CLINICAL MONOGRAPH · ENERGY & NUTRITIONAL

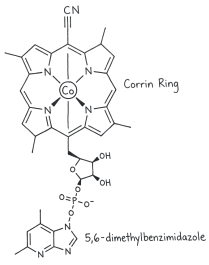
Cyanocobalamin

Standard injectable B12 form

Cyanocobalamin is one form of vitamin B12, the cobalt-containing vitamin your body uses to make red blood cells, build the myelin sheath around nerves, and recycle the amino acid homocysteine. Most people get B12 from animal foods; the body cannot make it.

The classic deficiency syndrome is pernicious anemia, in which the stomach stops producing intrinsic factor (the protein that lets the small intestine absorb B12). Without B12, red blood cells become large and fragile, and nerves can slowly fail, causing numbness, balance problems, and memory changes. Cyanocobalamin injection (1000 micrograms intramuscularly) corrects the deficiency [green2017]. High-dose oral cyanocobalamin (1000, 2000 micrograms daily) is also effective, even in pernicious anemia, because a small fraction of B12 is absorbed by passive diffusion at high doses [kuzminski1998; vidalalaball2005].

Cyanocobalamin injection is an FDA-approved generic product that has been used clinically for over half a century. Compounded cyanocobalamin from a 503A pharmacy is appropriate only when the manufactured product cannot meet a specific clinical need, for example, a custom concentration for an IV-push, a preservative-free formulation for a patient with benzyl-alcohol sensitivity, or a B-complex or methylation-cocktail injectable that combines B12 with other vitamins [stabler2013].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

State-licensed 503A	Pharmacist reviewed	Doctor led	Cold-chain ready	Patient choice preserved

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FOR CLINICIANS

Cyanocobalamin is a synthetic vitamin B12 vitamer used clinically for the treatment and prevention of vitamin B12 deficiency [vidalalaball2005; wang2018]. Intramuscular cyanocobalamin (1000 mcg/mL) has been FDA-approved as a generic for decades, and Nascobal intranasal spray (500 mcg/0.1 mL) provides a non-injectable maintenance option [fda_label_cyanocobalamin_injection]. Vitamin B12 functions as a cofactor for two enzymes: methionine synthase (cytosolic; methylcobalamin-dependent; remethylates homocysteine to methionine) and methylmalonyl-CoA mutase (mitochondrial; adenosylcobalamin-dependent; converts methylmalonyl-CoA to succinyl-CoA). Deficiency produces megaloblastic anemia and a characteristic neurological syndrome (subacute combined degeneration of the spinal cord, peripheral neuropathy, cognitive changes) [stabler2013, green2017, reynolds2006]. Lindenbaum and colleagues demonstrated that neuropsychiatric presentations can occur in the absence of anemia or macrocytosis [lindenbaum1988], and serum methylmalonic acid and total homocysteine are markedly more sensitive than serum B12 alone for biochemical diagnosis [savage1994, snow1999].

Epidemiology: B12 deficiency is common in older adults due to food-cobalamin malabsorption (loss of gastric acid and pepsin needed to release protein-bound B12) [andres2004, stabler1997, wolffenbuttel2019], in vegans and vegetarians who lack dietary intake [pawlak2014], in patients with autoimmune pernicious anemia (anti-intrinsic-factor or anti-parietal-cell antibodies), in patients on long-term metformin (DPPOS demonstrated a dose-dependent association between cumulative metformin exposure and biochemical B12 deficiency) [aroda2016], and in patients with terminal ileum disease or resection. Therapy: parenteral cyanocobalamin 1000 mcg IM (daily for one week, weekly for one month, monthly for maintenance) is the historical standard; oral cyanocobalamin 1000, 2000 mcg daily is equally effective for correction of biochemical and hematological abnormalities in randomized comparisons and a Cochrane systematic review [fda_label_cyanocobalamin_injection] [kuzminski1998; bolaman2003]. Nascobal intranasal (500 mcg weekly) is FDA-approved for maintenance after parenteral repletion [fda_label_nascobal]. Homocysteine-lowering with B vitamins did not produce a clinically meaningful slowing of cognitive decline in pooled trial data [smith2010], diagnose and replete B12 to correct deficiency, not to prevent dementia in B12-replete adults.

503A compounding: manufactured cyanocobalamin injection is a low-cost, widely available FDA-approved generic, so compounded cyanocobalamin must rest on a documented patient-specific clinical need that the manufactured product cannot meet [fda_essentially_a_copy] [fda_label_cyanocobalamin_injection]. Legitimate compounded use cases include: custom concentrations for standardized IV-push dosing (1, 5 mg) outside commercial 1000 mcg/mL strengths; preservative-free formulations for patients with benzyl-alcohol or chlorobutanol sensitivity; sublingual troches and high-strength oral preparations for patients who cannot tolerate injections; and multi-vitamin injectables (B12 plus folate, methylfolate, or B-complex) on a prescriber's individualized formula. Routine substitution of compounded cyanocobalamin for the manufactured generic is not appropriate under FDA's section 503A essentially-a-copy guidance.

Why Personalized Cyanocobalamin

The FDA-approved cyanocobalamin injection is a 1000 mcg/mL aqueous solution in a multi-dose vial, and the dose schedule (daily for a week, then weekly, then monthly) was calibrated for the average pernicious anemia patient. That product does not account for the patient who reacts to the benzyl alcohol preservative in the manufactured vial, the patient whose prescriber wants to deliver 1 to 5 mg as an IV push and needs a concentration that does not exist commercially, the patient who cannot tolerate injections at all, or the patient whose protocol calls for B12 combined with folate, methylfolate, or other B vitamins in one syringe.

That is the gap a compounding pharmacy fills. The molecule is the same cyanocobalamin the FDA reviewed. What changes is the concentration (5 or 10 mg/mL for IV-push protocols outside the commercial 1 mg/mL strength), the preservative profile (benzyl-alcohol-free and chlorobutanol-free formulations for documented sensitivity), the route (custom-strength sublingual troches for patients who refuse injections), and the formula (multi-vitamin injectables blending B12 with folate, methylfolate, B6, or hydroxocobalamin on a prescriber's individualized order). None of these are available off the shelf, which is the entire point. Routine substitution of compounded B12 for the cheap manufactured generic is not what 503A is for, and RonanRx does not do it.

This is what pharmacy looked like before mass manufacturing. A prescriber wrote the order for a specific patient, and a pharmacist prepared it on the bench. Compounded cyanocobalamin is that older arrangement, kept honest by state inspection and the named-patient prescription on file.

Quick Facts About Cyanocobalamin

Category: Water-soluble vitamin (cobalt-containing corrinoid; cobalamin / vitamin B12)

Active ingredient: Cyanocobalamin, a synthetic vitamin B12 vitamer in which the upper axial ligand on the central cobalt is a cyano group; converted intracellularly to the bioactive coenzymes methylcobalamin and 5'-deoxyadenosylcobalamin

FDA-approved branded and generic forms: Cyanocobalamin injection (1000 mcg/mL, IM or deep SC; FDA-approved generic, decades of clinical use); Nascobal nasal spray (500 mcg/0.1 mL intranasal); multiple OTC oral tablets and solutions

Route: Intramuscular, deep subcutaneous, oral, sublingual, and intranasal

Evidence posture: Decades of clinical use; randomized trials and a Cochrane systematic review establish oral and parenteral cyanocobalamin as effective for correcting vitamin B12 deficiency

FDA-approval status: Manufactured cyanocobalamin injection and Nascobal intranasal spray are FDA-approved. Compounded cyanocobalamin preparations are not FDA-approved.

Compounded under: 503A, patient-specific prescription, justified when commercial cyanocobalamin products cannot meet a documented clinical need (custom strengths, allergen-free formulations, IV-push concentrations, mixed-vitamin injectables)

Honest framing: FDA-approved cyanocobalamin injection is a generic, inexpensive, and widely available product. Compounding is appropriate only when individualization a manufactured product cannot provide is clinically required, not as a routine substitution.

> **SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY**
>
> Cyanocobalamin described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.
>
> - **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
> - **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
> - **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
> - **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
> - **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Cyanocobalamin?

Cyanocobalamin is a synthetic form of vitamin B12. Vitamin B12 (cobalamin) is a corrinoid: a tetrapyrrole macrocycle similar to heme but with a central cobalt ion. The corrin ring carries a lower axial ligand, 5,6-dimethylbenzimidazole linked via a ribose-phosphate-aminopropanol arm, and an upper axial ligand that varies between vitamers. In cyanocobalamin the upper ligand is a cyano group; in methylcobalamin it is a methyl group; in adenosylcobalamin it is a 5'-deoxyadenosyl group; in hydroxocobalamin it is a hydroxyl group [quadros2010, hannibal2022].

Cyanocobalamin is the most chemically stable cobalamin vitamer and is the form historically used in pharmaceuticals, food fortification, and most over-the-counter supplements. After absorption, cyanocobalamin is intracellularly converted by the MMACHC enzyme, which removes the cyano group, to a common cob(II)alamin intermediate that is then channeled into the two active coenzyme forms: methylcobalamin (cytosolic, cofactor for methionine synthase) and 5'-deoxyadenosylcobalamin (mitochondrial, cofactor for methylmalonyl-CoA mutase) [hannibal2022, quadros2010].

The FDA-approved manufactured cyanocobalamin products include parenteral cyanocobalamin injection (typically 1000 mcg/mL aqueous solution, intramuscular or deep subcutaneous), Nascobal nasal spray (500 mcg/0.1 mL intranasal), and multiple oral tablets and solutions available over the counter [fda_label_cyanocobalamin_injection, fda_label_nascobal]. The manufactured injection is a generic product that has been used clinically for more than half a century at a low unit cost.

How Cyanocobalamin Works

Vitamin B12 is an essential cofactor for two human enzymes. Methionine synthase, a cytosolic enzyme that uses methylcobalamin, transfers a methyl group from 5-methyltetrahydrofolate to homocysteine, producing methionine and tetrahydrofolate. Methylmalonyl-CoA mutase, a mitochondrial enzyme that uses 5'-deoxyadenosylcobalamin, isomerizes methylmalonyl-CoA (derived from odd-chain fatty acid and branched-chain amino acid catabolism) to succinyl-CoA, which then enters the citric acid cycle [stabler2013, green2017].

When B12 is deficient, methionine synthase activity falls, homocysteine accumulates, and 5-methyltetrahydrofolate becomes trapped (the 'methyl folate trap'), producing functional folate deficiency in marrow precursors and the megaloblastic anemia phenotype. In parallel, methylmalonyl-CoA mutase activity falls, methylmalonic acid accumulates, and abnormal odd-chain fatty acids are incorporated into myelin lipids, contributing to subacute combined degeneration of the spinal cord and peripheral neuropathy [stabler2013, reynolds2006, savage1994].

Cyanocobalamin itself is biologically inert until intracellular processing removes the cyano group; the MMACHC-mediated decyanation generates a reactive cob(II)alamin that is methylated to methylcobalamin or adenosylated to 5'-deoxyadenosylcobalamin [hannibal2022, quadros2010]. Methylmalonic acid and total plasma homocysteine therefore serve as functional markers of intracellular B12 status, both fall within days of effective repletion regardless of vitamer used [snow1999, savage1994].

Biological Role of Cyanocobalamin

Vitamin B12 is one of eight B vitamins and one of two single-carbon-metabolism cofactors (the other is folate). The methionine cycle, the folate cycle, and the methylmalonyl-CoA mutase reaction together situate B12 at the intersection of nucleotide synthesis, methylation, and odd-chain fatty acid catabolism.

Methionine produced by methionine synthase is the precursor of S-adenosylmethionine (SAM), the universal methyl donor for hundreds of methyltransferase reactions, including DNA methylation, neurotransmitter synthesis, and myelin basic protein methylation [reynolds2006, stabler2013].

Humans cannot synthesize cobalamin; it is produced exclusively by certain bacteria and archaea. Dietary sources are animal foods (meat, fish, eggs, dairy) and, to a smaller extent, B12-fortified foods. Plant foods do not contain meaningful amounts of bioavailable cobalamin; algae and fermented foods contain mostly inactive corrinoid analogs [watanabe2007, pawlak2014]. Recommended dietary intake in adults is 2.4 mcg/day; daily losses (biliary excretion and shedding of cobalamin-rich cells) are well below 1% of body stores per day, so deficiency manifests slowly, typically years after onset of malabsorption or dietary inadequacy [green2017].

Detailed Mechanism of Cyanocobalamin

Dietary vitamin B12 in animal foods is bound to proteins. Gastric acid and pepsin release B12 from food protein, after which it binds haptocorrin (R-binder) in saliva and gastric juice. In the duodenum, pancreatic proteases degrade haptocorrin and free B12 is transferred to intrinsic factor, a glycoprotein secreted by gastric parietal cells. The intrinsic factor-B12 complex traverses the small bowel and binds the cubilin-amnionless receptor (the cubam receptor) on enterocytes of the distal ileum, where it is internalized by receptor-mediated endocytosis [quadros2010, green2017]. Loss of any of these steps, achlorhydria from atrophic gastritis or chronic proton pump inhibitor use, autoimmune destruction of parietal cells (pernicious anemia), pancreatic exocrine insufficiency, ileal disease or resection, produces malabsorption.

After enterocyte uptake, B12 is exported into the portal circulation bound to transcobalamin II (the active transport carrier; the holotranscobalamin fraction is the metabolically available pool). Transcobalamin-B12 binds the transcobalamin receptor on target cells and is internalized to the lysosome, where the carrier is degraded and free cobalamin enters the cytosol. The MMACHC gene product processes incoming cobalamins by removing the upper axial ligand, including the cyano group of cyanocobalamin, to generate a common cob(II)alamin intermediate [hannibal2022]. This intermediate is methylated by methionine synthase reductase (MTRR) to produce methylcobalamin or trafficked to the mitochondrion and adenosylated by MMADHC and MMAB to produce 5'-deoxyadenosylcobalamin [hannibal2022, quadros2010].

Approximately 1, 3% of an oral dose of cyanocobalamin is absorbed by passive diffusion across the intestinal mucosa, independent of intrinsic factor [kuzminski1998, wang2018]. This mass-action absorption pathway is the mechanistic basis for high-dose oral cobalamin therapy in patients with pernicious anemia, food-cobalamin malabsorption, or terminal ileum disease: at 1000, 2000 mcg oral daily, the passively absorbed fraction (10, 60 mcg) exceeds daily requirements (2.4 mcg in adults). The Kuzminski 1998 randomized comparison and the Bolaman 2003 prospective trial established the clinical effectiveness of this approach, and the Vidal-Alaball 2005 and Wang 2018 Cochrane systematic reviews

confirmed equivalence of high-dose oral to intramuscular cyanocobalamin on hematological and biochemical endpoints [bolaman2003; vidalalaball2005].

Parenteral cyanocobalamin bypasses the absorption cascade entirely. After IM or deep SC injection, a substantial fraction is bound to plasma haptocorrin and to transcobalamin II; tissue uptake is rapid and the elimination half-life from plasma is short (hours), but cobalamin is sequestered in hepatic stores (1, 5 mg total body store in healthy adults, predominantly hepatic) that buffer total body status for years [green2017, quadros2010]. Renal handling is minor at therapeutic doses; very high parenteral doses produce dose-proportional urinary loss because the protein-binding pool saturates.

Cyanocobalamin Research History

The discovery of vitamin B12 emerged from the work on pernicious anemia in the 1920s. George Minot and William Murphy showed in 1926 that feeding large quantities of raw liver produced clinical and hematological remission in patients with pernicious anemia. William Castle in 1929 demonstrated that the gastric juice of healthy donors, but not of patients with pernicious anemia, contained an 'intrinsic factor' that worked together with an 'extrinsic factor' in food to produce the antianemic effect. The active substance was isolated in crystalline form in 1948 (Rickes, Smith, and Folkers at Merck; Lester Smith at Glaxo), and its molecular structure was determined by Dorothy Hodgkin and colleagues by X-ray crystallography in 1956 (a feat that contributed to her 1964 Nobel Prize in Chemistry). The Minot-Murphy work earned the 1934 Nobel Prize in Physiology or Medicine [green2017, stabler2013].

Clinical use of parenteral cyanocobalamin became standard within years of its isolation; the 1000 mcg IM repletion-then-maintenance schedule that remains in widespread use today originated in the 1950s. The Berlin group's mid-century work and subsequent trials established that high-dose oral cobalamin (1000, 2000 mcg daily) is absorbed by intrinsic-factor-independent passive diffusion at sufficient quantity to produce hematological remission even in pernicious anemia. Kuzminski et al. randomized 38 patients with newly diagnosed cobalamin deficiency to oral cyanocobalamin 2000 mcg daily or intramuscular cyanocobalamin 1000 mcg on the standard induction-then-maintenance schedule and found equivalent serum cobalamin, methylmalonic acid, and homocysteine normalization [kuzminski1998]. Bolaman et al. extended this comparison in patients with megaloblastic anemia [bolaman2003]. The Vidal-Alaball 2005 Cochrane systematic review pooled the available randomized evidence, and the updated Wang 2018 Cochrane review reaffirmed the conclusion: oral cyanocobalamin is equivalent to parenteral cyanocobalamin for correction of B12 deficiency at appropriate doses [vidalalaball2005, wang2018]. Practice guidelines from the British Committee for Standards in Haematology codified these findings in 2014 [devalia2014].

Parallel research extended the deficiency syndrome and its biochemical diagnosis. Lindenbaum and colleagues showed in 1988 that neuropsychiatric manifestations of cobalamin deficiency can occur in the absence of anemia or macrocytosis, undermining the historical reliance on the complete blood count as a

screen [lindenbaum1988]. Stabler, Allen, Savage, and Lindenbaum demonstrated that serum methylmalonic acid and total plasma homocysteine are markedly more sensitive than serum cobalamin for biochemical diagnosis [savage1994, stabler1990, snow1999]. Epidemiological work in elderly adults established food-cobalamin malabsorption, failure to release B12 from food protein in patients with atrophic gastritis and reduced gastric acid, as the dominant cause of B12 deficiency after age 65 [andres2004, stabler1997, wolffenbuttel2019], and dedicated studies established the prevalence of B12 deficiency in vegetarians and vegans [pawlak2014]. The DPPOS cohort showed a dose-dependent association between long-term metformin use and biochemical B12 deficiency in adults with type 2 diabetes [aroda2016]. The 2010 VITACOG trial demonstrated that homocysteine-lowering with B vitamins slowed the rate of brain atrophy in adults with mild cognitive impairment and elevated homocysteine [smith2010], although subsequent pooled analyses did not consistently translate to a clinically meaningful slowing of cognitive decline.

Cyanocobalamin Timeline

1926 • Minot and Murphy show that raw liver feeding produces remission in pernicious anemia [green2017]

1929 • William Castle demonstrates the gastric 'intrinsic factor' required for absorption of an 'extrinsic factor' in food [green2017]

1948 • Vitamin B12 isolated in crystalline form (Rickes, Smith, Folkers at Merck; Lester Smith at Glaxo) [green2017]

1956 • Dorothy Hodgkin solves the X-ray crystal structure of vitamin B12, the corrin ring with central cobalt [green2017]

1988 • Lindenbaum et al [lindenbaum1988]. (NEJM) demonstrate that neuropsychiatric manifestations of cobalamin deficiency occur in the absence of anemia or macrocytosis

1990 • Stabler et al [stabler1990]. (Blood) review the clinical spectrum and biochemical diagnosis of cobalamin deficiency, establishing methylmalonic acid and homocysteine as functional markers

1994 • Savage et al [savage1994]. (Am J Med) demonstrate the diagnostic sensitivity of serum methylmalonic acid and total homocysteine for cobalamin and folate deficiency

1998 • Kuzminski et al [kuzminski1998]. (Blood) randomize 38 patients to oral 2000 mcg vs IM 1000 mcg cyanocobalamin, equivalent biochemical correction; mechanistic basis for high-dose oral therapy

1999 • Snow (Arch Intern Med) primary-care guide to laboratory diagnosis of vitamin B12 and folate deficiency [snow1999]

2003 • Bolaman et al [bolaman2003]. (Clin Ther) prospective randomized comparison of oral vs IM cobalamin in megaloblastic anemia

2004 • Andrès (CMAJ) and Stabler (Annu Rev Nutr) review B12 deficiency in the elderly and as a worldwide problem; food-cobalamin malabsorption framed as dominant geriatric mechanism [andres2004; stabler2004]

2005 • Vidal-Alaball et al [vidalalaball2005]. publish the first Cochrane systematic review of oral vs intramuscular cyanocobalamin

2006 • Eussen et al [eussen2006; reynolds2006]. (AJCN) randomized trial of oral cyanocobalamin in elderly adults with mild B12 deficiency; Reynolds (Lancet Neurol) reviews B12 and the nervous system

2010 • Smith et al [smith2010]. (PLoS ONE), VITACOG randomized trial: homocysteine-lowering with B vitamins (folic acid, B12, B6) slows brain atrophy in mild cognitive impairment

2013 • Stabler (NEJM) Clinical Practice review of vitamin B12 deficiency [stabler2013]

2014 • Pawlak (Eur J Clin Nutr) reviews B12 deficiency prevalence among vegetarians; Devalia et al [pawlak2014; devalia2014; hunt2014]. publish BCSH guideline for diagnosis and treatment of cobalamin and folate disorders; Hunt (BMJ) primary-care review

2016 • Aroda et al [aroda2016]. (JCEM), DPPOS analysis demonstrates dose-dependent association of long-term metformin use with biochemical B12 deficiency in adults with type 2 diabetes

2017 • Green et al [green2017]. publish the Nature Reviews Disease Primers monograph on vitamin B12 deficiency

2018 • Wang et al [wang2018]. updated Cochrane systematic review confirms equivalence of oral vs IM cyanocobalamin for B12 deficiency

2019 • Wolffenbuttel et al [wolffenbuttel2019]. (Mayo Clin Proc IQO) review 'the many faces of cobalamin deficiency'

2020 • Andrès (QJM) state-of-the-art review of oral and nasal vitamin B12 therapy in the elderly [andres2020]

2022 • Hannibal (Vitam Horm) reviews intracellular cobalamin processing by MMACHC, the molecular step that decyanates cyanocobalamin [hannibal2022]

2024 • Lacombe et al [lacombe2024]. (AJCN) prospective cohort confirms effectiveness of oral cyanocobalamin in patients with pernicious anemia

Clinical Contexts for Cyanocobalamin

Treatment of vitamin B12 deficiency (megaloblastic anemia and neurological deficiency)

FDA APPROVED

FDA-approved indication for manufactured cyanocobalamin injection and Nascobal intranasal spray.

Cyanocobalamin injection is FDA-approved for the treatment of pernicious anemia and other causes of vitamin B12 deficiency including dietary inadequacy, malabsorption syndromes, and inadequate utilization [kuzminski1998; vidalalaball2005; wang2018]. The standard induction-then-maintenance schedule is 1000 mcg IM daily for one week, weekly for one month, then monthly for life in patients with permanent malabsorption [fda_label_cyanocobalamin_injection]. Randomized trials and Cochrane systematic reviews demonstrate that oral cyanocobalamin 1000, 2000 mcg daily achieves equivalent biochemical and hematological correction in patients with pernicious anemia and other malabsorption phenotypes [bolaman2003; lacombe2024]. Nascobal intranasal spray (500 mcg once weekly) is FDA-approved for maintenance after initial parenteral repletion in patients in hematological remission [fda_label_nascobal].

Branded product: Cyanocobalamin injection (multiple generic manufacturers) and Nascobal (cyanocobalamin nasal spray)

Pernicious anemia (autoimmune intrinsic factor deficiency)

FDA APPROVED

FDA-approved indication for parenteral cyanocobalamin; high-dose oral established by randomized trials.

Pernicious anemia is the autoimmune destruction of gastric parietal cells producing intrinsic factor deficiency and B12 malabsorption [wang2018; lacombe2024]. Anti-intrinsic-factor antibodies are highly specific; anti-parietal-cell antibodies are more sensitive but less specific. Parenteral cyanocobalamin produces complete hematological correction within weeks and neurological improvement over weeks to months [devalia2014; fda_label_cyanocobalamin_injection; fda_label_nascobal]. High-dose oral cyanocobalamin (1000, 2000 mcg daily) is an alternative for patients in whom adherence can be assured [kuzminski1998; bolaman2003; vidalalaball2005].

Branded product: Cyanocobalamin injection (generic) and Nascobal nasal spray

Food-cobalamin malabsorption (elderly atrophic gastritis) WELL STUDIED

Well-studied dominant geriatric mechanism of B12 deficiency; FDA-approved cyanocobalamin products are routinely used.

After age 65, the dominant cause of B12 deficiency is food-cobalamin malabsorption: atrophic gastritis with hypochlorhydria reduces the gastric acid and pepsin needed to release B12 from food protein, but crystalline (free) cyanocobalamin in tablets or injections is absorbed normally because it does not require this proteolytic release step [stabler1997; wolffenbuttel2019]. Oral cyanocobalamin therapy is therefore highly effective in this population [andres2020]. The prevalence of subclinical B12 deficiency in community-dwelling older adults is approximately 5, 20% depending on the diagnostic threshold and biomarker used [stabler2013, green2017] [andres2004].

Vitamin B12 deficiency in vegans and vegetarians WELL STUDIED

Well-studied dietary etiology; cyanocobalamin supplementation is the standard intervention.

Plant foods contain no biologically meaningful vitamin B12; cobalamin found in algae and fermented foods is predominantly inactive corrinoid analog [watanabe2007]. Pawlak et al. systematically reviewed cobalamin status across vegetarian and vegan populations and found prevalences of deficiency reaching 62% in pregnant vegetarian women and 86% in elderly vegans depending on biomarker definitions [pawlak2014]. Cyanocobalamin oral supplementation (typically 1000 mcg daily or 2000 mcg weekly) corrects and prevents deficiency in this population [green2017].

Metformin-induced vitamin B12 deficiency WELL STUDIED

Well-studied; B12 supplementation is recommended in patients on long-term metformin who develop biochemical deficiency.

The Diabetes Prevention Program Outcomes Study (DPPOS) demonstrated a dose-dependent association between cumulative metformin exposure and biochemical B12 deficiency in adults with type 2 diabetes, risk approximately doubled in long-term metformin users compared with placebo [aroda2016] [stabler2013; green2017]. The proposed mechanism is interference with calcium-dependent ileal uptake of the intrinsic factor-B12 complex. Periodic biochemical screening (serum B12, with reflex to methylmalonic acid or homocysteine when borderline) and oral cyanocobalamin supplementation are reasonable in patients on long-term metformin.

Neuropsychiatric manifestations of cobalamin deficiency WELL STUDIED

Well-studied syndrome; cyanocobalamin replacement is the standard of care.

Subacute combined degeneration of the spinal cord (posterior column and lateral corticospinal tract involvement), peripheral neuropathy, cognitive decline, depression, and psychotic presentations have all been described as B12 deficiency syndromes. Lindenbaum et al. demonstrated that 28% of 141 patients with neuropsychiatric manifestations of cobalamin deficiency had no anemia and no macrocytosis at presentation [lindenbaum1988] [stabler2013; green2017]. Reynolds reviewed the spectrum of neurological involvement and the rationale for prompt replacement [reynolds2006]. Neurological recovery is variable and incomplete when treatment is delayed; the urgency to recognize, biochemically confirm with methylmalonic acid and homocysteine, and replete is driven by this risk of permanent deficit.

Homocysteine-lowering for cognitive decline prevention WELL STUDIED

Studied in randomized trials with mixed and modest results; do not extrapolate to non-deficient adults.

The VITACOG randomized trial [smith2010] demonstrated that homocysteine-lowering with high-dose B vitamins (folic acid 0.8 mg, vitamin B12 0.5 mg, vitamin B6 20 mg daily) slowed the rate of brain atrophy on MRI in older adults with mild cognitive impairment and elevated homocysteine, the strongest available evidence of a biologically plausible MRI signal [smith2010]. Pooled trial data on cognitive outcomes have been less consistent, and the practical inference is to diagnose and replete true B12 deficiency rather than to administer B vitamins as a dementia prophylactic in B12-replete adults [stabler2013; green2017].

Off-Label Uses of Cyanocobalamin

'Energy' or fatigue indications in patients with normal serum B12 EMERGING

Common indication for prescribing in practice; not supported by randomized evidence in B12-replete adults.

Subjective improvements in energy, mood, or wellbeing are widely reported after B12 injection in patients without biochemical deficiency. Randomized placebo-controlled evidence does not support a specific B12 effect in adults with serum B12 in the normal range; the appropriate clinical approach is to confirm or exclude deficiency biochemically (serum B12 with reflex methylmalonic acid and homocysteine in borderline cases) before treating. When deficiency is confirmed, fatigue and cognitive symptoms commonly improve with replacement [stabler2013, green2017].

FDA-Approved Uses of Cyanocobalamin

Brand	Indication	Year	Route
Cyanocobalamin injection (generic)	Treatment of vitamin B12 deficiency, including pernicious anemia, dietary deficiency, malabsorption syndromes, and inadequate utilization; vitamin B12 absorption (Schilling) test	Decades, multiple generic NDAs / ANDAs	Intramuscular or deep subcutaneous injection
Nascobal (cyanocobalamin nasal spray)	Maintenance of normal hematologic status in patients with pernicious anemia who are in hematologic remission following intramuscular vitamin B12 therapy; supplemental B12 for patients with B12 deficiency from dietary deficiencies, malabsorption diseases, or inadequate utilization	2005	Intranasal

Cyanocobalamin has multiple FDA-approved manufactured products. Parenteral cyanocobalamin injection (1000 mcg/mL aqueous solution, intramuscular or deep subcutaneous) is a generic that has been used clinically for over half a century, labeled for treatment of vitamin B12 deficiency from pernicious anemia, malabsorption, dietary inadequacy, or increased requirements, and historically for the Schilling absorption test [fda_label_cyanocobalamin_injection]. Nascobal nasal spray (500 mcg/0.1 mL, one spray weekly) is FDA-approved for maintenance therapy after parenteral repletion in patients with pernicious anemia in hematological remission [fda_label_nascobal]. Multiple over-the-counter oral cyanocobalamin tablets and solutions are widely available.

Compounded cyanocobalamin preparations are not FDA-approved. The manufactured generic cyanocobalamin injection is widely available and inexpensive; compounded versions must rest on a documented patient-specific clinical reason that the manufactured product cannot meet, consistent with FDA's section 503A 'essentially a copy' guidance [fda_essentially_a_copy].

Compounded Cyanocobalamin (503A)

Cyanocobalamin is one of the more honestly framed compounding scenarios on the RonanRx formulary. The FDA-approved generic cyanocobalamin injection (1000 mcg/mL) is a low-cost, widely available drug [fda_label_cyanocobalamin_injection]. The legitimate role of 503A compounding is therefore narrow and specific: compounded cyanocobalamin should be dispensed only when a documented patient-specific clinical need cannot be met by the manufactured product [fda_essentially_a_copy, fda503a].

Documented patient-specific needs that justify a compounded cyanocobalamin preparation include: (1) custom concentration, for example, 5 mg/mL or 10 mg/mL for IV-push administration in protocols that deliver 1, 5 mg per dose, which is not a commercially available manufactured strength; (2) excipient sensitivity, preservative-free formulations for patients with documented benzyl alcohol or chlorobutanol hypersensitivity, since most multi-dose manufactured vials contain one of these preservatives; (3) custom-strength sublingual troches or oral preparations for patients who cannot tolerate injections and who require strengths not commercially available; (4) multi-vitamin injectables, B12 prepared as a component of a B-complex or methylation-cocktail injectable (with folate or methylfolate, hydroxocobalamin, B6, and other vitamins) on a prescriber's individualized formula. None of these use cases is met by the commercially available 1000 mcg/mL cyanocobalamin injection [fda_label_cyanocobalamin_injection].

Routine substitution of compounded cyanocobalamin for the manufactured generic, for example, the dispensing of a 1000 mcg/mL aqueous compounded injection identical in composition to the commercial product, is not appropriate under FDA's section 503A essentially-a-copy guidance and is not a service RonanRx provides [fda_essentially_a_copy]. The honest framing is that the manufactured cyanocobalamin injection works, is inexpensive, and is the appropriate product for the great majority of patients; compounding earns its place only where individualization the manufactured product cannot provide is clinically required [fda_label_cyanocobalamin_injection].

Compounded sterile cyanocobalamin preparations are prepared per USP General Chapter <797>; nonsterile preparative steps (when applicable) follow USP General Chapter <795> [usp_797; usp_795]. Stability, sterility, endotoxin testing, container closure, and beyond-use dating are documented per the pharmacy's quality-management system and per the relevant USP standards.

Cyanocobalamin Formulations and Routes

Form	Concentration	Description
Manufactured cyanocobalamin injection (reference product)	1000 mcg/mL (1 mg/mL) aqueous solution, single- or multi-dose vials; multi-dose vials typically contain benzyl alcohol as preservative	FDA-approved generic. Standard parenteral product for treatment of pernicious anemia and other causes of B12 deficiency. Routine repletion-then-maintenance schedule is 1000 mcg IM daily for one week, then weekly for one month, then monthly for life in permanent malabsorption.
Nascobal intranasal spray (reference product)	500 mcg per 0.1 mL spray; one spray weekly	FDA-approved intranasal cyanocobalamin for maintenance of B12 status after parenteral repletion in pernicious anemia.
Oral cyanocobalamin (OTC)	Typical tablets 100, 5000 mcg	Widely available over the counter. High-dose oral cyanocobalamin (1000, 2000 mcg daily) is equivalent to parenteral cyanocobalamin for

Form	Concentration	Description
		correction of B12 deficiency in randomized trials and Cochrane meta-analysis.
Compounded sterile injectable (custom concentration)	Custom, typical compounded strengths include 5 mg/mL and 10 mg/mL for IV-push or high-dose IM protocols not commercially available	Prepared under USP <797> on patient-specific prescriptions when the manufactured 1000 mcg/mL product cannot meet a documented clinical need (e.g., 1, 5 mg IV-push dosing, preservative-free formulation, B-complex injectable).
Compounded sublingual troche or high-strength oral preparation	Custom, patient-specific strengths and excipient profiles	Prepared under USP <795> for patients who require an oral or sublingual cyanocobalamin preparation at a strength or in an excipient profile not commercially available.

Routes used in published literature: intramuscular, subcutaneous, intravenous, oral, sublingual, intranasal.

Cyanocobalamin Dosing

Route	Population	Range	Duration	Study type
Intramuscular	Adults with vitamin B12 deficiency from pernicious anemia or other malabsorption (FDA-labeled regimen)	1000 mcg IM daily for one week; then 1000 mcg IM weekly for one month; then 1000 mcg IM monthly for life (or as long as the underlying cause persists). Alternative repletion schedules in the literature include 1000 mcg IM every other day for one to two weeks, then less frequently.	Indefinite in permanent malabsorption	FDA-approved labeled regimen
Oral	Adults with vitamin B12 deficiency from any cause (pernicious anemia, food-cobalamin malabsorption, dietary inadequacy)	1000, 2000 mcg orally once daily	Indefinite while underlying cause persists	Randomized trials and Cochrane systematic reviews
Intranasal	Adults with pernicious anemia in			

Route	Population	Range	Duration	Study type
	hematological remission after parenteral repletion (Nascobal labeled regimen)	500 mcg (one spray in one nostril) once weekly	Indefinite while clinically indicated	FDA-approved labeled regimen
Intravenous (IV push, custom-strength compounded)	Adults receiving high-dose B12 protocols in clinical settings where commercial 1000 mcg/mL strength is impractical	1, 5 mg per dose; frequency per prescriber protocol	Per prescriber protocol	Pharmacy compounding practice; no dedicated phase-3 program, supported by general pharmacology of cyanocobalamin
Subcutaneous (deep SC, manufactured or compounded)	Adults intolerant of IM injection or on patient-preference SC route per prescriber	1000 mcg SC, on the same induction-then-maintenance schedule as the IM route	Indefinite while underlying cause persists	FDA-approved alternative route on the cyanocobalamin injection label
Sublingual (compounded)	Adults requiring oral therapy who prefer or require a sublingual route	1000, 2000 mcg sublingually daily (mirroring oral regimen)	Indefinite while underlying cause persists	Pharmacy compounding practice; sublingual absorption likely similar to high-dose oral passive diffusion

Doctor-prescribed. The classic intramuscular cyanocobalamin schedule (1000 mcg daily for one week, weekly for one month, then monthly) was empirically chosen in the 1950s and has not been displaced by a single more efficient parenteral regimen. High-dose oral cyanocobalamin (1000, 2000 mcg daily) is an equally effective alternative for many patients including those with pernicious anemia, provided adherence can be reasonably assured [fda_label_cyanocobalamin_injection] [kuzminski1998; bolaman2003]. The choice between routes is typically practical: severe presentations with neurological involvement are often treated parenterally for at least the first few weeks before considering a switch to oral; food-cobalamin malabsorption in older adults often responds well to oral therapy from the outset [vidalalaball2005; wang2018; lacombe2024].

Biochemical correction is monitored by serum B12, methylmalonic acid, and homocysteine (the last two normalize within days of effective repletion); hematological correction is monitored by complete blood count and reticulocyte response (a reticulocytosis peaks at approximately one week) [fda_label_cyanocobalamin_injection] [devalia2014]. Neurological improvement is slower, variable, and

incomplete when treatment is delayed, the urgency to recognize and treat is driven by this risk of permanent deficit [stabler2013, reynolds2006, lindenbaum1988].

Cyanocobalamin Safety

Cyanocobalamin has an exceptionally favorable safety profile across more than half a century of clinical use. The most common adverse effects of parenteral administration are mild injection-site reactions (pain, pruritus, transient rash). Hypersensitivity reactions, including anaphylaxis, have been rarely reported and are typically attributable to cobalt or to excipients (benzyl alcohol in multi-dose vials) rather than to the cobalamin molecule itself [27] [5].

Hypokalemia has been reported during the rapid hematological response to B12 repletion in patients with severe megaloblastic anemia (potassium is consumed during rapid erythropoiesis); serum potassium should be monitored in patients with severe anemia or in those with pre-existing electrolyte disturbance during the first week of therapy [27][16]. Rare reports of thrombosis during repletion of severe megaloblastic anemia are reported in the older literature [26].

The cyano moiety of cyanocobalamin is released during intracellular processing in trace amounts, historically of theoretical concern in patients with Leber's hereditary optic neuropathy and in heavy smokers with tobacco amblyopia (hydroxocobalamin is preferred in these specific contexts because it does not contribute cyanide and indeed scavenges it). For the great majority of patients without these conditions, the cyanide released from a 1000 mcg therapeutic dose is biologically negligible [21][16].

There is no established upper intake level for vitamin B12; the Institute of Medicine did not set a tolerable upper intake limit because no toxic effect has been demonstrated at high doses. Oral cyanocobalamin 1000, 2000 mcg daily has been administered chronically in clinical trials without dose-limiting toxicity [10][22].

Contraindications

Cyanocobalamin is contraindicated in patients with known hypersensitivity to cobalt or to any component of the formulation (including benzyl alcohol in multi-dose preservative-containing vials) [27].
Cyanocobalamin is relatively contraindicated in Leber's hereditary optic neuropathy and in suspected tobacco amblyopia; hydroxocobalamin is preferred in these contexts because cyanocobalamin contributes trace cyanide that may exacerbate optic neuropathy.

Caution is warranted in patients with hypokalemia or polycythemia vera at the start of therapy because of potassium consumption during rapid erythropoiesis [27].

Drug interactions

Drugs that reduce B12 absorption over months to years include long-term metformin (dose-dependent, established in DPPOS) [20], long-term proton pump inhibitors and H2 receptor antagonists (which reduce gastric acid needed to release B12 from food protein), aminosalicylic acid, neomycin, colchicine, and

chloramphenicol (which can blunt the hematological response to B12 repletion). The clinical implication is periodic biochemical screening in patients on long-term metformin or acid-suppressive therapy, with oral cyanocobalamin supplementation when biochemical deficiency develops [27].

Cyanocobalamin is not metabolized by cytochrome P450 enzymes and does not participate in CYP-mediated drug-drug interactions [27]. Folic acid supplementation in the presence of unrecognized B12 deficiency can correct the megaloblastic anemia while neurological deficits progress, the historical reason to confirm B12 status before treating macrocytic anemia with folate alone [1621].

Adverse events

Reported adverse events with cyanocobalamin injection are uncommon and generally mild: injection-site pain, pruritus, transient rash, mild diarrhea, and headache. Anaphylaxis has been reported rarely; the cobalt ion and benzyl alcohol preservative (when present) are the typical culprits rather than the cobalamin molecule [27]. Hypokalemia during the rapid hematological response in severe megaloblastic anemia is well documented and managed by monitoring and replacement [2716].

Adverse events with Nascobal intranasal spray are predominantly local: rhinitis, sneezing, and headache [28]. Adverse events with oral cyanocobalamin are rare; in the Kuzminski 1998, Bolaman 2003, and Lacombe 2024 trials, oral 1000, 2000 mcg daily was well tolerated with no dose-limiting toxicity over the study durations [5726].

↗ Monitoring Cyanocobalamin Therapy

Baseline evaluation includes serum B12, complete blood count with mean corpuscular volume, reticulocyte count, and consideration of methylmalonic acid and total plasma homocysteine when serum B12 is borderline (200, 350 pg/mL) or when neurological symptoms are present without anemia [snow1999, savage1994, stabler2013]. In suspected pernicious anemia, anti-intrinsic-factor antibodies (highly specific) and anti-parietal-cell antibodies (more sensitive but less specific) help establish the etiology [devalia2014, green2017].

On therapy: reticulocyte response peaks at approximately one week; serum B12 rises rapidly with parenteral therapy. Methylmalonic acid and homocysteine normalize within days to weeks of effective repletion regardless of route [snow1999, savage1994]. Hematological normalization (Hb, MCV) typically completes by 6, 8 weeks. Neurological response is variable and may continue improving over 6, 12 months; incomplete recovery is associated with longer pre-treatment duration of deficit [reynolds2006, lindenbaum1988]. Serum potassium should be monitored during the first week of treatment in patients with severe megaloblastic anemia [fda_label_cyanocobalamin_injection].

Cyanocobalamin in Special Populations

Cyanocobalamin Evidence Quality

The evidence base for cyanocobalamin is mature and consistent. The biochemistry of cobalamin-dependent enzymes is well characterized [hannibal2022, quadros2010]. The clinical spectrum of vitamin B12 deficiency and the biochemical diagnostic markers (serum B12, methylmalonic acid, homocysteine) are codified across decades of work by Lindenbaum, Stabler, Allen, Savage, Snow, and others [stabler1997; wolffenbuttel2019; pawlak2014]. Epidemiology of deficiency in elderly adults, in vegetarians and vegans, and in patients on long-term metformin is well established [andres2004; aroda2016; lindenbaum1988]. The Nature Reviews Disease Primers monograph [green2017] and the NEJM Clinical Practice review [stabler2013] consolidate this evidence [green2017, stabler2013].

Randomized comparative effectiveness data are unusually strong for a generic vitamin [snow1999; lacombe2024]. The Kuzminski 1998 randomized comparison of oral 2000 mcg vs IM 1000 mcg cyanocobalamin and the Bolaman 2003 prospective randomized trial in megaloblastic anemia established equivalence of the two routes [kuzminski1998, bolaman2003] [andres2020]. The Vidal-Alaball 2005 Cochrane systematic review and the updated Wang 2018 Cochrane review pooled randomized evidence and reaffirmed the equivalence conclusion [vidalalaball2005, wang2018]. Practice guidelines from the British Committee for Standards in Haematology [devalia2014] and contemporary reviews [hunt2014] translate the evidence into clinical recommendations [stabler1990]. The VITACOG randomized trial [smith2010] is the leading evidence base for the homocysteine-lowering hypothesis in cognitive decline [smith2010] [savage1994].

Evidence specifically supporting compounded cyanocobalamin preparations is essentially absent, there is no separate efficacy program for compounded formulations because the manufactured FDA-approved cyanocobalamin injection is the reference product and is the basis for the pharmacology established above [aroda2016]. Compounded use is therefore an individualization-driven extrapolation from the manufactured-product evidence, justified case-by-case by documented patient-specific clinical factors that the manufactured product cannot accommodate.

Major Cyanocobalamin Clinical Studies

Study	Design	Participants	Duration	Finding
Lindenbaum et al. (1988, NEJM), Neuropsychiatric	Case series of 141 consecutive patients with neuropsychiatric disorders	141	—	28% of patients with neuropsychiatric manifestations of cobalamin

Study	Design	Participants	Duration	Finding
presentation without anemia	caused by cobalamin deficiency			deficiency had neither anemia nor macrocytosis at presentation, undermining reliance on the CBC as a screening tool [lindenbaum1988]
Stabler et al. (1990, Blood), Clinical spectrum of cobalamin deficiency	Review and case series characterizing the clinical and biochemical spectrum of cobalamin deficiency	—	—	Established serum methylmalonic acid and total plasma homocysteine as functional biochemical markers of cobalamin status, more sensitive than serum cobalamin alone [stabler1990]
Savage et al. (1994, Am J Med), Diagnostic sensitivity of MMA and Hcy	Prospective comparison of serum methylmalonic acid and total homocysteine to serum cobalamin and folate in patients with biochemically confirmed cobalamin or folate deficiency	434	—	Methylmalonic acid elevated in 98% of cobalamin-deficient and total homocysteine in 96%; either marker more sensitive than serum cobalamin alone for diagnosis [savage1994]
Kuzminski et al. (1998, Blood), Oral vs IM cobalamin randomized trial	Randomized, open-label, parallel-group comparison of oral cyanocobalamin 2000 mcg daily vs IM cyanocobalamin 1000 mcg on the standard induction-then-maintenance schedule in adults with newly diagnosed cobalamin deficiency	38	120 days	Equivalent normalization of serum cobalamin, methylmalonic acid, and homocysteine on oral 2000 mcg daily compared with IM 1000 mcg on the standard schedule; numerically higher serum cobalamin in the oral arm [kuzminski1998]
Snow (1999, Arch Intern Med), Lab diagnosis primary-care guide	Narrative review of laboratory tests for vitamin B12 and folate deficiency	—	—	Serum B12 has limited sensitivity; methylmalonic acid and total homocysteine provide functional confirmation; the practical diagnostic algorithm for primary care [snow1999]

Study	Design	Participants	Duration	Finding
Bolaman et al. (2003, Clin Ther), Oral vs IM cobalamin in megaloblastic anemia	Prospective, randomized, open-label, single-center trial of oral vs intramuscular cobalamin in adults with megaloblastic anemia	60	90 days	Equivalent hematological and biochemical correction with oral vs intramuscular cobalamin [bolaman2003]
Andrès (2004, CMAJ), Vitamin B12 deficiency in elderly patients	Review of B12 deficiency epidemiology, etiology, and treatment in elderly adults	—	—	Food-cobalamin malabsorption is the dominant geriatric mechanism; crystalline cyanocobalamin (oral or parenteral) is absorbed normally because it does not require gastric proteolytic release from food protein [andres2004]
Vidal-Alaball et al. (2005, Cochrane), Oral vs IM cyanocobalamin systematic review	Cochrane systematic review of randomized trials of oral vs intramuscular cyanocobalamin for vitamin B12 deficiency	—	—	Two trials [kuzminski1998] met inclusion; pooled results favored oral therapy on serum cobalamin and showed equivalent clinical correction [vidalalaball2005]
Eussen et al. (2006, AJCN), Oral B12 cognitive function in mild deficiency	Randomized, double-blind, placebo-controlled trial of oral cyanocobalamin 1000 mcg with or without folic acid 400 mcg daily in older adults with mild B12 deficiency	195	24 weeks	Significant biochemical correction without a measurable effect on cognitive function endpoints at the trial duration [eussen2006]
Smith et al. (2010, PLoS ONE), VITACOG B-vitamin brain atrophy trial	Randomized, double-blind, placebo-controlled trial of folic acid 0.8 mg, vitamin B12 0.5 mg (cyanocobalamin), and vitamin B6 20 mg daily in adults with mild cognitive impairment and elevated homocysteine	168	24 months	Significant slowing of whole-brain atrophy rate on MRI in the B-vitamin arm; effect concentrated in participants with higher baseline homocysteine [smith2010]

Study	Design	Participants	Duration	Finding
Stabler (2013, NEJM), Clinical Practice review of B12 deficiency	Clinical Practice review article	—	—	Comprehensive contemporary synthesis of vitamin B12 deficiency epidemiology, diagnosis, and treatment with case-based recommendations [stabler2013]
Pawlak (2014, Eur J Clin Nutr), Vegetarian B12 deficiency systematic review	Systematic review of cobalamin deficiency prevalence in vegetarian and vegan populations across age groups	—	—	Prevalences of biochemical deficiency reached 62% in pregnant vegetarians and 86% in elderly vegans depending on diagnostic threshold; supplementation is universally indicated for vegans [pawlak2014]
Devalia et al. (2014, Br J Haematol), BCSH guideline	British Committee for Standards in Haematology guideline for diagnosis and treatment of cobalamin and folate disorders	—	—	Practical evidence-based recommendations for screening, diagnosis (including thresholds for methylmalonic acid and homocysteine), and treatment routes [devalia2014]
Aroda et al. (2016, JCEM), DPPOS metformin and B12	Post-hoc analysis of the Diabetes Prevention Program Outcomes Study examining long-term metformin exposure and biochemical B12 status	2155	Median 13 years follow-up	Dose-dependent association between cumulative metformin exposure and biochemical B12 deficiency; risk of low B12 approximately doubled in long-term metformin users vs placebo [aroda2016]
Green et al. (2017, Nat Rev Dis Primers), Vitamin B12 deficiency monograph	Nature Reviews Disease Primers monograph	—	—	Comprehensive multidisciplinary synthesis of B12 biochemistry, epidemiology, diagnosis, and therapy [green2017]
Wang et al. (2018, Cochrane), Updated	Updated Cochrane systematic review of oral vs intramuscular	—	—	Oral cyanocobalamin produces equivalent hematological and

Study	Design	Participants	Duration	Finding
oral vs IM B12 systematic review	cyanocobalamin for vitamin B12 deficiency			biochemical correction to intramuscular cyanocobalamin at appropriate doses (typically 1000, 2000 mcg daily orally) [wang2018]
Wolffenbuttel et al. (2019, Mayo Clin Proc IQ&O), The many faces of cobalamin deficiency	Narrative review	—	—	Heterogeneity of clinical presentations and limited sensitivity of serum cobalamin as a single screening marker; argues for liberal use of MMA and homocysteine confirmation [wolffenbuttel2019]
Andrès (2020, QJM), Oral and nasal B12 in the elderly	State-of-the-art review of oral and intranasal cyanocobalamin therapy in older adults	—	—	Oral cyanocobalamin 1000 mcg daily is appropriate first-line therapy for B12 deficiency from food-cobalamin malabsorption in older adults; intranasal cyanocobalamin (Nascobal) is an alternative for maintenance [andres2020]
Hannibal (2022, Vitam Horm), Intracellular cobalamin processing	Review of MMACHC-mediated intracellular processing of cobalamins	—	—	MMACHC removes the upper axial ligand of incoming cobalamins (including the cyano group of cyanocobalamin) to generate a common cob(II)alamin intermediate that is then channeled into methylcobalamin and adenosylcobalamin [hannibal2022]
Lacombe et al. (2024, AJCN), Oral B12 in pernicious anemia prospective cohort	Prospective cohort study of oral cyanocobalamin in patients with pernicious anemia	—	—	Confirms effectiveness of high-dose oral cyanocobalamin in pernicious anemia in a contemporary clinical cohort; supports oral therapy as a reasonable first-

Study	Design	Participants	Duration	Finding
				line option in selected patients [lacombe2024]

Cyanocobalamin Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Cyanocobalamin is absorbed by two parallel mechanisms after oral administration [fda_label_cyanocobalamin_injection]. The physiological pathway requires gastric acid and pepsin to release B12 from food protein, binding to haptocorrin in the stomach, transfer to intrinsic factor in the duodenum, and receptor-mediated uptake of the intrinsic factor-B12 complex by the cubilin-amnionless receptor in the distal ileum. Absorption by this pathway saturates at approximately 1.5, 2 mcg per meal and accounts for nutritional B12 intake. The non-physiological pathway is intrinsic-factor-independent passive diffusion across the intestinal mucosa, which absorbs approximately 1, 3% of an oral dose and is the basis for high-dose oral cyanocobalamin therapy [quadros2010, green2017, kuzminski1998].

After absorption, cyanocobalamin is bound in plasma to transcobalamin II (active transport carrier, the holotranscobalamin pool) and haptocorrin. Tissue uptake is rapid; the plasma elimination half-life is short (hours) but the hepatic store (1, 5 mg in healthy adults) buffers total body status for years. Renal handling is minor at therapeutic doses; urinary loss becomes dose-proportional only at very high parenteral doses that saturate plasma protein binding. Cyanocobalamin itself is biologically inert until intracellular processing by MMACHC removes the cyano group; the resulting cob(II)alamin intermediate is methylated to methylcobalamin or adenosylated to 5'-deoxyadenosylcobalamin [hannibal2022, quadros2010] [fda_label_cyanocobalamin_injection].

Intramuscular and deep subcutaneous administration bypass the absorption cascade entirely; bioavailability is essentially complete. Intranasal cyanocobalamin (Nascobal) achieves bioavailability of approximately 7, 10% relative to intramuscular administration on a per-dose basis, supporting the 500 mcg weekly maintenance regimen [fda_label_nascobal] [fda_label_cyanocobalamin_injection].

Pharmacodynamics

Pharmacodynamic effects of cyanocobalamin repletion in deficiency include rapid reticulocytosis (peaking at approximately one week), normalization of mean corpuscular volume over 6, 8 weeks, and biochemical normalization of methylmalonic acid and total homocysteine within days to weeks [stabler2013, snow1999, savage1994]. Neurological response is slower (weeks to months) and incomplete when treatment is delayed [lindenbaum1988, reynolds2006].

There is no pharmacodynamic indication for cyanocobalamin in adults with normal serum B12 and normal functional markers (methylmalonic acid, homocysteine); subjective effects on energy or mood in B12-replete adults are not supported by randomized placebo-controlled evidence.

↓↑ Comparing Cyanocobalamin Formulations

The manufactured cyanocobalamin products are parenteral cyanocobalamin injection (1000 mcg/mL, IM or deep SC; FDA-approved generic) and Nascobal intranasal spray (500 mcg/0.1 mL, once weekly maintenance) [fda_label_cyanocobalamin_injection; fda_label_nascobal]. Over-the-counter oral cyanocobalamin tablets are widely available at 100, 5000 mcg strengths. Among other B12 vitamers: hydroxocobalamin injection (preferred for cyanide-related conditions and for Leber's hereditary optic neuropathy) is available as a generic; methylcobalamin and adenosylcobalamin are available as oral supplements but are not FDA-approved as drugs.

Cyanocobalamin and hydroxocobalamin behave nearly identically in routine B12 repletion because both vitamers feed the same intracellular MMACHC processing step before becoming biologically active [hannibal2022, quadros2010]. The empirical clinical choice between vitamers is driven by historical convention, specific contraindications (cyanocobalamin avoided in Leber's hereditary optic neuropathy; hydroxocobalamin preferred for cyanide poisoning), and availability rather than by demonstrable differences in routine repletion efficacy [fda_label_cyanocobalamin_injection].

Compounded sterile injectable cyanocobalamin preparations differ from the manufactured 1000 mcg/mL generic primarily in concentration (e.g., 5 mg/mL or 10 mg/mL for IV-push protocols) and excipient profile (e.g., preservative-free formulations) [fda_label_cyanocobalamin_injection]. They are not bioequivalent to the manufactured product without separate stability and PK data.

🌡 Cyanocobalamin Storage and Handling

Manufactured cyanocobalamin injection is stored at controlled room temperature (20, 25°C; 68, 77°F) protected from light [usp_797]. Light exposure degrades cobalamins by photolysis; the product is supplied in amber glass and should be returned to the carton when not in use [fda_label_cyanocobalamin_injection]. Nascobal nasal spray is stored upright at controlled room temperature; use within the labeled in-use period after activation [fda_label_nascobal].

Compounded sterile cyanocobalamin preparations are stored per the pharmacy's stability data and beyond-use-date assignment under USP <797>. Light protection (amber containers, opaque overwraps, light-blocking storage cabinets) is a routine requirement. Refrigerated storage extends beyond-use dates relative to room temperature for many compounded sterile aqueous preparations [usp_797].

Cyanocobalamin Compounding & Operations

503A compounding

Compounded cyanocobalamin is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares sterile injectable cyanocobalamin per USP General Chapter <797>, the official compendial standard for sterile pharmaceutical compounding, with documented active ingredient sourcing, gravimetric and analytical verification, sterility and endotoxin testing per the pharmacy's quality-management system, and full lot traceability [usp_797] [fda503a]. Nonsterile preparative steps (when applicable) follow USP General Chapter <795> [usp_795].

Compounded cyanocobalamin is dispensed only when the prescriber documents a patient-specific clinical need that the manufactured cyanocobalamin injection or Nascobal product cannot meet, consistent with FDA's section 503A guidance on compounded copies of commercially available drugs [fda_essentially_a_copy]. Routine compounding of a 1000 mcg/mL cyanocobalamin injection identical to the manufactured generic is not appropriate and is not performed at RonanRx [fda503a; fda_label_cyanocobalamin_injection].

Beyond-use dating, ingredient identity verification, sterility assurance, and stability assessment follow USP <797> requirements [fda503a]. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing.

Pharmacist review

Each prescription for compounded cyanocobalamin undergoes pharmacist review prior to dispensing [vidalalaball2005; wang2018; devalia2014]. The review confirms: a documented patient-specific clinical reason that the manufactured cyanocobalamin injection or Nascobal product is not appropriate (e.g., excipient sensitivity to benzyl alcohol or chlorobutanol; custom concentration for an IV-push protocol; a multi-vitamin injectable formula); absence of contraindications (cobalt hypersensitivity, Leber's hereditary optic neuropathy, tobacco amblyopia); appropriate biochemical evaluation of B12 status (serum B12, with reflex methylmalonic acid and homocysteine in borderline cases) where the prescription indication is treatment of suspected deficiency [snow1999, savage1994, stabler2013]; and a prescribed regimen consistent with the established clinical evidence on dose, route, and frequency [fda_label_cyanocobalamin_injection].

RonanRx does not fill prescriptions for compounded cyanocobalamin that read as routine substitution of compounded for manufactured product without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy] [fda_label_cyanocobalamin_injection] [kuzminski1998].

Quality and traceability

Cyanocobalamin active pharmaceutical ingredient is sourced from FDA-registered facilities with documented certificates of analysis (identity, purity, water content, residual solvents, microbial limits). Each compounded batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, sterility test result (for sterile preparations), endotoxin test result, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Cyanocobalamin is not strictly a cold-chain product, the manufactured injection is stored at controlled room temperature with light protection [fda_label_cyanocobalamin_injection]. Compounded sterile aqueous cyanocobalamin preparations may be refrigerated to extend beyond-use dating relative to room-temperature storage, per the pharmacy's stability data [usp_797]. Light protection (amber containers, opaque overwraps) is a routine requirement throughout storage and transport because cobalamins are photolabile.

Frequently Asked Questions About Cyanocobalamin

Is compounded cyanocobalamin the same as a generic B12 injection from the pharmacy?

No. FDA-approved cyanocobalamin injection (1000 mcg/mL) is a manufactured generic available at most pharmacies, inexpensive, and well established [fda_label_cyanocobalamin_injection]. Compounded cyanocobalamin is pharmacy-prepared on a patient-specific prescription and is appropriate only when the manufactured product cannot meet a documented clinical need, for example, a custom concentration for IV push, a preservative-free formulation, or a multi-vitamin injectable formula. Compounded drugs are not FDA-approved [fda_essentially_a_copy].

When is compounded cyanocobalamin appropriate instead of the manufactured product?

When a documented patient-specific clinical need cannot be met by the manufactured 1000 mcg/mL injection or by Nascobal nasal spray, for example, a custom concentration (5 mg/mL or 10 mg/mL for IV-push protocols), a preservative-free formulation for benzyl alcohol or chlorobutanol sensitivity, a custom-strength sublingual troche, or a B-complex/methylation-cocktail injectable on a prescriber's individualized formula. Cost or convenience does not justify compounding under section 503A [fda_essentially_a_copy].

Is oral B12 as good as B12 injections?

For most patients, yes. Two randomized trials (Kuzminski 1998 and Bolaman 2003) and two Cochrane systematic reviews (Vidal-Alaball 2005 and Wang 2018) showed that oral cyanocobalamin 1000, 2000 mcg daily produces equivalent biochemical and hematological correction to intramuscular cyanocobalamin 1000 mcg on the standard schedule, even in pernicious anemia [kuzminski1998; bolaman2003;

vidalalaball2005]. Injections may still be preferred initially when there are severe neurological symptoms or when adherence cannot be assured [wang2018].

Should everyone on metformin take a B12 supplement?

Long-term metformin use is associated with dose-dependent biochemical B12 deficiency (DPPOS, Aroda 2016) [aroda2016]. Routine biochemical screening (serum B12, with reflex to methylmalonic acid or homocysteine in borderline cases) is reasonable in patients on metformin for several years, with oral cyanocobalamin supplementation when deficiency develops. Universal supplementation in all metformin users without screening is not formally recommended by current guidelines [devalia2014].

Do vegans need to supplement vitamin B12?

Yes. Plant foods contain no biologically meaningful B12; algae and fermented foods contain mostly inactive corrinoid analogs. Pawlak et al. (2014) found that biochemical B12 deficiency was highly prevalent across vegan and vegetarian populations (reaching 86% in elderly vegans) [pawlak2014]. Oral cyanocobalamin (1000 mcg daily or 2000 mcg weekly) is the standard intervention [watanabe2007].

What are the most common side effects of cyanocobalamin injection?

Side effects are uncommon and generally mild: injection-site pain, transient rash, mild pruritus, and headache. Hypersensitivity reactions are rare and usually attributable to cobalt or to benzyl alcohol preservative in multi-dose vials. Hypokalemia is reported during the rapid hematological response in severe megaloblastic anemia and is managed by monitoring and replacement [fda_label_cyanocobalamin_injection; stabler2013].

Why is methylmalonic acid measured to diagnose B12 deficiency?

Serum B12 has limited sensitivity at borderline levels. Methylmalonic acid accumulates when the B12-dependent mitochondrial enzyme methylmalonyl-CoA mutase is functionally impaired; total plasma homocysteine accumulates when the B12-dependent cytosolic enzyme methionine synthase is functionally impaired [savage1994]. Both markers are more sensitive than serum B12 alone, are elevated in 96, 98% of biochemically confirmed deficiency cases (Savage 1994), and normalize within days to weeks of effective repletion [snow1999; stabler2013].

Does RonanRx sell compounded cyanocobalamin directly to patients?

No. Compounded cyanocobalamin requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the manufactured cyanocobalamin injection or Nascobal product is not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Cyanocobalamin

Compounded Cyanocobalamin is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Cyanocobalamin, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)