>
<td>1/1</td>
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<tr>
<td>Issar, 2013</td>
<td>Cohort</td>
<td>31 (20-53)</td>
<td>2/5</td>
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<td>Keen, 2014</td>
<td>Cohort</td>
<td>11 (8-17)</td>
<td>5/5</td>
</tr>
<tr>
<td>Sachdev, 2014</td>
<td>Cohort</td>
<td>29 (17-51)</td>
<td>5/17</td>
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<tr>
<td>Sobstyl, 2014</td>
<td>Case report</td>
<td>NR</td>
<td>NR/1</td>
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</table>
Mixed Age Cohort with ‘Other Movement Disorder’ Studies (n=9 studies)

- **Adverse events**: 7/9 studies reported.
  - Infection: 3/9 studies reported (36 instances)
  - Transient AEs reported in 4 studies (16 instances)
  - Kidney failure from battery depletion yielding status dystonicus in 1 study (1 instance)
  - Mistargeting leading to ineffective stimulation in 1 study (1 instance)

- **Device malfunction**: 4/9 studies reported.
  - EMI was reported in 1 study (1 instance)
  - Hardware malfunction was reported in 3 studies (8 instances)
Conclusions

• No new concerns regarding safety of the device were identified.

• More diligent post-op monitoring may mitigate observed AEs. (Sobstyl / Petrossian).

• Adherence to product labeling may mitigate AEs occurring at the end of the battery life or with technical malfunction.

• Strategies for increasing physician awareness of labeling should be considered.
FDA Recommendations and Question to the PAC

- FDA recommends continued surveillance and will report the following to the PAC in 2016:
  - Annual distribution number
  - PAS follow-up results
  - Literature review
  - MDR review

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