Alinity i Insulin-18

Prepared by: Yusra Othman /Director/Supervisor-Chem **Date:** May/24/2024
signature/title

Reviewed by: Jordan Dillard /Instructor **Date:** June 26 2024
signature/title

Approved by: Sanford N. Bauch, M.D /Chairman **Date:** June 28 2024
signature/title

BIENNIAL REVIEW:

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SUPERSEDES: Procedure titled _____

Instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from these instructions.

WARNING: The Insulin assay value in a given specimen, as determined with assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the Insulin assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining insulin levels serially

is changed, additional sequential testing should be carried out. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies. These specimens should not be assayed with the Alinity i Insulin assay. Refer to the section LIMITATIONS OF THE PROCEDURE in this package insert.

INTENDED USE

The Alinity i Insulin assay is a chemiluminescent microparticle immunoassay (CMIA) used for the quantitative determination of human insulin in human serum or plasma on the Alinity i analyzer.

SUMMARY AND EXPLANATION OF THE TEST

Insulin is a polypeptide hormone (MW 6000) composed of two nonidentical chains, A and B, which are joined by two disulfide bonds. Insulin is formed from a precursor, proinsulin (MW 9000), in the beta cells of the pancreas. In proinsulin, the A and B chains are joined by a connecting peptide, referred to as the C-peptide. Both insulin and C-peptide are stored in secretory granules of the islet cells of the pancreas and are then secreted.[1]

Insulin secretion follows two basic mechanisms, tonic secretion and biphasic secretion.[1] The basal or tonic secretion is independent of stimulation by exogenous glucose but is modulated by the fluctuations in physiological levels of glucose. The biphasic secretion is primarily a direct response from stimulation by exogenous glucose. Stimulation of insulin secretion can be caused by many factors including hyperglycemia, glucagon, amino acids, and by complex mechanisms involving growth hormone or catecholamines.[1] Increased levels of Insulin are found with obesity, Cushing's Syndrome, oral contraceptives, acromegaly, insulinoma and hyperthyroidism.[2, 3] Decreased levels of insulin are found in overt diabetes mellitus (although this may not be clearly expressed in early stages of the condition) and by part of a complex mechanism involving catecholamines.[1]

"Immunoreactive insulin" (IRI) is a term often used to refer to the component of circulating insulin and insulin-like biological activity which can be measured using antibodies against insulin. Insulinomas may produce various forms of insulin and proinsulin-like material and show total immunoreactive insulin at normal or elevated levels.[4, 5, 6, 7, 8] Since proinsulin and insulin both contain A and B polypeptide chains, there is a possible cross-reactivity with antibodies generated against insulin. This assay shows no cross-reactivity with proinsulin ($\leq 0.1\%$ at 10^6 pg/mL). Another possible interference is brought about by insulin antibodies which develop in patients treated with bovine or porcine insulin.[9]

Immunoassays for insulin have been widely used to provide supplementary information, first, for the diagnosis of diabetes mellitus and, second, for differential diagnosis of fasting hypoglycemia to discriminate between insulinoma and factitious hypoglycemia. **In these applications, the ratio of immunoreactive insulin to blood glucose (I/G) may be more valuable than the**

insulin level alone.[1] Furthermore, a single random blood sample may provide insufficient information due to wide variations in the time responses of insulin levels and blood glucose which are found among individuals and various clinical conditions. Other uses of insulin assays have been suggested by the finding of an increase in risk factors for coronary artery disease among healthy persons with hyperinsulinemia and normal glucose tolerance.[10]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

This assay is a one-step immunoassay for the quantitative determination of human insulin in human serum or plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

Sample, anti-insulin coated paramagnetic microparticles and anti-insulin acridinium-labeled conjugate are combined to create a reaction mixture and incubated. The insulin present in the sample binds to the anti-insulin coated microparticles and to the anti-insulin acridinium-labeled conjugate. Following a wash cycle, Pre-Trigger and Trigger Solutions are added.

The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of insulin in the sample and the RLUs detected by the system optics.

For additional information on system and assay technology, refer to the Alinity ci-series Operations Manual, Section 3.

REAGENTS

Kit Contents

Alinity i Insulin Reagent Kit 04T75

Volumes (mL) listed in the table below indicate the volume per cartridge.

REF	**04T7520**
Tests per cartridge	100
Number of cartridges per kit	2
Tests per kit	200
MICROPARTICLES	6.6 mL
CONJUGATE	6.1 mL
MICROPARTICLES Antibody to human insulin (mouse, monoclonal) coated microparticles in MOPS buffer with protein (bovine) stabilizer. Minimum concentration: 0.08% solids. Preservatives: sodium azide and other antimicrobial agents.	

REF	04T7520
CONJUGATE Antibody to human insulin (mouse, monoclonal) acridinium-labeled conjugate in MES buffer with protein (bovine) stabilizer. Minimum concentration: 0.09 µg/mL. Preservatives: sodium azide and other antimicrobial agents.	

Warnings and Precautions

- IVD
- For *In Vitro* Diagnostic Use
- Rx ONLY

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[11, 12, 13, 14]

The following warnings and precautions apply to: MICROPARTICLES	
WARNING	Contains 4-Morpholinopropanesulphonic acid* and sodium azide.
H316*	Causes mild skin irritation.
EUH032	Contact with acids liberates very toxic gas.
Response	
P332+P313*	If skin irritation occurs: Get medical advice / attention.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

* Not applicable where regulation EU 1272/2008 (CLP) or OSHA Hazard Communication 29CFR 1910.1200 (HCS) 2012 have been implemented.

The following warnings and precautions apply to: CONJUGATE	
Contains sodium azide.	
EUH032	Contact with acids liberates very toxic gas.
P501	Dispose of contents / container in accordance with local regulations.

Safety Data Sheets are available at www.abbottdiagnostics.com or/and SDS folder.

For a detailed discussion of safety precautions during system operation, **refer to the Alinity ci-series Operations Manual, Section 8.**

Reagent Handling

Upon receipt, gently invert the unopened reagent kit by rotating it over and back for a full 180 degrees, 5 times with green label stripe facing up and then 5 times with green label stripe facing down. This ensures that liquid covers all sides of the bottles within the cartridges. During reagent shipment, microparticles can settle on the reagent septum.

- Place a check in the square on the reagent kit to indicate to others that the inversions have been completed.
- After mixing, place reagent cartridges in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- If a reagent cartridge is dropped, place in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- Reagents are susceptible to the formation of foam and bubbles. Bubbles may interfere with the detection of the reagent level in the cartridge and cause insufficient reagent aspiration that may adversely affect results.

For a detailed discussion of reagent handling precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 7.

Reagent Storage

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened	2 to 8°C	Until expiration date	Store in upright position. If cartridge does not remain upright, gently invert the cartridge 10 times and place in an upright position for 1 hour before use.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Onboard	System Temperature	30 days	
Opened	2 to 8°C	Until expiration date	Store in upright position. If cartridge does not remain upright during storage, discard the cartridge. Do not reuse original reagent caps or replacement caps due to the risk of contamination and the potential to compromise reagent performance.

Reagents may be stored on or off the system. If removed from the system, store reagents with new replacement caps in an upright position at 2 to 8°C. For reagents stored off the system, it is recommended that they be stored in their original trays or boxes to ensure they remain upright.

For information on unloading reagents, refer to the Alinity ci-series Operations Manual, Section 5.

Indications of Reagent Deterioration

Deterioration of the reagents may be indicated when:

- a calibration error occurs
- a control value is out of the specified range

Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary.

For troubleshooting information, **refer to the Alinity ci-series Operations Manual, Section 10.**

INSTRUMENT PROCEDURE

The Alinity i Insulin assay file must be installed on the Alinity i analyzer prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, **refer to the Alinity ci-series Operations Manual, Section 2.**

For information on printing assay parameters, **refer to the Alinity ci-series Operations Manual, Section 5.**

For a detailed description of system procedures, **refer to the Alinity ci-series Operations Manual**.

Alternate Result Units

Edit assay parameter "Result Units" to select an alternate unit.

Conversion formula:

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

Default Result Unit	Conversion Factor	Alternate Result Unit
µU/mL	7.175	pmol/L

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

The specimen types listed below were verified for use with this assay.

Other specimen types and collection tube types have not been verified with this assay.

Specimen Types	Collection Tubes
Serum	Serum
	Serum separator
Plasma	Potassium EDTA
	Sodium EDTA
	Sodium heparin
	Sodium fluoride

- Do not use cadaveric specimens and other bodily fluids.
- Liquid anticoagulants may have a dilution effect resulting in lower concentration values for individual specimens.
- The instrument does not provide the capability to verify specimen types. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.

Specimen Conditions

- Analyze fresh specimens if possible.

Do not use:

- heat-inactivated specimens
- grossly hemolyzed specimens
- specimens with obvious microbial contamination

- For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter. Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
- Specimens should be free of bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross-contamination.
- Sample should be tested as soon as possible after drawing for the reason that the determined value may show lower levels because of insulin degrading enzyme existing in the red blood cell.

To ensure consistency in results, recentrifuge specimens prior to testing if

- they contain fibrin, red blood cells, or other particulate matter.

NOTE: If fibrin, red blood cells, or other particulate matter are observed, mix by low speed vortex or by inverting 10 times prior to recentrifugation.

Prepare frozen specimens as follows:

- Frozen specimens must be completely thawed before mixing.
- Mix thawed specimens thoroughly by low speed vortex or by inverting 10 times.
- Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous.
- If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Recentrifuge specimens.

Recentrifugation of Specimens

- Transfer specimens to a centrifuge tube and centrifuge.
- Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.

Specimen Storage

Analyze fresh specimens if possible.

Specimen Type	Temperature	Maximum Storage Time	Special Instructions
Serum/Plasma	**-10°C or colder**	7 days	Remove serum or plasma from the clot, red blood cells, or separator gel.

Avoid multiple freeze/thaw cycles.

Specimen Shipping

Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.

PROCEDURE

Materials Provided

04T75 Alinity i Insulin Reagent Kit

Materials Required but not Provided

- Alinity i Insulin assay file
- 04T7501 Alinity i Insulin Calibrators
- 04T7510 Alinity i Insulin Controls or other commercially available controls
- Alinity Pre-Trigger Solution
- Alinity Trigger Solution
- Alinity i-series Concentrated Wash Buffer

For information on materials required for operation of the instrument, refer to the Alinity ci-series Operations Manual, Section 1.

For information on materials required for maintenance procedures, refer to the Alinity ci-series Operations Manual, Section 9.

Assay Procedure

For a detailed description of how to run an assay, **refer to the Alinity ci-series Operations Manual, Section 5.**

- If using primary or aliquot tubes, refer to the Alinity ci-series Operations **Manual, Section 4 to ensure sufficient specimen is present.**
- To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.

Maximum number of replicates sampled from the same sample cup: 10

- Priority:
    - Sample volume for first test: 74 µL
    - Sample volume for each additional test from same sample cup: 24 µL
- ≤ 3 hours on the reagent and sample manager:
    - Sample volume for first test: 150 µL
    - Sample volume for each additional test from same sample cup: 24 µL
- 3 hours on the reagent and sample manager:
    - Replace with a fresh aliquot of sample.
- Refer to the Alinity i Insulin calibrator package insert and/or Alinity i Insulin control package insert for preparation and usage.
- For general operating procedures, **refer to the Alinity ci-series Operations Manual, Section 5.**
- For optimal performance, it is important to perform routine maintenance as described in the Alinity ci-series Operations Manual, Section **9. Perform maintenance more frequently when required by laboratory procedures.**

Sample Dilution Procedures

Samples with an insulin value exceeding 300 µU/mL (2152.5 pmol/L) are flagged with the code "> 300.0 µU/mL" ("> 2152.5 pmol/L") and may be diluted with either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a **1:2** dilution of the sample and automatically calculates the concentration by multiplying the result by the dilution factor.

Manual Dilution Procedure

Suggested dilution: 1:10

Add 20 µL of the sample to 180 µL of Alinity i Insulin Calibrator A.

To avoid contamination, use disposable pipettes or pipette tips when transferring Calibrator A for manual dilution. Refer to the Alinity i Insulin calibrator package insert for preparation and storage.

The operator must enter the dilution factor in the Specimen or Control tab of the Create Order screen. The system will use this dilution factor to automatically calculate the concentration of the sample and report the result.

The result should be ≥ 3.0 µU/mL (≥ 21.5 pmol/L) before the dilution factor is applied.

If the operator does not enter the dilution factor, the result must be manually multiplied by the appropriate dilution factor before reporting the result. If a diluted sample result is less than 3.0 µU/mL (21.5 pmol/L), do not report the result. Rerun using an appropriate dilution.

For detailed information on ordering dilutions, refer to the Alinity ci-series Operations Manual, Section 5.

Calibration

For instructions on performing a calibration**, refer to the Alinity ci-series Operations Manual, Section 5.**

Each assay control must be tested to evaluate the assay calibration.

Once a calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:

- A reagent kit with a new lot number is used.
- Daily quality control results are outside of statistically-based quality control limits used to monitor and control system performance, as described in the Quality Control Procedures section of this package insert.
    - **If statistically-based quality control limits** are not available, then the calibration should not exceed **a 30-day limit for recalibration** frequency.

This assay may require recalibration after maintenance to critical parts or subsystems or after service procedures have been performed.

Quality Control Procedures

The recommended control requirement for the Alinity i Insulin assay is that a single sample of each control level be tested once every day testing performed.

To establish statistically-based control limits, each laboratory should establish its own concentration target and ranges for new control lots at each clinically relevant control level. This can be accomplished by assaying a minimum of **20 replicates over several (3-5)** days and using the reported results to establish the expected average (target) and variability about this average (range) for the laboratory. Sources of variation that should be included in this study in order to be representative of future system performance include:

- Multiple stored calibrations
- Multiple reagent lots
- Multiple calibrator lots
- Multiple processing modules (if applicable)
- Data points collected at different times of the day

Refer to published guidelines for information or general control recommendation, for example Clinical and Laboratory Standards Institute (CLSI) Document C24-A3 or other published guidelines, for general quality control recommendations.*15*

- If quality control results do not meet the acceptance criteria defined by laboratory QC procedure, sample results may be suspect. Follow the established quality control procedures troubleshoot. Recalibration may be necessary**. For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.**
- Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

Commercial controls should be used according to the guidelines and recommendations of the control manufacturer. Concentration ranges provided in the control package insert should be used only for guidance.

For any control material in use, the laboratory should ensure that the matrix of the control material is suitable for use in the assay per the assay package insert.

Quality Control Guidance

Refer to “Basic QC Practices” by James O Westgard, Ph.D. for guidance on laboratory quality control practices.*16*

Verification of Assay Claims

For protocols to verify package insert claims, refer to Verification of Assay Claims in the Alinity ci-series Operations Manual.

RESULTS

Calculation

The Alinity i Insulin assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration and results.

For information on alternate result units, refer to the INSTRUMENT PROCEDURE, Alternate Result Units section of this package insert.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, **refer to the Alinity ci-series Operations Manual, Section 5.**

Measuring Interval

Measuring interval is defined as the range of values in µU/mL (pmol/L) which meets the limits of acceptable performance for linearity, imprecision, and bias.

The measuring interval of the Alinity i Insulin assay is **1.6 to 300.0 µU/mL** (11.5 to 2152.5 pmol/L).

LIMITATIONS OF THE PROCEDURE

- If the insulin results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.
- For diagnostic purposes, results should be used in conjunction with other data; e.g., symptoms, results of other tests, clinical impressions, etc.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed. Additional information may be required for diagnosis.[17]
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA).[18], [19] Specimens containing HAMA may produce anomalous values when tested with assay kits (such as Alinity i Insulin) that employ mouse monoclonal antibodies.[19]
- Insulin levels may be measured lower in patients with insulin autoimmune syndrome or familial high pro-insulinemia.
- Hemolyzed samples should not be used, since enzymatic degradation of insulin may occur and result in lower assay values.[20], [21] However, purified hemoglobin up to 500 mg/dL has been shown not to interfere.

- Specimens from patients treated with bovine or porcine insulin may contain insulin antibodies which could show interference in the assay.[9]

EXPECTED VALUES

It is recommended that each laboratory determine its own reference range based upon its particular locale and population characteristics. The reference ranges vary between countries due to differences in body size and nutrition.

CALIPER reference ranges: https://caliperdatabase.org

Reference Intervals (Female and Male)

Age	Lower Limit	Upper Limit	Sample Size	Lower Confidence Intervals	Higher Confidence Intervals
0 to < 1 year	0.96	23.5	96	(0.72, 1.22)	(20.8, 26.2)
1 to < 6 years	1.31	40.2	79	(0.92, 1.75)	(33.6, 47.5)
6 to < 19 years	2.19	49.7	190	(1.22, 3.14)	(39.3, 53.4)

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

The Alinity i analyzer and the ARCHITECT i System utilize the same reagents and sample/reagent ratios.

Unless otherwise specified, all studies were performed on the Alinity i analyzer.

Precision

Within-Laboratory Precision

A study was performed based on guidance from CLSI EP05-A2.[22] Testing was conducted using 1 lot of the Alinity i Insulin Reagent Kit, 1 lot of the Alinity i Insulin Calibrators, and 1 lot of the Alinity i Insulin Controls and 1 instrument. Three controls and 2 human serum panels were assayed in a minimum of 2 replicates at 2 separate times per day on 20 different days.

Sample	N	Mean (µU/mL)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV

Sample	N	Mean (µU/mL)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Low Control	120	8.2	0.15	1.8	0.15	1.8
Medium Control	120	38.5	0.53	1.4	0.57	1.5
High Control	120	120.5	1.74	1.4	1.96	1.6
Panel 1	120	8.7	0.18	2.1	0.20	2.2
Panel 2	120	150.3	2.35	1.6	2.45	1.6

[a]Includes within-run, between-run, and between-day variability.

Sample	N	Mean (pmol/L)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Low Control	120	59.0	1.09	1.8	1.09	1.8
Medium Control	120	276.1	3.77	1.4	4.12	1.5
High Control	120	864.3	12.45	1.4	14.05	1.6
Panel 1	120	62.5	1.33	2.1	1.40	2.2
Panel 2	120	1078.3	16.88	1.6	17.61	1.6

[a]Includes within-run, between-run, and between-day variability.

Lower Limits of Measurement

A study was performed based on guidance from CLSI EP17-A2.[23] Testing was conducted using 3 lots of the Alinity i Insulin Reagent Kit on each of 2 instruments over a minimum of 3 days. The maximum observed Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) values are summarized below.

	µU/mL	pmol/L
LoB[a]	0.1	0.7

	µU/mL	pmol/L
LoD[b]	0.4	2.9
LoQ[c]	**1.6**	11.5

[a]The LoB represents the 95th percentile from n ≥ 60 replicates of zero-analyte samples.

[b]The LoD represents the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

[c] The LoQ was determined from n ≥ 60 replicates of low-analyte level samples and is defined as the lowest concentration at which a total allowable error of 36.7% was met.

Linearity

A study was performed based on guidance from CLSI EP06-A.*24*

This assay is linear across the measuring interval of **1.6 to 300.0 µU/mL** (11.5 to 2152.5 pmol/L).

Cross-Reactants

This study was performed on the ARCHITECT i System.

The cross-reactivity with Proinsulin (1 000 000 pg/mL), with C-Peptide (10 000 000 pg/mL) and with Glucagon (10 000 000 pg/mL) was determined as below in the ARCHITECT Insulin assay.

Cross-Reactant	Cross-Reactant Concentration	% Cross-Reactivity
Proinsulin	10^6 pg/mL	≤ 0.1
C-Peptide	10^7 pg/mL	≤ 0.001
Glucagon	10^7 pg/mL	≤ 0.001

Interference

This study was performed on the ARCHITECT i System.

Potentially Interfering Endogenous Substances

The specificity of the ARCHITECT Insulin assay was determined by testing sera containing the potentially interfering substances listed below. These substances showed less than 10% interference in the ARCHITECT Insulin assay at the levels indicated.

Potentially Interfering Substance	Interferent Level
Bilirubin	≤ 20 mg/dL
Hemoglobin	≤ 500 mg/dL
Total Protein	≤ 12 g/dL
Triglycerides	≤ 3000 mg/dL

Method Comparison

A study was performed based on guidance from CLSI EP09-A3 using the Passing-Bablok regression method. [25]

		Units	n	Correlation Coefficient	Intercept	Slope	Concentration Range
Alinity i Insulin vs ARCHITECT Insulin	Serum	µU/mL (pmol/L)	174	1.00	-1.06 (-7.57)	0.98	2.0-286.3 (14.0-2054.2)

Carryover

No detectable carryover (less than 0.5 µU/mL) was observed when a sample containing 15 000 µU/mL of insulin was assayed.

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