DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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May 26, 2016

GENMARK DIAGNOSTICS, INCORPORATED
ALAN MADERAZO
VP, QUALITY, REGULATORY, & CLINICAL AFFAIRS
5964 LA PLACE COURT
CARLSBAD CA 92008

Re: k152612
Trade/Device Name: eSensor Warfarin Sensitivity Saliva Test
Regulation Number: 21 CFR §862.3360
Regulation Name: Drug Metabolism Enzyme Genotyping Test
Regulatory Class: II
Product Code: ODW, ODV, NSU
Dated: April 21, 2016
Received: April 22, 2016

Dear Mr. Maderazo:

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. 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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney H. Lias -S

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
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and Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K152612

Device Name
eSensor® Warfarin Sensitivity Saliva Test

Indications for Use *(Describe)*
The eSensor® Warfarin Sensitivity Saliva Test is an in vitro diagnostic for the detection and genotyping of the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the Vitamin K epoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A) from genomic DNA extracted from human saliva samples collected using the Oragene®•Dx and ORAcollect®•Dx devices, as an aid in the identification of patients at risk for increased warfarin sensitivity.

The eSensor® XT-8 instrument is an in vitro diagnostic device intended for genotyping multiple mutations or polymorphisms in an amplified DNA sample utilizing electrochemical detection technology.

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.

510(k) SUMMARY

eSensor® Warfarin Sensitivity Saliva Test

Attached is a 510(k) summary as described in 21 CFR 807.92

Sponsor Information

Submitted By:

Name:	GenMark Diagnostics, Incorporated
Address:	5964 La Place Court Carlsbad, CA 92008 (760) 448-4300

Company Contact:

Contact:	Alan Maderazo, Ph.D., RAC VP, Quality Assurance, Regulatory and Clinical Affairs
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Date Prepared: May 23, 2016

General Information

Trade Name: eSensor® Warfarin Sensitivity Saliva Test

eSensor® Warfarin Sensitivity Saliva Test

Device Description	Drug metabolizing enzyme genotyping test Prothrombin time test,
Medical Specialty	Hematology
Product Code	ODW, ODV
Device Class	2
Regulation number	862.3360, 864.7750

Instrument (XT-8)

Device Description	Instrumentation for clinical multiplex test systems
Medical Specialty	Clinical Chemistry
Product Code	NSU
Device Class	2
Regulation number	862.2570

Predicate device: eSensor® Warfarin Sensitivity Saliva Test, K110786

This premarket application is a labeling modification to a previously cleared device: addition of a new specimen collection kit.

Device Description

The kit consists of the eSensor® Warfarin Sensitivity Saliva Test cartridge, the eSensor® Warfarin Sensitivity Saliva Test amplification reagents (including PCR mix and DNA polymerase), the eSensor® Warfarin Sensitivity Saliva Test detection reagents (including exonuclease, probes and hybridization buffer ingredients) and the eSensor® XT-8 System. One eSensor® Warfarin Sensitivity Saliva Test Kit has sufficient materials for 24 tests.

The polymorphisms genotyped by the eSensor® Warfarin Sensitivity Saliva Test are shown in Table 1.

Table 1. Polymorphisms in the eSensor® Warfarin Sensitivity Saliva Test Panel

Polymorphism	Allele†
CYP450 2C9 430 C>T	*2
CYP450 2C9 1075A>C	*3
VKORC1 -1639G>A	GG, GA, or AA

† CYP450 2C9 allele designations as established by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (http://www.cypalleles.ki.se/cyp2c9.htm). The major alleles of these polymorphisms are designated as *1.

Intended Use

The eSensor® Warfarin Sensitivity Saliva Test is an *in vitro* diagnostic for the detection and genotyping of the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the Vitamin K epoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A) from genomic DNA extracted from human saliva samples collected using the Oragene®•Dx and ORAcollect®•Dx devices, as an aid in the identification of patients at risk for increased warfarin sensitivity.

The eSensor® XT-8 instrument is an *in vitro* diagnostic device intended for genotyping multiple mutations or polymorphisms in an amplified DNA sample utilizing electrochemical detection technology.

Comparison to Predicate

This premarket application is a labeling modification to a previously cleared device: addition of a new specimen collection kit (the ORAcollect®·Dx Device manufactured by DNA Gentek). The data supporting the use of this specimen collection kit are provided in K152464.

Similarities		
Item	**Proposed Device**	**Predicate Device (K110786)**
Intended Use	For the detection and genotyping of the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the Vitamin K epoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A)	Same
Indications for Use	as an aid in the identification of patients at risk for increased warfarin sensitivity	Same
Device Components	Test cartridge, amplification reagents (including PCR mix and DNA polymerase), detection reagents (including exonuclease, probes and hybridization buffer ingredients) and the eSensor® XT-8 System.	Same
Differences		
Item	**Proposed Device**	**Predicate Device (K110786)**
Specimen Collection Kit	ORAcollect®·Dx Device	Oragene®•Dx Device
DNA Extraction Method	QIAAMP DNA Mini Kit extraction method; provided in Attachment B of the package insert	Manual ethanol extraction method; provided in Attachment A of the package insert

Performance Data

The following studies were conducted to validate the performance of the ORAcollect·Dx device:

- Reproducibility
- Method Comparison
- Interfering Substances

Summaries of the study results are provided. The formal study reports are provided in K152464.

Reproducibility

Reproducibility of the performance of the ORAcollect·Dx device was evaluated to establish multi-center (site-to-site), lot-to-lot, sample-to-sample, day-to-day extraction and operator-to-operator reproducibility.

Sample-to-Sample, Lot-to-Lot, Day-to-Day and Operator-to-Operator Reproducibility

Three samples (collected using three lots of ORAcollect·Dx format OCD-100) from each of ten donors, were processed by three different operators on multiple days. Each operator extracted DNA from each sample using the same Qiagen QIAamp DNA mini kit, followed by determination of DNA concentration and A_{260}/A_{280} ratio for all samples. Three operators tested the extracted DNA samples on the eSensor Warfarin Saliva Sensitivity Test. Genotyping data was evaluated after first-pass results and all samples were concordant to bi-directional sequencing.

Summary of Results Stratified by Operator

	SNP	Samples Tested	Correct Calls	Incorrect Calls	No-Calls	% Agreement
Operator 1	2C9*2	20	20	0	0	100%
	2C9*3	20	20	0	0	100%
	VKOR	20	20	0	0	100%
Operator 2	2C9*2	20	20	0	0	100%
	2C9*3	20	20	0	0	100%
	VKOR	20	20	0	0	100%
Operator 3	2C9*2	20	20	0	0	100%
	2C9*3	20	20	0	0	100%
	VKOR	20	20	0	0	100%
Combined	2C9*2	60	60	0	0	100%
	2C9*3	60	60	0	0	100%
	VKOR	60	60	0	0	100%

Summary of Results by Sample and Genotype

Donor ID	Genotype by sequencing			Number of Samples Tested by eSensor	Number of Correct Calls	% Agreement
	2C9*2	2C9*3	VKOR			
REP01	WT	WT	HET	12	12	100%
REP02	HET	WT	WT	12	12	100%
REP03	HET	WT	MUT	12	12	100%
REP04	HET	WT	WT	12	12	100%
REP05	HET	HET	HET	12	12	100%
REP06	WT	MUT	MUT	12	12	100%
REP07	MUT	WT	WT	12	12	100%
REP08	HET	HET	HET	12	12	100%
REP09	WT	WT	HET	12	12	100%
REP10	MUT	WT	WT	12	12	100%
Total				**120**	**120**	100%

Multi-center reproducibility

Thirty (30) donors collected multiple saliva samples each from 3 sites; 2 of the 3 sites were in a professional setting and had supervised collections compared to unsupervised collections at the third site. The 30 donors were selected to encompass a diverse genotype distribution for CYP2C9 and VKORC1 genotype distribution. After sample collection, one sample from each donor was transported at ambient temperatures to three (3) independent sites. Each site had one operator for a study total of 3 operators. Following sample extraction using the QIAamp DNA

mini kit, all purified genomic DNA samples were tested for DNA concentration, yield and A260/A280 at the sites where they were extracted. All purified genomic DNA samples were transported to Site 1 for testing on the eSensor Warfarin Sensitivity Saliva Test where one extracted DNA aliquot from each sample from each site was tested on the Warfarin assay, excluding a single sample that did not meet assay input criteria. When data from all three sites are combined, only one (1) sample did not meet the eSensor Warfarin Sensitivity Saliva Test input requirements. After final pass there was 100% agreement (89/89) with bidirectional sequencing.

Summary of Results by Site (Final Pass)

eSensor Warfarin Sensitivity Saliva Test* **					
Site of sample extraction*	Number of Samples Tested**	Correct Calls	Incorrect Calls	No-calls	% Agreement with Bi-directional Sequencing
Site 1	30	30	0	0	100%
Site 2	30	30	0	0	100%
Site 3****	29	29	0	0	100%

* DNA extraction using QIAGEN QIAMP DNA Mini kit.

** Donor genotype representation: CYP2C9 (*1, *2, *3); VKOR

*** All eSensor Warfarin Sensitivity Saliva testing was conducted at Site 1 (by Operator 1). Only sample aliquots meeting the WST input criteria were tested.

**** One sample was excluded from WST testing

Method Comparison

In a method comparison study, a total of 156 saliva samples were genotyped using the eSensor® Warfarin Sensitivity Saliva Test and DNA sequencing. The genotyping calls by the eSensor® Warfarin Sensitivity Saliva Test method were 99.4% concordant with genotypes determined by DNA sequencing for all polymorphisms, with a 98.1% first-pass call rate and 99.4% final pass call rate. The following tables summarize the results of the method comparison study after re-tests.

eSensor® Warfarin Sensitivity Saliva Test Method Comparison After Retest			
DNA Sequencing Result	**2C9 wt/wt**	**2C9 wt/*2**	**2C9*2/*2**
Correct Calls	104	46	5
No-Calls*	1	0	0
Miscalls	0	0	0
%Agreement	99.0%	100.0%	100.0%
95% LCB	95.6%	93.7%	54.9%
DNA Sequencing Result	**2C9 wt/wt**	**2C9 wt/*3**	**2C9 *3/*3**
Correct Calls	135	19	1
No-Calls*	0	1	0
Miscalls	0	0	0
%Agreement	100.0%	95.0%	100.0%
95% LCB	97.8%	78.4%	5.0%
DNA Sequencing Result	**VKORC1 G/G**	**VKORC1 G/A**	**VKORC1 A/A**
Correct Calls	63	71	21
No-Calls*	1	0	0
Miscalls	0	0	0
%Agreement	98.4%	100.0%	100.0%
95% LCB	92.8%	95.9%	86.7%

On First pass there were 2 miscalls due to operator error (sample mix-up) occurring during the first XT8 testing.
* After Final pass, one no call remained unresolved, likely due to an operator error at the purification step of the protocol.

Interfering Substances

Interfering substances including salivary α-amylase, hemoglobin, immunoglobulin A (IgA) and total protein were spiked into saliva samples at the highest amounts found in literature. 14 donors provided four saliva samples each which were each spiked with one of the four interfering substances. There was 100% agreement between the eSensor® Warfarin Sensitivity Saliva Test results and bidirectional DNA sequencing for all test substances after re-test, demonstrating no effect of any interfering substances on genotyping.

Substance	Samples Tested	Correct Calls	Incorrect Calls	No-Calls	% Agreement
Amylase	14	14	0	0	100%
Hemoglobin	14	14	0	0	100%
IgA	14	14	0	0	100%
Total Protein	14	14	0	0	100%

Effect of Exogenous Interfering Substances:

Potentially interfering exogenous substances introduced into saliva samples through various activities (eating, drinking, chewing gum, using mouthwash, smoking and brushing teeth) were tested. Each activity group was composed of five to nine donors who each provided samples immediately after activity and 30 minutes post-activity. There was 100% agreement between the eSensor® Warfarin Sensitivity Saliva Test results and bidirectional DNA sequencing for all activities tested in first pass, demonstrating no effect of any interfering substances on genotyping.

Activity	Time-point	Samples Tested	Correct Call	Incorrect Call	No-call	% Agreement
Eating	Immediate	8	8	0	0	100%
	30 minutes	9	9	0	0	100%
Drinking	Immediate	8	8	0	0	100%
	30 minutes	9	9	0	0	100%
Chewing Gum	Immediate	7	7	0	0	100%
	30 minutes	7	7	0	0	100%
Smoking	Immediate	5	5	0	0	100%
	30 minutes	5	5	0	0	100%
Mouthwash	Immediate	5	5	0	0	100%
	30 minutes	5	5	0	0	100%
Brushing Teeth	Immediate	9	9	0	0	100%
	30 minutes	9	9	0	0	100%

Conclusion

The above test results support the safety and effectiveness of the eSensor® Warfarin Sensitivity Saliva Test on the eSensor® XT-8 System, and demonstrate substantial equivalence to the predicate device.