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ELECTRONIC SUBMISSION

Tamara Syrek Jensen
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services (CMS)
7500 Security Boulevard
Baltimore, MD 21244

RE: A Formal Request for a National Coverage Determination for Renal Denervation

Dear Ms. Syrek Jensen:

Medtronic is the world's leading medical technology company, specializing in implantable and interventional therapies that alleviate pain, restore health, and extend life. We are committed to the continual research and development necessary to produce high-quality products and innovative therapies that improve health outcomes for all patients, including Medicare beneficiaries.

Pursuant to the "Medicare Program; Revised Process for Making National Coverage Determinations" notice published in the *Federal Register* on August 7, 2013 (78 FR 48164), we hereby formally request CMS issuance of a National Coverage Determination (NCD) for renal denervation (RDN) for the treatment of uncontrolled hypertension. As described in greater detail below, the epidemic of hypertension in the U.S. and the health risk to Medicare beneficiaries – including higher risk of cardiovascular events such as heart attack, stroke, heart failure, and kidney failure – indicate that there is an important unmet need in how hypertension is managed today. The Medtronic Symplicity Spyral™ RDN System is an FDA-designated Breakthrough Device that provides an option for hypertension treatment that is

adjunctive to medications to help lower blood pressure. Granted FDA premarket approval on November 17, 2023, the Symplicity system is backed by a rigorous, multi-year, global clinical program and experience in treating more than 25,000 patients world-wide.

Medtronic greatly appreciates the opportunity to have collaborated with CMS on RDN as a pilot to test processes and concepts during development of the Transitional Coverage for Emerging Technologies (TCET) pathway, which was made effective via final notice on August 12, 2024 (89 FR 65724) – including key components such as the Evidence Preview and Evidence Development Plan. Thank you for your consideration of this complete, formal request for CMS to initiate an NCD for RDN. If you have questions or need further information, please contact me at (202) 441-1938 or carrie.w.bullock@medtronic.com.

Regards,

Carrie Bullock
Vice President, Health Policy, Reimbursement & CMS Strategy
Medtronic

Contents

Request for a National Coverage Determination

Medtronic formally requests a National Coverage Determination (NCD) for coverage of renal denervation (RDN) for the treatment of uncontrolled hypertension.

Benefit Category

The following statutorily defined benefit categories would be applicable to RDN:

- Inpatient hospital services
- Outpatient hospital services incident to a physician's service
- Physicians' services
- Ambulatory Surgical Center facility services

Description of Renal Denervation and the Symplicity System

Overview

On November 17, 2023, the U.S. Food and Drug Administration (FDA) granted premarket approval (PMA) for the Symplicity Spyral™ Renal Denervation System (Symplicity Spyral Multi-Electrode Renal Denervation Catheter & Symplicity G3 Renal Denervation RF Generator; hereafter "Symplicity system"). The Symplicity system, an FDA-designated Breakthrough Device, is indicated to reduce blood pressure (BP) as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control BP.[1] This approval is the culmination of a rigorous, multi-year, global clinical program and is backed by experience in more than 25,000 patients treated globally.[2]

The Symplicity system is used to perform RDN, a minimally invasive, catheter-based approach to lower BP by ablating overactive renal nerves, without permanent implantation. It is specifically designed to provide consistent performance to reduce BP independent of a patient's medication adherence by decreasing sympathetic signaling. The system is comprised of a single-use, disposable catheter (Symplicity Spyral catheter) and reusable radiofrequency (RF) generator (Symplicity G3 RF generator). During the procedure, an interventionalist uses the Symplicity system to supply precisely controlled and targeted RF energy to the renal nerves, safely disrupting the overactive signaling between the kidneys and brain to help reduce BP.[3] This one-time procedure takes around one hour and is usually performed by an interventional cardiologist in a catheterization laboratory under analgesic or conscious sedation.

Technology Design

The Symplicity system consists of the Symplicity Spyral Multi-Electrode Renal Denervation Catheter and the Symplicity G3 Renal Denervation RF Generator. The catheter consists of a distal, self-expanding array of four gold electrodes radially spaced for quadratic ablation. The catheter has an effective length of 117 cm and is compatible with a 6Fr guide catheter. It has the deliverability to treat a wide range of anatomy (vessels 3-8 mm in diameter). A radiopaque marker is embedded in the catheter tip, approximately 1 mm proximal from the distal end to assist in the positioning of the catheter using fluoroscopic guidance. The self-expanding electrode array consists of nitinol stranded tubing to maintain the spiral shape-set and guidewire lumen integrity during the procedure. The gold electrodes are connected to individual, insulated bi-filar wires that deliver energy and measure temperature. The electrodes are placed over a polymer outer cover (array jacket) that provides insulation from the nitinol tubing and bi-filar wires. The proximal end of the self-expanding electrode array assembly is attached to an intermediate shaft assembly, which balances the flexibility between the array and a proximal shaft. This intermediate shaft assembly contains a guidewire lumen that terminates at the rapid exchange guidewire exit port. A jacketed stainless steel hypotube in the proximal shaft joins the delivery system to the catheter handle and integrated cable. The cable connector connects directly into the Symplicity G3 generator. The generator employs a real-time responsive algorithm that controls and monitors the safe distribution of energy to target nerves. A straightening tool sits on the proximal shaft of the catheter and can slide distally to assist during loading of the guidewire in the catheter tip lumen. When loaded onto a guidewire, the catheter is in a low-profile straight configuration that allows it to be inserted in a 6F guide-catheter for delivery to the renal artery.

Procedure Description

The Symplicity Spyral catheter, when used with the Symplicity G3 generator, is introduced through an endovascular approach into the renal arteries and delivers minimally invasive RF ablation of the renal sympathetic nerves. RDN using the Symplicity system aims to lower blood pressure by modulating an elevated sympathetic drive through the ablation of the renal artery nerves. It has four electrodes in a spiral array, which allows simultaneous ablation in all four quadrants of a single vessel. The catheter is inserted through a small femoral incision and guided to the renal artery via the abdominal aorta. Once the catheter is positioned at the desired treatment location(s) within the renal artery, the guidewire is retracted, allowing the self-expanding catheter to expand and fit the renal arterial vessel walls. A treatment is the delivery of RF energy to ablate the renal nerves through the activation of the catheter electrodes, controlled using the generator. The treatment delivers precisely focused energy of up to 6.5W to each electrode simultaneously through the wall of the renal artery to disrupt the surrounding renal nerves. This low-power ablation has been shown to effectively disrupt the renal nerves without damaging the artery walls or surrounding organs. The single-use catheter is used to deliver multiple ablations in both kidneys, in the renal main, accessory, and branch arteries (based on artery size). The guidewire may be used to reposition the catheter for additional ablations.

Supporting Scientific Evidence

Overview

Data in clinical trials from over 1,500 Symplicity Spyral procedures have demonstrated consistent, clinically meaningful, and sustained reductions in BP across a wide range of patients through three years, along with a strong safety profile.[4] As described in more detail below, the supporting evidence includes prospective, randomized, sham-controlled studies (RCTs), both in the absence (OFF MED)[5,6] and presence (ON MED)[7,8] of antihypertensive medications; real-world evidence from a large global registry;[9,10] and longer-term follow-up from independent, single-center observational studies. Further, recent consensus statements from U.S. and European cardiology societies, as well as 2024 and 2023 European HTN clinical practice guidelines, recognize RDN as an evidence-based approach to reduce BP in patients with uncontrolled hypertension.

The evidence on the Symplicity RDN system shows:

- Statistically significant and clinically meaningful BP reductions vs. sham, in the presence and absence of antihypertensive medication, in RCTs;

- Durable and consistent BP reduction in a RCT to three-years, in real-word registry to three-years, and in independent studies up to a decade;
- A robust safety profile with no significant increase in adverse events vs. sham in RCTs out to three-years, and renal function is preserved; and
- RDN is recommended by medical societies in the U.S. and globally in the management of hypertension.

SPYRAL HTN-OFF MED Trial

The OFF MED trial enrolled 331 patients and successfully demonstrated the benefit of RDN in 24-hour and office systolic BP (SBP) in the absence of antihypertensive medications from baseline to 3 months (24-hour: RDN −4.7 mmHg, Sham −0.6 mmHg, baseline ANCOVA-adjusted treatment difference -4.0 mmHg, p<0.0005; Office: RDN −9.2 mmHg, Sham −2.5 mmHg, baseline ANCOVA-adjusted treatment difference -6.6 mmHg, p<0.0001).[6] This off-medication study was critical to understand the true BP-lowering effect of RDN free of potential confounding factors, such as the effect of medications. Importantly, an "always on" effect of RDN was observed with sustained BP reductions throughout the entire 24-hour period, including significant reductions in the "high-risk zone" that occurs late-night/early-morning, which overcomes the dosing and pharmacokinetic limitations of medications to prevent large swings of BP throughout the day. This may be particularly helpful for patients with nighttime hypertension and higher cardiovascular (CV) risk.[11]

SPYRAL HTN-ON MED Trial

The ON MED trial evaluated the effects of RDN in 337 patients in the presence of antihypertensive medications and demonstrated consistent BP reductions with 20% lower medication burden* at 6 months with RDN (Medication burden: 2.9 RDN vs. 3.5 sham, p=0.04).[8] Notably, three times as many RDN patients were able to achieve target SBP <140 mmHg versus sham (Target SBP: 20% RDN, 6% Sham, p=0.001). The absolute reduction in 24-hour SBP for RDN (-6.5mmHg) was consistent and larger than that seen in the OFF MED trial, although there was not a significant treatment difference in the overall 24-hour SBP reduction between the RDN and sham limbs. Multiple, pre-specified secondary endpoints demonstrated a statistically significant difference favoring RDN over sham, including office and nighttime SBP (Office: RDN −9.9 mmHg, Sham −5.1 mmHg, baseline ANCOVA-adjusted treatment difference −4.9 mmHg, p=0.002; Nighttime: RDN −6.7 mmHg, Sham −3.0 mmHg, baseline ANCOVA-adjusted treatment difference −3.7 mmHg,

* Based on number, class and dosage, where all medication classes are considered of equivalent potency

p=0.01). Nighttime and office SBP reductions are clinically relevant and important measures that have strong correlation with improvement in long-term CV outcomes.[12] The main possible confounder for the 24-hour SBP results was that the significant differences in medication prescription and burden were disproportionate in favor of sham, with a 10-fold higher proportion of sham patients exhibiting an increase in medications. Finally, the study met its primary safety endpoint, with a low incidence of procedure-related adverse events.

At three-year follow-up in the ON MED Pilot cohort (the first 80 subjects enrolled),[7] RDN demonstrated significantly greater reductions in 24-hour SBP (24-hour: RDN −18.7 mmHg, Sham −8.6 mmHg, ANCOVA-adjusted treatment difference -10 mmHg, p=0.004) as well as office and nighttime SBP compared to sham (Office: RDN -20.9, Sham -12.5, p=0.073; Nighttime: RDN -19.3, Sham -6.6, p=0.00017).[13] Importantly, the BP reductions favoring RDN were achieved with a numerically lower medication burden (Medication burden: 7.6 RDN vs. 10.3 Sham).

Furthermore, a validated lifetime cost-effectiveness analysis using ON MED trial results quantified the impact of RDN on clinical outcomes, QALYs,[†] and costs associated with treating uncontrolled hypertension.[14] RDN demonstrated as a high-economic value treatment by yielding meaningful relative risk ratios in clinical events of 0.80 for stroke, 0.88 for myocardial infarction, and 0.85 for CV death modeled over 10 years and a base case ICER[‡] of $32,732/QALY.

Global Symplicity Registry

In addition to the ON MED and OFF MED RCTs, evidence of RDN long-term efficacy and safety is further demonstrated in a large global registry (Global Symplicity Registry)[§] in multiple high-risk patient subgroups, including those with resistant hypertension, diabetes, chronic kidney disease, elderly patients, and Isolated Systolic Hypertension. At three years, this registry of over 3,000 patients demonstrated significantly decreased 24-hour and office SBP, independent of medications (24-hour: -8.9, p<0.0001; Office: -19.0, p<0.0001). There was also a decrease in the number of prescribed antihypertensive medications compared to baseline (Baseline: 4.6±1.4, 3-yr: 4.3±1.5, p<0.0001) when typically, an increase in medications over time is expected. Importantly, 38.4% of patients were able to achieve target SBP <140 mmHg (Baseline: 13.5%, p<0.001).[10] These three-year results have calculated event reduction rates of 31 composite major

[†] QALY = quality-adjusted life year: a summary outcome measure commonly used in health economic analysis to quantify the effectiveness of a particular intervention, combining the impact of gains in quality and in quantity of life (i.e., life expectancy) associated with an intervention or treatment.
‡ ICER = Incremental Cost-Effectiveness Ratio: the key outcome of a cost-effectiveness analysis. It is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect – usually expressed as QALYs) to provide a ratio of "extra cost per extra unit of health effect" – i.e., for the more expensive therapy vs. the alternative or comparator therapy.
[§] Includes patients treated with both Symplicity Spyral™ and Flex™ catheters.

adverse CV events avoided for every 1,000 patients (33 Number Needed to Treat (NNT)), 23 strokes avoided per 1,000 (43 NNT), 7 myocardial infarctions avoided per 1,000 (151 NNT), and 6 CV deaths avoided per 1,000 (171 NNT).[15]

Independent Studies

The durable BP-lowering results in the Global Symplicity Registry are supported by longer-term follow-up from independent, single-center observational studies. These studies demonstrate that the BP-lowering effects of RDN remain durable through 8-9 years without an increase in medications.[16,17,18]

Safety

The Symplicity system has demonstrated a robust safety profile. The pooled ON MED and OFF MED RCTs primary safety endpoint was met with a low rate of major adverse events.[13] Long-term analysis of the ON MED Pilot trial reported long-term safety results associated with RDN through three years, with zero device or procedural safety events, and no negative effect on kidney function.[13] Kidney function decline over three years in the Global Symplicity Registry was within the expected range for severe antihypertensive patients (-7.1 ± 16.7 mL/min/1.73 m^2 and -3.7 ± 16.2 mL/min/1.73 m^2 for patients with and without chronic kidney disease, respectively).[9]

Recent Society Statements & Guidelines

After completing a thorough review of RDN evidence, outlined above, recent consensus statements from major U.S. and European cardiology societies, as well as 2024 and 2023 European HTN clinical practice guidelines, recognize RDN as an evidence-based approach to reduce BP in patients with uncontrolled hypertension. These societies include the American Heart Association (AHA),[19] U.S. Society for Cardiovascular Angiography & Interventions (SCAI)/National Kidney Foundation (NKF),[20] European Society of Cardiology (ESC)[21,22] and European Society of Hypertension (ESH).[23] Positive recommendations supporting the safety, efficacy, and sustained effects of RDN in the management of uncontrolled hypertension have been increasing, with 12 medical societies worldwide publishing statements or guidelines in just the last two years, most recently the Japan Society of Hypertension (JSH),[24] a panel of physician experts in Ireland,[25] and the French National Authority for Health (HAS).[26]

Benefits and Relevance to the Medicare Population

Uncontrolled hypertension remains a global health burden. In the U.S., nearly half of adults have hypertension, of whom about 75% do not have their hypertension under control.[27] It is the most

prevalent risk factor for stroke and a major risk factor for other CV diseases such as coronary artery disease, heart failure, and chronic kidney disease.[28] Furthermore, prevalence of hypertension increases with age: the U.S. Centers for Disease Control and Prevention (CDC) estimates that 77% of Americans over the age of 65 have hypertension, and 15.8 million are treated for hypertension with medication but remain uncontrolled (representing 57.3% of the total population ≥65 years old who are indicated for antihypertensive pharmacological treatment).[29]

Hypertension is the leading modifiable risk factor associated with death,[30] and uncontrolled hypertension is associated with higher risk of CV events, including heart attack, stroke, heart failure and kidney failure.[31,32] Hospitalizations for Medicare beneficiaries for acute hypertension increased by more than double between 2009 and 2019, with greater increase in hospitalization rate by race and ethnic disparities.[33]

BP reduction is strongly associated with reduced CV risk. In clinical trials for hypertension treatments, the clinical benefit of improving BP is well understood, and measuring BP as a surrogate endpoint is accepted as valid by the FDA and European Medicines Agency (EMA).[34,35] Meta-regression analyses of placebo-controlled BP trials demonstrate a continuous linear reduction in relative risk of major cerebral-CV events that is independent of baseline BP and comorbidities.[28,36] This strong association supports the validity of BP reduction as a surrogate clinical trial outcome and further indicates that relatively modest reductions in BP result in substantial and meaningful reductions in CV risk. For example, a 10mmHg reduction in office SBP leads to 20% reduction in CV events. [28]

The current American College of Cardiology and AHA HTN Guidelines recommend lifestyle modifications and antihypertensive medications for patients with hypertension.[37] However, despite available treatments, hypertension control rates within the U.S. remain low and have been decreasing over the last decade. Among U.S. adults taking hypertension medications, over 32% remain uncontrolled.[38] Patients may be intolerant to medication or experience adverse side effects from medication, or they may be non-adherent to medication due to a multidimensional array of economic, psychological, and social influences.[39,40]

The epidemic of hypertension in the U.S. and the health risk to Medicare patients indicate that there is an important unmet need in how hypertension is managed today. Radiofrequency RDN using the Symplicity system provides Medicare beneficiaries an option for hypertension treatment that is adjunctive to medications to help improve blood pressure management.

Attachment A: FDA PMA Approval Letter

Attachment B: Symplicity Spyral Summary of Safety and Effectiveness Data (SSED)

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