PHOSPHORUS

Diagnostic reagent for determination of Phosphorus 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
A2290	160 mL	D2290	540 mL	MD290	450 mL	PL2290	240 mL
A2291N	500 mL	D2291	280 mL	MD291	150 mL	PL2291	150 mL
A2292N	200 mL	HN290	400 mL	M2290	500 mL	RD2290	400 mL
A2293N	100 mL	HN291	230 mL	M2291	300 mL	S2291	100 mL
A2294N	200 mL	K2291	240 mL	M2290	500 mL	S2292	200 mL
BB145	160 mL	LB290	160 mL	M3290	320 mL	S2293	100 mL
BY2290	500 mL	LM067	240 mL	M3291	120 mL	TB2290	400 mL
BY2291	350 mL	L2290	600 mL	M4290	500 mL	TB2291	150 mL
BZ2155	240 mL	L2291	400 mL	M4291	300 mL	T2290	800 mL
DM2290	333 mL	L2292	160 Ml	At2290	188 mL	T2291	250 mL
		MD291	150 mL	MS-120	120 mL	8A2290	500 mL
						8A2291	350 mL

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

INTENDED USE

The test is applied for the quantitative determination of phosphorus in serum, plasma and urine.

GENERAL INFORMATION

Phosphate is often called phosphorus; however, only phosphate circulates and is measured in the blood, not elemental phosphorus.[1] An adult has about 600 g of phosphorus, or about 20 mol of inorganic and organic phosphate, of which about 85% is in the skeleton and the rest mainly in soft tissue.[2,3] Although plasma contains both inorganic and organic phosphate, only inorganic phosphate is measured. Inorganic phosphate exists as both monovalent ($H_2PO_4^-$) and divalent (HPO_4^{-2}) phosphate anions. The ratio of $H_2PO_4^-$ to HPO_4^{-2} is pH dependent and varies from approximately 1:1 in acidosis to 1:4 at pH 7.4 and 1:9 in alkalosis. Approximately 10% of the phosphate in serum is protein bound, 35% forms complexes with sodium, calcium and magnesium, and the remaining 55% is free. Organic phosphate esters are found primarily in the cellular elements of the blood. Inorganic phosphate is the major component of hydroxyapatite in bone, thus playing an important role in the structural support of the body and providing phosphate for extracellular and intracellular pooling. In soft tissue, most phosphate is intracellular. Although both inorganic and organic phosphate is present in cells, most is organic and is found in nucleic acids, phospholipids, phosphoproteins and high-energy compounds involved in metabolism. Other phosphates, such as ATP and creatine phosphate, are involved in many high-energy physiological functions such as muscle contraction, neurological function and electrolyte transport. Phosphate is also an essential element of cyclic nucleotides (such as cAMP) and cofactors such as nicotinamide-adenine dinucleotide phosphate (NADP). It is important for the activity of many enzymes, including adenylate cyclase, 25-hydroxyvitamin D-1α-hydroxylase and its role in the production of 2,3-diphosphoglycerate, the key compound that regulates the oxygen affinity of hemoglobin.

Intracellular phosphate is therefore involved in the regulation of the intermediary metabolism of proteins, fats and carbohydrates and in gene transcription and cell growth. Phosphate regulation is a complex process involving the kidneys, intestines and skeletal system. In adults, plasma phosphate is kept in the range of 0.7 to 1.4 mmol/L.[1]

$1,25(OH)_2D$ can induce intestinal absorption of phosphate and calcium and increase phosphate mobilization from bone by stimulating osteoclastic resorption of bone mineral containing hydroxyapatite as a storage form of phosphate.[4] Parathormone (PTH) downregulates NPT2a by increasing the expression of the type IIa sodium-phosphate cotransporter (NPT2a) in the proximal tubules and decreasing the residence time of the transporter at the apical membrane of the tubules, and can act on phosphate through the kidneys.[5]

PTH action in the tubules indirectly reduces circulating phosphate by increasing phosphaturia.[1] PTH can stimulate both bone resorption and bone formation, depending on the fluctuation in PTH, and thus phosphate can be released or stored in the bone.[6,7]

It is clear that the observed changes in PTH and $1,25(OH)_2D$ in health and disease do not fully explain the changes in phosphate homeostasis, and therefore some researchers believe that the regulatory effects of "phosphatonin(s)" such as FGF23 contribute to this process.[8] FGF23 increases the fractional excretion of phosphate from the kidneys by decreasing the reabsorption of phosphate from the proximal tubules. It also decreases the production of the active form of vitamin D, $1,25(OH)_2D$, by decreasing the activity of the enzyme responsible for its formation (25-hydroxyvitamin D1-alpha-hydroxylase) and increasing the activity of 24-hydroxylase.

It forms the inactive form of vitamin D. There are also other phosphonins involved in phosphate metabolism.[1]
Hypophosphatemia, defined as a serum inorganic phosphate concentration below the reference range (usually <2.5 mg/dL [<0.81 mmol/L]), is relatively common in hospitalized inpatients (≈2%). Hypophosphatemia is not necessarily associated with intracellular phosphate depletion. Hypophosphatemia may be present despite normal cellular concentrations. Conversely, cellular phosphate depletion may be present when plasma concentrations are normal or even high.[1] Hypophosphatemia or phosphate depletion in the blood may result from a shift of phosphate from extracellular to intracellular sites, loss of renal phosphate, decreased intestinal absorption and loss of intracellular phosphate.[2,3,9] Many medications such as paracetamol, diuretics, estrogen, niacin, some antiviral drugs (HIV treatment) and bisphosphonates are also among the causes of hypophosphatemia.[1] The main cause of low plasma phosphate is stimulation of carbohydrate-derived insulin secretion, which promotes the transport of glucose and phosphate into insulin-sensitive cells where phosphate is incorporated into sugar phosphates and ATP. Re-feeding malnourished individuals can create an anabolic state, causing intracellular phosphate alterations. Respiratory alkalosis leads to an increase in intracellular pH, which activates phosphofructokinase and accelerates glycolysis, causing a shift of phosphate into the cell. Renal phosphate loss can also cause hypophosphatemia. Any cause of excessive PTH secretion (primary and secondary hyperparathyroidism) lowers the renal phosphate threshold and can cause hypophosphatemia and phosphate depletion. The renal phosphate threshold decreases in Fanconi syndrome, X-linked hypophosphatemic rickets and tumor-induced osteomalacia. Hypophosphatemia and phosphate depletion may result from inadequate intestinal phosphate absorption. Antacids containing aluminum or magnesium can cause hypophosphatemia by binding phosphate in the intestine, preventing its absorption. Hypophosphatemia observed in patients with malabsorption may be more closely related to secondary hyperparathyroidism rather than malabsorption of phosphate. Since phosphate is abundant in most foods, dietary deprivation is not usually a cause of phosphate depletion in patients with normal bowel function and adequate nutrition. In acidosis, intracellular phosphate loss may occur as a result of catabolism of intracellular organic compounds. Thus, patients treated for diabetic ketoacidosis may experience both intracellular phosphate loss and hypophosphatemia. If hypophosphatemia is chronic, impaired mineralization of bone may lead to rickets in children and osteomalacia in adults.[1]

The most common cause of hyperphosphatemia is the inability of the kidneys to excrete phosphate.[3,9] Decrease in glomerular filtration rate in acute kidney injury and chronic renal failure causes hyperphosphatemia by decreasing phosphate excretion from the kidneys. Moderate increases in plasma phosphate occur in people with low PTH (hypoparathyroidism), PTH resistance (pseudohypoparathyroidism) or acromegaly (increased growth hormone) caused by an increased renal phosphate threshold. Excessive oral, rectal or intravenous administration of phosphate for the treatment of phosphate depletion is a common cause of hyperphosphatemia. Phosphate release as a result of cell lysis due to rhabdomyolysis, intravascular hemolysis or chemotherapy in some malignancies can cause hyperphosphatemia. Hyperphosphatemia may also be associated with acidosis, which is a result of hydrolysis of intracellular organic phosphate-containing compounds and release of phosphate into the plasma.[1]

TEST PRINCIPLE

UV spectrophotometric method

Inorganic phosphate forms a phosphomolybdate complex with ammonium molybdate in the presence of sulfuric acid. The concentration of the formed phosphomolybdate complex is directly proportional to the concentration of inorganic phosphate and is measured photometrically at a wavelength of 340 nm.

Annotation:

- There is no reference method for the measurement of serum phosphorus. Currently, most laboratories perform phosphate analysis using direct analysis of the phosphorus-molybdate complex.[10]
- Although an acidic pH environment is required for the measurement reaction, the reaction is greatly slowed when the pH drops to 1.0; above 2.0, molybdate is self-reduced.[11,12]
- In automated methods, a serum blind is needed because of the large number of compounds and drugs that absorb at 340 nm wavelength. It needs to contain surfactant to prevent turbidity in the serum and sulfuric acid to correct the pH effect on the absorption of many compounds at ultraviolet wavelengths.[10]

REAGENT COMPONENT

Ammonium molibdate	≤ 0.6 mmol/L,
Sulphuric acid	≤ 0.25 mol/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 45 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.[13]

SAMPLE REQUIREMENTS

Serum and heparinised plasma can be used and are collected according to the standard procedures. Multiple sample freezing and thawing should be avoided. The sample should be homogenized before testing

Phosphorus activity stability in serum and plasma[35]:

-1 day at +15/+25°C
-7 days at +2/+8°C
-1 year at -20°C

Phosphorus activity stability in urine[36]

- 2 days at +15/+25°C

Annotation:

- *Serum and plasma samples*
  - Inorganic phosphate concentrations are approximately 0.2 to 0.3 mg/dL lower in heparinized plasma than in serum.[1,14] This difference is due to intracellular phosphate release during coagulation.[10] However, some studies have found no difference between serum and plasma concentrations.[15]
  - Other anticoagulants such as citrate, oxalate and EDTA may interfere with the formation of the phosphomolybdate complex and are therefore not suitable for use.[16]
  - The concentration of inorganic phosphate in whole blood samples may decrease or increase over time depending on the type of sample, storage temperature and storage time.[1] Serum or plasma should be separated immediately after collection.[10]
  - Glucose phosphate, creatine phosphate and other organic phosphates may be hydrolyzed depending on test conditions, which may lead inorganic phosphate concentrations to be over-measured.[1]
- *Urine samples*
  - Glucose phosphate, creatine phosphate and other organic phosphates may be hydrolyzed depending on test conditions, which may lead inorganic phosphate concentrations to be over-measured.[1]
  - Urine should be collected in 6 mol/L HCl (20 to 30 mL for a 24-hour sample) to avoid precipitation of phosphate complexes.[1]
  - Simultaneous measurement of phosphate and creatinine levels in serum and urine in the morning on an empty stomach or in timed samples of 1 to 2 hours allows calculation of the renal phosphate threshold ($TmPO_4$/GFR), which is considered to be the best method to assess renal tubular reabsorption of phosphate.[17]

CALIBRATION AND QUALITY CONTROL

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

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

Phosphorus Calibrator
Ref.No: A229S
Ref.No: A229D

Calibration stability is 20 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 Control Level 1 - Lyophilized
Ref.No: A3910
Ref.No: A3912 (for Olympus AU series.)
Ref.No: A3913 (for BS Series.)
Ref.No: A3914 (for Erba.)

Arcon P Control Level 2 - 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

Serum/plasma

Adults[37] : 2.5 - 4.5 mg/dL

Children[38] :

Age	Male (mg/dL)	Female (mg/dL)
1-30 days	3.9-6.9	4.3-7.7
1-12 months	3.5-6.6	3.7-6.5
1-3 ages	3.1-6.0	3.4-6.0
4-6 ages	3.3-5.6	3.2-5.5
7-9 ages	3.0-5.4	3.1-5.5
10-12 ages	3.2-5.7	3.3-5.3
13-15 ages	2.9-5.1	2.8-4.8
16-18 ages	2.7-4.9	2.5-4.8

Urine[39] (Unrestricted Diet) : 0.4 -1.3 g/24h

Annotation:

- *Blood phosphate levels*

- Moderate hypophosphatemia of 1.5 to 2.4 mg/dL (0.48 to 0.77 mmol/L) is usually not associated with clinical signs and symptoms.[1]
- Plasma phosphate concentrations of <1.5 mg/dL (<0.48 mmol/L) may cause clinical signs and symptoms. Muscle weakness, acute respiratory failure, cardiac arrhythmia and decreased cardiac output may occur.[1]
- At very low plasma phosphate concentrations of <1 mg/dL (<0.32 mmol/L), rhabdomyolysis may occur.[1]
- Severe hypophosphatemia [plasma phosphate concentration <0.5 mg/dL (<0.16 mmol/L)] may result in hemolysis. Mental confusion and coma may occur secondary to low ATP and tissue hypoxia.[1]
- Serum phosphate concentrations are approximately 50% higher in infants than in adults and decrease throughout childhood as a result of the ability of growth hormone to increase the renal phosphate threshold.[18]
- The reference range for serum phosphate in older women is similar to that of young adult women. As for older men, it is lower than that of young adult men.[19,20]
- Since a significant daily variation in plasma phosphate has been reported, sampling in the morning on an empty stomach is recommended.[17] Concentrations are higher in the afternoon and evening.[1]
- Plasma phosphate concentrations are influenced by dietary intake and meals, and increase with exercise.[1]

- *Urine phosphate levels*
  - Urinary phosphate excretion varies with age, muscle mass, renal function, PTH, time of day and other factors. It depends greatly on diet and is essentially equivalent to dietary intake.[21]

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.[22]

Unit Conversion:
mg/dL x 0.3229 = mmol/L

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).[23]

The determined analytic measuring interval for Phosphorus is 0.8 – 20 mg/dL.

Detection Capability

Limit of Detection (LoD): 0.4 mg/dL

Limit of Quantitation (LoQ): 0.8 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.[24]

Linearity

This method shows measurement linearity in the activities up to 20 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.[25]

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.[26]

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

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

Mean Concentration	SD	CV%	n
3.80 mg/dL	0.04	1.05	80
7.33 mg/dL	0.06	0.81	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[27]

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

Mean Concentration	SD	CV%	n
3.80 mg/dL	0.08	2.35	80
7.33 mg/dL	0.19	2.59	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[27]

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

Passing-Bablok equation:[28]
y= 1.005x – 0.109 mg/dL
r=0.975

Interference

Endogenous interferant and analyte concentrations that have been used in the Phosphorus scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[29,30]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Phosphorus interference scanning test is appropriate, is determined as ±10%.[31]

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

Interferant-Concentration	Phosphorus Target (mg/dL)	N*	Observed Recovery %
Lipemia 2149,2 mg/dL	3,33	3	103

** 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).*[30]

Annotation:

- Non- icteric samples should be used.
- Hemolyzed samples are unacceptable since erythrocytes contain high concentrations of organic phosphate esters that can be hydrolyzed to inorganic phosphate during storage. Inorganic phosphate increases by 4 to 5 mg/dL in 24 hours in hemolyzed samples stored at 4°C, whereas this increase occurs more rapidly at room temperature or 37°C.[1]
- Mannitol[32] fluoride and monoclonal immunoglobulins.[33,34]

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.[30]

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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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