GLUCOSE

Diagnostic reagent for determination of glucose concentration.
Liquid. Monoreagent. Store at +2/+8°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**

Ref No	Package	Ref No	Package	Ref No	Package	Ref No	Package
A2191N	400 mL	HN190	600 mL	MD190	450 mL	PL2190	240 mL
A2192N	200 mL	HN191	400 mL	MD191	225 mL	PL2191	150 mL
BB105	220 mL	K2191	320 mL	M2192	400 mL	RD2190	400 mL
BY2190	700 mL	LB190	240 mL	M3190	320 mL	S2191	400 mL
BY2191	500 mL	LM155	240 mL	M3191	120 mL	S2192	200 mL
BZ2105	360 mL	L2190	600 mL	M4191	400 mL	TB2190	400 mL
DM2190	333 mL	L2191	400 mL	M4192	560 mL	TB2191	200 mL
D2190	900 mL	L2192	240 mL			8A2190	700 mL
D2191	500 mL	A2193N	500 mL			8A2191	500 mL
D2192	250 mL						

Changes made in the instructions for use are marked as grey.

INTENDED USE

The test is applied for the quantitative determination of glucose in serum, plasma, urine and CSF (Cerebrospinal Fluid).

GENERAL INFORMATION

Carbohydrates are aldehyde or ketone derivatives of polyhydroxy (more than one OH group) alcohols or compounds that yield these derivatives during hydrolysis. Glucose is a monosaccharide aldohexose sugar with the chemical formula $C_6H_{12}O_6$ [or $C_6(H_2O)_6$].[1] Compounds with the same chemical formula but different structures are called isomers. For example, fructose, mannose and galactose are all isomers of each other, including glucose, and have the same chemical formula ($C_6H_{12}O_6$).[2] Since most sugars in humans are in the d-configuration, the D-glucose form is available.[1]

Glucose is obtained from the breakdown of carbohydrates in the diet (cereals, starchy vegetables and legumes) and body stores (glycogen), as well as by endogenous synthesis from protein or the glycerol portion of triglycerides. Dietary carbohydrates are digested and absorbed in the gastrointestinal tract. When energy intake exceeds expenditure, the excess is converted into fat and glycogen to be stored in adipose tissue, liver or muscle, respectively. When energy expenditure exceeds caloric intake, endogenous glucose formation occurs from the breakdown of carbohydrate stores and from non-carbohydrate sources (e.g. amino acids, lactate, glycerol). The concentration of glucose in the blood is maintained within a fairly narrow range by various hormones under various conditions (feeding, fasting or vigorous exercise).[1] The hormones mainly involved in the regulation of glucose metabolism in fasted and fed states are insulin, glucagon, GH, adrenaline and cortisol. Of these, insulin has the most pronounced effect and is the only hormone that lowers blood glucose. Glucagon, GH, adrenaline and cortisol generally tend to antagonize the effects of insulin.[3]

Diabetes mellitus (DM) is a chronic disease characterized by chronic hyperglycemia accompanied by glucosuria and other biochemical abnormalities. It includes a wide range of clinical conditions, from asymptomatic patients with relatively mild biochemical abnormalities to patients admitted to hospitals with rapid onset of severe metabolic decompensation leading to coma. Long-term complications such as retinopathy, neuropathy and nephropathy may develop. It is a major risk factor for cardiovascular disease. In type 1 DM, there is essentially no insulin secretion, whereas in type 2 DM, insulin is secreted but the amount is insufficient to prevent hyperglycemia or there is resistance to its action. Type 1 DM usually presents acutely within a few days or weeks in young, non-obese people, but can occur at any age. Type 2 DM usually appears in older (>40 years) and obese patients, with a less acute course; in many patients it is evident some time (even years) before diagnosis. In addition to types 1 and 2 DM, there are many other types of DM, including gestational diabetes mellitus (GDM), neonatal diabetes, maturity onset diabetes of the young (MODY), MODY2 and MODY3.[3]

Hypoglycemia is a blood glucose concentration below the fasting value, but it is difficult to define a specific threshold. The most commonly recommended threshold is 50 mg/dL,[4] although some suggest 60 mg/dL.[5] A transient drop in glucose level may occur 1.5 to 2 hours after a meal, and it is not unusual to see a plasma glucose concentration as low as 40 mg/dL 2 hours after receiving an oral glucose load. Similarly, extremely low fasting blood glucose levels can sometimes be recognized without any symptoms or signs of underlying disease.[1] The brain cannot store and produce glucose. In resting adults, the central nervous system (CNS) consumes about 50% of the glucose used by the body.[6] Very low plasma glucose concentrations (<20 or 30 mg/dL) may lead to severe CNS dysfunction.[1] Neonatal blood glucose concentrations are much lower than adult concentrations (average <35 mg/dL) and fall shortly after birth as liver glycogen stores are depleted. Glucose concentrations as low as 30 mg/dL in a term infant and 20 mg/dL in a premature infant can occur without clinical evidence of hypoglycemia. The most common causes of hypoglycemia in the neonatal period include prematurity and maternal DM, GDM and eclampsia. These

are usually transient. Hypoglycemia that begins in early infancy is rarely transient and may be due to congenital metabolic disorders or ketotic hypoglycemia. It usually occurs after starvation or a febrile illness.[1] The Pediatric Endocrine Society published guidelines for the evaluation of persistent hypoglycemia in newborns and infants in 2015.[7]

The most common cause of hypoglycemia is drugs.[8] A wide range of drugs such as pentamidine, gatifloxacin and quinine can cause hypoglycemia. Oral hypoglycemic agents with a long half-life (35 hours for chlorpropamide) are the most common cause of drug-induced hypoglycemia. Sulfonylureas stimulate insulin, proinsulin and C-peptide secretion and may mimic insulinoma. Ethanol causes hypoglycemia by inhibiting gluconeogenesis. This is exacerbated by malnutrition (low glycogen stores) in patients with chronic alcoholism. Decreased glucose production caused by impaired gluconeogenesis or glycogen storage in liver failure (e.g. viral hepatitis, toxins) may cause hypoglycemia. Growth hormone deficiency (especially in combination with ACTH deficiency), glucocorticoids, thyroid hormone or glucagon deficiency can cause hypoglycemia.[1] Various medications and a group of disorders can cause hypoglycemia in the postprandial period.[9] These include antibodies against insulin or the insulin receptor and congenital disorders (e.g. fructose-1,6-diphosphatase deficiency). It also includes reactive hypoglycemia (referred to as functional hypoglycemia), which is the subject of much debate.[5] Hypoglycemia is common in both type 1 DM and type 2 DM.[10-12] Hypoglycemia is a limiting factor in the glycemic management of DM. Patients on insulin experience approximately one to two episodes of symptomatic hypoglycemia per week, and severe hypoglycemia (requiring assistance from others or associated with loss of consciousness) affects approximately 10% of this population annually.[1] An estimated 2 to 4% of people with type 1 DM die from hypoglycemia.[13] Similarly, hypoglycemia can occur in patients with type 2 DM (caused by oral hypoglycemic agents or insulin), but less frequently than in type 1 DM.[1]

In addition to blood, glucose can also be measured in urine or cerebrospinal fluid (CSF). Glucose appears in the urine when the maximum tubular absorption capacity of the kidney is exceeded; although variable, this occurs at blood glucose concentrations of approximately 180 mg/dL (10 mmol/L). Although a positive urine glucose level supports the diagnosis of DM and indicates the need for further investigation, it is not a diagnostic criterion for the disease. Because of variability in tubular absorption of both water and glucose, urine glucose is not used to estimate plasma glucose concentration.[14]

A decrease in CSF glucose level is an important indicator for the diagnosis of CNS infection and carcinoma. Glucose is the main substance providing energy in CSF. CSF glucose levels decrease when energy-consuming diseases are present.[15] Therefore, CSF glucose levels are important in the diagnosis and evaluation of treatment of infectious CNS diseases, as well as in the differentiation of bacterial and non-bacterial infections.[16] CSF glucose concentrations should be approximately 60% of plasma concentrations (approximately 45-70 mg/dL). For adequate clinical interpretation, they should always be compared with simultaneously measured plasma glucose.[1]

TEST PRINCIPLE

Enzymatic, colorimetric method

The glucose oxidase method uses two coupled enzyme reactions. The first reaction is specific, while the indicator reaction is not. The first reaction uses glucose oxidase to oxidize glucose to gluconic acid and hydrogen peroxide (H_2O_2). H_2O_2 reacts with phenol and 4-aminoantipyrine in the presence of peroxidase to form quinonimine dye. The intensity of the formed color is proportional to the glucose concentration and can be measured photometrically between 480 and 520 nm.

1) $\text{Glucose} + O_2 \xrightarrow{\text{Glucose Oxidase}} \text{Gluconic acid} + H_2O_2$

2) $H_2O_2 + \text{4-aminoantipyrine} + \text{Phenol} \xrightarrow{\text{Peroxidase}}$ Quinonimine dye complex

The first reaction uses glucose oxidase (GO) to oxidize glucose to glucuronic acid and hydrogen peroxide. Glucose in solution is 36% α-form and 64% β-form. Since GO is highly specific for β-D-glucose, glucose requires mutation to the β form and most GO preparations contain the enzyme mutarotase to catalyze the conversion of α-D-glucose to the β form. Otherwise, the prolonged incubation time allows for spontaneous conversion.

Glucose oxidase methods are suitable for glucose measurement in CSF but not for glucose measurement in urine, because urine contains high concentrations of substances (such as uric acid) that interfere with the peroxidase reaction and cause erroneous low results. Therefore, the glucose oxidase method should not be used for urine. A method is described in which urine is first pretreated with an ion exchange resin to remove interfering substances.

REAGENT COMPONENTS

Phosphate buffer pH 6.50	: ≤ 240 mmol/L
Glucose oxidase	: ≥1500 U/L
Peroxidase	: ≥500 U/L
4-AAP	:≤ 1 mmol/L
Phenol	:≤ 15 mmol/L
Surfactant	

REAGENT PREPARATION

Reagent is ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8°C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 60 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[17]

SAMPLE REQUIREMENTS

Serum, plasma, urine and CSF can be used and are collected according to the standard procedures. Sample collection tubes containing Li-heparin, K2-EDTA, K3-EDTA can be used for plasma. Multiple sample freezing and thawing should be avoided.

Urine: Protect 24-hour samples by adding 5 mL glacial acetic acid to the collection container prior to collection.

CSF: It should be processed immediately to avoid erroneous low results.

Glucose activity stability in serum and plasma[28,29,30]:

2 days at +20/+25ºC
7 days at +2/+8ºC
3 months at -20°C

Glucose activity stability in urine[28,29,30]:

2 hours at +2/+8ºC
2 hours at +20/+25ºC
2 days at -20°C

Glucose activity stability in CSF[28,29,30]:

5 hours at +20/+25ºC
3 days at +2/+8ºC
1 month at -20°C

Annotation:

- *Blood:*
  - Methods for self-monitoring of glucose use whole blood samples, but glucose concentration in the plasma phase can be measured.[1]
  - In individuals with normal hematocrit, the fasting whole blood glucose concentration is approximately 10% to 12% lower than plasma glucose.[1]
  - Venous plasma is recommended for the diagnosis of diabetes.[19,20]
  - Although older methods of analysis reported that glucose concentrations in plasma were 5% lower than in serum[21] later studies have shown that glucose values measured in serum and plasma are essentially the same.[22,23]
  - During fasting, the capillary blood glucose concentration is only 2 to 5 mg/dL higher than that of the venous blood, while after glucose loading the difference increases to 20 to 70 mg/dL.[24,25]
  - Glycolysis made by red and white blood cells reduces serum glucose by approximately 5 to 7% in 1 hour in normal non-centrifuged clotted blood at room temperature.[26,27] The rate of in vitro glycolysis is higher in the presence of leukocytes or bacterial contamination.[1]
  - A sterile plasma without cells has no glycolytic activity, whereas a plasma separated from cells after moderate centrifugation contains leukocytes that will metabolize glucose.[1]

- *Urine:*
  - Urine samples lose up to 40% of their glucose content after 24 hours at room temperature.[1,31]
  - Glucose can be preserved by adding 5 mL of glacial acetic acid to the container before starting 24-hour urine collection. Bacterial activity is inhibited when the final pH of the urine is between 4 and 5. Other recommended preservatives include 5 g sodium benzoate or chlorhexidine and 0.01% benzethonium chloride and 0.1% sodium nitrate ($NaNO_3$) per 24-hour sample. Urine should be stored at 4°C during collection. [1]

- *CSF*
  - It may be contaminated with bacteria or other cells and should be analyzed immediately with regard to glucose. If a delay in measurement is unavoidable, the sample should be centrifuged and stored at 4°C or -20°C.
    Samples requiring storage can be collected in a fluoride/oxalate sample tube.[1] CSF fluid should be clear; if not, it should be centrifuged.[18]

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of an Arcal Auto Calibrator or Glucose Calibrator.

Arcal Auto Calibrator - Lyophilized
Ref.No: A39052
Ref.No: A39054
Ref.No: A39055 (For Olympus AU series)

Glucose Calibrator - Liquid
Ref.No: A219S
Ref.No: A219D

Calibration stability is 60 days. Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used.

Control: Commercially available control material with established values determined by this method can be used. We recommend:

Arcon N Level 1 Control- Lyophilized
Ref.No: A3910
Ref.No: A3912 (For Olympus AU series.)
Ref.No: A3913 (For BS series.)
Ref.No: A3914 (For Erba.)

Arcon P Level 2 Control- Lyophilized
Ref.No: A3920
Ref.No: A3922 (For Olympus AU series.)
Ref.No: A3923 (For BS series.)
Ref.No: A3924 (For Erba.)

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVALS / MEDICAL DECISION LEVELS

Plasma/serum (fasting)[1]
Adults: 74 - 99 mg/dL
Children: 60 - 100 mg/dL
Premature newborn: 20 - 60 mg/dL
Normal newborn: 30 - 60 mg/dL
CSF: 40 - 70 mg/dL

Urine
Random: 1 - 15 mg/dL
24-hour: < 500 mg/24s

CSF
Infant and Children: 60 - 80 mg/dL
Adults: 40 - 70 mg/dL

For 24-hour urine excretion, to convert results from mg/dL to mg/day;

24 h urine = [(V x c) / 100] mg/day

V = 24 hour urine volume
c = analyte concentration (mg/dL)

Annotation:

- The American Diabetes Association (ADA)[19] and the World Health Organization (WHO)[20] accept a fasting plasma glucose (APG) concentration of ≥126 mg/dL as the medical decision level for the diagnosis of DM instead of the reference range.
- The threshold for the diagnosis of hypoglycemia is variable and considerably lower than the lower limit of the reference range.[1] It is difficult to define a specific limit.[4] The most commonly recommended threshold is 50 mg/dL, but some authors suggest 60 mg/dL (3.3 mmol/L).[5]
- An APG value below 100 mg/dL or a random glucose concentration below 140 mg/dL is sufficient to exclude the diagnosis of DM.[32]
- A plasma glucose concentration of ≥200 mg/dL at any time during the Oral Glucose Tolerance Test (OGGT) is sufficient for the diagnosis of DM.[33]
- ADA does not recommend the use of OGTT for the diagnosis of type 1 or 2 DM. However, it recommends the use of the OGTT test for the diagnosis of GDM.[34] Other expert organizations, such as the WHO and the Australian Diabetes Association, recommend the use of the OGTT for screening for type 2 DM.[35,36]
- Pre-diabetes (pre-diabetic), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG): Values between 100-125 mg/dL are recognized by the ADA as pre-diabetic.[37] Values between 100-110 mg/dL are defined as IGT; values between 110-125 mg/dL are defined as IFG.[36,37]
- **Glucose medical decision levels for the diagnosis of GDM after 75 g OGTT:**
  Fasting plasma glucose: 92 mg/dL
  1st hour plasma glucose: 180 mg/dL
  2nd hour plasma glucose: 153 mg/dL
- Any exceeding value is sufficient for the diagnosis of GDM.[33]
- *Some medical decision levels for diabetic ketoacidosis:* > 200 or > 250 mg/dL; diagnostic predictive values of plasma glucose concentration differ between organizations.[32]
- *Plasma glucose concentrations for hyperosmolar hyperglycemic nonketotic syndrome:* > 596 or > 600 mg/dL. There are small differences among some sources in the plasma glucose concentrations used as diagnostic criteria.[32]

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval has been verified by using CLSI EP28-A3c protocol.[38]

Unit Conversion:
mg/dL × 0.0555 = mmol/L
mmol/L × 18.02 = mg/dL

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[39]

The determined analytic measuring interval for Glucose is 3 – 400 mg/dL.

Detection Capability

Limit of Detection (LoD): 1 mg/dL

Limit of Quantitation (LoQ): 3 mg/dL

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[40]

Linearity

This method shows measurement linearity in the activities up to 400 mg/dL.Autoanaylzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For the manual dilution procedure, dilute the sample 1:5 using 0.90% isotonic. After this process, multiply the result of the reworked sample by the dilution factor. Do not report

the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[41]

Precision

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[42]

Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of Glucose have been given in the table 1 and 2 respectively.

Table 1. Glucose Repeatability (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
89 mg/dL	1.30	1.46	80
285 mg/dL	2.22	0.78	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[43]

Table 2. Glucose Repeatability (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
89 mg/dL	1.53	1.71	80
285 mg/dL	4.40	1.54	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[43]

Method Comparison

As a result of the statistical evaluation of the method comparison data:

Passing-Bablok equation:[44]
y= 0.98x + 1.05 mg/dL
r=0.99

Interference

Endogenous interferant and analyte concentrations that have been used in the Glucose scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[45,46]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Glucose interference scanning test is appropriate, is determined as ±10%.[47]

In Glucose test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Interferant-Concentration	Glucose Target (mg/dL)	N*	Observed Recovery %
Hemoglobin 990 mg/dL	103,0	3	109
Bilirubin 23,6 mg/dL	108,5	3	90
Lipemia 433,4 mg/dL	106,6	3	108

** Total acceptable error rate determined as interference limit and repeatability (within run) pre-detected for the related method were used for the calculations of how many times the control and test samples prepared as a serum pool are going to be run repetitively. In the calculations, the accepted error rate for type 1 (α error) was 5% and for type 2 (β error) was 10% (90% power).*[46]

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[46]

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.
Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA (Occupational Safety and Health Administration) standards.

Danger

EUH032 :Releases a very toxic gas if contacts with acid.
H317 :May cause allergic skin reaction.

Precaution

P280 :Use protective gloves / clothes / glasses / mask.

P264	:Wash your hands properly after using.
P272	:Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

P302+P352	:Wash with plenty of water and soap if it contacts with skin.
P333+P313	:Seek medical help if it irritates your skin or develops rash.
P362+P364	:Remove contaminated clothes and wash properly before using.

Disposal

P501	:Dispose the vials and contents according to the local regulations.

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CE

SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practices
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests