

Summary of Safety and Effectiveness**Assay Principles**

The Osteomark NTx Serum EIA is a competitive-inhibition enzyme-linked immunosorbent assay (ELISA/EIA) for quantitative determination of NTx present in human serum.

NTx is adsorbed to a 96-well microplate. Diluted samples are added to the microplate wells, followed by a horseradish peroxidase labeled monoclonal antibody. NTx in the specimen competes with the NTx epitope on the microtiter plate for antibody binding sites. Following a wash step, the amount of labeled antibody bound is measured by colorimetric generation of a peroxide substrate. NTx concentration is determined spectrophotometrically and calculated using a standard calibration curve. Assay values are reported in nanomoles Bone Collagen Equivalents per liter (nM BCE).

Kit Components

Supplied Materials sufficient for 96 wells

Instructions for Use	1 booklet
Antigen Coated 96-Well Plate, 12 1x8 well strips	1 plate
Specimen Diluent	40 mL bottle
Calibrators:	
0 nM BCE Calibrator	20.0 mL vial
1 nM BCE Calibrator	0.4 mL vial
5 nM BCE Calibrator	0.4 mL vial
10 nM BCE Calibrator	0.4 mL vial
20 nM BCE Calibrator	0.4 mL vial
40 nM BCE Calibrator	0.4 mL vial
Level I Serum Control	0.4 mL vial
Level II Serum Control	0.4 mL vial
Antibody Conjugate Concentrate	0.4 mL vial
Antibody Conjugate Diluent	25 mL bottle
30X Wash Concentrate	125 mL bottle
Chromogen Reagent	0.9 mL vial
Buffered Substrate	30 mL bottle
Stopping Reagent	30 mL bottle
Plate Sealers	1 pad

Expected Values

A multi-center, cross-sectional study was conducted at five regional sites to determine the reference range for normal premenopausal women (mean age 36 years, range 25-49).

Male reference range was determined from a multi-center, cross-sectional study conducted at three regional sites (mean age 51 years, range 31-80).⁶

	Mean*	Std Dev	Range (mean \pm 2 Std Dev)	N
Women	12.6	3.2	6.2 - 19.0	257
Men	14.8	4.7	5.4 - 24.2	176

*expressed as nM BCE

When the premenopausal women expected value range is log-transformed, the range is 7.7 - 19.3 nM BCE. The log-transformed male reference range is 8.1 - 24.8 nM BCE. These reference ranges are provided as guidelines only. Each laboratory should establish their own reference range.

In a study of postmenopausal women⁷, short-term (3 days) and long-term (2 months) intra-subject variability was determined to be 7.3% (n=271) and 8.7% (n=261), respectively. In a subset of the above male reference range study population, the short-term (4 days) intra-subject variability was 9.1% (n=32), and the long-term (3 months) intra-subject variability was 9.5% (n=27).

Performance Characteristics

Assay Reproducibility and Precision

Intra-assay variability was determined by testing four human serum specimens following NCCLS Precision Performance Guideline EP5-T2 with BCE values distributed throughout the calibration range of the assay. From these test results the Osteomark NTx Serum EIA intra-assay variability is established as 2.6%.

Inter-assay variability was determined by testing eight human serum specimens with BCE values distributed throughout the calibration range of the assay. From these test results the Osteomark NTx Serum EIA inter-assay variability is established as 6.9%.

Total assay precision was evaluated by testing the Level I Serum Control and the Level II Serum Control at four clinical laboratories. Estimate of the total precision percent coefficient of variation for the Level I Serum Control was 13.99% and for the Level II Serum Control was 11.92%.

Antigen Recovery was evaluated by adding known amounts of NTx to each of nine serum specimens of known NTx concentration. Recovery represented the observed assay value of the “spiked” specimens, calculated as a percent of the expected serum value (baseline serum value plus added antigen (NTx) value). Results demonstrated an average antigen recovery of 100% across the assay range.

Dilutional linearity was evaluated by performing serial dilutions of five serum specimens with high nM BCE values into a serum specimen with a known low nM BCE value. Percent linearity was determined as the measured value divided by the expected value multiplied by 100. Results demonstrated an average linearity of 98%.

Clinical Studies

Use of Osteomark NTx Serum EIA in Postmenopausal Women Treated With HRT

A clinical trial was conducted to determine the ability of the Osteomark NTx Serum EIA to monitor the effect of hormone replacement therapy (HRT) on bone resorption and to determine the probability for a decrease in bone mineral density (BMD) after one year if treated with only calcium supplements relative to those treated with supplements and HRT.⁴ Results of the study supported these clinical uses. Prior to HRT initiation,

Osteomark NTx Serum EIA mean baseline values in this group were 15.9 nM BCE, significantly higher than the premenopausal mean of 12.6 nM BCE. In the HRT group, mean values fell significantly after 3 months of therapy to 12.2 nM BCE, a -22.9% decrease. Mean values in the calcium group remained constant throughout the 12 month study; 15.4 nM BCE at baseline and 15.8 nM BCE after 12 months. Examination of the contrast between the HRT and calcium only groups provides information regarding risk of BMD loss. In the lowest NTx quartile (≤ 12.5 nM BCE), there was no statistically significant difference between the HRT and calcium groups in the likelihood of bone loss over 1 year. A high baseline NTx (≥ 18.1 nM BCE) indicated a 6 times higher risk of BMD loss if not treated with HRT.

Use of Osteomark NTx Serum EIA in Postmenopausal Women Treated With Bisphosphonate

A study was conducted at a regional specialty hospital in the northeast United States to determine if early changes in Osteomark NTx Serum EIA following treatment with the bisphosphonate alendronate sodium predicts an increase in BMD.⁵ In this randomized, double-blind clinical study, women were randomized to either placebo or 5-10 mg alendronate sodium. In the alendronate treated group, mean Osteomark NTx Serum EIA values after 6 months of treatment, 11.0 nM BCE, were significantly lower than baseline, 16.1 nM BCE. Stratification of baseline Osteomark NTx Serum EIA demonstrate that subjects with the highest values (≥ 16.6 nM BCE) had the greatest gain in PA spine BMD (5.76%).

References

1. Garnero P., et. al. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. *J Clin Endo and Met.* 79:1963-1700. 1994.
2. Garnero P., et. al. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res.* 11:337-349. 1996.
3. Prestwood K.M., et. al. The short-term effects of conjugated estrogen on bone turnover in older women. *J. Clin Endo and Met.* 79:366-371. 1994
4. Chesnut C.H., et. al. Hormone replacement therapy in postmenopausal women: Urinary N-telopeptide of type I collagen monitors therapeutic effect and predicts response of bone mineral density. *Am J Med.* 102:29-37. 1997.
5. Greenspan S.L., et. al. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: A randomized clinical trial. *J Bone Miner Res.* 13:1431-1438. 1998.
6. Orwoll E.S., et. al. Collagen N-telopeptide excretion in men: The effects of age and intra-subject variability. *J. Clin Endo and Met.* In Press.
7. Weiss S., et. al. Determination of the intrasubject variability in NTx excretion in postmenopausal women. *J Bone Miner Res.* Vol. 12. Suppl. 1, pp. S506. 1997.

OSTEOMARK NTx SERUM EIA QUICK REFERENCE GUIDE

1. Thoroughly read the Assay Procedure before you begin.
2. Allow all specimens and kit components to come to room temperature. Mix all reagents thoroughly.
3. Prepare working strength wash solution. Dilute 30X Wash Concentrate 1:30 with deionized water.
4. Plan the plate configuration, and create a plate map.
5. Prepare working strength antibody conjugate solution at a 1:101 dilution. You will need approximately 1 mL per strip.
6. Prepare 1:5 dilutions of all Calibrators, Controls and specimens in Specimen Diluent using microtubes or equivalent.
7. Pipette, in duplicate wells, 100 μ L of each diluted Calibrator, Control or specimen into the microplate according to the plate map.
8. Pipette 100 μ L of working strength antibody conjugate solution into each microwell. Gently swirl to mix, cover the plate with a plate sealer and incubate the plate at room temperature for 90 ± 5 minutes.
9. Prepare Chromogen Reagent/Buffered Substrate solution at a 1:101 dilution during the last 5 minutes of incubation. You will need approximately 2 mL per strip.
10. Wash microwells five (5) times with working strength wash solution. Blot on absorbent paper after the final wash.
11. Add 200 μ L diluted Chromogen Reagent/Buffered Substrate to each microwell, gently swirl to mix, and incubate at room temperature for 30 ± 2 minutes.
12. Add 100 μ L of Stopping Reagent to each microwell. Gently swirl the plate to mix.
13. Incubate at room temperature for five minutes and read the absorbance of each microwell at 450 nm-630 nm. Calculate the results using a 4-parameter logistic curve fit.



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Re: K983457
Trade Name: Osteomark NTx Serum EIA
Regulatory Class: I
Product Code: JMM
Dated: December 18, 1998
Received: December 22, 1998

Dear Ms. Mallinak:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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). 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 (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895.

A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

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Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

This letter will allow you to begin marketing your device as described in your 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 Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive style.

Steven I. Gutman, M.D, M.B.A.
Director
Division of Clinical
Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) NUMBER (IF KNOWN): K983457

DEVICE NAME: OSTEOMARK® NTx SERUM EIA

INDICATIONS FOR USE:

Osteomark® NTx Serum EIA provides a quantitative measure of cross-linked N-telopeptides of type I collagen (NTx) in serum as an indicator of human bone resorption. Serum NTx level is used to aid in predicting skeletal response (bone mineral density) to antiresorptive therapy and in monitoring bone resorption changes following initiation of antiresorptive therapy. Prior to initiating antiresorptive therapy, serum NTx level is used to determine the probability for a decrease in bone mineral density after one year in postmenopausal women treated with hormonal antiresorptive therapy relative to those treated with calcium supplement.

Jean Cooper
(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K983457

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

Concurrence of CDRH, - Office of Device Evaluation (ODE)

Prescription Use
(Per 21 CFR 801.109)

OR

Over-The-Counter-Use
(Optional Format 1-2-96)