K962873

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SUMMARY: SAFETY AND EFFECTIVENESS INFORMATION FOR CEP 12 SpectrumOrange DNA Probe Kit

The CEP 12 SpectrumOrange DNA Probe is a SpectrumOrange fluorescent labeled DNA probe specific for the centromeric region of chromosome 12. This assay is designed to provide a rapid and reliable method for the detection and quantification of chromosome 12 in interphase nuclei by fluorescence *in situ* hybridization (FISH).

Standard cytogenetic analysis detects cytogenetic abnormalities such as trisomy 12 by karyotyping metaphase spreads after staining the chromosomes with a dye in cultured tissue cells.

Safety and effectiveness issues relevant to FISH assays such as the CEP 12 assay may include cross-reactivity, poor sensitivity, poor specificity, or poor reproducibility.

Analytical Sensitivity and Specificity

Hybridization Efficiency

In a pivotal study, the average percentage of cells with no hybridization signal was 0.43% (S.D.=1.48%) on 402 peripheral blood specimens. Thus, <2% cells with no signal is a realistic standard of acceptance.

Analytical Sensitivity

The analytical sensitivity of the CEP 12 probe was tested in the reproducibility study described below. In that study, the 0% specimen was estimated with a mean of 1.72% (S.D.= 1.09%) tri-signaled nuclei and the 5% specimen, 4.87% (S.D.= 0.99%). There was slight overlap between the 0% and 5% specimens; the upper 95% confidence limit for the 0% specimen was 3.86% and the lower 95% confidence limit for the 5% specimen was 2.93%. Thus, the limit of detection for CEP 12 is estimated to be 4.0%.

Analytical Specificity

Locus specificity studies were performed with metaphase spreads according to standard Vysis QC protocols. A total of 56 metaphase spreads were examined sequentially by G-banding to identify chromosome 12, followed by FISH. No cross-hybridization to other chromosome loci was observed in any of the 56 cells examined; hybridization was limited to the centromere region of chromosome 12.

Reproducibility

To assess the reproducibility of the CEP 12 assay, CEP 12 analyses for the percentage of tri-signaled cells were assessed for inter-site, inter-lot, inter-day, and inter-observer reproducibility. Four mixtures of hematologically derived human cells with known percentages of trisomy 12 (approximately 0%, 5%, 10%, and 13%) were evaluated for the percentage of tri-signaled cells according to the instructions for signal enumeration in the package insert. For intra assay variation, the N, mean, SD, and percent CV of the observed percentage of tri-signaled nuclei were 22, 1.72%, 1.09%, and 63.1%, respectively, for the 0% specimen; 23, 4.87%, 0.99%, and 20.4%, respectively, for the 5% specimen; 23, 9.19%, 1.78%, and 19.4%, respectively, for the 10% specimen; and 24, 12.07%, 1.61%, and 13.3%, respectively, for the 13% specimen. For inter assay reproducibility, statistically significant site-to-site and observer-to-observer variations were observed, reflecting the subjectivity of the visual enumeration process.

Methods Comparison: Clinical Specimens

A multi-center, blinded, controlled, comparative study was conducted to further define the performance of the CEP 12 SpectrumOrange DNA probe kit relative to standard cytogenetic analysis. Peripheral blood specimens were obtained from a total of 402 patients with B-cell chronic lymphocytic leukemia (B-CLL) for standard cytogenetic and FISH analysis. Specimens were evaluated at three sites; 97 specimens were analyzed at site 1, 205 at site 2, and 100 at site 3. All sites utilized cultured specimens for standard cytogenetic and FISH analyses except site 1; it utilized direct preparations for FISH only, but the same patient specimen was utilized for both methods. Each site followed its own in-house protocol for standard cytogenetic analysis; FISH analyses were performed according to the instructions in the CEP 12 SpectrumOrange DNA probe kit package insert*.

A total of 177 specimens had a sufficient number of metaphase cells (≥20, or at least two metaphases with trisomy 12) for standard cytogenetic analysis. In addition, 157 specimens from one site had insufficient metaphases for complete cytogenetic analysis, but were evaluated by FISH.

Of those specimens with sufficient metaphases for analysis, 41 were classified as positive for trisomy 12; 132 negative; and 4 ambiguous (one trisomy 12 cell per 30 metaphases), by standard cytogenetic analysis. By interphase FISH analysis, 53 specimens were classified as positive for trisomy 12; 119 were negative; and 5 were uninformative (with less than 500 evaluable interphase nuclei).

When results between interphase FISH and standard cytogenetics were compared utilizing only specimens with sufficient metaphases for analysis, the CEP 12 DNA probe kit showed a relative sensitivity of 100% (95% CI 91.2% to 100%), and a relative specificity of 91.47% (95% CI 86.66% to 96.22%). FISH interphase analysis designated 54 specimens as positive; 13 more than were positive by standard cytogenetic analysis.

One study site (from the United Kingdom) evaluated a significant number of specimens (157) with less than the minimum number (20) of metaphases required by the International System for Human Cytogenetic Nomenclature (ISCN) standards for standard cytogenetic analysis. At this site, a minimum of 10 metaphase cells were examined and specimens were designated as negative or ambiguous if 0 or 1 cells, respectively, showed trisomy 12. If >2 cells were positive for trisomy 12, the specimen was reported as positive. FISH analysis designated 25 of these 157 specimens as positive for trisomy 12; they were reported as negative or ambiguous at this site by standard cytogenetic analysis.

Although the true status of specimens designated as trisomy 12 by FISH and negative or ambiguous by standard cytogenetic analysis has not been established, these discrepancies may, in part, be a reflection of the difference in the reported analytic sensitivity between the two methods.

Conclusions

Performance of CEP 12 is supported by the Vysis Quality Control Procedures and is demonstrated in the clinical studies. When the CEP 12 SpectrumOrange DNA Probe is used as instructed in the package insert, the above statements describe its performance.

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* Site 2 used a slight modification to the recommended time and temperature for the FISH hybridization step.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

AUG 26 2011

Vysis
c/o Dr. Russel K. Enns
Vice President, Regulatory Affairs
3100 Woodcreek Dr.
Downers Grove, IL 60515

Re: k962873
Trade/Device Name: CEP 12 SpectrumOrange Direct Labeled Chromosome Enumeration DNA Probe
Regulation Number: 21 CFR §866.6040
Regulation Name: Gene expression profiling test system for breast cancer prognosis.
Regulatory Class: Class II
Product Code: OVQ, KIR
Dated: October 29, 1996
Received: October 30, 1996

Dear Dr. Enns:

This letter corrects our substantially equivalent letter of January 13, 1997.

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 class II (Special Controls), 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); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); 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 advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. 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 Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K962873

Device Name: CEP 12 SpectrumOrange Direct Labeled Chromosome Enumeration DNA Probe Kit

Indications For Use:

The CEP 12 SpectrumOrange Direct Labeled Chromosome Enumeration DNA Probe Kit is designed to be an adjunct to standard cytogenetic analysis for in vitro diagnostic use in identifying and enumerating chromosome 12 via fluorescence *in situ* hybridization (FISH) in interphase nuclei of cells obtained from peripheral blood lymphocytes in patients with chronic lymphocytic leukemia (CLL). Results from the CEP 12 SpectrumOrange Direct Labeled Chromosome Enumeration DNA Probe Kit are intended for use in conjunction with standard cytogenetics and for further assessing the trisomy 12 status in normal and abnormal tissue specimens characterized by standard cytogenetics, in patients with and/or without clinical symptoms of CLL. It is not intended to be a stand alone assay for test reporting.

Peter J. Martin

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K962873

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use √ OR Over-The-Counter Use ___
(Per 21 CFR 801.109)

(Optional Format 1-2-96)