DE NOVO CLASSIFICATION REQUEST FOR VIBRANT SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Orally ingested transient device for constipation. An orally ingested transient device for constipation is an electric swallowable capsule that naturally passes through the gastrointestinal tract for the treatment of constipation.

NEW REGULATION NUMBER: 21 CFR 876.5940

CLASSIFICATION: Class II

PRODUCT CODE: QTN

BACKGROUND

DEVICE NAME: Vibrant System

SUBMISSION NUMBER: DEN210052

DATE DE NOVO RECEIVED: December 1, 2021

SPONSOR INFORMATION:
Vibrant Ltd.
Hakochav P.O. Box 516
Yokneam, Israel, 2069206

INDICATIONS FOR USE

The Vibrant System is an orally administered Capsule that is indicated for the treatment of adults with chronic idiopathic constipation who have not experienced relief of their bowel symptoms by using laxative therapies at the recommended dosage for at least one month.

LIMITATIONS

The sale, distribution, and use of the Vibrant System is restricted to prescription use in accordance with 21 CFR 801.109.

The Vibrant capsules are contraindicated for use under the following conditions:

- History of complicated/obstructive diverticular disease
- History of intestinal or colonic obstruction, or suspected intestinal obstruction
- Clinical evidence of current and significant gastroparesis

- History of significant gastrointestinal disorder, including any form of inflammatory bowel disease or gastrointestinal malignancy (celiac disease is accepted if the subject has been treated and is in remission), and/or anal fissures and fistulas
- History of Zenker's diverticulum, dysphagia, esophageal stricture, eosinophilic esophagitis, or achalasia
- Women who are pregnant or lactating

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Vibrant System is comprised of two components: a Pod and a single use Capsule. The Pod activates the Capsule using radio frequency (RF) communication. After activation, the Capsules are taken orally. After a pre-programmed activation delay, the Capsules begin to vibrate. The marketed device will have an activation delay of 14 hours. (The 14 hours activation delay corresponds to Active Mode 1 of the pivotal study described below; the pivotal study also included an Active Mode 2 with a 9 hour activation delay.) As they pass through the gastrointestinal tract, the Capsules vibrate for four pre-programmed periods of 100 min, 120 min, 100 min, 180 min. It takes about three days for the Capsules to pass through the gastrointestinal tract, at which point they are excreted in a bowel movement.

The Capsule is comprised of a motor that vibrates (2.5 Vdc, 70 ma), electronic card, batteries (2x 1.5V 60 mAh, alkaline/0% Hg coin battery) and connector. The capsule is a two-piece shell made from Polycarbonate Makrolon 2458. The Capsule dimensions are as follows: length: 24.5 ± 0.1 mm; diameter: 11.20 ± 0.05 mm; weight 4.0 ± 0.1 g. The Capsules have a vibration force between 200 and 550 gf, with vibration cycles of 3 seconds on and16 seconds off (190 cycles per hour).

Figure 1: Vibrant System: Capsule

Figure 2: Vibrant System: Pod

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOBURDEN AND SHELF LIFE

The Vibrant System is not provided sterile. Vibrant Capsules are routinely monitored during manufacturing for bioburden levels to ensure the total bioburden is no greater than (b)(4) forming units per capsule. Packaging and shelf-life testing confirmed the Vibrant System packaging maintained integrity and device performance over the 1-year labeled shelf life. See Table 1 for list of bench testing conducted to support shelf-life.

SOFTWARE

The Vibrant System contains software to control the operation and vibration of the Capsule and for activation and time calibration of the Capsule by the Pod. Software verification and validation testing was performed and the results demonstrated the software functions as intended and all requirements specifications were met. The software/firmware was reviewed according to the "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005. The software has a moderate level of concern.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Vibrant System conforms to the requirements for electrical safety and electromagnetic compatibility in ANSI AAMI ES60601-1:2005/®2012, A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012; IEC 60601-1-11:2015; IEC 60601-1-2:2014.

BIOCOMPATIBILITY

The Vibrant capsules are classified as mucosal membrane contacting with a cumulative duration of exposure of >30 days. Capsule biocompatibility was evaluated in accordance with ISO 10993-1, Biological evaluation of medical devices and FDA Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". The following biocompatibility endpoints were evaluated with testing and chemical characterization/toxicological risk assessment:

- cytotoxicity
- sensitization
- irritation
- acute systemic toxicity
- materials mediated pyrogenicity
- subchronic toxicity
- genotoxicity
- chronic toxicity

The results of these evaluations support the biocompatibility of the Vibrant Capsules.

The Vibrant System Pod is non-patient contacting and biocompatibility assessment was not necessary.

PERFORMANCE TESTING - BENCH

The performance of the Vibrant Capsule was evaluated with the nonclinical bench testing summarized in Table 1.

Table 1: Summary of Performance Testing – Bench Studies

Test	Test Methods	Acceptance Criteria	Results
Mechanical Integrity	Capsules were placed under loads ranging from (b)(4) to (b)(4) The capsule was subjected to (b)(4) for (b)(4)	No cracks, ruptures, loose particles, or debris are observable following (b)(4) application of (b)(4)	Pass
Seal test	Capsule ultrasonic welds were evaluated for seal integrity using leak tester (b)(4)	No major leak, and the pressure of the test capsule must be less than (b)(4) the control capsule pressure.	Pass
pH Resistance	Capsules were incubated for (b)(4) in the worse-case pH conditions of pH (b)(4)	Capsules must not show defects in the seal, no ruptures, no shell cracks, or any other damage to the capsule. The Capsules must also pass the sealing	Pass

Test	Test Methods	Acceptance Criteria	Results
		and mechanical integrity tests successfully.	
Mode of Operation	Following Capsule activation, the following parameters were recorded: vibration start time, vibration duration, vibration force, vibration sequence and rest time. These parameters were recorded for each of the four vibration rounds.	Capsules must meet the predefined specifications for start time, duration, vibrational force, vibrational sequence.	Pass
Dimensional Verification	A digital caliper was used to measure the length and diameter of the capsules.	Capsule length must be (b)(4) Capsule diameter must be (b)(4) (b)(4)	Pass
Visual Inspection	The Capsules were visually inspected with a magnifying glass to check the Capsule for correct assembly of the shell components, check for any damage to the shell (e.g., scratches, kinks), and to check for the presence of extraneous matter on the shell.	External surface of Capsule is free of surface defects and extraneous matter.	Pass

PERFORMANCE TESTING - ANIMAL

An earlier version of the Vibrant Capsule was evaluated in (b)(4) proof-of-concept (b)(4) studies. The testing evaluated preliminary safety and performance of the capsules. The studies did not identify any significant safety signals.

SUMMARY OF CLINICAL INFORMATION

A pivotal study (V270) was conducted to evaluate the safety and effectiveness of the Vibrant Capsules. The study was conducted in compliance with 21 CFR parts 50, 56, and 812. V270 was a prospective, randomized, multi-center, double-blinded, placebo-controlled pivotal study. The study included two active treatment arms that used different vibration patterns (i.e., Active Mode 1 and Active Mode 2) and a control arm. For the first part of the study, subjects were randomized equally to each arm in a 1:1:1 ratio, for a treatment period of 8 weeks. A "drop the loser" design was pre-specified, whereby the lower performing active treatment was dropped from the study following an interim analysis. After the lower performing active arm was dropped, future subjects were randomized to each of the remaining arms on a 1:1 ratio. The alpha value was adjusted to two-sided 0.025 to account for this design.

Vibrant Capsules were administered 5 times per week, and the treatment arm was compared to a control arm. The sham used in the control arm was a placebo consisting of a biodegradable soft-gel capsule filled with soybean oil, beeswax, and calcium carbonate. The study population was comprised of subjects with chronic idiopathic constipation (CIC) who were refractory to existing OTC or Rx treatments or could not tolerate with the side effects. Patient eligibility was assessed during the initial screening visit and was re-assessed and confirmed during the Baseline visit following a 2–3-week run-in period. Randomization occurred following the 2–3-week run-in

period and verification that the patient satisfied all inclusion criteria and did not meet any exclusion criteria.

Endpoints

Primary Effectiveness endpoint

- Complete Spontaneous Bowel Movements (CSBM1) success rate, defined as an increase from the run-in period of at least one weekly CSBM during at least 6 of the 8 weeks of treatment.
- Complete Spontaneous Bowel Movements (CSBM2) success rate, defined as an increase from the run-in period of at least two weekly CSBM during at least 6 of the 8 weeks of treatment.

Study success was defined as either the CSBM1 or the CSBM2 success rate being statistically significantly higher in the active arm that was continued after interim analysis, than in the control arm, as evaluated in the modified Intent to Treat (mITT) population, which is described in the "Subject Accountability" section, below.

Primary Safety endpoint

All adverse events (AEs) related and unrelated to the study treatment, in the Intent to Treat (ITT) population, as described in the "Subject Accountability" section, below.

Secondary endpoints

- Change from baseline in average straining, using a scale from 0 (no straining) to 10 (unbearable straining).
- Change from baseline in average stool consistency, using the Bristol Stool Scale.
- Change from baseline in average bloating, using a scale from 0 (no bloating) to 10 (unbearable bloating).

Selected additional secondary endpoints

- Treatment satisfaction score using the Treatment Satisfaction Questionnaire for Medication (TSQM)
- Change from baseline in quality of life using the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL) questionnaire

Subject accountability

A total of 904 subjects were consented and screened. 555 subjects were not randomized: 89% (493/555) were considered screen failures, 5% (28/555) withdrew consent prior to randomization, 2% (10/555) were lost to follow up before randomization, and the other 4% (24/555) for other reasons. A total of 349 consenting subjects were enrolled in the study and randomized. It was subsequently determined that one of the 349 randomized subjects did not meet the eligibility criteria, and 12/349 subjects had less than 2 weeks of diary entries with at least 5 days/week (requirement for randomization); these subjects were thus included in the Intention to Treat (ITT) analysis set but excluded from the modified ITT (mITT) analysis set. Three subjects in the mITT analysis set had major protocol deviations and were thus excluded from the Per Protocol (PP) analysis set. Subjects with less than 6 weeks of diary data were

considered as failures for the CSBM1, and CSBM2 success rates. The final treatment allocation and analysis sets are shown in Table 2.

Table 2: Treatment Allocation

	Active Mode 1	Active Mode 2	Control	Total
ITT analysis set	163	37	149	349
mITT analysis set	158	34	144	336
PP analysis set	155	34	144	333

Patient demographics are shown in Table 3.

Table 3: Demographic Characteristics – ITT

			Active Mode 1	Active Mode 2	Control	Total	p-value (Active Mode 1 vs Control)
Age, years		N	163	37	149	349	0.4391(*)
		Mean (SD)	47.1 (13.33)	45.0 (12.25)	45.9 (13.47)	46.4 (13.26)	
		Median [Range]	47.4 [20.6;77.8]	44.0 [22.2;76.0]	44.8 [22.1;78.1]	45.0 [20.6;78.1]	
Gender	Male	% (n/N)	12.3% (20/163)	24.3% (9/37)	15.4% (23/149)	14.9% (52/349)	0.4177(#)
	Female	% (n/N)	87.7% (143/163)	75.7% (28/37)	84.6% (126/149)	85.1% (297/349)	
Race/Ethnicity	Caucasian	% (n/N)	47.2% (77/163)	59.5% (22/37)	40.3% (60/149)	45.6% (159/349)	0.7624(#)
	Hispanic or Latino	% (n/N)	19.0% (31/163)	8.1% (3/37)	22.8% (34/149)	19.5% (68/349)	
	Black or African American	% (n/N)	25.2% (41/163)	29.7% (11/37)	26.2% (39/149)	26.1% (91/349)	
	Asian/ Pacific Islander	% (n/N)	6.1% (10/163)	2.7% (1/37)	8.1% (12/149)	6.6% (23/349)	
	Other	% (n/N)	2.5% (4/163)	-	2.7% (4/149)	2.3% (8/349)	

(*) t-test
(#) x^2 test

Effectiveness results

The pre-specified interim analysis was conducted on the results available from 116 enrolled subjects. At the interim analysis timepoint, the Active Mode 2 arm was dropped, and the study continued with only 2 arms: the most promising effectiveness treatment arm (Active Mode 1) and the control arm. The effectiveness results presented below are for the Active Mode 1 treatment arm and the control arm.

Table 4 presents the CSBM1 and CSBM2 success rates by study arm and analysis set. In the primary analysis population, the mITT set, the CSBM1 success rate was 40.51% in the treatment arm, compared to 22.92% in the control arm, a difference of 17.6% (chi-square p-value = 0.0011); and the CSBM2 success rate was 23.42% in the treatment arm, compared to 11.81% in the control arm, a difference of 10.0% (chi-square p-value = 0.0085). The primary effectiveness results met the study success criteria with both the CSBM1 and the CSBM2 success rates

statistically significantly higher in the active arm compared to the control. Similar results were also found in the PP and ITT analysis sets.

Table 4: CSBM1 and CSBM2 Success Rates in mITT, ITT, and PP Analysis Sets

		Treatment		Control		p-value (chi-square)
		% (n/N)	97.5% CI (Wilson Score)	% (n/N)	97.5% CI (Wilson Score)	
mITT	Improve by ≥ 1 CSBM, 6 out of 8 weeks	40.51% (64/158)	[32.18%;49.42%]	22.92% (33/144)	[16.06%;31.60%]	0.0011
	Improve by ≥ 2 CSBM, 6 out of 8 weeks	23.42% (37/158)	[16.76%;31.72%]	11.81% (17/144)	[7.03%;19.16%]	0.0085
PP	Improve by ≥ 1 CSBM, 6 out of 8 weeks	40.65% (63/155)	[32.23%;49.65%]	22.92% (33/144)	[16.06%;31.60%]	0.0010
	Improve by ≥ 2 CSBM, 6 out of 8 weeks	23.23% (36/155)	[16.54%;31.60%]	11.81% (17/144)	[7.03%;19.16%]	0.0098
ITT	Improve by ≥ 1 CSBM, 6 out of 8 weeks	39.26% (64/163)	[31.13%;48.04%]	22.15% (33/149)	[15.50%;30.61%]	0.0011
	Improve by ≥ 2 CSBM, 6 out of 8 weeks	22.70% (37/163)	[16.23%;30.80%]	11.41% (17/149)	[6.79%;18.55%]	0.0085

Secondary endpoints

There was an observed reduction in straining in the active arm compared to the control arm (Table 5). Staining was measured using a subject reported scale from 0 (no straining) to 10 (unbearable straining).

Table 5: Change from Baseline in Straining (Adjusted Baseline)

		Adj. Mean	SE	Two-sided 97.5% CI
mITT	Treatment	-1.78	0.15	[-2.12;-1.44]
	Control	-1.32	0.16	[-1.68;-0.97]
	Diff. (Treatment-Control)	-0.46	0.22	[-0.95;0.03]
PP	Treatment	-1.80	0.15	[-2.15;-1.46]
	Control	-1.33	0.16	[-1.69;-0.98]
	Diff. (Treatment-Control)	-0.47	0.22	[-0.96;0.02]
ITT	Treatment	-1.71	0.15	[-2.04;-1.37]
	Control	-1.29	0.16	[-1.65;-0.94]
	Diff. (Treatment-Control)	-0.41	0.22	[-0.90;0.08]

There was an observed improvement in stool consistency (rated using the Bristol Stool scale) in the active arm compared to the control arm (Table 6).

Table 6: Change from Baseline in Stool Consistency (Adjusted for Baseline)

		Adj. Mean	SE	Two-sided 97.5% CI
mITT	Treatment	1.03	0.08	[0.85;1.21]
	Control	0.58	0.08	[0.39;0.76]
	Diff. (Treatment-Control)	0.45	0.11	[0.19;0.71]
PP	Treatment	1.02	0.08	[0.84;1.20]
	Control	0.58	0.08	[0.40;0.77]
	Diff. (Treatment-Control)	0.44	0.12	[0.18;0.70]
ITT	Treatment	0.99	0.08	[0.81;1.16]
	Control	0.57	0.08	[0.38;0.75]
	Diff. (Treatment-Control)	0.42	0.11	[0.16;0.68]

No difference was observed in the bloating sensation endpoint (Table 7). Bloating was measured using a subject reported scale from 0 (no bloating) to 10 (unbearable bloating).

Table 7: Change from Baseline in Bloating Sensation (Adjusted for Baseline)

		Adj. Mean	SE	Two-sided 97.5% CI
mITT	Treatment	-0.42	0.11	[-0.67;-0.17]
	Control	-0.37	0.12	[-0.63;-0.10]
	Diff. (Treatment-Control)	-0.06	0.16	[-0.42;0.30]
PP	Treatment	-0.44	0.11	[-0.70;-0.19]
	Control	-0.37	0.12	[-0.63;-0.11]
	Diff. (Treatment-Control)	-0.08	0.16	[-0.44;0.29]
ITT	Treatment	-0.40	0.11	[-0.64;-0.15]
	Control	-0.36	0.11	[-0.62;-0.10]
	Diff. (Treatment-Control)	-0.04	0.16	[-0.39;0.32]

Safety results

The ITT data analysis set served as the principal set for the safety analysis: 200 treatment subjects (37 from Active Mode 2 arm and 163 from Active Mode 1 arm) and 149 control subjects. A total of 114 AEs were reported during the study: 74 AEs experienced by 62 treatment subjects (31.0%), and 40 AEs experienced by 26 subjects (17.45%) in the control arm. Two AEs, both in the control arm, were classified as serious adverse events (SAEs), but were not considered related to the study treatment. There were no SAEs reported in the treatment arms.

49 AEs were considered possibly, probably, or definitely related to the study treatment or procedure (41 in the treatment arm, and 8 in the control arm) by study investigators (Table 8). Device and procedure related AEs reported in the study included abdominal pain, abdominal distension, abdominal discomfort, vomiting, nausea, diarrhea, flatulence, and proctalgia (rectal spasm or cramp). Medical device discomfort events characterized as sensation of vibration were the most commonly reported device related AE, with 19 subjects (9.5%) in the Active Mode 1 and 2 treatment arms reporting 21 events (none in the control).

Table 8: Related adverse events that are possibly, probably, or definitely related to the study treatment or procedure, by system organ class, preferred term and relationship (ITT)

			Treatment (Active Modes 1 and 2)			Control		
System Organ Class	Preferred Term	Relation to Device	# of reports	# of subjects	Incidence	# of reports	# of subjects	Incidence
Total	*Total*	Total	41	29	14.50%	8	5	3.36%
		Possibly related	12	7	3.50%	7	4	2.68%
		Probably related	8	6	3.00%	1	1	0.67%
		Related	18	15	7.50%	.	.	.
		Related to procedure	3	2	1.00%	.	.	.

Gastrointestinal disorders	*Total*	Possibly related	9	5	2.50%	7	4	2.68%
		Probably related	5	5	2.50%	1	1	0.67%
	Abdominal pain	Possibly related	1	1	0.50%	2	2	1.34%
	Vomiting	Possibly related	3	3	1.50%	.	.	.
	Nausea	Possibly related	1	1	0.50%	.	.	.
		Probably related	1	1	0.50%	.	.	.
	Diarrhoea	Possibly related	1	1	0.50%	.	.	.
		Probably related	1	1	0.50%	.	.	.
	Abdominal distension	Possibly related	1	1	0.50%	1	1	0.67%
	Flatulence	Possibly related	1	1	0.50%	.	.	.
	Constipation	Possibly related	1	1	0.50%	.	.	.
	Proctalgia	Possibly related	.	.	.	1	1	0.67%
		Probably related	1	1	0.50%	.	.	.
	Abdominal discomfort	Probably related	2	2	1.00%	.	.	.
	Anorectal discomfort	Possibly related	.	.	.	2	1	0.67%
	Abdominal pain lower	Possibly related	.	.	.	1	1	0.67%
	Abdominal pain upper	Probably related	.	.	.	1	1	0.67%
General disorders and administration site conditions	*Total*	Possibly related	1	1	0.50%	.	.	.
		Probably related	3	3	1.50%	.	.	.
		Related	16	14	7.00%	.	.	.
		Related to procedure	2	1	0.50%	.	.	.
	Medical device discomfort	Possibly related	1	1	0.50%	.	.	.
		Probably related	3	3	1.50%	.	.	.
		Related	16	14	7.00%	.	.	.
		Related to procedure	1	1	0.50%	.	.	.
	Discomfort	Related to procedure	1	1	0.50%	.	.	.
Reproductive system and breast disorders	*Total*	Possibly related	1	1	0.50%	.	.	.
	Amenorrhoea	Possibly related	1	1	0.50%	.	.	.
Nervous system disorders	*Total*	Possibly related	1	1	0.50%	.	.	.
	Headache	Possibly related	1	1	0.50%	.	.	.
Psychiatric disorders	*Total*	Related	1	1	0.50%	.	.	.
	Sleep disorder	Related	1	1	0.50%	.	.	.
	Total	Related	1	1	0.50%	.	.	.

Injury, poisoning and procedural complications	*Intentional device misuse*	Related	1	1	0.50%	.	.	.
Investigations	*Total*	Related to procedure	1	1	0.50%	.	.	.
	Weight decreased	Related to procedure	1	1	0.50%	.	.	.

ADDITIONAL CLINICAL INFORMATION

Five smaller clinical trials were conducted prior to the V270 pivotal study. The studies included a total of 499 subjects and varied from the V270 study treatment protocol in the dosing regimen, number of capsule vibration sets while passing through the large intestine, and/or the number of capsule administered per week. The prior studies do not support effectiveness of the Vibrant System. However, FDA considered the cumulative safety data in these studies to support safety of the Vibrant System. Safety data from these prior studies are consistent in the type, severity and frequency of adverse events reported in the V270 pivotal study.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

Physician labeling includes the device indications for use, a description of the device, warnings and precautions, clinical data on the device, and instructions for the safe and effective use of the device. The labeling satisfies the requirements of 21 CFR 801.109 Prescription devices. Per the Special Controls for this generic type of device, labeling includes a summary of device effectiveness and device related adverse events.

RISKS TO HEALTH

Table 9 identifies the risks to health that may be associated with use of an orally ingested transient device for constipation, and the measures necessary to mitigate these risks.

Table 9 Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Infection	Bioburden testing Labeling Shelf life testing
Adverse tissue reaction	Biocompatibility evaluation
Device malfunction leading to injury	Electrical safety testing Software validation, verification, and hazard analysis Non-clinical performance testing Labeling Shelf life testing
Interference with other devices	Electromagnetic compatibility testing
Failure to excrete capsule	Clinical data

	Labeling
Device related adverse events including: • Choking • Abdominal pain • Abdominal distension • Abdominal discomfort • Vomiting • Nausea • Proctalgia • Diarrhea	Clinical data Non-clinical performance testing Labeling
Device ineffective leading to constipation and effects of delayed treatment	Clinical data Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, an orally ingested transient device for constipation is subject to the following special controls:

(1) Clinical data must demonstrate the device performs as intended and evaluate the following:
   (i) Treatment of constipation; and
   (ii) All adverse events.

(2) Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (i) Dimensional testing must verify device dimensions;
   (ii) Performance bench testing must verify functional aspects of the device design;
   (iii) Leak testing must verify device integrity under worst case clinical conditions;
   (iv) Bite testing must demonstrate that the device can withstand bite forces;
   (v) pH resistance testing must evaluate integrity of the capsule when exposed to a physiological relevant range of pH values; and
   (vi) Bioburden testing must demonstrate the device does not pose an infection risk throughout the labeled shelf life.

(3) The patient-contacting components of the device must be demonstrated to be biocompatible.

(4) Performance data must support the shelf life of the device by demonstrating continued package integrity and device functionality over the labeled shelf life.

(5) Software validation, verification, and hazard analysis must be performed.

(6) Electrical safety and electromagnetic compatibility (EMC) testing must be performed for any electrical components of the device.

(7) Labeling for the device must include:
   (i) A summary of clinical data for the device, including a discussion of adverse events and clinical benefit; and
   (ii) A shelf life.

BENEFIT-RISK DETERMINATION

Nonclinical laboratory studies as well as clinical data from a pivotal study (V270) and prior studies were used to evaluate the safety and effectiveness of the Vibrant System.

Summary of Benefits

The V270 pivotal study demonstrated a statistically significant and clinically meaningful benefit over the control. The study met both components of the primary endpoint with higher success rates in the treatment arm compared to the control arm. In 6 out of the 8 weeks of the study, 40.51% in the treatment arm had at least one more weekly CSBM, compared to 22.92% in the control arm, a difference of 17.6% (chi-square p-value = 0.0011, mITT, CSBM1). In 6 out of the 8 weeks of the study, 23.42% in the treatment arm had at least two more weekly CSBM, compared to 11.81% in the control arm, a difference of 10% (chi-square p-value = 0.0085, mITT, CSBM2). The improvements in the number of complete spontaneous bowel movements was statistically significant and clinically meaningful when considering an improvement of 1 and 2 bowel movements during at least 6 of the 8 weeks of treatment in a patient population with chronic idiopathic constipation who have not experienced relief of bowel symptoms by using laxative therapies at the recommended dosage for at least one month.

Factors that increase uncertainty in determining probable benefits for the Vibrant Systems include:

- Inconsistent or conflicting results between studies. Five clinical trials were conducted prior to the V270 pivotal study. The studies included a total of 499 subjects and varied from the V270 study treatment protocol in the dosing regimen, number of capsule vibration sets while passing through the large intestine, and/or the number of capsule administered per week. The prior studies did not support effectiveness of the Vibrant System.

- The effectiveness endpoint required an increase of at least one weekly complete spontaneous bowel movement (CSBM) during at least 6 of the 8 weeks of treatment. The study met the primary effectiveness endpoint; however, effectiveness in the CSBM1 treatment arm was 40.5% indicating the response to the Vibrant capsule treatment was not experienced by 59.5% of the treated subjects.

- The long-term effectiveness of the device has not been studied beyond 8 weeks.

Summary of Risks

A total of 114 AEs were reported during the study. Two AEs were classified as serious adverse events (SAEs) in the control arm that were not considered related to the study treatment. There were no SAEs reported in the treatment arms. 49 AEs were considered possibly, probably, or definitely related to the study treatment or procedure (41 in the treatment arm, and 8 in the control arm). Device and procedure related adverse events reported in the study included abdominal pain, abdominal distension, abdominal discomfort, vomiting, nausea, diarrhea,

flatulence, and proctalgia. Medical device discomfort events characterized as sensation of vibration were the most commonly reported device related AE, with 19 subjects (9.5%) in the Active Mode 1 and 2 treatment arms reporting 21 events (none in the control).

Factors that increase uncertainty in determining probable risks for the Vibrant System include:

- Insufficient patient numbers to detect less common serious events.
- Insufficient duration of follow-up to detect delayed/late events. The long-term risks associated with continued repeat use of the device beyond 8 weeks are unknown. The pivotal study collected safety data for 8 weeks.
- The V270 pivotal study did not include evaluation for capsule retrievals once they passed through the GI tract. An earlier safety study (V111) evaluated capsule retrieval directly in a 28 subject safety study and reported a capsule retrieval rate of 85%; however, subjects in the V111 study had difficulty identifying the capsules in bowel movements.

Patient Perspectives

Patient perspectives were measured in the V270 trial as an additional endpoint assessment. Treatment Satisfaction Questionnaire for Medication (TSQM)[1] scores were evaluated in the V270 study. The TSQM score for effectiveness was reported to be higher in the treatment arm relative to the control arm. The mean scores for side-effects, convenience, and global satisfaction were similar in both groups.

Change from baseline in quality of life using the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL) questionnaire[2] was evaluated in the V270 study. More subjects reported an improvement in quality of life from baseline on the PAC-QOL in the active arm 1 than in the control arm (77.9% of active arm 1 subjects versus 66.2% of control arm subjects).

Benefit/Risk Conclusion

The V270 pivotal study reports a statistically significant and clinically meaningful clinical benefit for the Vibrant System treatment of chronic idiopathic constipation with an improvement in the number of complete spontaneous bowel movements per week over an 8-week treatment course. Considering the types, numbers, and mild-to-moderate severity of adverse events in the treatment arm compared to the control arm, there is an overall favorable benefit-risk profile that supports granting this De Novo request.

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[1] Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004 Feb 26;2:12. doi: 10.1186/1477-7525-2-12. PMID: 14987333; PMCID: PMC398419.

[2] Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scand J Gastroenterol. 2005 May;40(5):540-51. doi: 10.1080/00365520510012208. PMID: 16036506.

In conclusion, given the available information above, the probable benefits outweigh the probable risks for the Vibrant System when used as indicated. The device provides benefits, and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Vibrant System is granted and the device is classified as follows:

Product Code: QTN
Device Type: Orally ingested transient device for constipation
Regulation Number: 21 CFR 876.5940
Class: II