BECKMAN COULTER

CE 2797

ACTIVE® Renin IRMA

Instruction for use in local language is available at beckmancoulter.com/techdocs.

REVISION HISTORY

Previous version:	Current version:
IFU-DSL25100-02	IFU-DSL25100-03
—	Adding Dutch to the IFU.

REF DSL25100

FOR PROFESSIONAL USE ONLY

INTENDED PURPOSE

ACTIVE® Renin IRMA is an in vitro diagnostic manual medical device intended to be used by healthcare professionals for the quantitative measurement of renin in human plasma. Measurement of renin is intended to be used as an aid in diagnosis and differential diagnosis of primary and secondary hyperaldosteronism and hypoaldosteronism [1, 2].

PRINCIPLE

The immunoradiometric assay of renin is a sandwich-type assay. Mouse monoclonal antibodies directed against two different epitopes of renin and hence not competing are used. Samples or calibrators are incubated in tubes coated with the first monoclonal antibody in the presence of the second monoclonal antibody labeled with iodine 125. After incubation, the contents of the tubes are rinsed so as to remove unbound ^{125}I-labeled antibody. The bound radioactivity is then determined in a gamma counter. The renin concentrations in the samples are obtained by interpolation from the standard curve. The concentration of renin in the samples is directly proportional to the radioactivity.

WARNING AND PRECAUTIONS

General remarks:

- The vials with calibrators and controls should be opened as shortly as possible to avoid excessive evaporation.
- Do not mix the reagents from kits of different lots.
- A standard curve must be established with each assay.
- It is recommended to perform the assay in duplicate.
- Each tube must be used only once.

Basic rules of radiation safety

The purchase, possession, utilization, and transfer of radioactive material are subject to the regulations of the country of use. Adherence to the basic rules of radiation safety should provide adequate protection:

- No eating, drinking, smoking or application of cosmetics should be carried out in the presence of radioactive materials.
- No pipetting of radioactive solutions by mouth.
- Avoid all contact with radioactive materials by using gloves and laboratory overalls.
- All manipulation of radioactive substances should be done in an appropriate place, distant from corridors and other busy places.
- Radioactive materials should be stored in the container provided in a designated area.
- A record of receipt and storage of all radioactive products should be kept up to date.
- Laboratory equipment and glassware which are subject to contamination should be segregated to prevent cross-contamination of different radioisotopes.
- Each case of radioactive contamination or loss of radioactive material should be resolved according to established procedures.
- Radioactive waste should be handled according to the rules established in the country of use.

Sodium azide

Some reagents contain sodium azide as a preservative. Sodium azide can react with lead, copper or brass to form explosive metal azides. Sodium azide disposal must be in accordance with appropriate local regulations.

Material of human origin

All patient specimens should be handled as potentially infectious and waste should be discarded according to the country rules.

GHS HAZARD CLASSIFICATION

Calibrators / Control samples / Sample Diluent	WARNING	
		
	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) <0.05%

SDS Safety Data Sheet is available at beckmancoulter.com/techdocs

SPECIMEN COLLECTION, PROCESSING, STORAGE AND DILUTION

- EDTA plasma is the ONLY recommended sample type.
- It must be noted that cryoactivation of prorenin may occur giving falsely high active renin levels if samples are stored at 2-8°C [3]. Adhering to special sample collection and processing procedures will prevent cryoactivation. Therefore, samples should be collected in tubes stored at room temperature and NOT placed on ice prior to processing. A dry ice/ethanol bath can be used for rapid freezing procedures.
- After collection, centrifuge samples immediately, at room temperature and store frozen at < -20°C (1 year maximum) [4] if not tested within 4 hours of primary collection. It is recommended to prepare aliquots to avoid repeated freezing and thawing.
- It is recommended to rapidly freeze and thaw processed samples avoiding the temperature range of 2-8°C [5].
- If samples have concentrations greater than the highest calibrator, they must be diluted in Sample diluent.

MATERIALS PROVIDED

All reagents of the kit are stable until the expiry date indicated on the kit label, if stored at 2-8°C. Expiry dates printed on vial labels apply to the long-term storage of components by the manufacturer only, prior to assembly of the kit. Do not take into account.

Storage conditions for reagents after reconstitution are indicated in paragraph Procedure.

Tubes: 2 x 50 (ready-to-use)

^{125}I-Tracer: one 11 mL vial (ready-to-use)

The vial contains 370 kBq, at the time of manufacture, of ^{125}I-labeled anti-renin antibody in buffer with proteins and sodium azide (<0.1%).

Calibrators: five vials (lyophilized)

The calibrator vials contain from 0 to approximately 500 pg/mL of renin in buffer with proteins and ProClin 300. The exact concentration is indicated on each vial label. The calibrators are traceable to the international standard, WHO 1st IS 68/356.

Control samples: two vials (lyophilized)

The vials contain renin in buffer with proteins and ProClin 300. The concentration range is indicated on a supplement. The control samples are traceable to the international standard, WHO 1st IS 68/356.

Sample Diluent: one 5 mL vial (ready-to-use)

The vial contains a serum-based sample diluent with ProClin 300.

MATERIALS REQUIRED, BUT NOT PROVIDED

In addition to standard laboratory equipment, the following items are required:

- Precision micropipette (200 µL).
- Semi-automatic pipette (100 µL, 2 mL).
- Vortex type mixer.
- Horizontal or orbital shaker.
- A sponge rack or similar device for decantation.
- Absorbent material for blotting tubes.
- Gamma counter set for ^{125}I.

PROCEDURE

Preparation of reagents

Let all the reagents come to room temperature.

Reconstitution of calibrators and control samples

The content of the vials is reconstituted with the volume of distilled water indicated on the vial label. Wait for 10 min following reconstitution and mix gently to avoid foaming. Store the reconstituted solutions at 2-8°C for up to 14 days.

Assay procedure

Step 1 Additions*	Step 2 Incubation	Step 3 Counting
To coated tubes add successively:		Aspirate or decant all tubes (except «total cpm» tubes) by simultaneous inversion with a sponge rack into a radioactive waste receptacle.
200 µL of calibrator, control or sample, then immediately add 100 µL of tracer.	Incubate 3 hours at 18-25°C with shaking (≥180 rpm).	Wash three times with 2 mL of deionized water.
Vortex gently 1-2 seconds.		Count bound cpm (B) and total cpm (T) for 1 minute.

*. Add 100 µL of tracer to 2 additional tubes to obtain «total cpm».

RESULTS

Results are obtained from the calibrator curve by interpolation. The curve serves for the determination of analyte concentrations in samples measured at the same time as the calibrators.

Standard curve

The results in the quality control department were calculated using *spline* curve fit with determined radioactivity *(cpm_{cal}-cpm_{cal0})* on the log vertical axis and analyte concentration of the calibrators on the log horizontal axis.

Other calculation methods may give slightly different results.

Total activity: 135,553 cpm				
Calibrators	**Renin (pg/mL)**	**cpm (n=3)**	**B/T (%)**	**$cpm_{cal} - cpm_{cal0}$**
0	0	35	-	-
1	5	611	0.45	576
2	20	2,284	1.68	2,249
3	100	11,021	8.13	10,986
4	500	45,991	33.93	45,956

· *(Example of standard curve, do not use for calculation)*

Samples

For each sample, locate the cpm (cpm_{sample} - cpm_{cal0}) or B/T value on the vertical axis and read off the corresponding analyte concentration on the horizontal axis.

EXPECTED VALUES

We recommend each laboratory to establish its own reference values. The following values obtained with healthy adult subjects are indicative only. The results give a logarithmic normal distribution.

Population	n	Mean (pg/mL)	Median (pg/mL)	95% range (pg/mL)
Normal healthy adults	54	11.98	9.44	3.18 - 32.61
Supine	27	7.18	6.10	2.71 - 16.51
Upright	27	16.78	14.24	5.41 - 34.53

Detail information about expected values for children (sorted according to age) can be found in the data sheet "APPENDIX".

QUALITY CONTROL

Good laboratory practices imply that control samples be used regularly to ensure the quality of the results obtained. These samples must be processed exactly in the same way as the assay samples, and it is recommended that their results be analyzed using appropriate statistical methods.

Failure to obtain the appropriate values for controls may indicate imprecise manipulations, improper sample handling or deterioration of reagents.

In case of packaging deterioration or if data obtained show some performance alteration, please contact your local distributor or use the following e-mail address: imunochem@beckman.com

According to EU regulation 2017/746, any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of EU Member State in which the user and/or patient is located.

PERFORMANCE CHARACTERISTICS

(For more details, see the data sheet "APPENDIX")

Representative data are provided for illustration only. Performance obtained in individual laboratories may vary.

Sensitivity

Analytical sensitivity: 0.81 pg/mL

Functional sensitivity: 2.31 pg/mL

Specificity

The antibodies used in the immunoassay are highly specific for renin. Extremely low or non-detectable cross reactivities were obtained with several molecules.

Precision

Intra-assay

Samples were assayed 25 times in the same run. The coefficients of variation were ≤ 2.17%.

Inter-assay

Samples were assayed in duplicate in 10 different runs. The coefficients of variation were ≤ 13.28%.

Accuracy

Dilution test

High-concentration plasma samples were serially diluted with Sample Diluent. The recovery percentages ranged from 82.10% to 102.0%.

Recovery test

Low-concentration plasma samples were spiked with known quantities of renin. The recovery percentages ranged from 90.23% to 119.1%.

Measurement range (from analytical sensitivity to the highest calibrator): 0.81 to approximately 500 pg/mL.

LIMITATIONS

Failure to follow these instructions for use (IFU) may significantly affect results.

Results should be interpreted in the light of the total clinical presentation of the patient, including clinical history, data from additional tests and other appropriate information.

Do not use hemolyzed, lipemic or icteric samples. For more details, see Appendix, § Interference.

In immunoassays, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Immunoassays may be also affected by presence of anti-avidin or anti-streptavidin antibodies, as well as by the presence of autoantibodies directed against the determined analyte. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies [6, 7, 8].

"Hook effect": no hook effect was observed until 20,000 pg/mL.

It is recommended to finish pipetation within 30 minutes.

Failure to blot tubes adequately following decantation may result in poor replication and spurious values.

When evaluating human plasma renin levels, there are many physiological factors that influence stimulation or suppression of plasma renin activity. Posture, salt intake, antihypertensive drugs, oral contraceptives, age, race, and menstrual cycle may affect renin values [9].

APPENDIX

PERFORMANCE CHARACTERISTICS

ACTIVE is a trademark of BECKMAN COULTER Inc. and its subsidiaries.

Representative data are provided for illustration only. Performance obtained in individual laboratories may vary.

Summary and explanation of the test

Renin is an enzyme that belongs to the family of aspartyl proteases, a classification that is based on the properties of having two aspartic acid residues at the active site and its susceptibility to inhibition by pepstatin [10,11,12]. Renin synthesis was first discovered in the juxtaglomerular cells of the kidney. At present there is evidence that renin synthesis can also occur in other organs such as brain, heart and arterial smooth muscle [13,14]. Renin circulates in two different forms, prorenin and the active renin forms. Prorenin is the enzymatically inactive biosynthetic precursor of renin. In the secretory granules of the juxtaglomerular cell, prorenin is processed to active renin by a thiol protease resembling cathepsin B. An amino terminal prosegment of 42 amino acids is cleaved from the prorenin which allows the exposure of the active site of renin [15,16,17].

Renin is substrate specific and is capable of converting circulating angiotensinogen into biologically inactive decapeptide angiotension I. Angiotension I in turn is converted to the octapeptide angiotension II by means of the angiotension converting enzyme (ACE). ACE is localized on the endothelium and smooth muscle cells of the blood vessels from the kidney, lung and many other organs. Renin substrate, angiotension I and II and ACE are collectively known as the renin angiotension system or RAS. Under normal conditions and in many pathological situations it is the amount of renin secreted by the kidney that determines the activity of the whole system. Measurement of plasma renin is therefore a good index of RAS activity. Theoretically the plasma level of angiotension II would seem to offer an even better index, but for practical purposes angiotension measurements are difficult, in part because of the very short half life [18].

Angiotension II causes constriction of the small arteries or arterioles. It also promotes sodium and water reabsorption in tubules both directly and indirectly via aldosterone. Aldosterone is a steroid hormone produced by the adrenal gland. Its secretion is stimulated by angiotension II. Angiotension II and aldosterone act at different levels of the kidney tubule. Aldosterone does not only promote sodium reabsorption but also potassium excretion. Vasoconstriction, insufficient urinary sodium and water excretion cause a rise in blood pressure or hypertension, and an increase in the urinary excretion of potassium, which lowers blood levels of potassium or hypokalemia [19,20]. Renin is produced in the juxtaglomerular cells of the kidney. These cells are innervated by sympathetic nerves. Renin secretion is increased when blood pressure in the arterioles is low and by sympathetic stimulation. Sympathetic stimulation occurs under circumstances of physical stress.

RAS is activated in hemorrhagic and cardiogenic shock, after fluid loss by diarrhea and the use of diuretics, and in edematogenic conditions such as liver or kidney disease. The RAS is also activated in patients with stenosis of the renal artery, in such patients it is partly responsible for the development of hypertension. Autonomous, angiotension II independent hypersecretion of aldosterone, as in adrenal tumor, also leads to hypertension. In such cases plasma renin is low, as opposed to secondary aldosteronism where the hypersecretion of aldosterone is caused by angiotension II [21,22]. In most patients with primary or essential hypertension the cause of the hypertension is unknown. Plasma renin levels in these cases are normal or low. Within a subgroup of patients with essential hypertension, plasma renin is high. These patients seem to have a higher risk for stroke and myocardial infarction.

The clinical utility of plasma renin assays is mainly centered around the diagnosis of and management of patients with hypertension due to renal artery stenosis or renovascular hypertension. Approximately 10% of the adult population suffers from hypertension. Renal vascular stenosis is the cause of this hypertension in a subgroup of these patients. This subgroup constitutes 1% of the total hypertensive population. Renin assays can also help the clinician decide whether or not to perform X-ray studies of the renal blood vessels [23,22]. Renin assays are also important for the diagnosis of primary aldosteronism. Surgical removal of the adrenal tumor will often cure the hypertension [24]. Renin assay may also provide some information on the risk of cardiovascular complications in patients with essential hypertension [25].

These assays are also used in the management of patients with adrenal insufficiency receiving steroid substitution. With insufficient substitution, plasma renin is high; with adequate therapy, plasma renin will be normal. In some patients with edema of unknown etiology, renin measurements are useful in making the diagnosis of secondary aldosteronism. Finally, in patients with secondary hypoaldosteronism plasma renin levels are abnormally low. Elderly patients with diabetes mellitus sometimes develop secondary aldosteronism [21]. Thus, in summary, renin assays are an important diagnostic work-up for patients with renovascular hypertension. They are also important in hypertension, edema and hypo- or hyperkalemia.

Interference

Plasma samples containing renin concentrations (low and high) were spiked with multiple concentrations of the substances listed below and assayed using ACTIVE® Renin IRMA. Values were calculated as described in CLSI EP07, 3rd ed. [26] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). No interference (defined as a shift in dose > 15 %) was found for addition of interferent up to concentration stated in the table below.

Interferent	Test concentration
Biotin	1,728 ng/mL
Conjugated bilirubin	411.1 µg/mL
Hemoglobin	1,013 µg/mL
Triglycerides	14.50 mg/mL
Unconjugated bilirubin	333.0 µg/mL

In spite of hemoglobin, bilirubin (conjugated, unconjugated) and triglyceride interference data in the table, we advise to avoid using hemolyzed, lipemic or icteric samples.

Specificity

The cross-reactivity of the renin antibody has been measured against the following compounds:

COMPOUND	% CROSS-REACTIVITY
Plasmin	ND
Trypsin	ND
Cathepsin B	ND
Cathepsin D	ND
ACE	ND
Albumin	ND

· *ND = Non-detectable (<0.1%)*

Precision

Intra-assay

EDTA plasma samples	P1	P2	P3
Number of determinations	25	25	25
Mean value (pg/mL)	33.31	141.1	427.1
C.V., %	1.97	2.09	2.17

Inter-assay

EDTA plasma samples	P1	P2	P3
Number of determinations	10	10	10
Mean value (pg/mL)	5.68	15.31	265.2
C.V., %	11.66	13.28	5.69

Accuracy

Dilution test

Samples were diluted with the Sample diluent and assayed according to the assay procedure of the kit.

EDTA plasma samples	Dilution factor	Expected (pg/mL)	Measured (pg/mL)	Ratio Measured/ Expected (%)
P1	Undiluted	—	100.4	—
	1:2	50.19	45.86	91.37
	1:4	25.10	22.18	88.38
	1:8	12.55	11.76	93.72
	1:16	6.27	6.30	100.4
	1:32	3.14	3.20	102.0
P2	Undiluted	—	211.1	—
	1:2	105.5	95.20	90.21
	1:4	52.77	44.55	84.43
	1:8	26.38	21.66	82.10
	1:16	13.19	11.47	86.90
	1:32	6.60	6.00	91.00
P3	Undiluted	—	184.4	—
	1:2	92.22	83.43	90.50
	1:4	46.11	40.76	88.40
	1:8	23.05	20.49	88.88
	1:16	11.53	10.05	87.19
	1:32	5.76	5.50	95.43

Recovery test

Samples were spiked with known quantities of renin and assayed according to the assay procedure of the kit.

EDTA plasma samples	Endog. (pg/mL)	Added (pg/mL)	Expected (pg/mL)	Measured (pg/mL)	Ratio Measured/ Expected (%)
P1	42.83	266.1	308.9	336.1	108.8
	43.89	6.82	50.71	56.75	111.9
	43.18	20.12	63.30	60.21	95.12
P2	17.69	68.17	85.87	102.2	119.1
	17.26	266.1	283.4	258.2	91.12
	16.47	634.5	651.0	587.4	90.23
P3	288.7	13.52	302.3	303.2	100.3
	281.8	33.00	314.8	308.0	97.85
	271.0	63.45	334.4	328.6	98.26

Expected data for children

Results are sorted according to age.

			Renin (pg/mL)			
Children - upright position	**N**	**Median**	**Min.**	**Max.**	**2.5th percentile**	**97.5th percentile**
2-9 years	38	34.80	2.83	122.9	7.22	117.4
10-16 years	22	18.81	6.00	58.76	6.96	57.30

^{125}I Characteristics

$T_{1/2}$ (^{125}I) = 1443 h = 60.14 d

^{125}I Characteristics	E (MeV)	%
γ	0.035	6.5
K_α X-ray	0.027	112.5
K_β X-ray	0.031	25.4

Symbols Key

WARNING — WARNING / AVERTISSEMENT / WARNUNG / AVVERTENZA / ADVERTENCIA / AVISO / VARNING / ΠΡΟΕΙΔΟΠΟΙΗΣΗ / 警告 / ĮSPĖJIMAS / VIGYÁZAT! / OSTRZEŻENIE / VAROVÁNÍ / VÝSTRAHA / 경고 / UYARI / ОСТОРОЖНО / ПРЕДУПРЕЖДЕНИЕ / 警告

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Biohazard / Risque biologique / Biogefährdung / Rischio biologico / Riesgo biológico / Risco biológico / Biologisk fara / Βιολογικός κίνδυνος / 生物危害 / Biologisk fara / Veszélyes biológiai anyag / Zagrożenie biologiczne / Biologické riziko / Biologické riziko / 생물학적 위험 / Biyolojik tehlike / Биологическая опасность / Биологична опасност / 生物危害

Radioactive / Radioactif / Radioaktiv / Radioattivo / Radiactivo / Radioactivo / Radioaktivt / Ραδιενεργό / 放射性 / Radioaktyvioji medžiaga / Radioaktív / Radioaktywny / Radioaktivní / Rádioaktívny / 방사성 / Radyoaktif / Радиоактивный / Радиоактивен / 具放射性

Ag 125I / Ab 125I — Tracer / Traceur / Tracer / Marcato / Trazador / Marcador / Tracer / Ανιχνευτής / 追踪剂 / Atsekamoji medžiaga / Nyomjelző / Znacznik / Radioindikátor / Indikátor (tracer) / 트레이서 / Tracer´lar / метка / Индикатор / 追蹤劑

CAL / CAL 0 — Calibrator / Calibrateur / Kalibrator / Calibratore / Calibrador / Calibrador / Kalibrator / Βαθμονομητής / 校准品 / Kalibravimo medžiaga / Kalibrátor / Kalibrator / kalibrátor / Kalibrátor / 보정 물질 / Kalibratör / Калибратор / Калибратор / 校正液

CTRL — Control / Contrôle / Kontrolle / Controllo / Control / Controlo / Kontrolle / Μάρτυρας / 质控品 / Kontrolinė / Kontroll / Kontrola / Kontrola / Kontrola / 정도관리 / Kontrol / Контроль / Контролна / 質控品

TUBE — Tubes / tubes / Röhrchen / provette / tubos / Tubos de amostra / Provrör / σωληνάρια / 试管 / Mėgintuvėliai / Csövek / Probówki / Zkumavky / Skúmavky / 튜브 / Tüpler / пробирки / Епруветки / 試管

IFU — Instruction for Use / Mode d'emploi / Gebrauchsanweisung / Istruzioni per l'uso / Instrucciones de uso / Instruções de utilização / Bruksanvisning / Οδηγίες χρήσης / 使用说明 / Naudojimo instrukcija / Használati utasítás / Instrukcja użycia / Návod k použití / Návod na použitie / 사용 안내 / Kullanma Talimatı / Инструкции / Инструкции за употреба / 使用說明

DIL — Diluent / Diluant / Diluent / Diluente / Diluyente / Diluente / Spädmedel / Αραιωτικό / 稀释液 / Skiediklis / Diluens / Rozcieńczalnik / Ředidlo / Riediaci roztok / 희석액 / Dilüent / Дилюент / Дилуент / 稀釋劑

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