FDA Executive Summary

Prepared for the
September 26, 2019, Meeting of the
FDA's Pediatric Advisory Committee

H160002

PulseRider Aneurysm Neck Reconstruction Device

Table of Contents

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 PulseRider Aneurysm Neck Reconstruction Device (PulseRider) in pediatric patients since approval in 2017. 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 appropriate for pediatric use.

II. DEVICE DESCRIPTION

The PulseRider is a permanent self-expanding nitinol (nickel titanium) implant for the treatment of wide-necked intracranial aneurysms (IAs) located at or near artery branch points in the brain. The device's Y or T shape allows the device to be implanted within the vessel while providing support for the placement of neurovascular embolic coils (flexible strands of thin coiled wire) and holding them in place inside the aneurysm sac (Figure 1). The coils remain inside the aneurysm and a clot will form around them, preventing blood from entering the aneurysm. The PulseRider is comprised of a torque device, delivery wire, introducer, and implant (see Figures 1, 2, and 3).

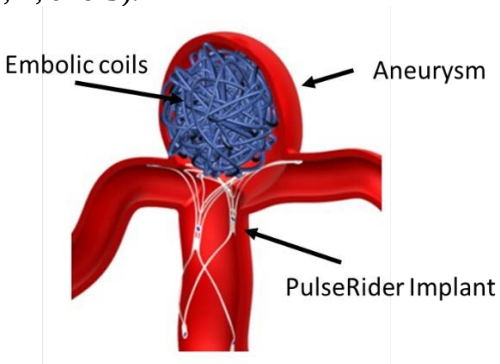


Figure 1: Treatment of an intracranial aneurysm at a vessel branch point using the PulseRider Implant and embolic coils.

Figure 2: PulseRider device (not to scale)

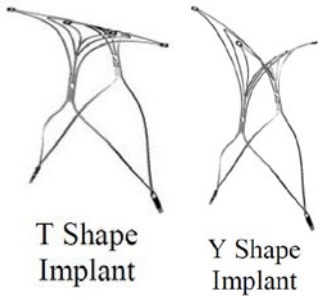


Figure 3: PulseRider implants - T and Y shapes

III. REGULATORY HISTORY

The HUD designation (HUD #09-0223) was approved on March 11, 2010. HDE (H160002) was approved on June 19, 2017. The applicant has been compliant with submitting HDE annual reports and post-approval study reports on time.

IV. INDICATIONS FOR USE

This device is indicated for use with neurovascular embolic coils in patients ≥ 18 years of age for the treatment of unruptured wide-necked intracranial aneurysms with neck widths ≥ 4 mm or dome to neck ratio < 2 originating on or near a vessel bifurcation of the basilar tip or carotid terminus with at least a portion of the aneurysm neck overlapping the lumen of the parent artery. The inflow vessels should have diameters from 2.7 mm to 4.5 mm.

The PulseRider is contraindicated in patients with:

1) Vascular anatomy or dimensions at the targeted treatment site for which the available PulseRider® sizes are not appropriate (refer to package label for sizing information).
2) Severe vascular tortuosity or anatomy that would preclude the safe introduction of the PulseRider® device or the use of other devices involved with the procedure.
3) Preoperative coagulation disorder, or with contraindications to antiplatelet or anticoagulant therapy.
4) Known hypersensitivity to nickel.

V. SUMMARY OF CLINICAL DATA USED TO SUPPORT HDE APPROVAL

A clinical study was performed to support the safety and probable benefit of the PulseRider device. The clinical study (ANSWER study) enrolled and treated 34 patients.

The mean age was 60.9 years with a preponderance of women (85.3%) as is common in studies of intracranial aneurysms. The range of ages treated in the study was 26 to 86 years. The aneurysms treated were located at the basilar artery bifurcation or the bifurcation of the carotid artery terminus. There were no reported neurological deaths or major ipsilateral or downstream strokes within 180 days of the PulseRider procedure. The upper limit of a one-sided 95% confidence interval for neurological death or major ipsilateral or downstream stroke at 180 days post-procedure was 8.4% based on the observed rate of 0%. While not included in this primary safety endpoint definition, there were 5 minor strokes or neurological deficits potentially due to strokes that occurred in 5 patients as a result of device treatment.

Immediately following implant of the PulseRider device , aneurysm occlusion assessed as Raymond I or II were obtained in the majority of cases (79.4% or n/N = 27/34). This result demonstrates that the majority of treated patients achieved 100% occlusion or near complete occlusion of their unruptured wide-neck intracranial aneurysm originating near or at a vessel bifurcation of the basilar tip or carotid terminus immediately post-procedure. This combined aneurysm occlusion rate of Raymond I or II assessed at 180-days post-procedure increased to 87.9% (n/N = 29/33 patients), which was adjudicated by a blinded Core Laboratory. In addition, in 34/34 (100%) cases, the treating physicians viewed the procedure as a technical success if they were able to access the target aneurysm, deploy the device accurately, and detach the device successfully. Therefore, the PulseRider device demonstrated in the ANSWER clinical study that there is probable benefit in successfully stabilizing the intracranial aneurysm using endovascular embolization coiling assisted by the PulseRider to retain the neurovascular embolization coils within the aneurysm sac to achieve 100% or near complete aneurysm occlusion from cerebral blood flow.

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the ANSWER clinical study conducted to support HDE approval. The most common observed adverse event in the ANSWER clinical study was headache (29.4% (n/N = 10/34)) followed by respiratory problems (20.6% (n/N = 7/34)), stroke (14.7% (5/34)), nausea and/or vomiting (11.8% (n/N = 4/34)), hypotension (8.8% (n/N = 3/34)), shortness of breath (8.8% (n/N= 3/34)), and anemia or drop in hemoglobin (8.8% (n/N = 3/34)). All of the 5 stroke patients recovered to a modified Rankin Scale (mRS) score of 0-2 at 180 days post-procedure with minimal disabilities except for one patient who was wheelchair bound due to an ongoing mass effect of the aneurysm unrelated to stroke. There were no adverse events of neurological death caused by the device or procedure and no major debilitating strokes. For all 34 treated patients, there was a low rate of peri-procedural complications (8.8% ongoing neurological events) and a mRS 0 – 2 was achieved in 94.1% of patients (n/N = 32/34) at the 180-day follow-up visit. The two subjects with mRS greater than 2 at the 180-day follow-up visit include the stroke subject described previously with ongoing mass effect of the aneurysm and one subject with ongoing leg numbness that resulted in decreased mobility.

The youngest patient in the clinical study was 26 years old. The clinical study protocol was approved to treat patients as young as 18 years old. With respect to sizing and placement of the device, reviewed data demonstrated no significant difference between

vascular anatomies between the 18-21 year-old group and adults 22 years of age and older. Also, the incidence of intracranial aneurysms in this age group is much less than older adults (> 45 years old). Given the risk and benefit profile of this device in the population studied and the similarities between young adults ≥ 22 years of age and the 18-21-year-old population with respect to target anatomies and intracranial aneurysm presentation, it was considered reasonable to include the "Transitional Adolescent (18 to 21 years old but treated as an adult)" population within the indications for use of this device during review for approval of the HDE.

Limitations to the ANSWER clinical study design were its single arm study design, which limits the ability to draw comparisons to alternative treatments, financial conflicts of interest as some of the investigators had a significant payment from Pulsar Vascular, Inc., the study was not statistically powered for hypothesis testing of the safety and probable benefit endpoints, and the mRS evaluations were not conducted by an unblinded assessor at the 180-day follow-up visit.

Considering all of these limitations to the clinical study design and after a thorough review of all of the clinical data including the individual subject Case Report Forms (CRFs), the results generally support that the risks of the PulseRider are similar to marketed HDE neurovascular embolization coil-assist stents and probable benefit is demonstrated through the majority of patients in the study were able to achieve adequate or complete occlusion of their unruptured, wide-necked, intracranial aneurysm originating on or near a vessel bifurcation of the basilar tip and carotid terminus arteries as assessed by Raymond I and II scores. An additional benefit of the device is that the PulseRider is specifically designed to be implanted at a vessel bifurcation and not intended to affect the blood flow within the parent vessel. This is unlike alternative endovascular treatment modalities such as neurovascular embolization coil-assist stents which have a tubular design and may be more limited in treating wide-necked IAs arising from a true vessel bifurcation.

VI. 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). 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. The number of PulseRider devices distributed in the US between May 2, 2018, and May 1, 2019 is 330.

VII. POST MARKET DATA: POST APPROVAL STUDY

The clinical study used to support the original HDE approval studied subjects out to six months (180 days) post-operative. Longer term clinical data is necessary to confirm the benefit to risk profile of the device. Therefore, as a condition of approval, the following post-approval study (PAS) was requested to collect data on the original ANSWER study cohort out to one year post-operative.

Study Title: Adjunctive Neurovascular Support for Wide-Neck Aneurysm Embolization and Reconstruction (ANSWER)

Study Objective: The PAS is a continuation of the ANSWER study, collecting longer term data in the original patient cohort out to one-year post-operative. The primary objective of the study is to evaluate the safety and probable benefit of the PulseRider when used in conjunction with embolic coils in the treatment of wide-neck intracranial aneurysms originating at or near a vessel bifurcation of the basilar artery or carotid terminus.

Study Design: This study is a prospective, multi-center, single-arm, non-randomized study. It is continued follow-up of the pre-market cohort up to 1-year (365 days) post-operative without any new enrollment.

Primary Endpoints:

- Safety – neurological death or major ipsilateral stroke or downstream stroke up to 365 days post-procedure. Major stroke is defined as a stroke, which is present after seven days and increases the National Institute of Health Stroke Scale (NIHSS) of the patient by greater than or equal to 4 points.

Additional Evaluations:

- Incidence of new neurological deficits
- Complication rate (neurological and non-neurological)
- Rate of occlusion at 365 days
- Device movement or migration
- Stenosis at implant site

Study Population: The study population consists of both male and female subjects, aged 26 years of age and older, who presented with a wide neck (neck width $\geq$ 4 mm or dome to neck ratio < 2) basilar or carotid terminus aneurysm located at a bifurcation. Subjects with acutely ruptured aneurysms were excluded from the study. The aneurysm parent vessel measurements were required to be between 2.7 mm and 4.5 mm to be suitable for the procedure. Patients were required to take dual antiplatelet therapy starting prior to the procedure and post-procedure.

Sample Size: 34 patients that were enrolled in the pre-market cohort.

The one-year follow-up for the ANSWER study has completed and the PAS requirement has been satisfied. There were 4 missing subjects without 1-year follow-up data because one subject died due to metastatic cancer and 3 subjects were lost-to-follow-up. In summary, based on the 30 subjects with available 1-year post-operative data, no device migration or stenosis defined as greater than 50% at the implant site was reported at 1-year follow-up. Clinical outcomes at 1-year post-operative as measured by the mRS and the NIHSS were consistent with the reported 180-day outcomes and there were no new neurological deficits. The IA occlusion rate and durability were consistent between the 6-months and 1-year post-operative results. No unanticipated adverse device effects were reported out to 1-year post-operative. Therefore, it is concluded that the safety and probable benefit profile of the PulseRider device approved under H160002 remain unchanged between 6-months and 1-year post-operative.

VIII. POST-MARKET 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 clinical practice setting, including:
  - rare, serious, or unexpected adverse events;
  - adverse events that occur during long-term device use;
  - adverse events associated with vulnerable populations; and
  - use error.

Although MDRs are a valuable source of information, this passive surveillance system has limitations that are described below. Because of this, MDRs comprise only one of the FDA's several important post-market 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 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, 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 PulseRider Aneurysm Neck Reconstruction Device

The Agency searched the MDR database to identify reports associated with the PulseRider device entered between May 31, 2018, and May 31, 2019. The search identified 18 MDRs (associated with 13 unique events), 17 of which were submitted by the manufacturer and one of which was submitted by a user facility. The 18 MDRs included two death reports (associated with one unique event), 6 injury reports (associated with 5 unique events) and 10 malfunction reports (associated with 7 unique events). Patient age was reported in 10 MDRs and the minimum age was 49 years old, the maximum age was 75 years old, and the median patient age was 60 years old. There were no MDRs associated with pediatric patients (age less than 22 years old). Patient gender was reported in 13 MDRs, with 11 MDRs associated with female patients and two MDRs associated with male patients. The reporting country was available in all 18 MDRs and included the United States (N=16 MDRs), the Netherlands (N=1 MDR) and Sweden (N=1 MDR).

All MDRs were individually reviewed to identify the most frequently reported patient and device problems. Please note that more than one patient or device problem may be reported within a single MDR. The reported patient problems included stroke (N=5 MDRs, 4 unique events), hemorrhage (N=5 MDRs, 3 unique events), headache (N=3 MDRs, 2 unique events), thrombosis/emboli (N=2 MDRs, 2 unique events), pseudoaneurysm (N=2 MDRs, 1 unique event) and vasospasm (N=1 MDR, 1 unique event). The reported patient death (2 MDRs, 1 unique event) was associated with a 49-year-old female patient with a medical history of sleep apnea, obesity, hypertension, headaches and chronic sinus issues who passed away in her home from a stroke eight days after her PulseRider procedure. There were no reported complications during the procedure and the physician attributed the stroke to the patient's complex medical history and anti-coagulation regimen, which included 6000 units of heparin given intra-procedure, and Plavix (75 mg daily) and aspirin (325 mg daily) which were prescribed five days prior to the procedure and at patient discharge. Although the physician did not attribute the patient death to the PulseRider device, the device cannot be ruled out as a potential contributor to the patient death.

The reported device problems were primarily deployment and device placement related (N=10 MDRs, 7 unique events). There were four MDRs (3 unique events) associated with use of the device in tortuous anatomy, which is warned against in the device labeling.

MDR Conclusions

A total of 18 MDRs, reporting 13 unique events, were associated with use of the PulseRider device. There were no known MDRs associated with pediatric patients. The most frequently reported patient problems included stroke, hemorrhage and headache. The most frequently reported device problems were deployment related. The patient and device problems reported in the MDRs are either noted in the device labeling or are known risks associated with endovascular treatment of intracranial aneurysms. Based on the information provided in the MDRs, no new patient or device problems, or reports associated with pediatric patients, were identified.

IX. LITERATURE REVIEW

Methods

This systematic literature review aimed to examine the current body of literature on the use of PulseRider in the adolescent population following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The years of publication eligibility ranged from 2018 to 2019. These years were utilized to identify articles published since the previous PulseRider literature review that was performed in 2018 by CDRH. The following search was initially conducted in PubMed and Embase:

('pulserider'/exp OR pulserider) AND ('pediatric'/exp OR pediatric OR newborn* OR infant* OR child* OR adolescent*)

For Embase, this search identified 28 articles, and for PubMed, this search identified zero articles. Thus, a more general search using only "Pulserider" in all fields was also conducted in PubMed to ensure that all pertinent articles were captured. A total of 10 additional articles were found in PubMed after this search criterion was employed.

Exclusion Criteria and Accountability of Publications

After conducting these searches, a review of titles and abstracts was performed followed by full- text assessment. The full exclusion criteria included the following: duplicates, conference abstracts and oral presentations, letters to the editor, commentaries, and editorials, review articles, not the device of interest, no adolescent specific analysis, no humans in the study (e.g., animal study), not written in English, and unrelated topic. Review articles were individually examined to check for other potential articles for inclusion.

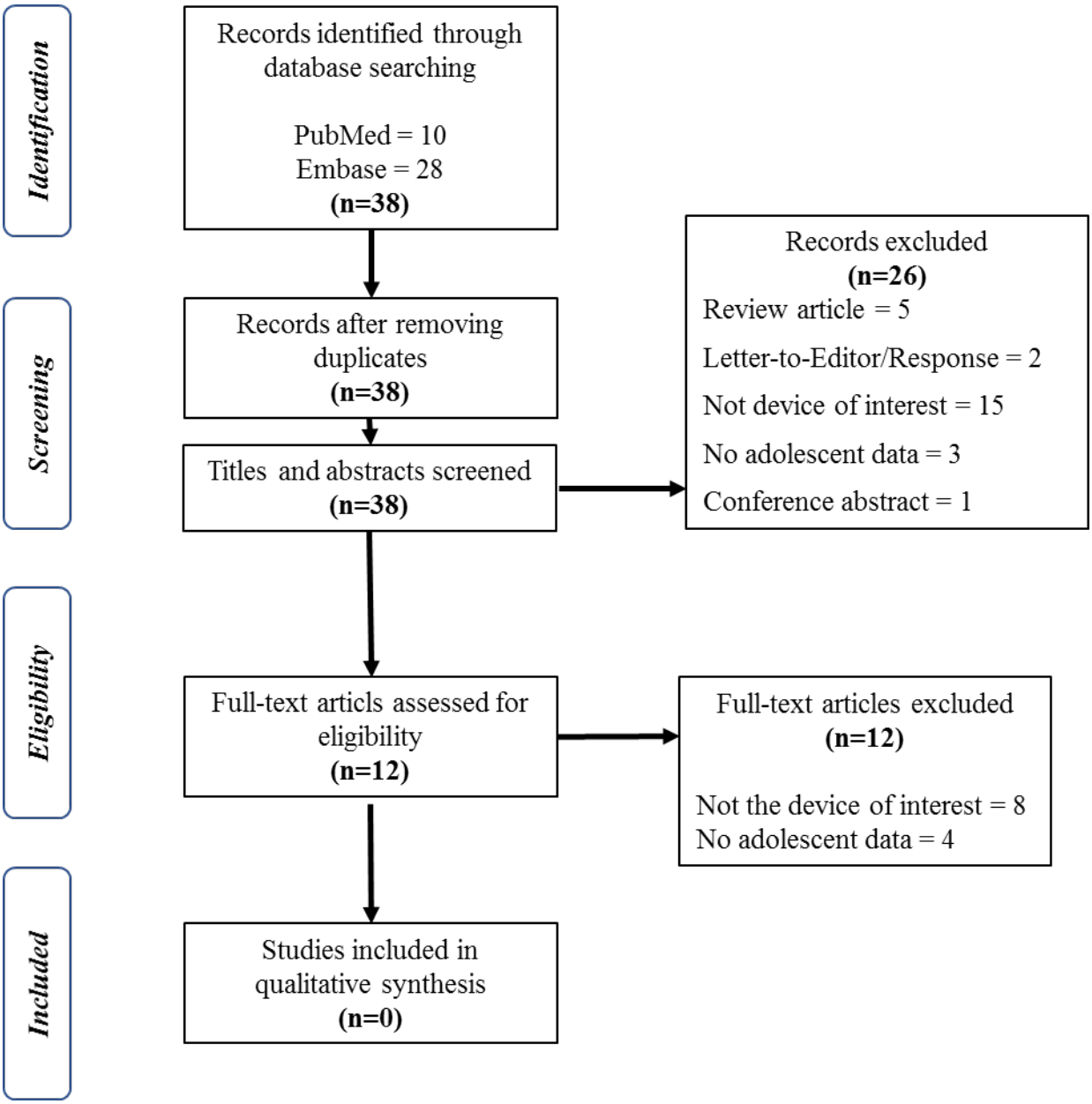
Figure 1 presents the article screening process. All 38 articles were excluded for the following reasons: review article (5), letter-to-editor and response (2), not the device of interest (23), no adolescent data (7), and conference abstract (1).

Literature Review Conclusions

Given the current searches of the literature, we did not find any studies published on

the PulseRider that report results for the use of this device in the adolescent population. Consequently, conclusions regarding the safety and probable benefit of the use of the PulseRider in the adolescent population cannot be obtained from the published literature.

Figure 1. Search Strategy based on PRISMA for Relevant Articles



X. SUMMARY

Based on the existing available evidence for the PulseRider device from the ANSWER study with up to 1-year post-operative data, an MDR analysis, and literature review from May 2018 to May 2019, there are no reported cases of device use in the pediatric population and no new safety concerns identified. FDA will continue post-market surveillance of this device through review of MDRs received for this device, HDE annual reports and annual device distribution number, and literature review. Any new information will be presented to the PAC in 2020.