GlucoMen LX PLUS
blood glucose and blood ketone meter

Accuracy Evaluation to New ISO 15197:2013, with Technical and Specification Data

GlucoMen® LX PLUS+

Reference Book, July 2013

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System accuracy evaluation of GlucoMen LX PLUS according to the INTERNATIONAL STANDARD ISO 15197:2013

IKFE GMBH (Institut für Klinische Forschung und Entwicklung / Institute for Clinical Research and Development). Mainz, Germany. Data obtained during the study MEN – BGM – 001a

1 Introduction to New ISO 15197:2013

New accuracy criteria for blood glucose meters have been published in the new EN ISO 15197:2013[(1)] guidelines. The new minimum acceptable accuracy criteria for results produced by a glucose monitoring system are as follows:

Accuracy Requirement A:

At glucose concentrations <5.55 mmol/L (100 mg/dL), ninety five percent (95%) of the individual glucose results shall fall within ± 0.83 mmol/L (15 mg/dL) of the results of the reference measurement.

At glucose concentrations ≥5.56 mmol/L (100 mg/dL), ninety five percent (95%) of the individual glucose results shall fall within ± 15% of the results of the reference measurement

Accuracy Requirement B:

Ninety nine percent (99%) of individual glucose results shall fall within zones A and B of the Consensus Error Grid (CEG).

In addition to the changed criteria, the system accuracy evaluation must include data from three different reagent system lots (three test strip lots), each with 100 fresh capillary blood samples.

Haematocrit Interference Evaluation:

Evaluation of haematocrit (packed cell volume) effect upon accuracy must be carried out with a minimum of five haematocrit levels at each of three glucose concentrations.
This evaluation is detailed separately, on pages 6 to 12 of this report

2. Objective of Accuracy Study

To investigate the blood glucose measuring accuracy of the GlucoMen LX PLUS system, compared to the established laboratory reference method YSI 2300 STAT Plus. Evaluation was carried out to the accuracy requirements of ISO 15197:2013. Haematocrit Interference Evaluation is the subject of a separate study – see pages 8 to 13 of this report.

3. Method

This evaluation follows the revised procedures and requirements of the new ISO 15197:2013, including the following:

1 Data from three tested lots is included in the evaluation. For each strip lot, 210 measurements were collected. These measurements were performed using two different GlucoMen LX PLUS meters for each lot (a total of 6 meters, with 105 measurements per meter).

2 The distribution from low to high glucose concentrations obtained ensured that the correct percentages of samples (%) fall within defined glucose concentrations (mmol/L).

ISO category	Percentage of samples (%)	ISO and Study Glucose Concentration (mmol/L)
1	5	≤ 2.8
2	15	> 2.8 to 4.4
3	20	> 4.4 to 6.7
4	30	> 6.7 to 11.1
5	15	> 11.1 to 16.7
6	10	> 16.7 to 22.2
7	5	> 22.2

Samples were assigned to the respective category according to their glucose concentration as measured with the YSI 2300 STAT PLUS.

In accordance with ISO 15197:2013, since it was not possible to fill the extreme categories of 1 and 7 (table above) without risk to patients, heparinised venous blood samples from subjects were obtained and manipulated in-vitro by IKFE Laboratory staff to achieve the desired blood glucose levels. The same was necessary for parts of categories 2 and 6.

Acceptable ranges and calculation procedures are all in line with the new ISO 15197:2013.

4. Results and Conclusion of Accuracy Study

Results: Accuracy Requirement A - Bias:

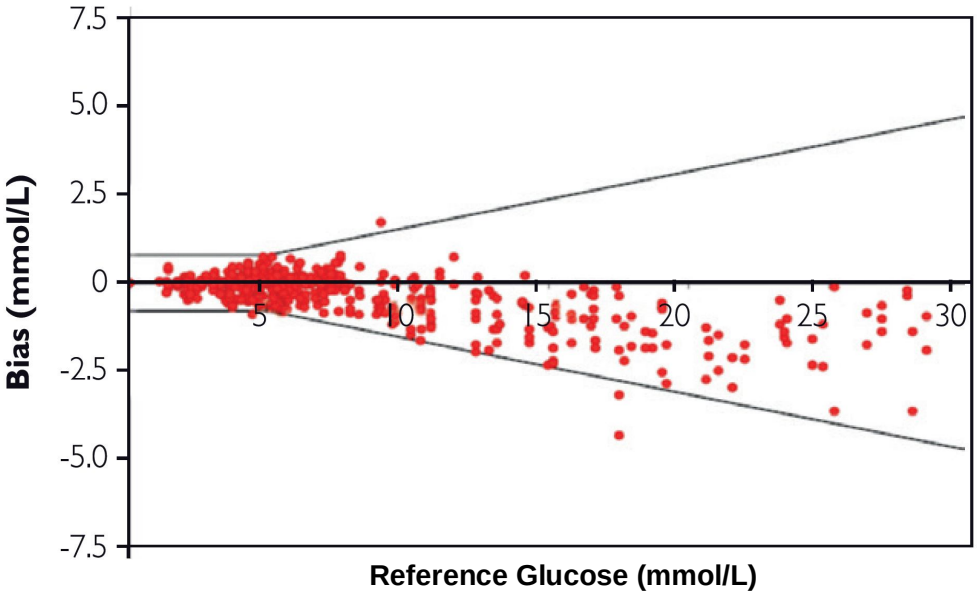
At glucose levels < 5.6mmol/L, 96% of results are within ± 0.83mmol/L of laboratory results.

At glucose levels ≥ 5.6mmol/L, 99% of results are within ± 15% of laboratory results.

Combined system accuracy was 98%

Conclusion: GlucoMen LX PLUS_exceeds ISO 15197:2013 requirement of 95% within ± 0.83mmol/L and ± 15% of laboratory results respectively.

Figure 1. Bias Plot for GlucoMen LX PLUS



System accuracy results for glucose concentrations < 5.55mmol/L		
Within ± 0.28mmol/L	Within ± 0.56mmol/L	**Within ± 0.83mmol/L**
124 / 192 (70%)	174 / 192 (91%)	**184 / 192 (96%)**

System accuracy results for glucose concentrations ≥ 5.55mmol/L		
Within ± 5%	Within ± 10%	**Within ± 15%**
273 / 438 (62%)	397 / 438 (91%)	**434 / 438 (99%)**

Combined system accuracy results (absolute and relative deviations)

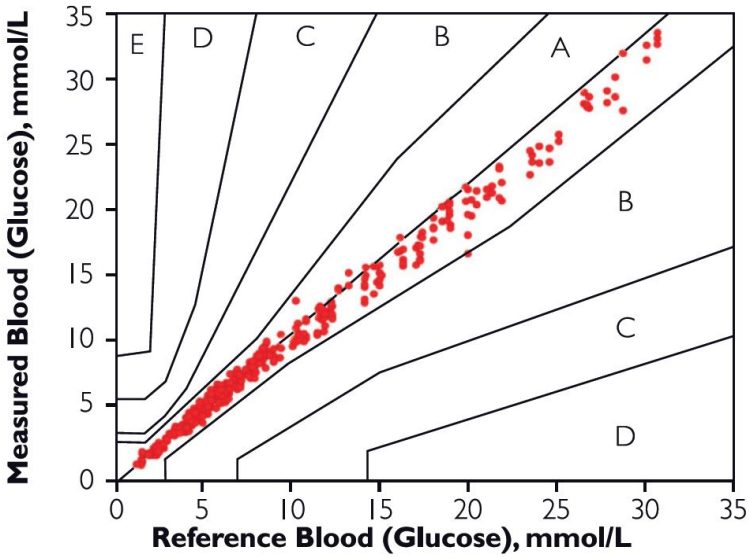
Within ± 0.83mmol/L and 15%
618 / 630 (98%)

Results: Accuracy Requirement B – Error Grid:

100% of results are within Zone A and B of the Consenses Error Grid, with 99.7% in Zone A

Conclusion: GlucoMen LX PLUS exceeds ISO 15197:2013 requirement of 99% of results within zones A and B of the Consensus Error Grid.

Figure 2. Consensus Error Grid Plot for GlucoMen LX PLUS



Zone	A	B	C	D	E
Cases	628	2	0	0	0
Percentage	99.7	0.3	0	0	0

The Consensus Error Grid (CEG) represents the results of a survey of 100 endocrinologists attending the American Diabetes Association Annual Meetinf 1994. The CEG is divided into five zones, which are defined by estimated risk to the patient if a result falls in a given zone. The risk levels defined by the CEG's zones are classified as:

Risk Level / CEG Zone	Risk to diabetic patient
A	No effect on clinical action
B	Altered clinical action - little or no effect on clinical outcomes
C	Altered clinical action - likely to affect clinical outcomes
D	Altered clinical action - could have significant medical risk
E	Altered clinical action - could have dangerous consequences

Haematocrit Interference Evaluation, ISO 15197:2013

Background

Varying haematocrit: is a potential source of error in blood glucose monitoring

Abnormal haematocrit levels interfere with glucose readings of patient self-testing blood glucose meters and are potentially a very significant source of inaccuracy.

How commonly will haematocrit levels vary from the normal level of approximately 42%?

A recent investigation, analyzing data from 15,108 community patients has reported haematocrit ranging from 20 to 60% [(1)].
Such deviations from normal haematocrit levels of approximately 42% can be induced by lifestyle interventions (e.g. smoking or prolonged exercise), environmental conditions (e.g. altitude or seasonal variations), demographic factors (e.g. age) and disease and drug related conditions (e.g. haematological disorders, hypermenorrhea, pregnancy or renal disease). [(1)]
Within subject variability also exists, indicated by a 15% relative change [(2)].

Why can varying haematocrit dramatically affect a blood glucose test?

Haematocrit that is lower than normal can lead to overestimation of glucose values and haematocrit that is higher than normal can lead to underestimation of glucose values. The impact of abnormal haematocrit on blood glucose testing may be explained by a change in diffusion kinetics, and / or increased packed red cell volume and displacement of plasma volume leading to insufficient plasma volume for accurate testing. The impact of abnormal haematocrit will vary depending upon the technology of the blood glucose monitoring system.

Requirement: Haematocrit Interference Evaluation

The haematocrit operating range described within the test strip insert must be such that:

At glucose concentrations <5.55 mmol/L (100 mg/dL), the difference between the average measured value at each haematocrit level and the average measured value at the mid-level haematocrit should not exceed 0.55 mmol/L.

At glucose concentrations ≥5.56 mmol/L (100 mg/dL), the difference between the average measured value at each haematocrit level and the average measured value at the mid-level haematocrit should not exceed ± 10%.

Two studies have been carried out to evaluate the potential effect of haematocrit level upon the accuracy of GlucoMen LX PLUS, described on the following pages.

References:

1. Lyon ME, Lyon AW. Patient acuity exacerbates discrepancy between whole blood and plasma methods through error in molality to molarity conversion: “Mind the gap!”. Clin Biochem. 2011;44(5-6):412–7.
2. Thirup P. Haematocrit: within-subject and seasonal variation. Sports Med. 2003;33(3):231–43.

Haematocrit Interference Evaluation: Study 1

Haematocrit Interference and Blood Glucose Meters for Patient Self-Measurement

IKFE GMBH (Institut für Klinische Forschung und Entwicklung / Institute for Clinical Research and Development). Mainz, Germany
J. Diabetes Sci Technol 2013;7(1):179-189

Introduction:

This study assessed the potential influence of haematocrit variations on a variety of blood glucose meters, including GlucoMen LX PLUS.

Method:

Venous heparinised blood was manipulated to three different blood glucose concentrations, 2.8 – 5.0mmol/L (low), 6.7 – 10.0mmol/L (mid), and 15.6 – 19.4 mmol/L (high), and five different haematocrit levels (25%, 35%, 45%, 55%, 65%), a total of fifteen samples.
Each sample was used to perform eight glucose tests on GlucoMen LX PLUS.
The reference analyser used to determine the glucose level of samples was the YSI 2300 STAT Plus™.

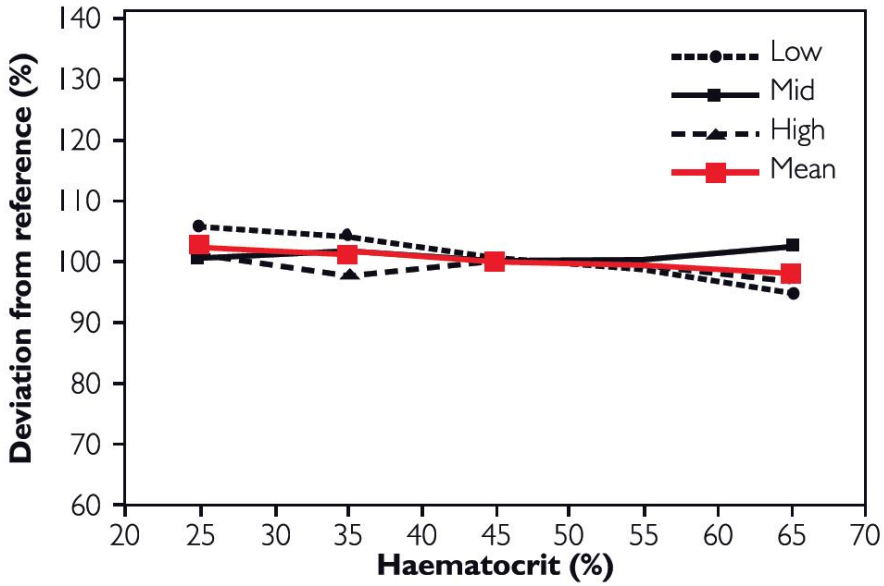
Interpretation of Results:

The mean glucose value determined at a haematocrit of 45% was used as the reference value from which to measure potential bias (percentage deviation) at other haematocrit levels tested.
The effect of haematocrit upon accuracy was determined by adding the largest observed bias above this reference glucose value to the largest observed bias below it (mean deviations over the entire glucose range were used). The result was termed the **Haematocrit Interference Factor (HIF)**.

According to the new ISO 15197:2013 guidelines, regulatory acceptance requires that results are within ±15% from the reference value at normal haematocrit (for values ≥5.5mmol/L). So any haematocrit induced error is additional to the allowed ±15%, confirming the importance of minimizing this potential source of error. Therefore the study arbitrarily defined that a mean Haematocrit Interference Factor (HIF) <10% is acceptable.

GlucoMen LX PLUS Results:

GlucoMen LX PLUS exhibits an Haematocrit Interference Factor of <4% at all levels of haematocrit and glucose, therefore exceeding ISO requirements at low and high glucose levels (both <5.5mmol/L and ≥5.5mmol/L).



Conclusion:

GlucoMen LX PLUS exceeds ISO 15197:2013 requirements.

Meters included in this evaluation showed Haematocrit Interference Factor's of up to 68%.

The paper concluded that the use of meters that are not affected by haematocrit interference should be encouraged.

Haematocrit Interference Evaluation: Study 2

A.MENARINI diagnostics Scientific & Technology Affairs	GlucoMen®LX PLUS system: investigation of accuracy variation with haematocrit level	Authors: F. Berti, C. Scuffi Date: 16/10/2012 Page 1 of 4

GlucoMen LX PLUS system: investigation of potential accuracy variation with haematocrit level

Background

The GlucoMen LX PLUS meter features haematocrit compensation, it calculates the haematocrit of the blood sample by measuring the inter-electrode impedance and corrects the glucose signal accordingly.

1. Aim

To evaluate the performance of GlucoMen LX PLUS at different haematocrit levels, in accordamce with the requirements of ISO15197:2013.

This study measured the effect on system accuracy of varying haematocrit (Hct%) levels, across five haematocrit levels. These levels included those within operating range of 25% to 60% haematocrit, and also at extremes.

The study is in line with ISO 15197:2013, which states that such investigation should include the range of haematocrit values specified in the labeling of the blood glucose monitoring system.

2. Method

Blood Sample Preparation

Venous blood samples from healthy subjects were analysed with the YSI 2300 STAT Plus, and manipulated to add or deplete glucose in order to obtain a low and a high concentration:

- **Level A** (low) 2.8 - 3.9 mmol/L
- **Level B** (high) 15.0 -16.1 mmol/L.

Five levels of haematocrit (Hct%) were investigated, according to the following distribution:

Level	Target HCT%	Achieved HCT% for Level A	Achieved HCT% for Level B
1	< 25%	15%	15%
2	30%	30%	28%
3	44%	49%	44%
4	58%	61%	60%
5	>60%	80%	65%

To manipulate haematocrit levels, blood was centrifuged and a calculated volume of supernatant plasma was either removed to achieve higher haematocrit levels, or added to achieve decreased haematocrit levels.

To obtain results comparable with capillary blood tests, the partial oxygen pressure (pO2) was maintained between 70 and 90 mmHg, either by allowing oxygenation of the venous sample to raise the pO2 or by adding venous blood if the sample oxygenation required reduction.

Blood Sample Testing

For both glucose concentrations (A and B), each haematocrit level was tested by performing 10 measurements (1 test on each of 10 GlucoMen LX PLUS meters). In total, 100 measurements were performed, 2 glucose levels x 5 haematocrit levels x 10 meters.

Each sample was analysed with the YSI 2300 STST Plus to obtain the reference glucose concentration.

Results:

Glucose level A (2.8 - 3.9 mmol/L)				**Glucose level B (15.0 - 16.1 mmol/L)**			
Hct % for level A	YSI Reference	Average meter reading	SD (meter)	Hct % for level B	YSI Reference	Average meter reading	SD (meter)
15%	3.1	3.3	0.1	15%	15.6	16.4	0.5
30%	2.9	3.3	0.1	28%	15.6	16.2	0.3
49%	3.9	4.1	0.2	44%	15.6	15.7	0.4
61%	3.4	3.9	0.2	60%	15.3	15.8	0.8
80%	3.6	E4*	n/a	65%	15.2	16.3	0.5
Results exceed requirements of ISO 15197:2013				**Results exceed requirements of ISO 15197:2013**			
40 / 40 (100%)				**40 / 40 (100%)**			

- E4 (Error 4) can be attributed to haematocrit of 80% which is out of the allowed range for glucose measurement

For glucose level A (low), 100% of results were within ± 0.83 mmol/L of the YSI reference method, for all the investigated haematocrit levels (Figure 1).

The exception is at haematocrit of 80%, E4 error was displayed as the meter had detected an extreme haematocrit level, dramatically exceeding the allowed operating range.

For glucose level B (high), 100% of results were within ± 15% of the YSI reference method, for all the investigated haematocrit levels (Figure 2).

Figure 1. Average bias variation v haematocrit level for low glucose (level A, 2.8 to 3.9 mmol/L)

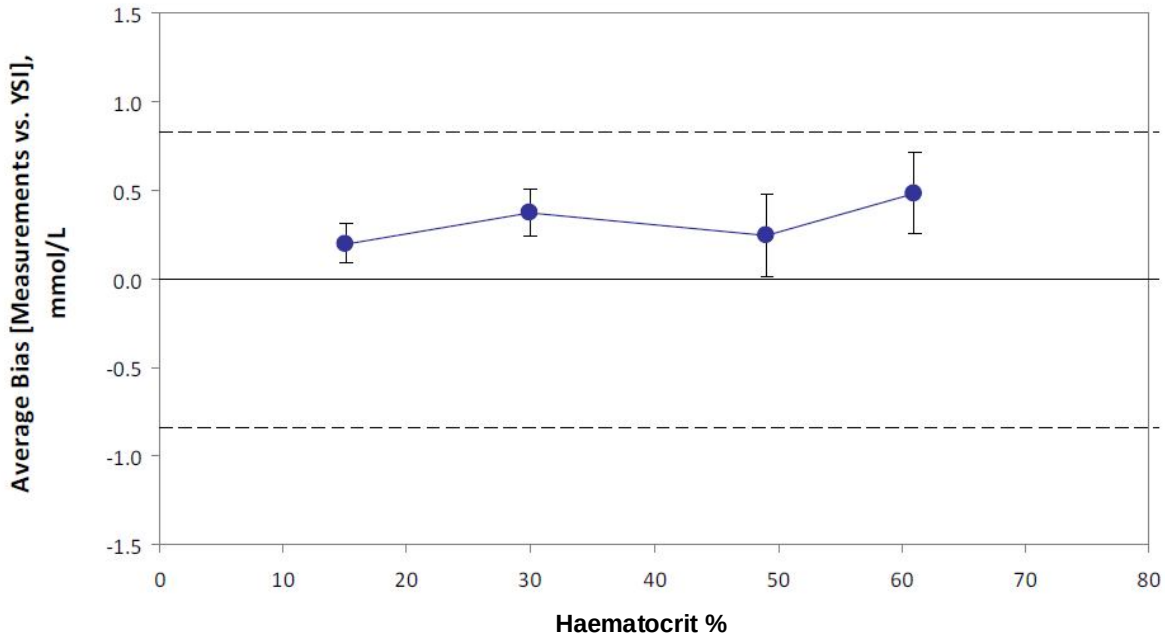
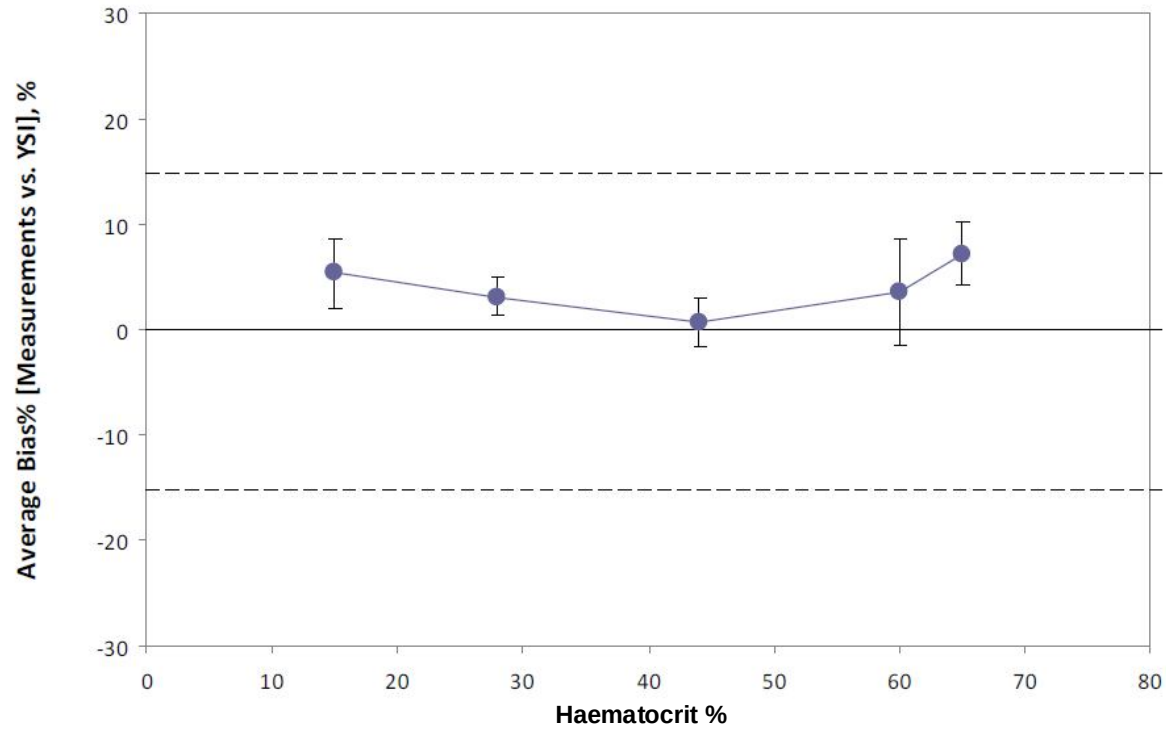


Figure 2. Average bias variation v haematocrit level for high glucose (level B, 15.0 to 16.1 mmol/L)



Conclusion:

GlucoMen LX PLUS exceeds ISO 15197:2013 requirements for accuracy across the system's haematocrit operating range of 25 to 60%

In addition the accuracy at extremely low haematocrit (15%), below the range stated within the product labeling, also exceeds ISO 15197:2013 requirements.

At extremely high haematocrit, outside of the possibility to accurately estimate blood glucose values, the meter displays an error message (a preferable outcome to an inaccurate result).

The GlucoMen LX PLUS meter calculates the haematocrit of the blood sample by measuring the inter-electrode impedance and corrects the glucose signal accordingly – haematocrit compensation.

Precision Final report

Background:

ISO 15197:2013 sets out the protocol and evaluation procedure for evaluation of measurement precision (repeatability), which requires a series of measurements within a short interval of time, by a single laboratory technician, using the same meter and reagent lot.

Method:

In a laboratory study, the precision (repeatability) evaluation was carried out following the ISO 15197:2013 procedure. The precision of GlucoMen LX PLUS was analysed using blood samples at five glucose concentrations across the operating range, performing 20 repeated tests with each sample.

Results:

ISO 15197:2013 requires that the average blood glucose value, the standard deviation and the coefficient of variation (CV) shall be calculated at each glucose concentration.

ISO 15197:2013 does not specify separate criteria for minimum acceptable precision and bias. The system accuracy requirements, as described on page 1, are designed to verify acceptability of the combined effects of precision and bias for the blood glucose monitoring system.

Average (mmol/L)	**3.0**	**5.4**	**14.5**	**23.0**	**31.3**
SD	**0.08**	**0.19**	**0.27**	**0.39**	**0.93**
CV%	**2.6**	**3.6**	**1.9**	**1.7**	**3.0**

Conclusion:

GlucoMen LX PLUS exhibits excellent precision across the range of blood glucose concentrations.

GlucoMen LX PLUS exceeds the accuracy requirements of ISO 15197:2013 which are designed to verify acceptability of the combined effects of precision and bias.

Technical and Analytical

General Specification, Glucose Testing:

No Coding	No coding procedure is needed with GlucoMen LX PLUS system (not for glucose nor ß-Ketone testing).
Enzyme specificity	Glucose Oxidase is specific for β D-glucose, it does not react with any other sugars e.g. Maltose (safe in peritoneal renal dialysis)
Maltose independent	Glucose Oxidase is specific for β D-glucose and independent of all other sugars
Calibration	GlucoMen LX PLUS blood glucose meter is plasma calibrated to allow easy comparison of results with laboratory methods (see below for further detail)
Blood Volume Control	The meter detect when enough blood has been applied to the test strip to enable a test (prevents under / over application)
Strip Expiry Date:	24 months shelf life 9 months after first opening vial
Test Range:	1.1 to 33.3mmol/L
Test Time:	4 seconds
Sample Volume:	0.3µl
Memory:	400 results with date and time; 1, 14, 30 day averages
Operating Temperature:	5 to 45°C
Haematocrit Range	25 – 60%
Operating Humidity:	10 to 90% Relative Humidity
Power Source:	3V Lithium Battery CR2450, available free to users
Battery Life:	Over 1000 Tests
Weight:	75g approximately
Size:	58 x 98 x 17mm approximately

Test Principle:

GlucoMen LX PLUS utilizes electrochemical test technology. Glucose in the blood sample mixes with reagent on the test strip which causes a small electric current. The amount of current that is created depends on how much glucose is in the blood. The GlucoMen LX PLUS blood glucose meter measures the current and converts the measurement to the amount of glucose in the blood. The result (blood glucose concentration) is displayed by the meter.

Reagent Composition:

The GlucoMen LX test strip enzyme is glucose oxidase (Aspergillus Niger) covalently bound to Flavin Adenine Dinucleotide (FAD), and utilizing a hexacyanoferrate(III) ion mediator.

Calibration / Traceability:

GlucoMen LX PLUS blood glucose meter is **plasma** calibrated to allow easy comparison of results with laboratory methods.

The GlucoMen LX PLUS system is calibrated versus capillary plasma values determined using a Yellow Springs 2300 analyser (YSI). The YSI analyser is calibrated (as secondary reference measurement procedure) using a series of NERL standards; the NERL standards (primary calibrators) are referenced directly to the NIST (National Institute of Standards and Technology, USA).

Testing for Endogenous and Exogenous Interfering Substances:

All of the 30 substances listed below could be present in the blood of intended users and could theoretically interfere with glucose measurement.

All 30 substances have been tested at two levels of glucose and found **not to interfere with the performance of the system at physiological or therapeutic levels**.

Glucose Level	3.9 mmol/L	13.3 mmol/L	Glucose Level	3.9 mmol/L	13.3 mmol/L
Acetaminophen	7 mg/dL	35 mg/dL	Triglycerides	3000 mg/dL	2000 mg/dL
Ascorbic acid	3 mg/dL	6 mg/dL	Uric Acid	9 mg/dL	12 mg/dL
Bilirubine	13 mg/dL	36 mg/dL	Creatinine	1000 mg/dL	3000 mg/dL
Cholesterol	2500 mg/dL	2000 mg/dL	Urea	500 mg/dL	1200 mg/dL
Dopamine	23 mg/dL	30 mg/dL	Sodium Citrate	400 mg/dL	400 mg/dL
Ephedrine	4 mg/dL	4 mg/dL	Sodium Heparin	3000 IU/dL	3000 IU/dL
Galactose	1700 mg/dL	700 mg/dL	Fetal Bilirubin	10 mg/dL	10 mg/dL
Gentisic Acid	6 mg/dL	25 mg/dL	Lactose	2000 mg/dL	3500 mg/dL
Ibuprofen	100 mg/dL	120 mg/dL	Maltose	3600 mg/dL	2400 mg/dL
L-Dopa	750 µg/dL	300 µg/dL	Xylitol	350 mg/dL	800 mg/dL
Methyl-Dopa	2 mg/dL	7 mg/dL	Xylose	3000 mg/dL	3000 mg/dL
Salicylate	150 mg/dL	200 mg/dL	Galactose	1700 mg/dL	700 mg/dL
Tetracycline	200 mg/dL	200 mg/dL	Fructose	1000 mg/dL	1500 mg/dL
Tolazamide	100 mg/dL	240 mg/dL	Mannose	800 mg/dL	1500 mg/dL
Tolbutamide	100 mg/dL	300 mg/dL	Sorbitol	3000 mg/dL	3000 mg/dL

Maltose independence:	Glucomen LX PLUS test strips (Glucose Oxidase enzyme) react specifically with β D-glucose and do not react with any other sugars that may be in the blood.
Lipaemic Samples:	Cholesterol up to 13.0 mmol/L and Triglycerides up to 38.0 mmol/L do not significantly affect test results.

For more information please call 0800 243 667

Or email

glucomen@menarinidiag.co.uk

GlucoMen® LX PLUS+

GlucoMen®
The Diabetes Diagnostics Company