




<b>REF IS-2400</b> 	<b>IDS-iSYS 1,25 Dihydroxy Vitamin D</b> 
Instructions for Use	<i>IN VITRO DIAGNOSTIC</i> 

## Intended Use

### For In Vitro Diagnostic Use

The IDS-iSYS 1,25-Dihydroxy Vitamin D kit is a complete assay system intended for the purification of 1,25-dihydroxyvitamin D [1,25D] in human serum or plasma by immunopurification followed by quantitative determination on the IDS-iSYS Multi-Discipline Automated System [System] to assess 1,25-dihydroxyvitamin D deficiency associated with renal disease. Results are to be used in conjunction with other clinical and laboratory data to assist the clinician in making patient management decisions.

### Summary and Explanation

There are two forms of vitamin D: vitamin D<sub>3</sub> and vitamin D<sub>2</sub>. Vitamin D<sub>3</sub>, cholecalciferol, is the naturally occurring vitamin D that is produced in the skin after exposure of 7-dehydrocholesterol to solar ultraviolet radiation (1). Vitamin D<sub>2</sub> is manufactured through the ultraviolet irradiation of ergosterol from yeast. Both are used in vitamin D supplements. The vitamin D compound is biologically inactive, but enters the circulation and is hydroxylated in the liver to 25-hydroxyvitamin D [25D], which is used to determine a patient's vitamin D status.

In the kidney, 25D is further hydroxylated to produce biologically active metabolite, 1,25-dihydroxyvitamin D [1,25D] (1). 1,25D is one of the major regulators of calcium and phosphate metabolism, stimulating intestinal calcium absorption and increasing bone resorption. It also inhibits parathyroid hormone (PTH) production both by direct action on the parathyroid glands and indirectly by raising serum calcium levels. 1,25D production is itself stimulated by parathyroid hormone (PTH), thus providing an effective control loop (1). Fibroblast growth factor 23 [FGF-23], secreted from the bone, causes the sodium-phosphate co-transporter to be internalized by the cells of the kidney and small intestine and also suppresses 1,25D synthesis (2).

In secondary hyperparathyroidism, a disease outside of the parathyroids causes all of the parathyroid glands to become enlarged and hyperactive. It is usually caused by kidney failure, a problem where the kidney is unable to clean the blood of phosphorus produced by the body and unable to make enough vitamin D, specifically 1,25D - the active form of vitamin D. The build-up of phosphorous leads to low levels of calcium in the blood, which stimulates the parathyroid glands to increase parathyroid hormone (PTH) production leading to the glands to enlarge. As the disease progresses, the parathyroid glands no longer respond normally to calcium and Vitamin D. The rationale for direct activated vitamin D therapy in CKD is to slow the progression of secondary hyperparathyroidism. The clinical practice guidelines such as the Kidney Disease Outcomes Quality Initiatives (KDOQI), and the Kidney Disease: Improving Global Outcomes (KDIGO) recommend activated vitamin D therapeutic regimens for CKD patients (3,4).

### Method Description

The IDS-iSYS 1,25-Dihydroxy Vitamin D kit is a complete assay system for the purification of 1,25D in patient samples by immunopurification followed by quantitation by one-site chemiluminescent immunoassay on the automated IDS-iSYS instrument.

150µL delipidated sample is added to an immunocapsule which contains a gel containing a monoclonal anti-1,25D antibody. 90 minutes rotation of the immunocapsule allows the binding of 1,25D to the monoclonal antibody. The gel is washed to remove potential interfering substances and the 1,25D eluted with ethanol. Eluates are then evaporated under

a gentle flow of nitrogen at 40°C and reconstituted in 200 µL assay buffer.

The reconstituted immunopurified samples are placed into the IDS-iSYS sample rack; the sample rack is then loaded on the IDS-iSYS system. 120 µL of the reconstituted immunopurified samples are incubated with the biotinylated sheep anti-1,25D antibody. The 1,25D-Acrininium conjugate is then added which competes for antibody binding sites. Streptavidin coated magnetic particles are then added and following a further incubation step, the particles are washed to remove unbound materials. Following the addition of Trigger Reagents, a flash chemiluminescent reaction is initiated. The light signal is measured by the photomultiplier as Relative Light Units (RLU) and is inversely proportional to the amount of 1,25D present in the samples.

### Warnings and Precautions

The IDS-iSYS 1,25-Dihydroxy Vitamin D kit is for in vitro diagnostic use only and is not for internal use in humans or animals. This product must be used strictly in accordance with the instructions set out in these Instructions for Use (IFU). IDS Limited will not be held responsible for any loss or damage (except as required by statute), howsoever caused arising out of non-compliance with the instructions provided.

**CAUTION:** This kit contains material of animal origin. Handle kit reagents as if capable of transmitting an infectious agent.

Appropriate precautions and good laboratory practice must be used in the storage, handling and disposal of the kit reagents. Disposal of kit reagents should be in accordance with local regulations.

#### Sodium Azide

Xn. Harmful: Calibrators contain sodium azide (NaN<sub>3</sub>) >0.1% (w/w) (<1%).

R22 Wear suitable protective clothing and gloves. R52/53 Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

S46 If swallowed, seek medical advice immediately and show this container or label.

S36/37 Wear suitable protective clothing and gloves.

S60 This material and/or its container must be disposed of as hazardous waste.

Some reagents in this kit contain sodium azide which may react with lead, copper or brass plumbing to form highly explosive metal azides. On disposal, flush with large volumes of water to prevent azide build up.

#### Elution Reagent

Elution reagent contains ethanol.

R11 Highly flammable (flashpoint 13°C).




S7 Keep container tightly closed.

S16 Keep away from sources of ignition – No smoking.

### Handling Precautions

Apart from the calibrators which are lyophilised, the reagents provided in the kit are ready to use. Refer to the calibrator section of the procedure for reconstitution methodology.

Before a new cartridge is loaded onto the IDS-iSYS system, mix the magnetic particles container by a brisk rotation motion. This will resuspend the magnetic particles that have settled during shipment. Ensure that there is no foam formation in the cartridge reagents. Should this occur, store the cartridge in an upright position in the dark at 2 to 8 °C until foaming has dissipated.

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### Shelf Life and Storage of Reagents

Prior to first use, store the cartridge and the calibrators in an **upright** position in the dark at 2 to 8 °C. Do not freeze the cartridge.

Reagent shelf life	Cartridge	Calibrators
Before opening at 2 - 8 °C	To the expiry date	
Cartridge, After opening at 2 - 8 °C	49 Days	N/A
On board the IDS-iSYS *	49 Days	3 Hours
Calibrators, After reconstitution at 2-8°C	N/A	6 Hours
Calibrators, After reconstitution at -20 °C or lower	N/A	28 Days
Calibrators, Freeze/thaw cycle(s)	N/A	2

\* Continuous on board stability.

### Sample Collection and Storage

The assay should be performed using serum (standard sampling tubes or tubes containing serum separating gel) or plasma (lithium heparin, sodium heparin or potassium EDTA) samples. Samples should be separated as soon as possible after collection.

Samples Storage Stability	Duration
Room temperature	24 Hours
2 - 8 °C	7 Days
-20 °C or lower	2.5 Months
Freeze/thaw cycles	2

To minimise possible evaporation effects, reconstituted calibrators should be measured within 3 hours and reconstituted immunopurified samples within 90 minutes after being placed on the system.

It is recommended to follow the instructions of the tube manufacturer especially when processing samples in primary tubes.

#### NOTE:

- Some sample collection tubes that are commercially available might affect the results of testing in particular cases.

### Procedure

#### Materials Provided

##### Immunoextraction Kit

###### SORB

Immunocapsules containing monoclonal antibody to 1,25D linked to solid phase particles in suspension with vitamin D binding protein inhibitor, 100 immunocapsules.

###### REAG 1

Delipidation Reagent, a solution of dextran sulphate and magnesium chloride, 1 bottle, 6 mL per bottle.

###### REAG 2

Elution Reagent, Ethanol, 2 bottles, 25 mL per bottle.

###### BUF

Assay buffer, a MOPS buffer containing bovine serum albumin with 0.01% sodium azide, 1 bottle, 22 mL per bottle.

### Reagent Cartridge

#### MP

Magnetic particles coated with streptavidin in a phosphate buffer containing bovine serum albumin and sodium azide as preservative (<0.1%), 1 vial, 2.6 mL per vial.

#### CONJ

Conjugate, 1,25D labelled with an acridinium ester derivative, in a phosphate buffer containing bovine serum albumin with sodium azide as preservative (<0.1%), 1 cartridge vial, 9.6 mL per vial.

#### Ab-BIOT

Antibody-Biotin, Anti-1,25D polyclonal antibody labelled with biotin, in a phosphate buffer containing sheep proteins with 0.01% sodium azide as preservative, 1 cartridge vial, 13mL per vial.

#### BUFD

Wash buffer, 1% proprietary detergent in PBS azide, 1 cartridge vial, 35mL per vial.

#### Calibrators

CAL A
CAL B

Lyophilised MOPS buffer containing bovine serum albumin, 1,25D and sodium azide as preservative (<1.0%), 2 each of 2 concentration levels, 1.2mL.

#### Mini CD

Contains IFU for IDS-iSYS 1,25D reagents and CRY files.

#### Materials Required But Not Provided

IDS-iSYS Multi-Discipline Automated System: IS-310400  
IDS-iSYS 1,25 Dihydroxy Vitamin D Control Set: IS-2430  
IDS-iSYS Cuvettes Cube: IS-CC100  
IDS-iSYS System Liquid: IS-CS100  
IDS-iSYS Wash Solution: IS-CW100  
IDS-iSYS Triggers Set A and B: IS-CT100  
IDS-iSYS Cartridge Check System: IS-6010  
Disposable 12 x 75 mm tubes  
Disposable polypropylene 2 mL, 10.8 mm diameter, conical skirted base, screw cap micro tubes, and screw cap with O-ring [Sarstedt 72.664 and 65.716 or equivalent.]  
Precision pipettes to deliver 150 µL, 200 µL, and 1 mL.  
Multi-tube vortexer or equivalent.  
End-over-end or roller mixer.  
Evaporation device or heating block/water bath at 40°C and nitrogen supply and manifold.  
Refrigerated centrifuge capable of achieving 2000 g.  
Distilled or deionised water.

#### Materials Available on Request




Certificate of Analysis

### Delipidation Procedure

- Label glass/plastic tubes, one for each sample/Extraction Control  
**Do not delipidate Calibrators/Assay Controls.**
- Pipette 500 µL of sample/Extraction Control to appropriately labelled tubes.
- Add 50 µL of Delipidation Reagent to each tube. Vortex all tubes.
- Centrifuge all tubes at 2000 g for 15 minutes.

#### NOTE:

**Be careful not to disturb the pellet when handling delipidated samples.** If the pellet becomes suspended or the sample is not clear, repeat the centrifugation.

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#### Alternative Sample Preparation

*When the available sample volume is less than 500 µL.*

1. Label conical-bottom plastic tubes or micro tubes, one for each sample.
2. Add sample (e.g. 300 µL) to appropriately labelled tubes
3. Add 0.1 x sample volume of Delipidation Reagent (e.g. 30 µL) to each tube. Vortex all tubes.
4. Centrifuge all tubes at 2000 g for 15 minutes.

#### Immunoextraction Procedure

1. Label Immunocapsules for each sample/extraction control.  
**Do not immunopurify Calibrators/Assay Controls.**

#### NOTE:

**DO NOT USE if an Immunocapsule shows signs of leakage or incorrect volume.**

2. Vortex Immunocapsules. Allow solid phase to settle. Stand Immunocapsules upright in provided cardboard inlay for 3-5 minutes.
3. Remove Immunocapsules screw caps. Add 150 µL of delipidated sample/extraction control to Immunocapsules. Replace caps securely.
4. Place Immunocapsules in cardboard inlay and rotate end over-end at 5-20 revolutions per minute for 90 minutes at room temperature (18-25°C).
5. Stand Immunocapsules upright for 3-5 minutes allowing gel to settle.
  - a. Tap to dislodge any gel adhering to the screw caps.
  - b. Allow gel to settle for a further 1-2 minutes.
6. Remove screw cap; break off (**do not twist off**) bottom stopper from Immunocapsules.
  - a. Place each Immunocapsule in a plastic/glass tube.
  - b. Centrifuge at low speed (500-1000 g) for approximately 1 minute.
7. Add 500 µL of distilled or deionised water to each Immunocapsule. **Add carefully to avoid solid phase splashing out of the Immunocapsule.**
  - a. Centrifuge at low speed (500-1000 g) for approximately 1 minute.
  - b. Repeat above step for further two (2) times for a total of 3 wash cycles.
8. Label 2 mL polypropylene conical skirted base, screw cap micro tubes, one for each Immunocapsule. Transfer Immunocapsules to the appropriated labelled micro tubes.
9. Add 150 µL of Elution Reagent to all Immunocapsules. Allow reagent to soak for 1 to 2 minutes.
  - a. Centrifuge at low speed (500-1000 g) for approximately 1 minute to collect eluate.
  - b. Repeat above step a further two times. The total elution volume collected is 450 µL for each sample/extraction control.
10. Discard Immunocapsules. Place micro tubes in a heating block or water bath set to 40°C.
11. Evaporate the eluates under a gentle flow, approximately 2-4 psi of nitrogen gas. Avoid splashing of the eluates. Evaporation should take approximately 45 minutes.

#### NOTE:

**Eluants must be completely dry.**

#### Alternative Evaporation Devices

*Other evaporation equipments such as vacuum centrifuge evaporator are feasible for use for Step 11. Laboratory should validate the procedure to ensure the optimal setting of their equipments.*

12. Add 200 µL of Assay Buffer to each tube. **Vortex for at least 5 seconds** to dissolve residues. The immunopurified samples/extraction controls are now ready for assay.
13. Load the immunopurified samples/Extraction Controls onto the IDS-iSYS System.

#### NOTE:

**Cap the immunopurified samples/Extraction Controls if they are not intended to be loaded onto and measured by the IDS-iSYS system within 90 minutes to minimise their evaporation.**

#### Immunopurified Samples Storage and Stability

The immunopurified samples must be loaded onto and measured by the IDS-iSYS System within 90 minutes after reconstitution. Otherwise, **cap** the immunopurified samples micro tubes; store in an **upright** position. Ensure the immunopurified samples are at room temperature before loading onto the system.

Immunopurified Samples Storage	Before reconstitution	Reconstituted
On board the IDS-iSYS *	N/A	90 Minutes
2 - 8 °C	4 Hours	2 Days
-20 °C or lower	1 Day	2 Days
Freeze/Thaw cycle(s)	N/A	2

\* Continuous on board stability.

#### Assay Procedure

##### IDS-iSYS Multi-Discipline Automated System Settings

The IDS-iSYS system's automatic validation of results feature should be disabled.

##### Reagent Cartridge




The reagents provided in the cartridge are ready to use. The system automatically performs the mixing of magnetic particles to maintain homogeneity. Before a new cartridge is loaded on board the system, mix the magnetic particles container by brisk rotation motion. Ensure that there is no foam formation in the cartridge reagents. Should this occur, store the cartridge in an upright position in the dark at 2 to 8 °C until foaming has dissipated.

The barcode is read when the cartridge is loaded on the reagent tray. If the label cannot be read by the system barcode reader, a manual procedure exists to enter the barcode data (see the IDS-iSYS User Manual).

Load the cartridge on the reagent tray and wait for at least 40 minutes before starting the assay. If the cartridge is removed from the reagent tray, store the cartridge vertically at 2 - 8 °C in the dark.

##### Calibrators

The 1,25D calibrators are lyophilised. Reconstitute immediately before use. Add 1.2 mL of distilled or deionised water to each bottle. Replace the stopper. Leave for 10 minutes to reconstitute. Invert calibrators gently before use. **Do not vortex the calibrators.** Pipette approximately 500 µL (120 µL per replicate) of calibrators into 2 mL polypropylene conical, skirted base micro tubes and place on the instrument within 15 minutes

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of reconstitution. Proceed according to the instructions of the IDS-iSYS User Manual.

If calibrators are to be used more than once, they should be stored at -20 °C or lower within 15 minutes of reconstitution. When re-using frozen calibrator vials, thaw at room temperature and mix well. Ensure that calibrators are at room temperature before pipetting approximately 500 µL of calibrators into 2 mL polypropylene conical, skirted based micro tubes and place on the instrument. Calibrators should be placed on the system within 15 minutes of reaching room temperature.

#### NOTE:

- DISCARD the material in the micro tubes after use.**
- DO NOT return material to the calibrator vials.**

#### System Calibration

Two 1,25D calibrators are required to perform the adjustment of the master curve. The calibrators are supplied with the kit; calibrators from another kit lot must not be used. The IDS-iSYS 1,25D Assay Controls (IS-2430) **MUST** be measured at the same time as the calibrators to perform a master curve adjustment.

All data required for the calibration of the cartridge batch can be found on the mini CD. Use calibrator levels A and B to adjust the master curve to the reagents on board the System. Check for the presence of a 1,25D cartridge on the reagent tray and the availability of the cartridge master curve in the database. If the data for the lot of calibrators is not available on board the system, load the data using the mini CD provided with the calibrator.

The calibration is carried out in triplicate. RLU CVs of  $\geq 7\%$  will result in a failed calibration. One replicate may be removed to meet the calibration requirements. The Assay Controls must also be measured in duplicate to calibrate the system. Verify and approve the calibration according to the calibration status displayed in the calibration windows and discard the calibrator after use.

#### Calibration

The IDS-iSYS 1,25D assay has been standardized against in-house reference standards.

#### Calibration Frequency

A new calibration is required:

- Each time a new lot of cartridge is loaded on board.
- Each time a new lot of trigger or cuvette is used.
- When the control values do not fall within the defined ranges.
- When the calibration interval of 21 days has expired.
- After System service.

Verification of the calibration is automatic and managed by the IDS-iSYS system.

#### Quality Control

The IDS-iSYS 1,25-Dihydroxy Vitamin D Control Set (IS-2430) is required for quality control.

The Assay Controls should be measured prior to loading the immunopurified samples/extraction controls onto the system to ensure the integrity of the system and the cartridge.

To verify the validity of sample results, the Extraction Controls should be immunopurified and measured at the same time as the patient samples. Extraction Controls should be tested at the beginning of every run containing patient samples or according to local regulations.

Refer to the IDS-iSYS 1,25D Control Set (IS-2430) Instructions for Use for preparation and handling procedures.

#### Determination of Sample 1,25D levels

Proceed according to the instructions of the IDS-iSYS User Manual for assaying samples.

#### Calculation of Results

The 1,25D concentration of each sample is calculated automatically. The display of the concentrations (screen or printed) is produced per user setting.

To convert results to SI units:  $\text{pmol/L} = \text{pg/mL} \times 2.4$

The IDS-iSYS 1,25D Assay uses a 4-parameter logistic curve fit (4PL) to calculate the 1,25D concentrations.

#### Validation of Samples Results

Verify the immunopurified Extraction Controls values against the acceptable limits specified in the Control Certificate. If an immunopurified Extraction Control value is outside the acceptable limits, the samples results are invalid. In this case, repeat the delipidation and immunopurification for the samples/Extraction Controls prior to the determination of 1,25D levels procedure.

#### Measurement Range (Reportable Range)

The reportable range of the assay is 6.5 – 210.0 pg/mL (15.6 – 504 pmol/L). Any value that reads below 6.5 pg/mL (15.6 pmol/L) should be reported as “< 6.5 pg/mL” (“<15.6 pmol/L”). The highest reportable value without dilution is 210.0 pg/mL (504 pmol/L).

#### Limitations of Use

- As in the case of any diagnostic procedure, results must be interpreted in conjunction with the patient's clinical presentation and other information available to the physician.
- The performance characteristics of this assay have not been established in a paediatric population.
- The following substances do not interfere in the IDS-iSYS 1,25D Assay when the concentrations presented in the following table are below the stated threshold.




Potentially Interfering Agent	Threshold Concentration
Triglycerides	1000 mg/dL
Haemoglobin	200 mg/dL
Bilirubin	20 mg/dL
Albumin	9.1 g/dL
Red Blood Cells	0.4%
Cholesterol	300 mg/dL
Biotin	300 nM
Rheumatoid Factor	1700 IU/mL

#### Expected Values

Each laboratory should determine ranges for their local population. The following range was determined using the IDS-iSYS 1,25D Assay and is provided for information only. The 95% reference interval for the following group was calculated by a non-parametric method following the NCCLS guideline C28-A2, “How to Define and Determine Reference Intervals in the Clinical Laboratory”.

Normal Adults: 26.1 – 95.0 pg/mL (n = 119)  
62.6 – 228 pmol/L (n = 119)



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## Performance Data

Representative performance data are shown. Results obtained at individual laboratories may vary.

### Sensitivity

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were determined with guidance from CLSI EP17-A, "Protocols for Determination of Limits of Detection and Limits of Quantitation" using 100 blanks and 50 low level samples.

LoB	2.8 pg/mL	6.7 pmol/L
LoD	6.5 pg/mL	15.6 pmol/L
LoQ	12.2 pg/mL	29.3 pmol/L

### Precision

Precision was evaluated in accordance with a modified protocol based on CLSI EP-5A2, "Evaluation of Precision Performance of Quantitative Measurement Methods". Three serum controls were assayed using three lots of reagents in duplicate twice per day for 20 days on three instruments.

Concentration (pg/mL)	n	Within-run		Total	
		SD	CV%	SD	CV%
21.7	80	2.5	11.5	3.1	14.5
64.1	80	4.6	7.2	5.9	9.2
154.3	80	8.1	5.2	15.2	9.9

Concentration (pmol/L)	n	Within-run		Total	
		SD	CV%	SD	CV%
52.1	80	6.0	11.5	7.4	14.5
153.8	80	11.0	7.2	14.2	9.2
370.3	80	19.4	5.2	36.5	9.9

### Linearity

Linearity was evaluated based on CLSI EP-6A, "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach". Samples containing varying concentrations of 1,25D were assayed in duplicate. The resulting mean concentrations were compared to predicted concentrations. Samples were prepared by diluting a high patient sample with a low patient sample prior to extraction.

12 sets of samples covering the range of the assay were measured, giving a total of 108 measured dilutions. Average Observed/Expected 1,25D values were 98.4%, with an r-squared of 0.98 defined by linear regression analysis.

### Method Comparison

The IDS-iSYS 1,25D Assay was compared against the IDS 1,25-Dihydroxy Vitamin D (AA-54) immunoassay for the quantitative determination of 1,25D, following CLSI EP-9A2, "Method Comparison and Bias Estimation Using Patient Samples". A total of 121 samples, selected to represent a wide range of 1,25D concentrations [10.7 – 197.5 pg/mL (25.7 – 474.0 pmol/L)], was assayed by each method.

Passing Bablok analysis was performed on the comparative data:

$$\text{IDS-iSYS} = 1.00 \times (\text{IDS RIA}) - 2.8$$

(95% CI of the slope and intercept were 0.93 to 1.07, and -6.3 to 0.4 respectively); correlation coefficient (r) = 0.95.

## Specificity

Analyte	Cross-Reactivity
1,25(OH) <sub>2</sub> D <sub>2</sub>	75%
1,24,25(OH) <sub>2</sub> D <sub>3</sub>	92%
25(OH)D <sub>3</sub>	0.0015%
25(OH)D <sub>2</sub>	0.0009%
Alfacalcidol	0.04%

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