



BRACCO DIAGNOSTICS

RUBRATOPE-57 Diagnostic Kit Cyanocobalamin Co 57 Diagnostic Kit

DESCRIPTION

Rubratope-57 Diagnostic Kit is a diagnostic radiopharmaceutical containing the following components:

- Rubratope-57 (Cyanocobalamin Co 57 Capsules USP) for oral administration, provides radioactive Cyanocobalamin in which a portion of the molecules contain Co 57 in the molecular structure (vitamin B₁₂-⁵⁷Co). The chemical structure of cyanocobalamin is given below:

Each Rubratope-57 capsule contains approximately 18.5 to 37 kBq (0.5 to 1.0 microcurie) of cyanocobalamin Co 57 at the time of calibration; the cyanocobalamin content of each capsule will vary with the specific activity of the cyanocobalamin Co 57 used. Complete assay data are provided on the vial label.

- Cobatope®-57 (Cobaltous Chloride Co 57 Reference Standard Solution), for laboratory use only as a standard of comparison to a companion lot of capsules. Each mL of clear red aqueous solution contains radioactive cobalt chloride Co 57 equivalent to 2 percent of the total radioactivity present in each accompanying Rubratope-57 diagnostic capsule.
- Intrinsic Factor Concentrate capsules (without vitamin B₁₂) for oral administration, providing 1 NF XI unit of intrinsic factor concentrate per capsule.
- Rubramin PC® (Cyanocobalamin Injection USP) in Unimatic® 1 mL syringes, containing a clear red, sterile, nonpyrogenic, aqueous solution for intramuscular administration. Each mL provides 1000 µg (cobalt content 40 µg) nonradioactive cyanocobalamin with 10 mg benzyl alcohol as a preservative and sodium chloride for isotonicity. The pH has been adjusted between 4.5 and 7.0 with sodium hydroxide or hydrochloric acid.

PHYSICAL CHARACTERISTICS

Cobalt 57 decays by electron capture with a physical half-life of 270.9 days.¹ Photons that are useful for detection and imaging studies are listed in Table 1.

Table 1.

Principal Radiation Emission Data		
Radiation	Mean % per Disintegration	Mean energy (keV)
Gamma-2	85.5	122.1
Gamma-3	10.6	136.5

¹kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026. (1981) p.77.

External Radiation

The specific gamma ray constant for Co 57 is 0.96 R/hour-millicurie at 1 cm. The first half-value thickness of Pb (lead) for Co 57 is 0.006 cm. To facilitate control of the radiation exposure, a range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. For example, the use of 1.6 cm of Pb will decrease the external radiation exposure by a factor of about 1,000.

TABLE 2
Radiation Attenuation by Lead Shielding

Shield Thickness (Pb)cm	Attenuation Factor
0.006	0.5
0.05	10 ⁻¹
0.14	10 ⁻²
1.6	10 ⁻³
3.5	10 ⁻⁴

To correct for physical decay of Co 57, the fractions that remain at selected intervals before and after calibration time are shown in Table 3. No decay corrections are necessary when the capsules are used with the companion vial of Cobatope-57.

TABLE 5

Days	Fraction Remaining	Days	Fraction Remaining
0*	1.000	75	0.825
5	0.987	90	0.794
10	0.975	105	0.764
15	0.962	120	0.736
30	0.926	135	0.708
45	0.891	150	0.681
60	0.858	165	0.656
		180	0.631

*Calibration time

CLINICAL PHARMACOLOGY

After oral administration, cyanocobalamin is normally bound by intrinsic factor and absorbed by the distal ileum. Following gastrointestinal absorption or parenteral administration, cyanocobalamin is bound to plasma proteins, stored in the liver, and slowly released when needed to carry out normal cellular metabolic functions. Within 48 hours, 50 to 98 percent of absorbed cyanocobalamin may appear in the urine. The major portion is excreted within the first eight hours. Any cyanocobalamin not bound by intrinsic factor is excreted in the stool.

INDICATIONS AND USAGE

Rubratope-57 Diagnostic Kit (Cyanocobalamin Co 57 Diagnostic Kit) is intended for the diagnosis of pernicious anemia and as a diagnostic adjunct in other defects of intestinal vitamin B¹² absorption.

CONTRAINDICATIONS

None known.

WARNINGS

None.

PRECAUTIONS General

In the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient and occupational workers consistent with proper patient management.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Because a large parenteral dose of vitamin B-12 may temporarily affect subsequent intestinal absorption and excretion of the vitamin, tests employing radioactive vitamin B-12 should not be performed for at least 24 hours after either a flushing dose for the Schilling test or a therapeutic injection (1000 µg) of vitamin B-12.

Since the parenterally administered flushing dose of vitamin B-12 may alter determinations made on bone marrow examinations, such examinations, if indicated, should be performed prior to conducting the Schilling test.

Drug Interactions

Most antibiotics, methotrexate, pyrimethamine, colchicine, para-aminosalicylic acid, or excessive alcohol intake for longer than two weeks may result in malabsorption of vitamin B-12.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate carcinogenic or mutagenic potential, or whether any kit agent for administration affects fertility in males or females.

Pregnancy: Teratogenic Effects

Category C

Animal reproduction studies have not been conducted with any of the agents for administration contained in the Cyanocobalamin Co 57 Diagnostic Kit. It is also not known whether these agents can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Since vitamin B-12-⁵⁷Co is taken up by the fetus, radiocyanocobalamin absorption tests in pregnant women should be postponed until after delivery unless the potential benefit justifies the potential risk to the fetus.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, in women of child-bearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

Since vitamin B-12-⁵⁷Co is excreted in human milk during lactation, formula feedings should be substituted for breast feedings.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

No adverse reactions specifically attributable to Cyanocobalamin Co 57 Capsules or Intrinsic Factor Concentrate capsules have been reported. The following adverse reactions have been reported with nonradioactive Cyanocobalamin: mild transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching, transitory exanthema, feeling of swelling of the entire body, congestive heart failure and pulmonary edema, anaphylactic shock, and death.

DOSAGE AND ADMINISTRATION

The suggested oral dose range for the average patient (70 kg) when performing a Schilling urinary excretion test is between 18.5 to 37 kBq (0.5 to 1 microcurie) of Cyanocobalamin Co 57; the suggested intramuscular (flushing) dose is 1000 µg of nonradioactive Cyanocobalamin. The usual dose of intrinsic factor is 1 NF XI unit.

The patient dose in each Cyanocobalamin Co 57 Capsule should be measured by a suitable radioactivity calibration system immediately prior to administration.

Schilling Urinary Excretion Test^{1,2}

Test Procedure

- The patient should be instructed to fast (patient may have water) for 12 hours prior to the test. Vitamin B¹² should not be administered orally or parenterally during the preceding 24 hours. It is important to establish the absence of any potentially interfering gamma-emitting radioisotopes in the patient's urine prior to starting the study.

After the patient voids, administer one Rubratope-57 (Cyanocobalamin Co 57) capsule. Inject 1000 µg Rubramin PC (Cyanocobalamin Injection) intramuscularly as a flushing dose two hours following administration of the capsule. Collect and pool all urine for 24 hours and mix thoroughly. Collect an additional 24 hour sample separately if renal function is impaired or if urinary excretion is delayed.

Determine 10-minute net radioactivity counts for a 4 mL sample of urine from each excretion period, and a 4 mL sample of diluted Cobatope-57 (Cobaltous Chloride Co 57 Reference Standard Solution). The working standard is prepared by diluting 0.5 mL Cobatope-57, which contains the equivalent of 1 percent of the total radioactivity in the oral dose, with 3.5 mL of water. Calculate as follows:

$$\frac{\text{Counts per minute per mL of urine} \times \text{volume of urine collected}^a}{\text{Counts per minute of standard}^b \times 100^c} \times 100\% = \% \text{ of administered dose}$$

(a)The measurement of radioactivity of the urine sample was a 10-minute count on a 4 mL sample. To convert to counts per minute per mL, divided by 40 (10 minutes x 4 mL).

(b)The count rate of the 4 mL standard is divided by 10 in order to obtain the counts per minute.

(c)1% standard, so dilution factor is 100.

Results

Values of 9 percent or more for samples excreted during either the first 24 hour period or first and second 24 hour periods combined, are generally considered to represent a normal state for vitamin B¹² absorption. The test should be repeated if a lower result is obtained.

Retest Procedure

The need for repeating a test should be carefully evaluated, especially in younger patients. A retest can be conducted four or five days following the primary test. Administer one Intrinsic Factor Concentrate capsule with a Rubratope-57 (Cyanocobalamin Co 57) capsule. Repeat all other steps of the primary procedure. Retest values greater than 9 percent are indicative of pernicious anemia; values of less than 9 percent are indicative of bacterial interference, malabsorption or ileal lesion.

An additional retest can be conducted to determine malabsorption or bacterial interference. Administer antibiotics, in lieu of Intrinsic Factor, 10 to 14 days prior to the second retest. Repeat all other steps of the primary procedure. Values greater than 9 percent are indicative of bacterial interference; values of less than 9 percent are indicative of lack of ileal absorption sites.

Radiation Dosimetry

The estimated absorbed radiation doses to an average patient (70 kg) from an oral dose of 37 kBq (1 microcurie) of vitamin B¹²⁻⁵⁷Co are shown in Table 4.

TABLE 4

Estimated Absorbed Radiation Doses				
Tissue	mGy/37 kBq		Co57 (rads/uCi)	
	Normal		Pernicious Anemia	
Liver	1.3*	(0.13)	0.26	(0.026)
Stomach	0.00081	(0.000081)	0.0011	(0.00011)
Small Intestine	0.0013	(0.00013)	0.0040	(0.00040)
Upper Large Intestine				•,,
Lower Large Intestine	0.0025	(0.00025)	0.0076	(0.00076)
Testes	0.0060	(0.00060)	0.018	(0.0018)
Ovaries	0.052	(0.0052)	0.0012	(0.00012)
Whole-body	0.065	(0.0065)	0.0057	(0.00057)
	0.099	(0.0099)	0.013	(0.0013)

Method of Calculation: "S" Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

*The administration of a flushing dose of nonradioactive vitamin B₁₂ will decrease the dose to the liver, gonads, and whole-body from Co 57 by about 30 percent.

HOW SUPPLIED

Rubratope-57 Diagnostic Kit (Cyanocobalamin Co 57 Diagnostic Kit) provides (Schilling test) material for primary testing for four patients or primary testing and initial retesting for two patients. Each kit contains:

- Four Rubratope-57 (Cyanocobalamin Co 57) two-piece blue/red capsules. Complete assay data are provided on the container.
- One 10 mL vial of Cobatope-57 (Cobaltous Chloride Co 57 Reference Standard Solution) bearing a lot number identical to that for the accompanying Rubratope-57 capsules.
- Two Intrinsic Factor Concentrate two-piece green capsules.
- Four Rubramin PC (Cyanocobalamin Injection) single-dose Unimatic syringes.

Also Available

- Rubratope-57 (Cyanocobalamin Co 57) supplied in bottles of 5 and 10 capsules.
- Cobatope-57 (Cobaltous Chloride Co 57 Reference Standard Solution) supplied in bottles of 10 mL.
- Intrinsic Factor Concentrate supplied in bottles of 2 capsules.

Storage

The kit should be stored at room temperature. In order to maintain the kit as a functional unit, the components should be stored in the platform in which they are packaged.

Rubramin PC (Cyanocobalamin Injection) should also be protected from light and freezing temperatures.

REFERENCES

1Mcintyre PA: "Use of Radioisotope Techniques in the Clinical Evaluation of Patients with Megaloblastic Anemia", Semin in Nucl. Med. 5:1 (1975), 79-94.

2 Nickoloff EL: "Alternatives to Vitamin B¹² Radioassays: The Schilling Test", The Ligand Quart 2: (1979), 27-29.

"This package conforms to the conditions and limitations specified in 49 CFR 173.421 for exempted radioactive material limited quantity, N.O.S., UN 2910".

Receipt, transfer, handling, possession or use of this product is subject to the radioactive materials regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreements States or Licensing States as appropriate.

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