K073720

510(k) Summary

JUL 17 2008

This summary of the 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1900 and CFR 807.92

510(k) number	
Summary Preparation Date	July 15, 2008
Submitted by	Osmetech Molecular Diagnostics 757 South Raymond Ave. Pasadena, CA 91105 Phone: 626 463-2000 Fax: 626 463-2012
Contact	Robert Dicheck, Vice President of Quality & Regulatory Affairs (Official Correspondent) Michael Reed, Ph.D., Director of Product Development & Project Manager
Proprietary names and classifications	*For the assay:* eSensor® Warfarin Sensitivity Test Regulations: 21CFR §862.3360 – Drug Metabolism Enzyme Genotyping Test 21CFR §864.7750 – Prothrombin Time Test Panels: 91 Toxicology & 81 Hematology Classification: II Product Codes: ODW Cytochrome P450 2C9 (CYP450 2C9) Drug Metabolizing Enzyme Genotyping System ODV Vitamin K epoxide reductase complex subunit 1 (VKORC1) Genotyping System *For the instrument:* eSensor® XT-8 System Regulation: 21CFR §862.2570 – Instrument for Clinical Multiplex Test Systems Panel: 75 Clinical Chemistry Classification: II Product Code: NSU Instrumentation for Clinical Multiplex Test Systems
Common names	*For the Assay:* Warfarin Sensitivity Test (*CYP2C9*2, CYP2C9*3, VKORC1*) *For the Instrument.* Bench-top molecular diagnostics workstation
Intended uses	• The eSensor® Warfarin Sensitivity 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 fresh whole blood samples preserved with EDTA, as an aid in the identification of patients at risk for increased warfarin sensitivity. The eSensor® Warfarin Sensitivity Test is for Rx only professional use within the confines of a licensed laboratory, as defined by the Clinical Laboratory Improvement Amendments (CLIA) of 1988. • 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.
Special conditions for use statement(s)	The eSensor® Warfarin Sensitivity Test is for Rx only professional use within the confines of a licensed laboratory, as defined by the Clinical Laboratory Improvement Amendments (CLIA) of 1988.
Predicate devices	Nanosphere Verigene® Warfarin Metabolism Nucleic Acid Test and Verigene® System

Device descriptions

The eSensor® XT-8 System is an *in vitro* diagnostic device for performing hybridization and genotyping of multiple mutations and/or polymorphisms in an amplified DNA sample. The XT-8 Instrument is configured with one to three processing towers which perform up to 8 simultaneous tests per tower. The XT-8 System uses a single-use, disposable test cartridge to perform hybridization and genotyping in approximately 30 minutes per sample. The cartridge contains an EEPROM chip which transmits the cartridge lot number, expiration date and protocol identity to the instrument.

The analysis process for each sample consists of three steps: 1) Genomic DNA isolated from whole blood obtained using EDTA as anti-coagulant is combined with PCR Mix and Taq polymerase enzyme and is subjected to amplification of target sequences by PCR using a thermal cycler. 2) Amplified DNA is treated with exonuclease enzyme to generate single-stranded target DNA. 3) Single-stranded, amplified target DNA is mixed with hybridization and genotyping reagents and transferred to an eSensor® Warfarin Sensitivity Test cartridge, and the cartridge is inserted in the eSensor® XT-8 Instrument. The instrument controls the circulation of the sample inside the cartridge containing to allow hybridization at a controlled temperature, and then detects and genotypes the sample by voltammetry.

Genotyping of the test panel polymorphisms is achieved by a sandwich assay principle: 1) Each pair of electrodes contains a different synthetic oligonucleotide capture probe which is complementary to one of the target DNA fragments. 2) The hybridization reagents contain pairs of ferrocene-labeled synthetic oligonucleotide signal probes; one member of each pair is complementary to the major allele sequence of the target polymorphism, while the second member of the pair is complementary to the minor allele sequence. Each member of the probe pair has a ferrocene label with a different oxidation potential for each allele. 3) Single-stranded, amplified target DNA hybridizes to its specific capture probe, and in turn hybridizes to the allele-specific, ferrocene-labeled signal probe. 4) Each electrode of the array is analyzed by voltammetry; the target polymorphism is determined by the location of the electrode containing the capture probe, and the genotype is identified by the ratio of signals from the allele-specific ferrocene labels. The array also includes positive and negative controls to confirm the hybridization reaction and detect non-specific signals.

Upon completion of the test, the EEPROM chip on the cartridge contains information that prevents its re-use with a new sample. The instrument analyzes the results and provides a report of the test results. The operator removes the used cartridge from the slot of the XT-8 Instrument, and that slot is ready to accept a new test.

Comparison to technological features of the predicate device

The following is a comparison of the Osmetech Molecular Diagnostics eSensor® Warfarin Sensitivity Test and XT-8 System to the Nanosphere, Inc. Verigene® Warfarin Metabolism Nucleic Acid Test and Verigene® System.

Characteristic	Verigene® Warfarin Metabolism Nucleic Acid Test and Verigene® System	eSensor® Warfarin Sensitivity Test and XT-8 System
Test type	Qualitative genetic test for single nucleotide polymorphism detection	Same as predicate
Sample Type	Genomic DNA obtained from a human whole blood sample	Same as predicate
Target of detection	Single-nucleotide polymorphism	Same as predicate
DNA extraction	Performed off-line	Same as predicate
Genes	Cytochrome P450 2C9 and VKORC1	Same as predicate
Number of Loci genotyped	3	Same as predicate
Genotyping reaction location	Test cartridge	Same as predicate
Genotyping principle	Sandwich hybridization test	Same as predicate
User interface	Graphical user interface with touch screen	Same as predicate
Instrument operating system	Random access compatible with multiple simultaneous test types	Same as predicate
Assay results	Assay signal results are interpreted by a software program and are assigned a genotype that is presented to the end-user in a report format	Same as predicate

Performance characteristics

Reproducibility:

Site to Site, Operator to Operator, Lot to Lot, Day to Day and Run to Run reproducibility

A reproducibility study was performed at three sites, two external and one internal. Five genomic DNA samples covering all possible genotypes for all three alleles in the Warfarin Sensitivity Test were tested in duplicate runs on a daily basis by the same operator for 5 days at 3 different sites. One site performed the same reproducibility testing twice each day, using two different operators and the same testing materials. Three kit lots were randomized throughout the study. An additional run using the same kit lot and sample as for the first-pass test were performed for tests that gave a no-call result.

The data were evaluated after first-pass results and following the additional run for no-calls. All samples gave 100% agreement with DNA sequencing. There were 9 first-pass no-calls: one was due to a cartridge manufacturing assembly error, and the remaining eight were due to operator error in set-up of the exonuclease reaction The following tables summarize the percent agreement between results obtained at each of the sites and DNA sequencing, before (first-pass) and after additional testing of no-calls (final):

Summary of Inter-laboratory and Inter-Operator Reproducibility Results

Site	Operator	Allele	Total tests	First-pass correct calls	First-pass no-calls	Final correct calls	Final incorrect calls	% Agreement (95% LCB)
1	1	2C9*2	50	42	8	50	0	100% (94.2%)
		2C9*3	50	42	8	50	0	100% (94.2%)
		VKORC1	50	42	8	50	0	100% (94.2%)
	2	2C9*2	50	49	1	50	0	100% (94.2%)
		2C9*3	50	49	1	50	0	100% (94.2%)
		VKORC1	50	49	1	50	0	100% (94.2%)
2	3	2C9*2	50	50	0	50	0	100% (94.2%)
		2C9*3	50	50	0	50	0	100% (94.2%)
		VKORC1	50	50	0	50	0	100% (94.2%)
3	4	2C9*2	50	50	0	50	0	100% (94.2%)
		2C9*3	50	50	0	50	0	100% (94.2%)
		VKORC1	50	50	0	50	0	100% (94.2%)
All	All	2C9*2	200	191	9	200	0	100% (98.5%)
		2C9*3	200	191	9	200	0	100% (98.5%)
		VKORC1	200	191	9	200	0	100% (98.5%)

Summary of Reproducibility Results sorted by sample and genotype.

Sample	Genotype	Total Tests	First-pass correct calls	First-pass no-calls	Final correct calls	Final incorrect calls	% Agreement (95% LCB)
01	2C9 *1/*1 VKORC1 G/G	40	37	3	40	0	100% (92.8%)
02	2C9 *2/*3 VKORC1 G/A	40	38	2	40	0	100% (92.8%)
03	2C9 *2/*2 VKORC1 G/G	40	39	1	40	0	100% (92.8%)
04	2C9 *3/*3 VKORC1 G/G	40	39	1	40	0	100% (92.8%)
05	2C9 *1/*3 VKORC1 A/A	40	38	2	40	0	100% (92.8%)

Genomic DNA extraction reproducibility

Three different sites extracted 7 whole blood samples of different genotypes in triplicate and tested them using the eSensor® Warfarin Sensitivity Test. Each site used a different commercially available extraction method, which yielded DNA with A260/280 ratios of 1.7 to 3.3. First pass results were in 100% agreement with DNA sequencing, as shown in the following tables:

Summary of Inter-laboratory Extraction Reproducibility Results

Site	Allele	# Total Tests	Correct Calls*	Incorrect Calls	No Calls	% Agreement (95% LCB)
1	2C9*2	21	21	0	0	100% (86.7%)
	2C9*3	21	21	0	0	100% (86.7%)
	VKORC1	21	21	0	0	100% (86.7%)
2	2C9*2	21	21	0	0	100% (86.7%)
	2C9*3	21	21	0	0	100% (86.7%)
	VKORC1	21	21	0	0	100% (86.7%)
3	2C9*2	21	21	0	0	100% (86.7%)
	2C9*3	21	21	0	0	100% (86.7%)
	VKORC1	21	21	0	0	100% (86.7%)

Summary of Extraction Reproducibility Results (sorted by sample and genotype).

Sample	Genotype	# Total Tests	Correct Calls	Incorrect Calls	No Calls	% Agreement
01	2C9 *1/*1 VKORC1 G/G	9	9	0	0	100%
02	2C9 *1/*2 VKORC1 G/G	9	9	0	0	100%
03	2C9 *1/*3 VKORC1 G/A	9	9	0	0	100%
04	2C9 *1/*3 VKORC1 G/G	9	9	0	0	100%
05	2C9 *3/*3 VKORC1 G/G	9	9	0	0	100%
06	2C9 *2/*3 VKORC1 A/A	9	9	0	0	100%
07	2C9 *2/*3 VKORC1 A/A	9	9	0	0	100%

Method comparison to bi-directional DNA sequencing:
In a method comparison study, a total of 157 samples with A260/280 ratios of 1.2 to 2.3 were genotyped using the eSensor® Warfarin Sensitivity Test and DNA Sequencing. All first-pass sample results (157/157) obtained with the eSensor® Warfarin Sensitivity Test agreed with the results obtained by DNA sequencing. The 95% lower confidence bound on a per-sample basis was 98.1%, and 99.4% on a per-SNP basis (471/471). The following table summarizes the results of the method comparison study:

DNA Sequencing Result	eSensor® Warfarin Sensitivity Test Result		
	2C9 *1/*1	2C9 *1/*2	2C9*2/*2
Result	111	43	3
No-Calls	0	0	0
Miscalls	0	0	0
%Agreement	100%	100%	100%
95% LCB	97.3%	93.3%	36.8%

DNA Sequencing Result	eSensor® Warfarin Sensitivity Test Result		
	2C9 *1/*1	2C9 *1/*3	2C9 *3/*3
Result	133	22	2
No-Calls	0	0	0
Miscalls	0	0	0
%Agreement	100%	100%	100%
95% LCB	97.7%	87.3%	22.4%

DNA Sequencing Result	eSensor® Warfarin Sensitivity Test Result		
	VKORC1 G/G	VKORC1 G/A	VKORC1 AA
Result	67	63	27
No-Calls	0	0	0
Miscalls	0	0	0
%Agreement	100%	100%	100%
95% LCB	95.6%	95.4%	89.5%

Other characteristics of the eSensor® Warfarin Sensitivity Test

Characteristic	Result
Limit of detection	Two genomic DNA samples of different genotypes were serially diluted to 1000, 100, 10, 1, and 0.1, nanograms and assayed 20 times each using the eSensor® Warfarin Sensitivity Test. An additional test was performed for tests that gave a first pass no call result. All input amounts for both samples gave equivalent first-pass and final performance. The lower detection limit was determined to be 0.1 ng of purified DNA per reaction and the upper detection limit was determined to be 1000 ng of purified DNA per reaction. The recommended range of DNA input amounts for the eSensor® Warfarin Sensitivity Test is from 10 to 1000 ng..
Interfering substances	Test performance was not affected by addition of the following substances to two whole blood samples of different genotypes prior to extraction: • Human serum albumin (3 g added/dL whole blood). • Bilurubin (50 µg added/mL whole blood). • Human immunoglobulin G (3 g added/dL whole blood). • Triglycerides (3 g added/dL whole blood). • Hemoglobin (20 g added as purified red blood cells/dL whole blood). • Warfarin (32.5 µM added to whole blood). • Heparin sodium (3,000 U/L added to whole blood). • EDTA (at a concentration equivalent to 5-fold higher than that provided by a standard EDTA blood collection tube).
Interfering mutations and polymorphisms	Samples containing the following CYP450 2C9 polymorphisms have been tested and found to give accurate results in the eSensor® Warfarin Sensitivity Test: • 1076T>C (*4) • 1080C>G (*5) • 818delA (*6) • 1003C>T (*11) • 374G>A (*14) • 485C>A (*15) • 895A>G (*16). In the VKORC1 gene, additional polymorphisms other than -1639G>A, as well as rare mutations have been observed. These additional polymorphisms and mutations are not detected by the eSensor® Warfarin Sensitivity Test.

Kit stability

eSensor® Warfarin Sensitivity Test kit components should be stored under the appropriate conditions until the expiration date printed on the label:

- PCR Box containing Warfarin Sensitivity Test PCR Mix and Taq Polymerase: Store at -20°C in a designated pre-PCR area.
- Cartridges: Store at 10° to 25°C
- Genotyping Box containing Exonuclease, Warfarin Sensitivity Test Signal Buffer, XT-Buffer 1 and XT-Buffer 2: Store at -20°C in a designated post-PCR area.

In-process stability has been established for the following components, working reagents and samples:

- Cartridges can be stored for up to 14 days after opening the foil pouches. If stored, cartridges should be kept in their original foil pouch at room temperature in a dry place with the zip-loc closure sealed.
- Once open, reagents can be stored at -20°C for up to 30 days.
- Reagents can be thawed up to 3 times.
- Whole blood stored in EDTA can be stored for up to 4 weeks after collection prior to extraction of gDNA for use in the eSensor® Warfarin Sensitivity Test.
- PCR product can be stored at 4°C or -20°C for up to 7 days.

	• Exonuclease-digested PCR product can be stored store at 4°C or -20°C for up to 7 days. • After combining the exonuclease-digested PCR with hybridization reagents, the hybridization reaction can be loaded on the cartridge and held at ambient temperature for up to 8 hours before initiating hybridization of the cartridge on the XT-8 instrument.
Conclusion	The above internal and clinical test results support the safety and effectiveness of the eSensor® Warfarin Sensitivity Test and the eSensor® XT-8 System, and demonstrate substantial equivalence to the predicate device.

eSensor® is a registered trademark of Osmetech and its subsidiaries.

Verigene® is a registered trademark of Nanosphere, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Osmetech Molecular Diagnostics
c/o Mr. Robert Dicheck
Vice President of Quality & Regularoty Affairs
757 South Raymond Avenue
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Re: k073720
Trade Name: eSensor® Warfarin Sensitivity Test, eSensor® XT-8 System
Regulation Number: 21 CFR 862.3360
Regulation Name: Drug Metabolism Enzyme Genotyping Test
Regulatory Class: Class II
Product Codes: ODW, ODV, NSU
Dated: May 22, 2008
Received: May 27, 2008

Dear Mr. Dicheck:

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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. 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); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0490. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number ~~(800) 638-2041 or (240) 276-3150 or at its Internet address at~~ http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Jean M. Cooper, M.S., D.V.M.

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Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
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Enclosure

Indications for Use

510(k) Number (if known): K073720

Device Name: eSensor® Warfarin Sensitivity Test and XT-8 System

Indications For Use:

The eSensor® Warfarin Sensitivity 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 whole blood samples preserved with EDTA, 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.

Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

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