

**510(K) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k070824

B. Purpose for Submission

New device

C. Measurand:

Creatinine

D. Type of Test:

Enzymatic colorimetric assay

E. Applicant:

Thermo Fisher Scientific

F. Proprietary and Established Names:

Creatinine (enzymatic); sCal; Nortrol; Abtrol

G. Regulatory Information:

1. Regulation Section

21 CFR §862.1225, Creatinine test system

21 CFR §862.1150, Calibrator

21 CFR §862.1660, Quality Control Material

2. Classification:

Class II (Reagent, Calibrator)

Class I, reserved (Control)

3. Product Code:

JFY, JIX, JJY

4. Panel

Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s)

See Indications for Use below.

2. Indication(s) for use:

The CREATININE (Enzymatic) is intended for quantitative *in-vitro* diagnostic determination of creatinine concentration in human serum, plasma (Li-heparin) or urine using T60 Clinical Chemistry Analyzers.

Measurement of creatinine levels aids in the diagnosis and treatment of certain renal disease, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

sCal is used as a multicalibrator for quantitative measurements using methods defined by Thermo Fisher Scientific Oy. For in vitro diagnostic use on T60 analyzer.

Nortrol is a control serum to monitor trueness and precision of the analytes listed in the separate Nortrol value sheet. The given values are valid for T60 Clinical Chemistry Analyzers using methods defined by Thermo Fisher Scientific Oy. For in vitro diagnostic use for quantitative testing on T60 analyzer.

Abtrol is a control serum to monitor trueness and precision of the analytes listed in the separate Abtrol value sheet. The given values are valid for T60 Clinical Chemistry Analyzers using methods defined by Thermo Fisher Scientific Oy. For in vitro diagnostic use for quantitative testing on T60 analyzer.

3. Special conditions for use statement(s):
For Prescription Use only

4. Special instrument requirements:
T60 Clinical Chemistry Analyzers

I. Device Description:

The CREATININE (enzymatic) is available as a kit only. It consists of 2 reagents. Reagent A contains TAPS buffer, pH 8.1, Creatinase (microorganisms), Sarcosine oxidase (microorganisms), Ascorbate oxidase (microorganisms), HTIB, Detergents, and Preservative. Reagent B contains TAPS** buffer, pH 8.0, Creatininase (microorganisms), Peroxidase (horseradish), 4-aminophenazone, Potassium hexacyanoferrate (II), Detergent, and Preservative. The calibrator and quality control are separate from the reagents and are provided in individual vials.

J. SUBSTANTIAL EQUIVALENCE INFORMATION

1. Predicate device name(s):
Roche Diagnostics Corporation COBAS Integra Creatinine plus ver.2
2. Predicate 510(k) number(s):
k024098
3. Comparison with predicate:

Item	Device CREATININE (enzymatic)	Predicate Roche Creatinine plus ver.2
Assay Protocol	Enzymatic colorimetric assay	Enzymatic colorimetric assay
Traceability/Standardization	The value of Creatinine has been assigned by using NIST SRM 967 (for serum) and NIST SRM 914a (for urine)	Method has been standardized against ID/MS
Sample Type	Serum, plasma (Li-heparin) and urine	Serum, plasma (Li-heparin, K3-EDTA) and urine
Reagent Storage	Reagents in unopened vials are stable at 2...8 °C until the expiry date printed on the label.	Shelf life at 2 to 8 °C until the expiration date on cassette.

Item	Device CREATININE (enzymatic)	Predicate Roche Creatinine plus ver.2
Instrument	T60 and T60i, T60i Kusti	Cobas Integra 700
Measuring Range	Serum, plasma: 0.11 – 28 mg/dL Urine: 2.3 – 452 mg/dL	Serum, plasma: 0 – 30.5 mg/dL Urine: 0 – 452 mg/dL

K. STANDARD/GUIDANCE DOCUMENT REFERENCED (IF APPLICABLE)

CLSI EP5-A2 Precision Performance of Clinical Chemistry Devices

CLSI EP6-A Evaluation of the Linearity of Quantitative Analytical Methods

CLSI EP9-A2 Method Comparison and Bias Estimation Using Patient Samples

CLSI EP7-A2 Interference Testing in Clinical Chemistry

L. Test Principle

Creatinine is determined by enzymatic colorimetric assay. Creatinine is converted to sarcosine with the aid of creatininase and creatinase. Sarcosine is then converted to glycine, formaldehyde and hydrogen peroxide in the presence of oxygen by sarcosine oxidase. The liberated hydrogen peroxide reacts with 4-aminophenazone and HTIB to form a quinone imine chromogen in a reaction catalyzed by peroxidase. The color intensity is directly proportional to the concentration of creatinine present and can be measured photometrically at 540nm.

M. Performance Characteristics (if/when applicable):

1. Analytical Performance:

a. Precision /Reproducibility:

Imprecision, serum/plasma:

A precision study was performed using CLSI EP5-A as a guideline varying calibrations and operators using one T60 for 20 days, with the number of measurements being n = 80 serum samples.

Result unit mg/dL

	Mean 0.43 mg/dL		Mean 1.75 mg/dL		Mean 5.47 mg/dL	
	SD	CV%	SD	CV%	SD	CV%
Within run	0.006	1.5	0.008	0.4	0.021	0.4
Between run	0.002	0.4	0.008	0.5	0.015	0.3
Total	0.009	2.2	0.026	1.5	0.076	1.4

Result unit $\mu\text{mol/L}$

	Mean 38 $\mu\text{mol/L}$		Mean 155 $\mu\text{mol/L}$		Mean 484 $\mu\text{mol/L}$	
	SD	CV%	SD	CV%	SD	CV%
Within run	0.6	1.5	0.7	0.4	1.8	0.4
Between run	0.2	0.4	0.7	0.5	1.3	0.3
Total	0.8	2.2	2.3	1.5	6.8	1.4

Imprecision, urine:

A precision study was performed using CLSI Document EP5-A as a guideline varying calibrations and operators using one T60 for 20/21 days, with the number of measurements being n = 80/84.

Result unit mg/dL

	Mean 76 mg/dL		Mean 165 mg/dL		Mean 251 mg/dL	
	SD	CV%	SD	CV%	SD	CV%
Within run	0.7	1.0	1.4	0.9	2.2	0.9
Between run	0.6	0.8	1.9	1.2	2.3	0.9
Total	2.7	3.5	5.7	3.5	8.7	3.5

Result unit mmol/L

	Mean 6.7 mmol/L		Mean 14.6 mmol/L		Mean 22.2 mmol/L	
	SD	CV%	SD	CV%	SD	CV%
Within run	0.06	1.0	0.13	0.9	0.20	0.9
Between run	0.05	0.8	0.17	1.2	0.21	0.9
Total	0.24	3.5	0.51	3.5	0.77	3.5

b. Linearity/ Assay reportable range.

Serum/plasma

The linearity study was performed using CLSI EP6-A as a guideline. Linearity was tested on serum samples medium and high for examination of various ranges of creatinine concentration. The samples were diluted in 11 steps (from 0% to 100%) with saline as diluent. Four replicate measurements were performed using one reagent lot. The linearity of CREATININE (Enzymatic) was analyzed on T60 over a measured range of 0.07 to 0.74 mg/dL with the linearity summary as Slope: 0.985; intercept: 0.000; Obs. Err: 4.4%; N: 11.

The Linearity of CREATININE (Enzymatic) was analyzed on T60 over a measured range of 0.798 to 34.945 mg/dL with the linearity summary as Slope: 0.969; intercept: 0.786; Obs. Err: 1.5%; N: 11. The claimed measuring range is 0.11 mg/dL to 28.0 mg/dL.

Urine:

The linearity study was performed using CLSI EP6-A as a guideline. Four parallel measurements were made in random order using one reagent lot. The samples were diluted in 11 steps. Urine was spiked with commercially available creatinine solution to a value of 536 mg/dL. The dilutions were made to urine and further diluted with saline. The Linearity of CREATININE (Enzymatic) was analyzed on T60 over a measured range of 2.3 to 452 mg/dL with the linearity summary as Slope: 1.001; intercept: 0.082; Obs. Err: 2.2%; N: 11. The claimed measuring range is 2.3 mg/dL to 452.0 mg/dL.

c. Traceability, Stability, Expected values (controls, calibrators or methods)

The stability claim was verified using an accelerated stability protocol. The assay was calibrated using a valid calibrator and accelerated calibrator material was measured as sample in triplicates. The verification of the real time stability is on going. The acceptance criteria for the calibrator were $\pm 5\%$ of the target value. The open vial

stability of the sCal, Nortrol and Abtrol were established. The opened vials were stored tightly capped at 2°C - 8°C for nine days. Three vials of calibrator/control material were measured as samples in triplicates at time points of 4, 7 and 9 days. The acceptance criteria for the calibrator were $\pm 5\%$ of the initial value. The acceptance criteria for the controls were $\pm 10\%$ of the initial value.

Reagents in unopened vials are stable at 2°C - 8°C until the expiry date printed on the label. Refer to the Application Notes of T60 instrument for the on board stability of reagents.

Calibration material

The sCal, kit code 981831, when used according to the instructions provided for T60 instrument may remain on the instrument for a maximum of one hour.

Traceability:

The calibrator values were obtained by multi determinations performed by Thermo Fisher Scientific Oy. The assigned value is the median of all values obtained. The assigned value of the calibrator is traceable to NIST reference material (SRM 967).

Quality Control materials

The values on control materials are traceable to the reference material, NIST SRM 967. Users are instructed in the labeling to use quality control samples at least once a day and after each calibration and every time a new bottle of reagent is used. It is recommended to use at least two levels (low and high) of controls. Available controls are Nortrol, kit code: 981043 and Abtrol, kit code: 981044.

d. Detection Limit:

The study was performed using CLSI EP17-A as a guideline. In the limit of blank study thirty replicates of a blank sample (0.9% NaCl) were assayed using two T60 instruments and two reagent lots with the total number of measurements being 60.

Limit Of Blank (LOB): The Limit Of Blank (LOB) represents the highest measurement result that is likely to be observed for a blank sample (0.9% NaCl, n=60). Based upon the studies conducted for LOB, the following results were obtained:

Serum/plasma: 0.01 mg/dL; Urine: 0.11 mg/dL

In the Limit of Detection study five low level samples were assayed in ten replicates with two T60 instruments and two reagent lots during two days with the total number of measurements being 100. Based upon the studies conducted for LOD, the following results were obtained:

Limit of Detection (LOD): Limit of Detection (LOD) represents the lowest amount of analyte in a sample that can be detected (n=100).

Serum/plasma: 0.02 mg/dL; Urine: 0.23 mg/dL

e. Analytical Specificity

Serum/plasma:

Unconjugated Bilirubin: No interference found up to 23 mg/dL (400 $\mu\text{mol/L}$). Higher bilirubin concentrations cause erroneously low creatinine values.

Conjugated Bilirubin: No interference found up to 17 mg/dL (300 $\mu\text{mol/L}$). Higher bilirubin concentrations cause erroneously low creatinine values.

Hemoglobin / Hemolysis: No interference found up to 1000 mg/dL (10 g/L) of hemoglobin in hemolysate.

Lipemia: No interference found up to 1000 mg/dL (10 g/L) of Intralipid™ (trademark of Fresenius Kabi AB) or 12 mmol/L (1062mg/dL) of triglycerides.

Ascorbic acid: No interference found up to 30 mg/dL (1.70 mmol/L) of ascorbic acid.

Creatine: No interference found up to 20 mg/dL (1.53 mmol/L) of creatine.

Monoclonal immunoglobulins (or parts of them) may interfere with the assay. The labeling includes the statement that results from patients suspected of having such antibodies should be carefully evaluated.

Levodopa and Calcium Dobesilate cause artificially low creatinine levels.

The sponsor stated that the acceptance criterion for recovery is within $\pm 10\%$ or ± 0.085 mg/dL (7.5 $\mu\text{mol/L}$) of initial values.

Urine:

Conjugated Bilirubin: No interference found up to 58 mg/dL (1000 $\mu\text{mol/L}$).

Hemoglobin / Hemolysis: No interference found up to 1000 mg/dL (10 g/L) of hemoglobin in hemolysate.

Glucose: No interference found up to 2500 mg/dL (139 mmol/L).

Ascorbic acid: No interference found up to 100 mg/dL (5.7 mmol/L).

The labeling includes the statement that calcium dobesilate and α -methyldopa cause erroneously low creatinine values and that levodopa causes artificially low results.

f. Assay Cut-off

Not applicable

2. Comparison Studies:

a. Method comparison with predicate device:

Serum:

A comparison study was performed using CLSI EP9-A as a guideline and commercially available enzymatic method as a reference.

Linear regression (Deming) (result unit mg/dL):

$$y = 1.01x - 0.001; r = 1.000; n = 41$$

The sample concentrations were between 0.12 to 24 mg/dL.

Plasma:

A comparison study was performed with matched serum and plasma (Li-heparin) samples on T60 instrument using CLSI EP9-A as a guideline.

Linear regression (Deming)(result unit mg/dL):

$$y = 0.97x - 0.02; r = 1.000; n = 52$$

The sample concentrations were between 0.27 to 27.58 mg/dL.

Urine:

A comparison study was performed using CLSI Document EP9-A as a guideline and commercially available enzymatic method as a reference.

Linear regression (result unit mg/dL):

$$y = 1.03x + 1.34; r = 0.999; n = 135$$

The sample concentrations were between 2.33 to 422 mg/dL.

b. Matrix comparison

Fifty-two matched serum and plasma (Li-heparin) samples were assayed on the T60 instrument to demonstrate the use of plasma (Li-heparin) samples. Both serum and plasma samples were assayed in duplicate and each individual measurement is compared to one individual measurement.

Linear regression (result unit mg/dL):

$$y = 0.97x - 0.02$$

$$r = 1.000; n = 52$$

Range from 0.27 to 27.58 mg/dL

3. Clinical Studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical Specificity:

Not applicable

c. Other Clinical Supportive Data (when a. and b. are not applicable)

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected Values/ Reference Ranges:

Serum/plasma:

Male: 0.67 – 1.17 mg/dL (59 – 104 μ mol/L)

Female: 0.51 – 0.95 mg/dL (45 – 84 μ mol/L)

Urine (1st morning urine):

Male: 40 – 278 mg/dL (3.54 – 24.6 mmol/L)

Female: 29 – 226 mg/dL (2.55 – 20.0 mmol/L)

In the labeling, the statements that the quoted values should serve as a guide only and that it is recommended that each laboratory verify this range or derive a reference interval for the population that it serves are included.

Conversion factor:

μ mol/L x 0.0113 → mg/dL

mmol/L x 11.3 → mg/dL

N. Proposed Labeling:

The labeling is sufficient to and satisfies the requirements of 21 CFR Part 809.10

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.