FDA Executive Summary

Prepared for the
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FDA's Pediatric Advisory Committee

H020007

Medtronic Activa Neurostimulator for Dystonia Treatment

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-market experience with the use of the Medtronic Activa® Dystonia Therapy in pediatric patients since approval in 2003. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-market safety data so the committee can advise the Food and Drug Administration (FDA) on whether they have any new safety concerns and whether they believe that the HDE remains appropriately approved for pediatric use.

The Medtronic Activa® Dystonia Therapy system 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.

II. ANNUAL DISTRIBUTION NUMBER (ADN) AND US DEVICE DISTRIBUTION DATA

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The number of devices implanted in the U.S. in 2016: 836 implants The number of devices implanted in pediatric patients (<22 years of age) in the U.S. in 2016: 139 implants. The number of active implants in pediatric patients in is 581 with a total of 3440 active implants in all populations.

III. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type.
- Detect actual or potential device problems used in a “real world” setting, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used

in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.

- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Medtronic Activa Neurostimulator for Dystonia Treatment

The Agency searched the MDR database to identify reports associated with the Medtronic Activa neurostimulator for dystonia treatment entered September 28, 2015 – September 27, 2016. The searches resulted in the identification of 324 unique MDR reports. For the purpose of this MDR analysis, these 324 MDRs will be referred to as the 2017 Pediatric Advisory Committee (PAC) data. One of the reports was submitted by a user facility and the remaining 323 MDRs were submitted by the manufacturer. Patient gender information was reported in 154 of the MDRs of which 101 were female and 53 were male patients. The event types by age category are presented in Table 1.

Table 1. Event types by age category for MDRs included in the 2014, 2015, 2016 and 2017 PAC data sets.

	PAC 2014			PAC 2015			PAC 2016			PAC 2017		
Event Type	Pediatric	Adult	Unknown	Pediatric	Adult	Unknown	Pediatric	Adult	Unknown	Pediatric	Adult	Unknown
Malfunction	14	46	11	19	91	26	22	101	22	27	107	35
Injury	35	101	65	22	84	38	34	122	29	31	90	33
Death	0	2	0	1	1	0	0	0	3	0	1	0
Total	49	149	76	42	176	64	56	223	54	58	198	68

The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2017 PAC data is presented by age category in Table 2. The majority of MDRs originated from within the US.

Table 2. Number of US and OUS MDRs by Age Category (2017 PAC Data Set)

Reporter Country	Pediatric	Adult	Unknown	Total
US	47	159	45	251
OUS	6	21	15	42
Unknown	5	18	8	31
Total	58	198	68	324

Pediatric MDR Review

Patient age was available in 256 of the MDRs, which included 58 pediatric reports and 198 adult reports. The patient age was unknown in 68 reports. Pediatric patient age ranged from 5 to 21 years of age. The average age of the pediatric patients was 14.4 years compared to 15.7 years in the 2016 PAC data set. The reason that patients were slightly younger in the 2017 PAC data set is unknown, but in the 2017 PAC data there was an increase in the number of MDRs associated with 12 year old patients (N=15) compared with the 2016 PAC data set (N=2). These 15 MDRs were associated with 10 unique events and did not

indentify any new concerns related to patient age. The reporting country was available in 53 of the 58 pediatric MDRs and included the United States (N=47), Japan (N=2), Italy (N=2) and the United Kingdom (N=2). Within the pediatric reports, 16 MDRs were associated with female patients, 17 MDRs were associated with male patients. There were 25 MDRs in which the patient gender was not reported.

Although the majority of the pediatric MDRs reported on-label use of the device (N=56 MDRs), it should be noted that off-label use of the device (in patients under the age of seven) was reported in a five year old patient and a six year old patient in the 2017 PAC data. A five year old patient experienced skin erosion at the neurostimulator pocket which required device explant. Additionally, a six year old patient experienced an infection that resulted in device explant. Both on label and off label MDRs were included in the analysis (N=58 MDRs).

Time to Event (TTE) for Pediatric MDRs

In an effort to separate reports for events that occurred zero to 30 days post implant from those that occurred greater than 30 days post implant, an analysis of the time to event (TTE) was conducted on the pediatric MDRs. The TTE was calculated based on implant date provided, date of event provided, and the event text for each report. The TTE could be calculated for 38 of the pediatric reports received. Reported problems and event types for pediatric MDRs by TTE are presented in Tables 3 and 4. There were five reports in which the event occurred between 0 and 30 days post implant procedure and 33 reports in which the event occurred more than 30 days post implant procedure. It should be noted that Tables 3 and 4 only reference the 38 MDRs for which a TTE could be calculated. This was a subset of the 58 MDRs which are the subject of later analyses.

Table 3. Reported problems and event types for pediatric MDRs by TTE ≤ 30 days (N=5) (2017 PAC Data Set)

Reported Problem	Injury	Malfunction
Intraoperative lead failure	3	2
Total	3	2

*Please note that intraoperative lead failure included lead break/fracture (N=1 injury, N=1 malfunction) as well as other intraoperative lead failures (N=2 injury, N=1 malfunction).

Table 4. Reported problems and event types for pediatric MDRs by TTE > 30 days (N=33 MDRs) (2017 PAC Data Set)

Reported Problem	Injury	Malfunction
Explanted due to infection	6	0
Normal battery depletion	2	3
Potential electromagnetic interference	0	5
Battery charging issue	0	3
Potential growth related issues	0	3
Explanted due to skin erosion	3	0
Lead break/fracture	3	0
Impedance issue of unknown cause	0	2
Return of symptoms due to unknown cause	1	0
Patient discomfort	0	1
Impedance issue due to head injury	0	1
Total	15	18

*Please note that "normal battery depletion" and "battery charging issues" are both related to battery/charging issues.

All pediatric reports were individually reviewed to identify events that were previously determined to be clinically significant or concerning by CDRH clinicians with input from previous PAC panel members, and to be consistent with the prior MDR analyses. The specific adverse events are presented in Table 5 and explained in detail in the appropriate subsections below. Please note that more than one contributing factor may have been associated with each of the events presented in Table 5 and described below in detail.

Table 5. Clinically concerning pediatric reports (N=58 MDRs) (2017 PAC Data Set)

Adverse Event	Count
Device explanted	24
Return or worsening of symptoms	15
Battery/charging issue	14
Device replaced	12
Infection	8
Potential electromagnetic interference	8
Growth related issues	5
Lead break/fracture	5
Stroke	0
Cognitive issues	0

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

- *Device Explant (N=24 MDRs, 16 unique events) and Device Replacement (N=12 MDRs, 7 unique events):* All 12 MDRs associated with the 7 unique events reporting device replacement also reported device explant. Further, device explant and replacement were associated with similar clinical issues. In the 12 MDRs that reported both device explant and replacement, the associated problems included battery/charging issues (N=3), lead fracture (N=3), impedance issues (N=2), infection (N=2), and potential patient growth related issues (N=2).

In the 12 MDRs associated with device explant without replacement, the associated problems included infection (N=6), battery/charging issues (N=2), skin erosion (N=2), decubitus ulcer (N=1) and lack of therapeutic benefit (N=1). Please refer to the sub-sections on infection and battery/charging issues for additional information on these MDRs.

- *Worsening or Return of Dystonia Symptoms (N=15 MDRs, 11 unique events):* MDRs reporting worsening or return of dystonia symptoms were associated with several different device problems. The reported problems that contributed to worsening or return of symptoms were battery/charging issues (N=5), impedance issues (N=3), device reset due to potential electromagnetic interference (EMI) (N=1), issues potentially due to patient growth (N=3), skin erosion (N=2) and intermittent device shut off (N=1). These issues resulted in device explant (N=8, five replaced) and unknown or unresolved patient outcome (N=7).

- *Battery/Charging issue (N= 14 MDRs, 12 unique events):* Battery/charging issues were associated with recharging issues (N=4), premature battery depletion (N=3), normal battery depletion (N=2), overstimulation (N=2), intermittent continuity (N=2) and unknown battery issue (N=1). These battery/charging related issues resulted in device replacement (N=3), no known impact on patient (N=3) and loss of therapy (N=1). Patient outcome was unknown in seven MDRs.

- *Infection (N=8 MDRs, 5 unique events):* Limited information was provided on the potential causes of the reported infections. The only organism identified within the MDRs reporting infection was *Staphylococcus aureus* (N=4). The remaining MDRs associated with infection (N=4) did not report a specific organism. The location of the infections was reported in five of the eight MDRs and included three pocket site/pulse generator infections and two lead site infections. The location of the infection was not reported in three MDRs. All MDRs associated with infections resulted in device explant.

- *Electromagnetic Interference (EMI) (N=8 MDRs, 6 unique events):* There were eight pediatric MDRs associated with potential EMI. Sources of EMI included exposure to a computer tablet on a wheel chair (N=1), "using software with a digital imaging system that puts out ultrasonic waves" as part of a "class" (N=2), security gates at a school library (N=1), a security gate at an unknown location (N=1), "working with magnets at school" (N=2) and unknown sources (N=1). Based on the limited information provided in the MDRs, the impact of EMI on the device is unclear, but may be associated with EMI inadvertently changing device settings or turning off the device.

- *Patient Growth Related Issues (N=5 MDRs, 3 unique events):* Potential growth-related issues were reported in five MDRs and were associated with "scar tissue wrapped around the extension" requiring device replacement (N=2) and patient discomfort (tingling, burning, shocking sensations, "wires pulling", N=3). The MDRs associated with patient discomfort were addressed by turning off the device and/or seeing a pain specialist. The ages of the patients associated with these reports ranged between 9 and 12 years old and occurred two to six years after implant.

- *Lead break/fracture (N=5 MDRs, 4 unique events):* There were five MDRs associated with lead break/fracture. Three of these MDRs resulted in device replacement and in two MDRs it is unknown if or how the issue was resolved. The reports of lead break included intraoperative lead fracture (N=3), fracture due to the patient's torticollis (N=1) and lead fracture with unknown cause (N=1). Please note that in addition to the five MDRs reporting lead break/fracture, there

were three interoperative lead failures (see Table 3) that were not lead breaks and these MDRs were not included as lead break/fracture.

MDR Conclusions

The 2017 PAC Data Set includes a total of 58 MDRs (entered September 28, 2015 – September 27, 2016), reporting 43 unique events, that were associated with use of the dystonia indication of the Activa neurostimulator in pediatric patients. Infection and a return or worsening of dystonia symptoms (loss of therapeutic effect) were the most frequently reported pediatric patient problems. The labeling does address the issue of symptom return/worsening and these events are known to occur with use of other neurostimulators. Other reported patient problems, including infection and patient growth related issues, are noted in either the device labeling or clinical summary.

The most frequently reported device problems were battery/charging issues and impedance issues. Very limited information on the battery/charging issues was provided within the MDRs. The device labeling states that issues with open circuits (high impedance) can occur without warning and impedance issues are also known to occur in other neurostimulators. Other device problems (such as charging issues, lead fractures or electromagnetic interference) that occurred within the MDRs are either noted in the device labeling or are known device issues with neurostimulator devices in general.

As opposed to the 2016 PAC data set, non MDRs associated with pediatric stroke or cognitive changes were reported within the 2017 PAC data set. No new patient or device problems were identified in the 2017 PAC data when it was compared to previous years.

IV. POSTMARKET DATA: LITERATURE REVIEW WITH FOCUS ON SAFETY DATA

Purpose

The intent of this systematic literature review is to provide an update of adverse events associated with the use of the Medtronic Activa neurostimulator since the previous literature review for the 2016 PAC meeting. Specifically, the systematic review was conducted to address the following question: What is the safety of Medtronic Activa neurostimulator devices in the pediatric population treated for dystonia?

Methods

The review team agreed on the following search string for conducting the search: (medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR (activa) OR (dbs) AND (pediatric) AND (Dystonia). PubMed and EMBASE databases were systematically searched on November 6, 2016. Papers published since the last search, i.e. during the period of November 5, 2015 until November 5, 2016 (both dates inclusive) were evaluated. Then, the following exclusion criteria were applied, either from reading of the abstracts or the full article:

1. Conference abstracts
2. Duplicates
3. No primary dystonia
4. Non-pediatric population or mixed (pediatric and adult) population where pediatric and adult subjects are not analyzed separately
5. No humans in the study (i.e. animal study)
6. Not written in English
7. Unavailable article
8. Unrelated topic
9. No Medtronic software used

The adverse events reported in the publications were described.

Results

The PubMed search yielded 8 articles (1-8) and the EMBASE search yielded 12 articles (9-20). When both PubMed and EMBASE searches were combined and duplicates were removed, a total of 15 unique articles were identified (1, 3-9, 11-15, 17, 18). Based on the pre-specified list of exclusion criteria, a total of 14 articles were excluded for various reasons, namely, unrelated topic (n=12) (1, 3, 4, 6-8, 11-14, 17, 18), duplicates (n=2) (6, 15), no primary dystonia (n=1) (13), non-pediatric population or mixed (pediatric and adult) population where pediatric and adult subjects are not analyzed separately (n=1) (9) and conference abstract (n=1) (9). Of the 12 articles excluded based on the criterion of 'unrelated topic', 2 were methodology papers (6, 18) and 1 was a review article (3). We examined the review article by Cif and Coubes and found it was not systematic in nature with no pertinent cross-references that can be added to this review update (3). Thus, 1 article by Krause et al. (5) was retained for the final review (See Flowchart).

A retrospective chart review involving a case series by Krause et al. (5) examined the long-term safety (up to 13 years) of pallidal deep brain stimulation (DBS) in 8 pediatric patients with generalized idiopathic or hereditary isolated dystonia (five males, mean age at surgery 12.5 ± 3.5 years). The main reason for surgical intervention or revision after successful implantation was replacement of the implantable pulse generator (IPG) after battery expiry, necessitating ten replacements in four patients. On average, the time interval between expiry and replacement of IPG batteries for these 4 patients was 34.1 ± 3.3 months. One patient needed revision of the IPG due to dislocation 11 years after the initial electrode implantation. Another patient underwent bilateral electrode revision 3 years after the initial pallidal DBS. Stimulation-induced dysarthria limited further increase of stimulation amplitude in two patients, and bradykinesia was induced by DBS in one severely affected patient with high stimulation amplitudes. Finally, one patient underwent several orthopedic surgeries due to severe contractures and musculoskeletal deformities resulting from longer disease duration before DBS surgery. None of the remaining patients experienced any further complication or serious adverse effect due to DBS.

Literature Review Conclusions

Premarket data suggested that DBS was a safe alternative for dystonia in the pediatric population refractory to standard of care therapies, and previously conducted literature reviews did not identify safety concerns not reported in premarket data. However, DBS requires implantation of a device into the brain, and therefore the device is not without risk. The systematic literature review conducted for the 2016 PAC meeting revealed that, in terms of safety, the most frequent adverse event was infection. Other adverse events included incorrect stimulation parameters leading to normal and expected transient side effects; partial seizures in a case of lead movement to temporal lobes; transient events like anxiety, dyskinesia, and depression; motor and sensory symptoms from the direct effect of stimulation; and ineffectiveness.

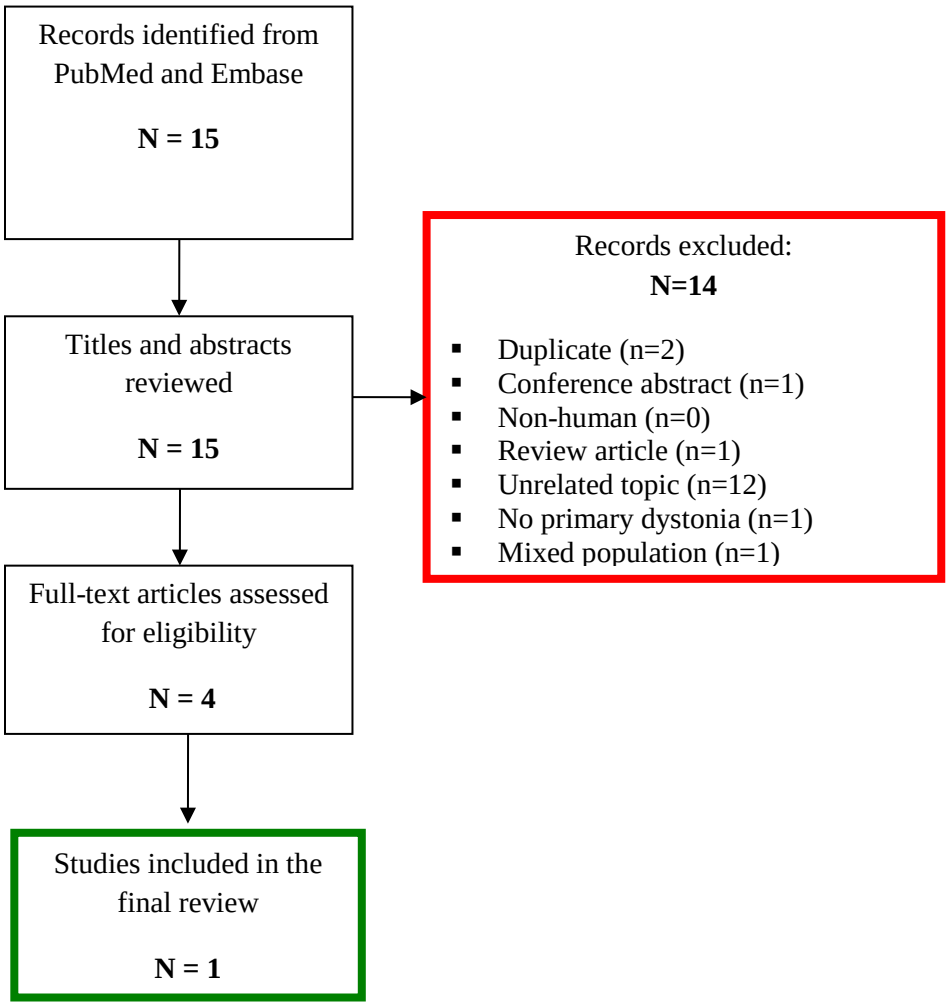
We provided a literature review update for the 2017 PAC meeting. Our PubMed and EMBASE literature search for the period of November 5, 2015 until November 5, 2016 yielded 15 unique articles, of which 14 articles (1, 3, 4, 6-9, 11-15, 17, 18) were excluded, based on pre-specified criteria and 1 case series by Krause et al. (5) was retained for the final review. This article identified IPG replacement after battery expiry as the main reason for surgical intervention after successful implantation, affecting 4/8 (50%) children. In addition, 2/8 (25%) children underwent revision surgery because of medical device (IPG or electrode) dislocation, 2/8 (25%) children experienced stimulation-induced dysarthria and 1/8 (12.5%) children experienced bradykinesia. (5)

The overall evidence suggests that infection and dislocation of medical device components are key adverse events related to use of the DBS among pediatric patients diagnosed with primary dystonia.

However, this evidence is based on a limited number of studies – 3 case-series (2 from 2016 PAC and 1 from 2017 PAC) – with sample sizes ranging between 6 and 11 patients.

Overall Summary

FDA's Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003. Based on the available data, and taking into account the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for pediatric use. FDA will continue routine surveillance including MDR and literature reviews. FDA will provide focused updated safety and use data to the PAC in 2018.



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