January 16, 2019

Dosis, Inc.
% E.J. Smith
Consultant
Smith Associates
1468 Harwell Ave.
Crofton, MD 21114

Re: K180410
Trade/Device Name: Smart Anemia Manager (SAM)
Regulation Number: 21 CFR§ 876.5820
Regulation Name: Hemodialysis System and Accessories
Regulatory Class: II
Product Code: MQS
Dated: December 7, 2018
Received: December 11, 2018

Dear E.J. Smith:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies.

You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Carolyn Y. Neuland -S

for
Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K180410

Device Name
Smart Anemia Manager (SAM)

Indications for Use *(Describe)*
SAM is a web application used to obtain, track and trend patient data pertaining to the management of anemia, and to provide a schedule of erythropoiesis-stimulating agent (ESA) dosage recommendations to help achieve and maintain target hemoglobin (Hgb) levels in hemodialysis patients. The device is intended to help clinicians manage chronic anemia.

The device is not a substitute for, but rather intended to assist, clinical judgment. The ESA dosing regimen options calculated by this device are intended to inform the optimization of the dosage of ESAs in accordance with their approved labeling in conjunction with clinical history, symptoms, and other diagnostic measurements, as well as the clinicians' judgment. No medical decision should be based solely on the patient Hgb response to dosing regimen options calculated by this device.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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510(k) Summary

Company Name: Dosis, Inc.
Company Address: 353 Sacramento Street
Suite 1811
San Francisco, CA 94111

Telephone: 650 383 0186
Contact Person: Shivrat Chhabra

Summary Preparation Date: 01/14/2019

Device Description:
Device Name: Smart Anemia Manager (SAM)
Common Name: Anemia Software Management
Classification Name Hemodialysis System and Accessories
Regulatory Class: Class II
Product Code: MQS
C.F.R. Section: 21 CFR 876.5820

PREDICATE DEVICE:

Manufacturer	Product Name	510(k) Number
Physician Software Systems, LLC	PhySoft AMS™	K130579

DEVICE DESCRIPTION:

SAM is a web application used to obtain, track and trend patient data pertaining to the management of anemia, and to provide a schedule of erythropoiesis-stimulating agent (ESA) dosage recommendations to help achieve and maintain target hemoglobin (Hgb) levels in hemodialysis patients. The device is intended to help clinicians manage chronic anemia.

Healthcare professionals access SAM using a web-enabled application (for example, a web browser or a web-enabled electronic health record system) communicating with the SAM web application server. Patient information is obtained by SAM from healthcare provider Electronic Medical Records. No components of SAM are required to be installed at end user or healthcare provider locations.

SAM estimates individual patient's Hgb response to ESAs. The results of this estimation are used to generate new patient-specific ESA dose recommendation to achieve target Hgb level specified by the physician. The ESA dose recommendation is reviewed by the physician, who after considering any additional relevant information about patient's condition, decides whether to follow or override the presented ESA dose recommendation.

INDICATIONS FOR USE:

SAM is a web application used to obtain, track and trend patient data pertaining to the management of anemia, and to provide a schedule of erythropoiesis-stimulating agent (ESA) dosage recommendations to help achieve and maintain target hemoglobin (Hgb) levels in hemodialysis patients. The device is intended to help clinicians manage chronic anemia.

The device is not a substitute for, but rather intended to assist, clinical judgment. The ESA dosing regimen options calculated by this device are intended to inform the optimization of the dosage of ESAs in accordance with their approved labeling in conjunction with clinical history, symptoms, and other diagnostic measurements, as well as the clinicians' judgment. No medical decision should be based solely on the patient Hgb response to dosing regimen options calculated by this device.

SUBSTANTIALLY EQUIVALENCE DISCUSSION:

	Dosis	Physicians Software System, LLC	Similarities and Difference
Product Name	SAM	PhySoft AMS™	
Indications for Use Statement	SAM is a web application used to obtain, track and trend patient data pertaining to the management of anemia, and to provide a schedule of erythropoiesis-stimulating agent (ESA) dosage recommendations to help achieve and maintain target hemoglobin (Hgb) levels in hemodialysis patients. The device is intended to help clinicians manage chronic anemia. The device is not a substitute for, but rather intended to assist, clinical judgment. The ESA dosing regimen options calculated by this device are intended to inform the optimization of the dosage of ESAs in accordance with their approved labeling in conjunction with clinical history, symptoms, and other diagnostic measurements, as well as the clinicians' judgment. No medical decision should be	PhySoft AMS™ is a web application used to obtain, track and trend patient data pertaining to the management of anemia, and to provide a schedule of erythropoiesis-stimulating agent (ESA) dosage recommendations to help achieve and maintain target hemoglobin levels in dialysis patients. PhySoft AMS™ is intended to help physicians, nurses, clinicians and anemia managers manage anemia in adult stage 5 chronic kidney disease (CKD) patients. The PhySoft AMS™ is not a substitute for, but rather intended to assist, clinical judgment. The ESA dosing regimen options calculated by this device are intended to be used by qualified and trained medical personnel to inform the optimization of the dosage of ESAs in accordance with their approved labeling in conjunction with clinical history, symptoms, and other diagnostic measurements, as	Same

	based solely on the patient Hgb response to dosing regimen options calculated by this device.	well as the medical professional's clinical judgment. No medical decision should be based solely on the patient Hgb response to dosing regimen options calculated by this device.	

Technological Characteristics			
Parameters	Dosis	Physicians Software System, LLC	Similarities and Differences
510(k) Number:		K130579	
Product Code	MQS	MQS	Same
Regulation Number	21 CFR 876.5820	21 CFR 876.5820	Same
Principle of Operation	Track and trend Hgb and ESA dosages which can be used to determine future ESA dosages	Track and trend Hgb and ESA dosages which can be used to determine future ESA dosages	Same
Technology	Application used to trend patient data collected during each dialysis treatment	Application used to trend patient data collected during each dialysis treatment	Same
Patient Demographics	Adult stage 5 chronic kidney disease patients	Adult stage 5 chronic kidney disease patients	Same
Intended User	Physician/Clinicians/Nurses	Physician/Clinicians/Nurses	Same
Data Storage	Data is stored electronically	Data is stored electronically	Same
Data Management	Generates reports and graphs to assist anemia management	Generates reports and graphs to assist anemia management	Same
Safeguards/Alerts	System flags patients who exceed limits	System flags patients who exceed limits	Same

Technological Characteristics			
Parameters	Dosis	Physicians Software System, LLC	Similarities and Differences
510(k) Number:		K130579	
Product Code	MQS	MQS	Same
Regulation Number	21 CFR 876.5820	21 CFR 876.5820	Same
Principle of Operation	Track and trend Hgb and ESA dosages which can be used to determine future ESA dosages	Track and trend Hgb and ESA dosages which can be used to determine future ESA dosages	Same
Technology	Application used to trend patient data collected during each dialysis treatment	Application used to trend patient data collected during each dialysis treatment	Same
Patient Demographics	Adult stage 5 chronic kidney disease patients	Adult stage 5 chronic kidney disease patients	Same
Intended User	Physician/Clinicians/Nurses	Physician/Clinicians/Nurses	Same
Data Storage	Data is stored electronically	Data is stored electronically	Same
Data Management	Generates reports and graphs to assist anemia management	Generates reports and graphs to assist anemia management	Same
Technology/Algorithm	Uses individualized dose response model to compute patient dose response.	Uses individualized dose response model to compute patient dose response.	Same
	Account for effects of last ESA dose.	Account for effects of multiple prior ESA dosages.	In SAM effect of multiple prior ESA dose is embedded in Hgb trend.
	Estimates ongoing dosing schedules to achieve target Hgb levels using close-loop approach.	Estimates ongoing dosing schedules to achieve target Hgb levels using open-loop approach.	In SAM close-loop allows for potential mismatch

Technological Characteristics			
Parameters	Dosis	Physicians Software System, LLC	Similarities and Differences
			between model and patient.
Data Entry	Patient data is transferred electronically from existing healthcare provider information systems.	Patient data is transferred electronically from existing healthcare provider information systems.	Same
Data Storage	Data is stored electronically in a remote database server	Data is stored electronically on local or remote database server	SAM does not store data locally
Data Network Access	Data is accessed over secure internet connections.	Data is accessed over secure internet connections.	Same
Safeguards/Alerts	System flags patients who exceed limits	System flags patients who do not respond as predicted and may have undetected health issues that do not fit the most probable model.	SAM does not flag undetected health issues.
Minimum Data Requirement		Evaluates patient readiness for application of algorithm to model ESA dose-Hgb response (sufficient history of Hgb and ESA dosing).	SAM does not have a minimum dosing history requirement only requires a single HgB measurement.

Discussion of Similarities and Differences:

Similarities

- SAM has the same indications for use, principle of operation, technology, patient demographics, intended users, data storage, data management, safe guards and alerts, technology/algorithm, data entry, and data network access and raises no new issues of safety and effectiveness, as a result of this submission.
- SAM has a similar algorithm as the predicate device. Both software systems were verified and validated using the recommendations found in FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,

Document issued on: May 11, 2005 and the results raises no new issues of safety and effectiveness.

Differences

- The combination of past ESA doses will impact future HgB concentrations and SAM uses the most recent ESA dose as a predictor of future HgB. Additional information on past ESA dose is present in HgB trend. Both methods use past ESA dose in different ways for the same end result.
- SAM uses close loop control and therefore can better acknowledge and adjust for errors in drug dosing and the measurement of HgB. This should lead to at least similar accuracy compared to the predicate and is a superior method when compared to open loop control.
- SAM only stores data on a remote HIPPA compliant server and avoids the potential problem with local data storage and potential data incursion. There is no effect on predictive performance due to data storage methods.
- SAM and the predicate both identify when the observed HgB is different from the prediction. SAM uses this information in the close loop control methodology to improve the prediction in the future. The predicate only flags the individual as not responding as expected and might be able to suggest the cause but does not adjust the prediction to account for this error like a close loop control method. The impact should not be substantially different between methods except that close loop control can potentially lead to improved future predictions.
- SAM does not have a minimum data requirement to estimate patient response and can make recommendations based on a single HgB measurement. This difference will allow SAM to make recommendations in patients that the predicate cannot.

Non-clinical Performance Tests

Simulation Testing

The performance of the SAM software was tested through simulation and comparison to anemia management using usual practice in the form of an anemia management protocol in use at 2 large dialysis providers.

Purpose

Demonstrate the efficacy and safety of the SAM software in the dosing of erythropoietin (ESA) for the treatment of anemia in a simulated patient population compare to usual care.

Subjects

Anemic subjects were simulated based on their response to an ESA using the concepts published on the pharmacodynamics of erythropoietin (Uehlinger et al. Clin Pharmacol

Ther 51:76-89, 1992). Subject had a broad range of responsiveness that encompassed that observed in the target population.

Study Design

In silico three way cross over simulation.

Outcome Variables

Methods

A pool of 2430 patients were created based on a range of ESA response measures and red blood cell life spans essentially generating a cohort of test subjects that range to hyper to hypo responsive to ESA. ESA dosing was then simulated to achieve steady state hemoglobin concentrations using the SAM software or conventional therapy using an anemia management protocol 1 or 2 (AMP1 or AMP2). Noise was introduced into the system to simulate the uncertainty in the measurement of hemoglobin between 0.0 and 1.0 g/dL. We recorded the mean achieve hemoglobin, time to steady state, hemoglobin variability, percent in target range, and mean ESA/week. A total of 26,730 simulations were run for each protocol. Target range was a hemoglobin between 10.0 and 12.0 g/dL. The goal was to demonstrate non-inferiority to AMP 1 and 2 in mean hemoglobin, percent in target range and hemoglobin standard deviation.

Results

The results of the simulations are shown in the following tables:

Time to target, Mean achieved Hgb, and Standard Deviation for AMP1, AMP2, and SAM

	Time to Target (weeks)			Mean Hgb (g/dL)			Hgb Standard Deviation (g/dL)		
Noise (g/dL)	AMP1	AMP2	SAM	AMP1	AMP2	Dosis SAM	AMP1	AMP2	Dosis SAM
0.0	5.2	4.5	12.6	11.2	12.3	10.9	0.5	1.4	0.2
0.1	5.4	4.5	12.4	11.2	12.3	10.9	0.6	1.4	0.3
0.2	5.3	4.6	11.9	11.1	12.3	10.9	0.6	1.5	0.4
0.3	5.3	4.8	11.6	11.1	12.4	10.9	0.7	1.6	0.4
0.4	5.5	4.5	11.0	11.1	12.4	10.9	0.8	1.7	0.5
0.5	5.5	4.7	10.2	11.0	12.4	10.9	0.9	1.8	0.6
0.6	5.5	4.5	9.8	11.0	12.4	10.9	1.0	1.8	0.7
0.7	5.2	4.8	9.5	11.0	12.5	10.8	1.1	1.9	0.9
0.8	5.2	4.7	8.9	11.0	12.6	10.8	1.2	2.0	0.9
0.9	5.7	4.7	8.3	11.0	12.7	10.8	1.3	2.1	1.1
1.0	5.7	4.5	7.7	11.0	12.7	10.8	1.4	2.2	1.2

The approaches resulted in differences in respect to time to target with SAM taking longer to reach the target Hgb. The mean Hgb achieved was similar between SAM and AMP1, but AMP2 routinely exceeded the target Hgb range of 10 to 12 g/dL. SAM had lower Hgb variability. The impact of these observations can be seen in the next table

comparing the percent of Hgb concentrations within the target range of 10 to 12 g/dL and the amount of ESA used to achieve this result.

	Percent Hgb 10 to 12			ESA Dose (units)		
Noise (g/dL)	AMP1	AMP2	SAM	AMP1	AMP2	Dosis SAM
0.0	67.7	50.1	74.1	11217	11554	7356
0.1	67.2	50.6	74.0	11186	11575	7352
0.2	65.5	49.3	73.9	11116	11759	7344
0.3	61.4	47.5	72.7	10869	11834	7337
0.4	57.6	46.1	70.6	10709	11910	7338
0.5	53.5	44.1	66.8	10455	12013	7307
0.6	51.0	41.7	62.7	10282	12147	7289
0.7	47.4	38.1	58.2	10252	12560	7277
0.8	45.4	36.7	55.8	10218	12651	7239
0.9	42.9	34.7	51.0	10131	12925	7232
1.0	40.2	33.2	48.0	9852	13074	7167

SAM resulted in a greater percent of Hgb observations within the target range and a lower utilization of ESA.

Other Testing

- ISO 14971 Second edition 2007-03-01, Medical devices - Application of risk management to medical devices.
- Software Verification and Validation were conducted based on the use of Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, Document issued on: May 11, 2005

Clinical Studies

Executive Summary

SAM software was tested in 2 clinical trials. The first trial was a randomized, controlled, double blind trial against standard of care conducted in 62 subjects over a 12 month period. 52 subject completed the study. The proportion of hemoglobin concentrations within the target range was greater for SAM (72.5%) than control (61.9%) (p=0.003). There was no difference in a Composite Safety Event (CSE) as a combination of All-Cause Mortality (ACM), Myocardial Infarction (MI), Cerebrovascular Accident (CVA), and (exacerbation of) Congestive Heart Failure (CHF). The second trial was a combination of a case controlled and cross sectional study. Efficacy was maintained over the 45 month long term follow up where hemoglobin concentrations within the target range ranged from 76.8% to 86.3% for SAM compared to 73.5% to 89.1% for PhySoft AMS™. Safety was maintained over the 45 month long term follow up where hemoglobin concentrations above 12.9 g/dL ranged from 1.5% to 8.7% for SAM compared to 5.9% to 9.4% for PhySoft AMS™. No statistical difference was observed between SAM and PhySoft AMS™ performance.

Conclusion

Smart Anemia Manager (SAM) is substantially equivalent in Indications for Use, principle of operation and technological characteristics to the predicate device. SAM is substantially equivalent in clinical performance as demonstrated in comparison of published performance measures with the predicate device. Dosis. Inc.'s software validation and verification has demonstrated the safety and effectiveness of the SAM software in anemia management for hemodialysis patients and it is the conclusion of Dosis, Inc., that the SAM raises no new questions of safety and effectiveness and is substantially equivalent to the predicate device.