FDA Executive Summary

Prepared for the
April 8, 2019 meeting of the
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.

This memorandum summarizes the safety data regarding H020007 through the present day including pre-market clinical data, post-market medical device reporting (MDR) for adverse events, and peer-reviewed literature regarding safety data associated with the device.

At this time, in review of the safety and effectiveness data, FDA believes the HDE remains appropriately approved for pediatric use.

II. ANNUAL DISTRIBUTION NUMBER (ADN)

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). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual.

Number of devices implanted in 2018	**2018 (cut-off date: 11/19/2018)**
Number of Dystonia Kits sold	3310: 7 3317: 0 3320: 10 3337: 3 3339: 0 Total: 20

# of devices implanted	604
# of active implants in the year	3618
# implanted in pediatric patients	96
# of active implants in pediatric patients	549

[1]

III. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives over 1.4 million 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.

[1] The number of devices sold in a year may not represent the total number of implants per year due to prior sales and pending implants. The number of active implants in 2018 is incorporated in the number of total active implants through the reporting period of 2018.

- 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 between September 28, 2017 and September 27, 2018. The reports entered during this timeframe are related to devices implanted between January 23, 2004 through August 20, 2018. The searches resulted in the identification of 227 MDRs. For the purpose of this MDR analysis, these 227 MDRs will be referred to as the 2019 Pediatric Advisory Committee (PAC) data. All of the 227 MDRs were submitted by the manufacturer. Patient gender information was reported in 210 of the MDRs of which 124 were female and 86 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 2015, 2016, 2017, 2018 and 2019 PAC data sets.

	PAC 2015			PAC 2016			PAC 2017			PAC 2018			PAC 2019		
Event Type	**PEDS**	**ADULT**	**UNK**	**PEDS**	**ADULT**	**UNK**	**PEDS**	**ADULT**	**UNK**	**PEDS**	**ADULT**	**UNK**	**PEDS**	**ADULT**	**UNK**
Malfunction	19	91	26	22	101	22	27	107	35	29	136	22	22	102	11
Injury	22	84	38	34	122	29	31	90	33	18	102	28	19	56	14
Death	1	1	0	0	0	3	0	1	0	6	2	0	0	3	0
Total	42	176	64	56	223	54	58	198	68	53	240	50	41	161	25

The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2019 PAC data is presented by age category in Table 2. The majority of MDRs originated from within the US.

Table 2. The Number of US and OUS MDRs by Age Category

Reporter Country	Pediatric	Adult	Unknown	Total
US	40	159	5	204
OUS	0	1	19	20
Unknown	1	1	1	3
Total	41	161	25	227

Pediatric MDR Review

Patient age was available in 202 of the MDRs, which included 41 pediatric reports and 161 adult reports. The patient age was unknown in 25 reports. Pediatric patient age ranged from 8 to 21 years of age. The average age of the patients in the pediatric reports was 16 years. The percentages of pediatric reports within the 2015, 2016, 2017, 2018 and 2019 PAC data sets were similar (15%, 17%, 18%,15%, and 18% respectively).

The reporting country for 40 Pediatric MDRs was the United States. 1 Pediatric MDR did not include the reporting country. Within the pediatric reports, 23 MDRs were associated with female patients, 18 MDRs were associated with male patients.

Time to Event (TTE) for Pediatric MDRs

In an effort to separate reports for events that occurred zero to 30 days 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 was only able to be conclusively calculated for 32 of the pediatric reports received. Reported problems and event types for pediatric MDRs by TTE are presented in Tables 3 and 4. The range of TTE was from 0 to 1904 days with an average of 498 days and median of 381 days.

There were 7 reports in which the event occurred between zero and 30 days post-implant procedure and 25 reports in which the event occurred greater than 30 days post-implant procedure.

Table 3. Reported problems and event types for pediatric MDRs* with TTE ≤ 30 days (n=7)

Reported Problem	Inury	Malfunction
Battery charging issue	0	4
Impendence issue	0	1
Infection	1	0
Device explanted due to infection	1	0
Device explanted	1	0
Lead break/fracture	0	1
Shelf-life exceeded	0	1

* A single MDR may be associated with more than one problem of clinical interest.

Table 4. Reported problems and event types for pediatric MDRs* with TTE > 30 days (n=25)

Reported Problem	Inury	Malfunction
Impendence issue	7	3
Battery charging issue	3	6
Lead break/fracture	2	0
Worsening symptoms	3	4
Infection	4	0
Device explanted due to infection	2	0
Device explanted	7	2
Device replaced	6	2
Communication Issue	0	2
Cognitive Issues	1	0
Discomfort	3	0
Electromagnetic Interference	0	1

* A single MDR may be associated with more than one problem of clinical interest.

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 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.

Table 5. Clinically concerning pediatric reports*

Adverse Event	MDR Report Count	Number of Patients
Battery/Charging issue	17	14
Device explanted	13	11
Device replaced	9	8
Return or worsening of symptoms	7	5
Infection	6	5
Lead break/fracture	3	2
Potential electromagnetic interference	1	1
Cognitive issues	1	1
Growth related issues	1	1
Stroke	0	0

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

- *Battery/Charging Issues (N=17 MDRs, 14 unique events):* Reports of battery/charging issues were associated with recharging issues (N=10), unknown battery issues (N=6), and a stretched extension wire (N=1). The reported battery/charging related issues also resulted in device replacement (N=3), and patient discomfort (N=2).
- *Device Explant (N=13 MDRs, 11 unique events) and Device Replacement (N=9 MDRs, 8 unique events):* Of the 13 reports of device explants, 9 noted device replacements due to: battery/charging issues (N=4), impedance issues (N=4), patient discomfort (N=4), and migration of device component due to possible growth related issues (N=1). Reports of device explants without reported replacements were due to infection (N=3), and battery/charging issues (N=1).
- *Return or Worsening of Dystonia Symptoms (N=7 MDRs,5 unique events):* MDRs reporting return or worsening dystonia symptoms were associated with several different device problems including impedance issues (N=3), battery/charging issue (N=2), lead break/fracture (N=2), failure to communicate (N=2), potential electromagnetic interference (EMI) (N=1), and a concomitant diagnosis of *Clostridium difficile* (N=1).
- *Infection (N= 6 MDRs, 5 unique events):* Reports of infection were from unknown causes (N=3), erosion/wound breakdown (N=2), and a post-operative infection (N=1). The reports did not include the types of infection or culture results. Due to infections, there were device explants (N=4) with one replacement (N=1), and one wound revision (N=1).
- *Lead break/fracture (N= 3 MDRs, 2 unique event):* High impendence and return/worsening of symptoms were associated with a fractured lead (N=2). Additionally, one MDR reported that during the lead and extension implant procedure, a lead cover slipped off the end of the lead with the distal metal contact still inside the cover. The distal contact was recovered and replaced onto the lead end and the procedure was completed with no reported patient problems.
- *Potential electromagnetic interference (EMI) (N=1 MDR):* On four different occasions, one patient experienced a return of symptoms with stimulation turning off on its own. The incidents were possibly related to having x-rays taken. Based on the limited information provided in the MDRs, the cause-effect of EMI on the device is unclear, but it may be associated with EMI inadvertently turning off the device.
- *Cognitive Issues (N=1 MDR):* Hallucinations were reported with and without stimulation in one MDR. The cause of cognitive changes were suspected to be from a catheter change in a concomitantly implanted intrathecal drug delivery pump. The manufacturer follow-up response noted "The patient outcome related to both the Pump and INS was complete recovery/return to baseline."
- *Growth Related Issues (N=1 MDR):* One MDR noted "when the patient moved their shoulder, the extensions would drag across their back area which was uncomfortable. It was unsure if this had been an issue for the patient since the implant of the INS or became an issue as the patient grew." A revision was completed to move the neurostimulator from the hip to the chest area and the extensions were replaced with shorter extensions.

MDR Conclusions

A total of 41 MDRs, reporting 35 unique events, were associated with use of the Dystonia indication of the Activa neurostimulator in pediatric patients. Battery/charging issues and return or worsening of symptoms 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 are noted in either the device labeling or clinical summary.

The most frequently reported device problem was battery/charging issues. Device problems (such as charging issues, lead fractures or electromagnetic interference) stated in the MDRs are either noted in the device labeling or are known device issues with neurostimulator devices in general. One MDR noted implantation of an expired device. The device was implanted on June 3, 2012 with a use before date of March 28, 2012. No patient or device problems were reported.

No MDRs associated with pediatric death or stroke were reported within the 2019 PAC data.

No new patient or device problems were identified in the 2019 PAC data when it was compared to previous years.

IV. POSTMARKET LITERATURE REVIEW: SAFETY DATA

Purpose

The objective of this systematic literature review is to provide an update of post-market safety/adverse events (AEs) associated with the use of the Medtronic Activa neurostimulator. This is an update on the systematic assessment of published literature since the 2017 PAC meeting.

Specifically, the systematic review was conducted to address the following question:

- What is the safety of Medtronic Activa neurostimulator device for the treatment of dystonia in the pediatric population?

Methods

On November 30, 2018, a literature search was conducted using the same search criteria applied in previous presentations to the PAC:

(medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR (activa) OR (dbs) AND (pediatric) AND (Dystonia).

The search was limited to PubMed and EMBASE databases for the period between November 6, 2017 and November 6, 2018 (dates included). The following exclusion criteria were used:

- Duplicates
- Conference abstracts/Oral presentations
- No primary dystonia
- Review articles
- Registries and/or No Device data
- Non-pediatric or combined (pediatric and adult) population where pediatric and adult subjects are not analyzed separately
- No humans in the study (e.g., animal study)
- Not written in English
- Unavailable article
- Unrelated topic
- No Medtronic software used in the device.

Review articles were individually examined to check for other potential articles for inclusion.

Through this search, 38 records were initially identified (Fig 1): 16 titles from PubMed and 22 from EMBASE. After removal of duplicates (n=11), there were 27 articles identified for title and abstract review. Based on the predefined exclusion criteria, 26 unique records were excluded for the following reasons: conference abstracts (n=6) (17, 22, 24-27), no primary dystonia (n=4) (3, 8, 18, 23), review article (n=4) (1, 2, 4, 15), no pediatric stratified analysis (n=6) (5, 9, 11, 19, 20, 21) and unrelated topic (n=6) (6, 7, 12, 13,14, 16). No additional articles were identified by the review articles. Among the 6 articles excluded based on the criterion of 'unrelated topic', 1 citation (6) assessed DBS effectiveness in patients with different GNA01 gene mutations and no device specified, 1 citation (7) was specific to robot assisted DBS surgery and no device is specified, 1 citation (12) was a genetic study in Japanese patients reporting phenotype variability and allelic heterogeneity in KMT2B-associated disease associated with complex early-onset dystonia, 1 citation (13) was a methodological paper related to clinical practice and a multidisciplinary approach to young-onset movement disorders with no device specified, 1 citation (14) was a case study reporting on the reversal of Status Dystonicus after relocation of pallidal electrodes in DYT6 generalized dystonia using the of interest (Medtronic Model 3387, Activa), and 1 citation (16) was an editorial related to clinical practice and whether clinical neurophysiology can assist in patient selection for DBS in pediatric dystonia.

There is one remaining publication that, although it does not identify the specific DBS device, includes authorship from Medtronic, Instanbul, Turkey (10). Since the article provides safety data, and potentially could be related to the device of interest, it was retained for review and is discussed below. Thus, 1 article was identified as *eligible and retained for final review*: article by *Canaz et al*. See Flowchart, Fig.1 (Article retrieval and selection).

Results

Canaz et al (10) present the results of a retrospective analysis of patients undergoing DBS from 2011-2017 at an institution in Instanbul, Turkey. All patients ≤ 17 years of age at the time of implantation of DBS were included in this series. Recorded data for analysis included gender, diagnosis, age of movement disorder onset, age at time of DBS, clinical outcomes, disability, movement and physical quality of life assessment 6 months after DBS surgery and complications of DBS therapy. Given the relatively small number of patients in this series, the authors only performed descriptive statistics to analyze the data.

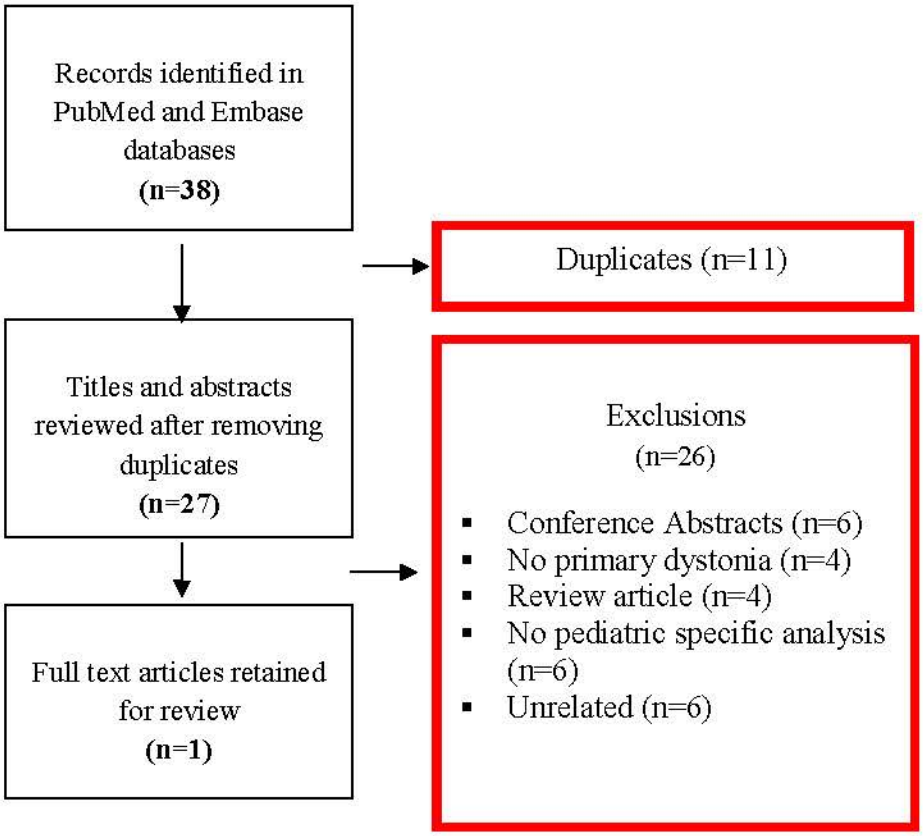
Between May 2014 and October 2017, 11 children underwent DBS procedures. Six of them were female and five were male. Mean age at surgery was 11.8 ± 4.06 years (range 5-17). In this series, 4 patients (all male; ages 5, 9, 15 and 16 at operation) had primary dystonia (36.3%), three patients had secondary dystonia, two patients had Juvenile parkinsonism (JP), and two patients had Tourette Syndrome (TS). Two JP patients underwent bilateral STN DBS while the other nine patients underwent bilateral GPi DBS. The target of DBS placement was GPi in patients with primary and secondary dystonia. None of the patients experienced any intracerebral hemorrhage or other serious adverse neurological effect related to the DBS. Wound complications occurred in two patients. One of these wound complications occurred in the primary dystonia cohort (case #4). In this case, the skin over the pulse generator was eroded. The system was totally removed while infection was diagnosed. Methicillin-sensitive *Staphylococcus aureus* was isolated in this patient. The system was reinserted after relevant antibiotherapy. The other wound complication occurred in a TS patient. Head skin was eroded on connection point of cable in one TS patient (patient #8) who had twitching due to TS. The system was totally removed while infection was diagnosed. *Escherichia coli* was isolated in patient 8. The system was also reinserted in this TS patient after relevant antibiotherapy.

Evidence Assessment: The experience reported from this study does not raise new safety concerns in pediatric patients treated with DBS for primary dystonia. However, the article is based on only one study (single institution) with important study design limitations including a small sample size, use of potentially different device models and/or device components or combination of them, inadequate patient follow-up and undefined criteria to determine infections and its relation/association with the device.

Literature Review Conclusions

The current literature review for the period between 11/06/2017 and 11/06/2018 did not identify new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003, and the annual literature reviews previously conducted. However, the report is based on one publication with important study design limitations such as a single study, a small sample size, use of potentially different device models and/or device components or combination of them, insufficient/inadequate patient follow-up, and undefined criteria to determine infections and its relation/association with the device, etc.

Fig. 1. Article Retrieval and Selection



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 2020.

Continued surveillance and will report the following to the PAC in 2020:

- Annual distribution number
- Literature review
- MDR review

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