RonanRx
PERSONALIZED MEDICINE

CLINICAL MONOGRAPH · ENERGY & NUTRITIONAL

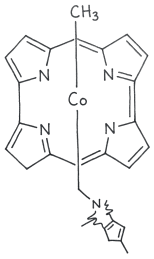
Methylcobalamin (B12)

Active form of vitamin B12 in injectable and oral preparations

Methylcobalamin is one of the two coenzyme forms of vitamin B12 that the body actually uses inside cells, the other is adenosylcobalamin. It is sometimes called the 'methylated' or 'active' form of B12.

Methylcobalamin works as a helper for an enzyme (methionine synthase) that converts homocysteine into methionine and supports DNA and neurotransmitter synthesis. People with diagnosed B12 deficiency from pernicious anemia, dietary restriction, gastric bypass, long-term metformin use, or recreational nitrous oxide exposure may need B12 replacement [green2017; niafar2015].

The standard FDA-approved injectable B12 is cyanocobalamin, the inexpensive form. Methylcobalamin is one of several alternative forms a doctor may prescribe, typically through a 503A compounding pharmacy as a sublingual tablet or subcutaneous injection, when there is a documented reason a patient should not use cyanocobalamin (for example, an excipient sensitivity, a clinician preference for the active form in the context of a confirmed MTHFR polymorphism, or another individualized clinical factor) [stabler2013; frosst1995].



EVIDENCE POSTURE WELL STUDIED EMERGING REVIEWED **2026-05-11**

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

Contents

Click any section to jump there. Page numbers update on render.

FOR CLINICIANS

Methylcobalamin (mecobalamin, MeCbl) is the cytosolic coenzyme form of vitamin B12 and the cofactor for methionine synthase, the enzyme that remethylates homocysteine to methionine using 5-methyltetrahydrofolate as the methyl donor and regenerates tetrahydrofolate for nucleotide synthesis [green2017, reynolds2006]. The second mammalian coenzyme form, adenosylcobalamin, is the cofactor for mitochondrial methylmalonyl-CoA mutase. Both coenzyme forms are generated intracellularly from any administered cobalamin precursor (cyanocobalamin, hydroxocobalamin, methylcobalamin, or adenosylcobalamin) by the cytoplasmic chaperone CblC and downstream enzymes [green2017] [devalia2014].

There is no FDA-approved standalone methylcobalamin drug product in the United States; cyanocobalamin injection (multiple ANDA generics) is the standard FDA-approved parenteral B12 and oral cyanocobalamin tablets are the standard FDA-approved oral form. Hydroxocobalamin is FDA-approved as an intramuscular B12 form and, at 5 g IV, as the cyanide antidote Cyanokit. Methylcobalamin is registered as a prescription drug in Japan and several Asian markets and has been studied in Japanese phase II/III trials in amyotrophic lateral sclerosis [kaji2019, oki2022, kaji2026] and in older trials in diabetic peripheral neuropathy [yaqub1992, deng2025, ran2024] and in Bell palsy [jalaludin1995] [fda503a]. RonanRx prepares methylcobalamin under 503A, sublingual tablets and sterile injections at custom strengths, only on a patient-specific prescription where the prescriber documents a clinical reason the FDA-approved cyanocobalamin or hydroxocobalamin product is not appropriate (excipient sensitivity, preference for the active form in patients with documented MTHFR C677T homozygosity [frosst1995], dose individualization, or other documented factor).

B12 deficiency replacement therapy (parenteral or high-dose oral) is well established across causes: autoimmune pernicious anemia [toh1997, carmel2005], food-cobalamin malabsorption in older adults [andres2004, andres2018, wolffenbuttel2019], post-gastric-bypass anatomy, dietary restriction, long-term metformin use [niafar2015, pflipsen2009, pratama2022], and nitrous-oxide-induced functional deficiency. Randomized comparisons of oral vs intramuscular cyanocobalamin [vidal2005, castelli2011] and of sublingual vs oral cyanocobalamin [sharabi2003] support high-dose oral and sublingual replacement for most causes other than acute neurological deficiency. Direct head-to-head trials of methylcobalamin vs cyanocobalamin on hard clinical outcomes are limited; the active-form rationale is mechanistic and individualized rather than population-level [stabler2013].

Why Personalized Methylcobalamin (B12)

The FDA-approved B12 products in the United States are cyanocobalamin and hydroxocobalamin, picked for chemical stability and population-level efficacy in trial cohorts. Those products were not picked for your particular biology: how severe your deficiency is, why you got it (pernicious anemia, gastric bypass, long-term metformin, nitrous-oxide exposure, food-cobalamin malabsorption), whether you carry a homozygous MTHFR C677T variant, whether you react to the standard excipients, or whether you respond better to a methylated coenzyme form. The cyanocobalamin generic is one shape and one strength for everyone.

Compounding closes that gap. A prescriber who knows your chart can ask a 503A pharmacy for the active coenzyme form (methylcobalamin) instead of the precursor, at a strength chosen for your deficiency severity (1,000 ug for routine maintenance, 5,000 ug for aggressive replacement, ultra-high-dose regimens studied in Japanese ALS trials at 25 to 50 mg twice weekly), by the route that fits your situation (subcutaneous self-injection at home, intramuscular in a clinic, or sublingual tablets for patients who cannot tolerate needles), in a preservative-free, allergen-free preparation if you have a documented excipient sensitivity. The same molecule the body uses inside the cell, prepared for the patient holding the prescription.

This is the older arrangement: a doctor writes the prescription, a pharmacist prepares it for the named patient, and the work is logged. Modern state inspection and USP-grade sourcing keep it honest.

Quick Facts About Methylcobalamin (B12)

Category: Active coenzyme form of vitamin B12 (cobalamin)

Common aliases: Mecobalamin, methyl-B12, MeCbl

Endogenous role: Cofactor for cytosolic methionine synthase; converts homocysteine to methionine and regenerates tetrahydrofolate for one-carbon metabolism

Routes used in 503A compounding: Subcutaneous and intramuscular injection; sublingual tablets and troches

FDA-approval status: No FDA-approved standalone methylcobalamin drug product is marketed in the United States. Cyanocobalamin is the FDA-approved generic injectable B12 form; hydroxocobalamin is FDA-approved as a cyanide antidote (Cyanokit) and as an intramuscular B12 replacement. Methylcobalamin is approved as a prescription drug in Japan and several other jurisdictions.

Compounded under: 503A, patient-specific prescription only

Evidence posture: B12 deficiency replacement (oral/IM cyanocobalamin or hydroxocobalamin) is well established; methylcobalamin-specific comparative pharmacology and clinical-outcome trials are more limited and concentrated in diabetic peripheral neuropathy and amyotrophic lateral sclerosis.

Important compounding caution: Methylcobalamin and cyanocobalamin are not interchangeable on a microgram-for-microgram basis without clinical justification. Compounded sublingual tablets and sterile injections must be prepared from USP-grade active pharmaceutical ingredient under USP <795> and <797> with documented stability and beyond-use dating.

> **SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY**
>
> Methylcobalamin (B12) 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 Methylcobalamin (B12)?

Methylcobalamin is a naturally occurring coenzyme form of vitamin B12 in which a methyl group occupies the upper axial coordination position of the central cobalt atom of the corrin ring [stabler2013]. Structurally, it is one of the four cobalamin forms encountered in pharmacology: cyanocobalamin (a synthetic stable form with a cyano group, used as the standard supplement and injectable), hydroxocobalamin (a hydroxyl group, used in cyanide poisoning and as long-acting IM B12),

methylcobalamin (a methyl group, the cytosolic active coenzyme), and adenosylcobalamin (a 5'-deoxyadenosyl group, the mitochondrial active coenzyme) [green2017].

Inside human cells, any administered cobalamin precursor is processed through the cytoplasmic protein MMACHC (CblC) which dealkylates or decyanates the upper axial ligand, generating a common cob(II)alamin intermediate [stabler2013]. That intermediate is then partitioned into the two coenzyme forms, methylcobalamin in the cytosol for methionine synthase and adenosylcobalamin in mitochondria for methylmalonyl-CoA mutase. This intracellular processing means that, in the absence of an inborn error of cobalamin metabolism (e.g., cblC, cblD, cblE, cblG disease), all four cobalamin forms can serve as B12 replacement [green2017].

In 503A compounding, methylcobalamin is supplied as a USP-grade active pharmaceutical ingredient and prepared as sublingual tablets (typical strengths 1,000, 5,000 µg) or as sterile injectable solutions for subcutaneous or intramuscular administration (typical strengths 1,000, 5,000 µg per mL) [usp_795; usp_797]. Methylcobalamin is photosensitive; finished preparations are stored protected from light.

How Methylcobalamin (B12) Works

Methylcobalamin functions as the direct cofactor for cytosolic methionine synthase [stabler2013]. The enzyme transfers a methyl group from 5-methyltetrahydrofolate to homocysteine, regenerating methionine and tetrahydrofolate. Methionine is then activated to S-adenosylmethionine (SAM), the universal methyl donor for DNA, RNA, protein, phospholipid, and neurotransmitter methylation reactions.

Adequate cellular methylcobalamin is required to keep this reaction running. When intracellular B12 is deficient, methionine synthase activity falls, homocysteine accumulates, 5-methyltetrahydrofolate accumulates because the folate one-carbon pool cannot be unloaded (the 'folate trap'), and SAM-dependent methylation reactions become substrate-limited [green2017, reynolds2006]. Methylmalonic acid also accumulates because the parallel adenosylcobalamin-dependent reaction in mitochondria is similarly affected. Elevated serum homocysteine and methylmalonic acid are the two metabolic biomarkers that confirm functional B12 deficiency at the cellular level [stabler2013].

Biological Role of Methylcobalamin (B12)

Vitamin B12 supports two essential enzymatic reactions in human cells. In the cytosol, methionine synthase uses methylcobalamin to transfer a methyl group from 5-methyltetrahydrofolate to homocysteine, regenerating methionine and tetrahydrofolate. In mitochondria, methylmalonyl-CoA mutase uses adenosylcobalamin to isomerize methylmalonyl-CoA to succinyl-CoA in the catabolism of branched-chain amino acids, odd-chain fatty acids, and cholesterol [green2017].

Both reactions matter for the central nervous system and the hematopoietic system. The methionine synthase reaction is the obligatory exit for the methylfolate pool, without it, the folate one-carbon machinery cannot supply methyl groups to SAM-dependent reactions, including phospholipid and myelin basic protein methylation. The methylmalonyl-CoA mutase reaction prevents accumulation of methylmalonyl-CoA and propionyl-CoA, which interfere with normal fatty-acid incorporation into myelin lipids. Functional B12 deficiency therefore causes the parallel clinical phenotype of megaloblastic anemia plus subacute combined degeneration of the spinal cord and peripheral neuropathy [reynolds2006, stabler2013].

Among the four cobalamin forms encountered in pharmacology, methylcobalamin is the upper-axial-ligand form that the body uses in the cytosolic reaction. After cellular uptake and processing through MMACHC and downstream enzymes, methylcobalamin is regenerated from any cobalamin precursor, methylcobalamin itself, adenosylcobalamin, cyanocobalamin, or hydroxocobalamin. The clinical implication is that, in patients without an inborn error of cobalamin metabolism, all four forms are functionally interconvertible at the cellular level [green2017].

Detailed Mechanism of Methylcobalamin (B12)

Cellular cobalamin metabolism has been mapped in detail through inborn errors of metabolism (cblA through cblJ) and their corresponding gene products [reynolds2006]. After receptor-mediated endocytosis of the transcobalamin-cobalamin complex, lysosomal release delivers cobalamin to the cytoplasm, where MMACHC (CblC) processes any upper-axial ligand (methyl, adenosyl, cyano, hydroxo) into a common cob(II)alamin pool [green2017]. Cob(II)alamin is then partitioned between cytosol, where methionine synthase (MTR, the CblG protein) uses methylcobalamin as cofactor with methionine synthase reductase (MTRR, CblE) as the activating partner, and mitochondria, where adenosylcobalamin is generated for methylmalonyl-CoA mutase. Patients with cblC disease (MMACHC mutations) are functionally deficient in both coenzyme forms despite normal serum B12 and respond preferentially to hydroxocobalamin, illustrating that all extracellular cobalamin forms converge on the same intracellular processing.

The methionine synthase reaction (homocysteine + 5-methyl-THF → methionine + THF) is the obligatory exit pathway for the methylfolate one-carbon pool. The methylenetetrahydrofolate reductase (MTHFR) enzyme, upstream of methionine synthase, is the rate-limiting step that commits one-carbon units to methylation. The MTHFR C677T polymorphism (Ala222Val, rs1801133) produces a thermolabile enzyme with reduced specific activity; homozygotes (TT genotype) have approximately 30% residual activity and demonstrate higher plasma homocysteine and lower red-cell folate than CC homozygotes [frosst1995]. Whether MTHFR genotype meaningfully alters cellular response to cyanocobalamin vs methylcobalamin replacement at population scale is not established by randomized comparative trials; the methylcobalamin preference in MTHFR variant carriers in clinical practice is mechanistic and individualized [stabler2013].

Excess folate intake in the absence of adequate B12 status has been hypothesized to mask cobalamin deficiency biochemically and possibly accelerate neurological decline, particularly in older adults with low B12 status; this interaction was reviewed by Paul and Selhub (2017) in the context of mandatory folic acid fortification [paul_selhub2017] [reynolds2006]. The interaction supports a one-carbon-balanced rather than folate-alone approach in patients with functional B12 deficiency.

Methylcobalamin (B12) Research History

Vitamin B12 was isolated from liver in 1948 and the structure (the largest non-polymeric natural product known at the time) was solved by Dorothy Hodgkin in 1956. The clinical syndrome of pernicious anemia, characterized by macrocytic anemia plus subacute combined degeneration of the spinal cord, had been described in the 19th century; the autoimmune pathophysiology, antibodies against parietal-cell H+/K+-ATPase and against intrinsic factor, was clarified in the 20th century and is reviewed in Toh, van Driel, and Gleeson (1997) [toh1997]. Carmel (2005) reviewed the limitations and contemporary use of serum cobalamin testing [carmel2005].

Cyanocobalamin became the dominant pharmaceutical form because it is the most chemically stable cobalamin. Hydroxocobalamin was developed for clinical use in the 1960s and has a longer plasma half-life than cyanocobalamin; it is also FDA-approved at 5 g intravenously as a cyanide antidote (Cyanokit). Methylcobalamin became commercially available as a prescription drug in Japan and was studied through the 1980s and 1990s in randomized trials in diabetic peripheral neuropathy, Yaqub, Siddique, and Sulimani (1992) reported a placebo-controlled trial in adults with diabetic neuropathy [yaqub1992], and in Bell's palsy, Jalaludin (1995) reported a comparative trial of methylcobalamin vs steroid therapy [jalaludin1995].

Subsequent research has clarified the comparative pharmacology of B12 replacement: Cochrane review by Vidal-Alaball et al. (2005) found that high-dose oral cyanocobalamin (1,000, 2,000 µg daily) is non-inferior to intramuscular cyanocobalamin for most causes of B12 deficiency [vidal2005]; Sharabi et al. (2003) reported equivalence of sublingual and oral cyanocobalamin in adults with B12 deficiency [sharabi2003]; Castelli et al. (2011) compared a daily oral B12 formulation with intermittent IM cyanocobalamin and reported comparable normalization of low cobalamin levels [castelli2011]. The British Society for Haematology guideline (Devalia, Hamilton, and Molloy, 2014) consolidates the evidence base for diagnosis and treatment of cobalamin and folate disorders [devalia2014]. Mayo Clinic Proceedings review by Wolffenbuttel et al. (2019) catalogs the heterogeneity of presentation in cobalamin deficiency [wolffenbuttel2019].

The largest dedicated methylcobalamin clinical-outcome program is in amyotrophic lateral sclerosis. Kaji et al. (2019) reported a long-term phase II/III randomized controlled trial of ultra-high-dose methylcobalamin (25 mg or 50 mg IM twice weekly) in adults with ALS [kaji2019]. Oki et al. (2022) published the phase III randomized clinical trial in early-stage ALS (JAMA Neurology), reporting that ultrahigh-dose methylcobalamin slowed ALSFRS-R decline at 16 weeks in patients enrolled within one year

of symptom onset [oki2022]. Kaji et al. (2026) reported the open-label extension safety data [kaji2026]. The metformin, B12 deficiency association was characterized in Pflipsen et al. (2009) [pflipsen2009] and meta-analytically confirmed by Niafar et al. (2015) [niafar2015] and Pratama et al. (2022) [pratama2022]. Frosst et al. (1995) identified the MTHFR C677T polymorphism that has motivated clinical preference for the methylated form of B12 in some practice settings [frosst1995].

Methylcobalamin (B12) Timeline

1948 • Vitamin B12 isolated from liver extract by Rickes (Merck) and Smith (Glaxo); structural work continued through the 1950s

1956 • Dorothy Hodgkin and colleagues solve the crystal structure of cyanocobalamin

1992 • Yaqub, Siddique, Sulimani, randomized placebo-controlled trial of methylcobalamin in diabetic neuropathy [yaqub1992]

1995 • Frosst et al [frosst1995]. (Nature Genetics) identify the MTHFR C677T thermolabile variant, common genetic determinant of homocysteine and folate-pool partitioning

1995 • Jalaludin, methylcobalamin treatment of Bell palsy compared with steroid [jalaludin1995]

1997 • Toh, van Driel, Gleeson (NEJM), pernicious anemia review consolidates the autoimmune gastritis pathophysiology [toh1997]

2003 • Sharabi et al [sharabi2003]. (Br J Clin Pharmacol), sublingual vs oral cyanocobalamin replacement: equivalent normalization of B12 status

2004 • Andrès et al [andres2004]. (CMAJ), review of vitamin B12 deficiency in elderly patients, including food-cobalamin malabsorption

2005 • Carmel (Blood), critical review of contemporary cobalamin testing [carmel2005]

2005 • Vidal-Alaball et al [vidal2005]. (Cochrane), oral cyanocobalamin 1,000, 2,000 µg daily non-inferior to IM cyanocobalamin for most causes of B12 deficiency

2006 • Reynolds (Lancet Neurology), vitamin B12, folic acid, and the nervous system [reynolds2006]

2009 • Pflipsen et al [pflipsen2009]. (J Am Board Fam Med), prevalence of B12 deficiency in adults with type 2 diabetes; metformin association

2011 • Castelli et al [castelli2011]. (Clin Ther), randomized comparison of a daily oral B12 formulation with intermittent IM cyanocobalamin

2013 • Stabler (NEJM Clinical Practice), vitamin B12 deficiency diagnosis and management [stabler2013]

2014 • Devalia, Hamilton, Molloy (BJH), BCSH guidelines for diagnosis and treatment of cobalamin and folate disorders [devalia2014]

2015 • Niafar et al [niafar2015]. (Intern Emerg Med), meta-analysis of metformin-induced vitamin B12 deficiency

2017 • Green et al [green2017]. (Nature Reviews Disease Primers), comprehensive review of vitamin B12 deficiency

2017 • Paul and Selhub (Mol Aspects Med), interaction between excess folate and low B12 status in the post-fortification era [paul_selhub2017]

2018 • Andrès et al [andres2018]. (J Clin Med), systematic review and pragmatic clinical approach to oral and nasal B12 in GI disorders

2019 • Kaji et al [kaji2019]. (JNNP), long-term phase II/III randomized trial of ultra-high-dose methylcobalamin in ALS

2019 • Wolffenbuttel et al [wolffenbuttel2019]. (Mayo Clin Proc Innov Qual Outcomes), many faces of cobalamin deficiency

2021 • Kaur et al [kaur2021]. (Indian J Pharmacol), randomized comparative trial of methylcobalamin, methylcobalamin + pregabalin, and methylcobalamin + duloxetine in diabetic neuropathy

2022 • Oki et al [oki2022]. (JAMA Neurology), phase III randomized trial of ultrahigh-dose methylcobalamin in early-stage ALS

2022 • Pratama et al [pratama2022]. (Diabetes Metab Syndr), systematic review of B12 supplementation for metformin-induced deficiency and peripheral neuropathy in T2DM

2024 • Ran et al [ran2024]. (J Diabetes Complications), systematic review and meta-analysis of disease-modifying therapies for diabetic peripheral neuropathy

2025 • Deng et al [deng2025]. (Front Endocrinol), meta-analysis of dapagliflozin combined with methylcobalamin for diabetic peripheral neuropathy

2026 • Kaji et al [kaji2026]. (J Neurol Sci), open-label extension of the ultra-high-dose methylcobalamin phase 2/3 ALS study; long-term safety data

Clinical Contexts for Methylcobalamin (B12)

Vitamin B12 deficiency replacement (any cause) WELL STUDIED

Well-studied indication for B12 replacement therapy. Standard FDA-approved replacement is cyanocobalamin or hydroxocobalamin; methylcobalamin is one of several active-form alternatives used under 503A on patient-specific clinical justification.

B12 replacement is the well-established indication. Cochrane review by Vidal-Alaball et al. (2005) found that high-dose oral cyanocobalamin (1,000, 2,000 µg daily) is non-inferior to IM cyanocobalamin for most causes of B12 deficiency [vidal2005]. Sharabi et al. (2003) reported equivalence of sublingual and oral cyanocobalamin in adults with B12 deficiency [sharabi2003]. Castelli et al. (2011) reported comparable normalization of low cobalamin levels with a daily oral formulation vs intermittent IM cyanocobalamin [castelli2011]. Andrès et al. (2018) provided a pragmatic systematic-review-based clinical approach for oral and nasal B12 in patients with GI disorders [andres2018]. Methylcobalamin is one of several cobalamin forms used in replacement therapy; the choice between cyanocobalamin, hydroxocobalamin, and methylcobalamin in a non-deficiency-specific patient is generally clinician preference and patient-specific factors rather than population-level outcome data. Devalia et al. (2014) BCSH guidelines describe diagnosis and replacement [devalia2014]; Green et al. (2017) and Stabler (2013) review the broader clinical landscape [green2017, stabler2013].

Autoimmune pernicious anemia WELL STUDIED

Well-studied indication for parenteral B12 replacement. Methylcobalamin is one of several parenteral cobalamin options.

Pernicious anemia is the classical autoimmune cause of B12 deficiency, characterized by parietal-cell H+/K+-ATPase and intrinsic-factor antibodies, atrophic gastritis, and intrinsic-factor-dependent ileal cobalamin malabsorption [toh1997, carmel2005]. The standard of care is lifelong parenteral B12 replacement (cyanocobalamin or hydroxocobalamin IM); the BCSH guidelines describe loading and maintenance regimens [devalia2014]. High-dose oral cyanocobalamin (1,000, 2,000 µg daily) is non-inferior to IM in most cases because passive intestinal absorption (~1%) is independent of intrinsic factor [vidal2005, castelli2011]. Compounded methylcobalamin SC or IM injection may be used on patient-specific clinical justification.

Food-cobalamin malabsorption (older adults, atrophic gastritis, PPI/H2 blocker use)

WELL STUDIED

Well-studied indication. Compounded methylcobalamin sublingual or injectable may substitute for FDA-approved cyanocobalamin where clinically justified.

Food-cobalamin malabsorption is the inability to release protein-bound dietary B12 in the stomach despite intact intrinsic-factor function. It is common in older adults with atrophic gastritis or proton-pump inhibitor or H2 blocker use, and accounts for the majority of B12 deficiency in adults over 65 [andres2004, wolffenbuttel2019, andres2018]. Free crystalline B12 (any form) is absorbed normally because it does not require gastric protein release; high-dose oral cyanocobalamin or sublingual cobalamin is generally adequate replacement [stabler2013].

Metformin-associated B12 deficiency in type 2 diabetes WELL STUDIED

Well-studied indication for B12 replacement; methylcobalamin is one option.

Long-term metformin use is associated with vitamin B12 deficiency through reduced ileal calcium-dependent absorption of the intrinsic-factor, B12 complex. Pflipsen et al. (2009) reported a 22% prevalence of B12 deficiency in adults with type 2 diabetes [pflipsen2009]. Meta-analysis by Niafar et al. (2015) confirmed a clinically meaningful pooled effect on serum B12 with metformin exposure [niafar2015]. Pratama et al. (2022) systematically reviewed B12 supplementation for metformin-induced deficiency and peripheral neuropathy in T2DM and supports routine replacement when deficiency is documented [pratama2022]. Replacement form (cyanocobalamin, methylcobalamin, or hydroxocobalamin) is generally clinician preference; methylcobalamin sublingual or SC injection is dispensed under 503A on patient-specific justification.

Diabetic peripheral neuropathy WELL STUDIED

Studied in randomized trials of methylcobalamin specifically; evidence base is modest and heterogeneous. Not an FDA-approved indication for any cobalamin form.

Methylcobalamin has been studied in diabetic peripheral neuropathy in multiple small randomized trials, including the early Yaqub, Siddique, and Sulimani (1992) placebo-controlled trial in adults with diabetic neuropathy [yaqub1992]. Kaur et al. (2021) reported a randomized comparative trial of methylcobalamin alone, methylcobalamin + pregabalin, and methylcobalamin + duloxetine in patients with diabetic neuropathy [kaur2021]. The recent meta-analysis by Ran et al. (2024) of disease-modifying therapies for diabetic peripheral neuropathy includes methylcobalamin among the agents reviewed [ran2024]. Deng et al. (2025) meta-analyzed dapagliflozin combined with methylcobalamin for T2DM with peripheral neuropathy [deng2025]. The clinical signal favors symptom improvement; effect sizes vary across trials and the field has not converged on a definitive recommendation.

Bell palsy EMERGING

Studied in older comparative trials; evidence base is limited and the standard-of-care is corticosteroid therapy. Not an FDA-approved indication.

Jalaludin (1995) reported a comparative trial of methylcobalamin vs steroid therapy and vs combination methylcobalamin + steroid in adults with Bell palsy [jalaludin1995]. The reported recovery times were shorter with methylcobalamin-containing arms than steroid alone. The trial was small and not blinded; modern Bell palsy management is centered on early corticosteroid therapy. Methylcobalamin in Bell palsy is best characterized as historical evidence of biological plausibility rather than a contemporary standard.

Amyotrophic lateral sclerosis (ALS), early-stage WELL STUDIED

Studied in dedicated Japanese phase II/III and phase III randomized trials of ultra-high-dose methylcobalamin; not an FDA-approved indication in the United States.

Kaji et al. (2019) reported a long-term phase II/III randomized double-blind placebo-controlled trial of ultra-high-dose methylcobalamin (25 mg or 50 mg IM twice weekly) in adults with ALS; the primary endpoint did not differ overall but a pre-specified early-treatment subgroup analysis suggested benefit [kaji2019]. Oki et al. (2022) reported the dedicated phase III randomized clinical trial in early-stage ALS (within 1 year of symptom onset), methylcobalamin 50 mg IM twice weekly slowed ALSFRS-R decline relative to placebo at 16 weeks [oki2022]. Kaji et al. (2026) reported the open-label extension safety data with no new safety signals at long-term follow-up [kaji2026]. Methylcobalamin is registered for ALS in Japan based on this evidence; it is not FDA-approved for ALS in the United States. Compounded methylcobalamin under 503A is not a substitute for an approved ALS therapy and is dispensed only on a patient-specific prescription with documented clinical rationale.

Hyperhomocysteinemia in patients with MTHFR C677T polymorphism EMERGING

Emerging individualized rationale for the methylated B12 form; not a labeled indication. Population-level randomized comparisons of methylcobalamin vs cyanocobalamin on clinical outcomes in MTHFR variant carriers are lacking.

Frosst et al. (1995) identified the MTHFR C677T polymorphism (rs1801133, Ala222Val) as a common thermolabile variant that produces reduced methylenetetrahydrofolate reductase activity, elevated plasma homocysteine, and altered folate one-carbon partitioning, especially in homozygotes (TT genotype) [frosst1995]. A clinical rationale for preferring the methylated B12 form in patients with documented MTHFR C677T homozygosity is that downstream methionine synthase has direct access to methylcobalamin without an additional remethylation step. Paul and Selhub (2017) reviewed the interaction between excess folate and low B12 status that is relevant to one-carbon-balanced replacement strategies in this group [paul_selhub2017]. Direct randomized comparisons of methylcobalamin vs cyanocobalamin on clinical outcomes (cardiovascular events, cognitive trajectories, neuropathy) in MTHFR variant carriers are not available; the methylcobalamin-preference rationale is mechanistic and individualized rather than evidence-based at population scale.

Off-Label Uses of Methylcobalamin (B12)

Cognitive and neurodegenerative conditions in older adults with low B12 status EMERGING

Emerging and heterogeneous evidence; not an FDA-approved indication. Routine B12 supplementation for cognitive protection in B12-replete older adults is not supported.

B12 status is associated with cognitive trajectory in older adults at the epidemiologic level, and homocysteine-lowering with B-vitamin combinations has been studied in mild cognitive impairment and Alzheimer's disease populations with mixed results. The methylated form of B12 is sometimes preferred mechanistically in this context but is not evidence-supported as superior to cyanocobalamin on cognitive outcomes [green2017, reynolds2006, paul_selhub2017].

Compounded Methylcobalamin (B12) (503A)

Methylcobalamin is dispensed under 503A only on a patient-specific prescription written by a licensed doctor for an identified patient [fda503a]. RonanRx does not sell methylcobalamin directly to patients and does not maintain a direct-to-consumer storefront.

Methylcobalamin compounding is generally framed as 'essentially-a-copy' relative to FDA-approved cyanocobalamin injection and oral cyanocobalamin tablets, the standard FDA-approved cobalamin products [fda503a] [devalia2014]. Hydroxocobalamin injection is also FDA-approved (as IM B12 replacement and, separately, as the IV cyanide antidote Cyanokit). Under section 503A and FDA guidance on compounded copies, a methylcobalamin preparation is dispensed only when the prescriber documents a patient-specific clinical reason that the manufactured cyanocobalamin or hydroxocobalamin product is not appropriate. Typical documented reasons fall into a small number of categories: (1) excipient sensitivity to a component of the manufactured product; (2) a documented MTHFR C677T homozygosity with a clinician decision to prefer the methylated cobalamin form on individualized metabolic grounds [frosst1995]; (3) a specific dose strength or sublingual dosage form not commercially available; (4) an allergen-free formulation requirement (preservative-free, dye-free, lactose-free) the manufactured product does not satisfy [sharabi2003; castelli2011].

Compounded methylcobalamin under 503A is not bioequivalent to FDA-approved cyanocobalamin or hydroxocobalamin. The compounded preparation does not have an FDA-reviewed efficacy or safety dossier; clinical outcomes are extrapolated from B12-replacement evidence generated mostly with cyanocobalamin and hydroxocobalamin together with methylcobalamin-specific evidence in diabetic peripheral neuropathy [yaqub1992, ran2024, deng2025] and amyotrophic lateral sclerosis [kaji2019, oki2022, kaji2026]. Compounded preparations are documented per USP <795> for nonsterile sublingual tablets and USP

<797> for sterile injectables, with finished-product stability and beyond-use dating per the pharmacy's quality management system [usp_795; usp_797].

The clinical case for an individualized methylcobalamin preference, especially in patients with documented MTHFR polymorphism, in patients with metformin-associated B12 deficiency for whom an active-form rationale is presented, or in patients with idiosyncratic excipient sensitivity to manufactured cyanocobalamin, is mechanistic and patient-specific rather than population-level outcome data [vidal2005]. RonanRx's role in 503A is to prepare a documented, sterile, traceable methylcobalamin preparation when the prescriber documents that rationale; it is not to advocate the methylated form as clinically superior to the FDA-approved generics on the basis of head-to-head outcome trials, because those trials do not exist [usp_797].

Methylcobalamin (B12) Formulations and Routes

Form	Concentration	Description
Sublingual tablet (compounded)	Custom, commonly 1,000 µg, 2,500 µg, or 5,000 µg per tablet	Nonsterile sublingual tablet prepared under USP General Chapter <795> for nonsterile pharmaceutical compounding. Tablets are dye-free and allergen-restricted on request. Sublingual administration bypasses gastric intrinsic-factor-dependent absorption.
Sterile subcutaneous or intramuscular injection (compounded)	Custom, commonly 1,000 µg/mL, 5,000 µg/mL, or 10,000 µg/mL	Sterile aqueous solution prepared under USP General Chapter <797> for sterile pharmaceutical compounding. Single-dose or limited-use multi-dose vials with documented stability and beyond-use dating. Light-protected during preparation, storage, and dispensing because methylcobalamin is photosensitive.
FDA-approved cyanocobalamin injection (comparator)	1,000 µg/mL multi-dose vial (and 100 µg/mL pediatric strength)	Generic cyanocobalamin injection is the standard FDA-approved parenteral B12 product in the United States. Used for treatment of B12 deficiency from pernicious anemia, food-cobalamin malabsorption, dietary restriction, gastric or ileal surgery, and other causes.
FDA-approved hydroxocobalamin injection (comparator)	1,000 µg/mL (IM B12 replacement) or 5 g/200 mL (Cyanokit, IV cyanide antidote)	Hydroxocobalamin is FDA-approved as IM B12 replacement (longer plasma half-life than cyanocobalamin) and at 5 g IV as the cyanide antidote Cyanokit.

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

Methylcobalamin (B12) Dosing

Route	Population	Range	Duration	Study type
Sublingual	Adults, B12 maintenance after deficiency replacement, or active-form supplementation on prescriber preference	1,000, 5,000 µg once daily	Indefinite while clinically indicated	Extrapolated from sublingual cyanocobalamin equivalence to oral cyanocobalamin
Subcutaneous	Adults, B12 deficiency replacement (loading and maintenance)	1,000 µg SC once weekly for 4, 8 weeks (loading), then 1,000 µg SC every 1, 3 months (maintenance). Higher individualized maintenance regimens at prescriber discretion.	Indefinite for autoimmune pernicious anemia and other irreversible causes	Extrapolated from BCSH cyanocobalamin/ hydroxocobalamin replacement regimens
Intramuscular	Adults, ALS (Japanese phase III regimen, ultra-high-dose investigational)	50 mg IM twice weekly (ultra-high-dose investigational regimen)	16-week primary endpoint in Oki 2022; longer-term in the open-label extension	Phase III randomized trial (Oki 2022); not an FDA-approved regimen in the United States
Oral	Adults, B12 deficiency replacement when high-dose oral is appropriate (food-cobalamin malabsorption, dietary restriction, vegan or vegetarian diet)	1,000, 2,000 µg once daily	Indefinite while clinically indicated	Extrapolated from oral cyanocobalamin trials

Methylcobalamin doses for B12 replacement parallel cyanocobalamin and hydroxocobalamin dosing rather than being established through independent dose-finding trials. Loading-and-maintenance regimens used in clinical practice are extrapolated from the BCSH cyanocobalamin guidelines [devalia2014] and review literature [stabler2013, green2017]. Ultra-high-dose IM methylcobalamin regimens (25, 50 mg twice weekly) used in the ALS literature [kaji2019, oki2022] are investigational and population-specific; they are not appropriate for B12 replacement.

Sublingual methylcobalamin (1,000, 5,000 µg daily) is convenient for patients with food-cobalamin malabsorption or intrinsic-factor-deficient absorption because it bypasses the gastric proteolytic step. The

Sharabi (2003) trial of sublingual vs oral cyanocobalamin found equivalent normalization of B12 status, supporting sublingual as a reasonable alternative to high-dose oral when patient preference favors it [sharabi2003].

Methylcobalamin (B12) Safety

Methylcobalamin has a wide therapeutic index. B12 in any form is water-soluble and excreted renally; oral, sublingual, and parenteral doses at the ranges used for replacement (1,000, 5,000 µg) have not been associated with dose-dependent toxicity in healthy adults [12]. Ultra-high-dose IM methylcobalamin (25, 50 mg twice weekly) used in the ALS literature was reported as well tolerated through 16 weeks of treatment and through long-term open-label follow-up, with no new safety signals at the long-term timepoint [131415].

Hypersensitivity reactions to injectable cobalamin preparations have been reported with all parenteral cobalamin forms (cyanocobalamin, hydroxocobalamin, and methylcobalamin) and are generally attributed to excipients or cross-reactivity rather than to the cobalamin moiety itself. Patients with documented allergy to one cobalamin form should be evaluated for cross-reactivity before switching to another form. Injection-site reactions (erythema, mild pain) are common and typically self-limited.

Acne or acneiform rashes have been reported with high-dose B12 supplementation, attributed to alteration of skin microbial metabolism rather than direct toxicity. Pseudo-tumor cerebri has been rarely reported with high-dose oral B12 supplementation; the causal relationship is not established. Polycythemia and thrombocytosis on B12 replacement reflect normalization of marrow function in previously deficient patients rather than a toxic effect. Patients with unrecognized severe folate deficiency may experience hypokalemia during the recovery from megaloblastic anemia after B12 replacement; potassium should be monitored in patients with severe macrocytic anemia at the start of replacement therapy [8].

Methylcobalamin is photosensitive, finished preparations must be stored protected from light to prevent degradation and the corresponding loss of potency.

Contraindications

Methylcobalamin is contraindicated in patients with a known hypersensitivity to cobalamin or to an excipient in the specific preparation [8]. Hereditary optic nerve atrophy (Leber optic atrophy) is a labeled contraindication for cyanocobalamin in some jurisdictions because of concern that cyanide release in the optic nerve may aggravate the lesion; in this specific group, hydroxocobalamin or methylcobalamin is preferred over cyanocobalamin.

Methylcobalamin is not contraindicated in pregnancy or lactation at replacement doses; B12 deficiency in pregnancy is itself associated with poor outcomes and replacement is indicated when deficiency is documented [1].

Drug interactions

Vitamin B12 has limited pharmacokinetic drug interactions. Long-term metformin use reduces ileal calcium-dependent absorption of the intrinsic-factor, B12 complex and is associated with measurable B12 deficiency in adults with type 2 diabetes [2][12][20][22]. Proton-pump inhibitors and H2 receptor antagonists reduce gastric acid and pepsin activity and contribute to food-cobalamin malabsorption (impaired release of protein-bound dietary B12) but do not affect absorption of free crystalline cobalamin in supplements or sublingual or parenteral preparations [4][19].

Recreational nitrous oxide (N2O) inhalation irreversibly oxidizes the cobalt center of intracellular cobalamin and produces a functional B12 deficiency state with megaloblastic anemia, myeloneuropathy, and subacute combined degeneration of the spinal cord. Patients with N2O exposure require parenteral B12 replacement; methylcobalamin, hydroxocobalamin, and cyanocobalamin have all been used in this context [1][3].

Co-administered folate corrects megaloblastic anemia but does not correct the neurologic component of B12 deficiency; serum B12 should be evaluated and replaced before initiating high-dose folate supplementation in patients with megaloblastic anemia of unclear cause [8][9].

Adverse events

Reported adverse events with methylcobalamin at B12 replacement doses are uncommon and generally mild [1]. Injection-site reactions (erythema, transient pain) are the most frequent. Hypersensitivity reactions including urticaria, pruritus, and rare anaphylaxis have been reported with all parenteral cobalamin forms; cross-reactivity between forms is variable and patients with reactions to one form should be carefully evaluated before substitution.

Headache, dizziness, and nausea have been reported sporadically but are not consistent dose-related findings. Acneiform eruption has been associated with high-dose B12 supplementation in case reports. In the ultra-high-dose IM methylcobalamin ALS program (25, 50 mg twice weekly), Kaji et al. (2019) and Oki et al. (2022) reported tolerability comparable to placebo over 12, 16 weeks of treatment, and the open-label extension reported no new safety signals at longer follow-up [13][14][15] [1].

Monitoring Methylcobalamin (B12) Therapy

Baseline assessment before starting B12 replacement should include serum B12, complete blood count with red-cell indices, and (when functional deficiency is suspected with a low-normal B12) methylmalonic acid and homocysteine. Folate status should be assessed in parallel because isolated folate replacement can mask B12 deficiency and accelerate its neurologic manifestations [carmel2005, devalia2014, paul_selhub2017] [stabler2013].

On replacement therapy: serum B12 should normalize within weeks of parenteral or high-dose oral therapy; macrocytic anemia resolves over 4, 8 weeks; neurologic recovery is variable and may be incomplete in long-

standing deficiency [stabler2013]. Methylmalonic acid and homocysteine return to normal range with adequate replacement. Re-evaluation at 3 and 6 months and annually thereafter is reasonable for patients on indefinite replacement [devalia2014].

Methylcobalamin (B12) in Special Populations

Methylcobalamin (B12) Evidence Quality

The evidence base for vitamin B12 replacement is well established across populations and routes. Multiple randomized comparisons of oral vs IM cyanocobalamin [vidal2005, castelli2011] and of sublingual vs oral cyanocobalamin [sharabi2003] support high-dose oral and sublingual replacement for most causes other than acute neurological deficiency. Guideline-level consolidation is provided by Devalia, Hamilton, and Molloy (2014) [devalia2014] and review-level synthesis by Green et al. (2017) [green2017], Stabler (2013) [stabler2013], Reynolds (2006) [reynolds2006], Andrès (2004, 2018) [andres2004, andres2018], and Wolffenbuttel (2019) [wolffenbuttel2019]. Pernicious anemia pathophysiology is reviewed by Toh, van Driel, and Gleeson (1997) [toh1997] and Carmel (2005) [carmel2005]. Metformin-associated B12 deficiency is meta-analytically established [niafar2015, pratama2022, pflipsen2009]. The MTHFR C677T polymorphism that motivates the methylated-form preference in some practice settings is identified in Frosst et al. (1995) [frosst1995] with the broader one-carbon interaction reviewed by Paul and Selhub (2017) [paul_selhub2017].

Methylcobalamin-specific clinical-outcome trials are concentrated in two areas. Diabetic peripheral neuropathy: Yaqub, Siddique, and Sulimani (1992) [yaqub1992] and Kaur et al. (2021) [kaur2021] reported small randomized trials, and meta-analyses by Ran et al. (2024) and Deng et al. (2025) consolidate the diabetic-neuropathy evidence including methylcobalamin-containing regimens [ran2024, deng2025]. Amyotrophic lateral sclerosis: Kaji et al. (2019) phase II/III [kaji2019], Oki et al. (2022) phase III in early-stage ALS [oki2022], and the Kaji et al. (2026) open-label extension [kaji2026] together comprise a dedicated ultra-high-dose IM methylcobalamin program in ALS that supports the Japanese registration. Bell palsy evidence [jalaludin1995] [jalaludin1995] is older and not contemporary standard-of-care. Direct head-to-head trials of methylcobalamin vs cyanocobalamin on hard clinical outcomes in non-deficient populations are not available, and the methylcobalamin-preference rationale in MTHFR variant carriers, in metformin-associated deficiency, and in cognitive-protection contexts remains mechanistic and individualized rather than evidence-based at population scale.

Major Methylcobalamin (B12) Clinical Studies

Study	Design	Participants	Duration	Finding
Yaqub et al. (1992, Clin Neurol Neurosurg), Methylcobalamin in diabetic neuropathy	Randomized placebo-controlled trial in adults with diabetic peripheral neuropathy	—	—	Methylcobalamin (oral, 500 µg three times daily for 4 months) produced improvement in symptoms and nerve conduction parameters relative to placebo [yaqub1992]
Jalaludin (1995, Methods Find Exp Clin Pharmacol), Methylcobalamin in Bell palsy	Comparative trial of methylcobalamin vs steroid vs combination methylcobalamin + steroid in adults with Bell palsy	—	—	Recovery times were shorter in methylcobalamin-containing arms than steroid alone in this small unblinded trial; not contemporary standard of care [jalaludin1995]
Frosst et al. (1995, Nature Genetics), MTHFR C677T identification	Genetic candidate-gene study identifying a common thermolabile MTHFR variant	—	—	MTHFR C677T (Ala222Val) produces a thermolabile enzyme with ~30% residual activity in TT homozygotes; elevated plasma homocysteine and altered folate one-carbon partitioning. Foundation for the methylated-B12-form rationale in carriers [frosst1995].
Toh, van Driel, Gleeson (1997, NEJM), Pernicious anemia review	Clinical review of the autoimmune pathophysiology of pernicious anemia	—	—	Autoimmune gastritis with parietal-cell H+/K+-ATPase and intrinsic-factor antibodies underlies intrinsic-factor-deficient B12 malabsorption and irreversible deficiency requiring lifelong replacement [toh1997]
Sharabi et al. (2003, Br J Clin Pharmacol), Sublingual vs oral cyanocobalamin	Randomized comparison of sublingual vs oral cyanocobalamin replacement in adults with B12 deficiency	—	—	Sublingual and oral cyanocobalamin produced equivalent normalization of serum B12 over the study period [sharabi2003]

Study	Design	Participants	Duration	Finding
Andrès et al. (2004, CMAJ), B12 deficiency in elderly	Clinical review of vitamin B12 (cobalamin) deficiency in elderly patients	—	—	Food-cobalamin malabsorption is the dominant mechanism of B12 deficiency in older adults; free crystalline B12 (oral or sublingual) is absorbed normally [andres2004]
Carmel (2005, Blood), Cobalamin testing	Editorial/critical review of clinical cobalamin testing	—	—	Reviews the limitations of serum cobalamin assays and the role of methylmalonic acid and homocysteine in confirming functional deficiency [carmel2005]
Vidal-Alaball et al. (2005, Cochrane), Oral vs IM B12	Cochrane systematic review of randomized trials of oral vs intramuscular cyanocobalamin	—	—	Oral cyanocobalamin 1,000, 2,000 µg daily is non-inferior to intramuscular cyanocobalamin for serum B12 normalization in most causes of B12 deficiency [vidal2005]
Reynolds (2006, Lancet Neurology), B12, folate, and the nervous system	Clinical review	—	—	Consolidates the neurology of B12 and folate deficiency including the methylation and folate-trap hypotheses [reynolds2006]
Pflipsen et al. (2009, J Am Board Fam Med), B12 deficiency in T2DM	Cross-sectional study of B12 prevalence in adults with type 2 diabetes	—	—	22% of adults with T2DM had biochemical B12 deficiency; metformin use was a significant predictor [pflipsen2009]
Castelli et al. (2011, Clin Ther), Daily oral B12 vs intermittent IM	Randomized, open-label, parallel-group study of a daily oral B12 formulation vs intermittent IM cyanocobalamin	—	—	Comparable normalization of low cobalamin levels between the daily oral and intermittent IM regimens [castelli2011]
Stabler (2013, NEJM Clinical Practice),	Clinical practice review	—	—	Diagnostic approach using serum B12, methylmalonic acid, and homocysteine;

Study	Design	Participants	Duration	Finding
Vitamin B12 deficiency				treatment regimens for parenteral and oral replacement [stabler2013]
Devalia, Hamilton, Molloy (2014, BJH), BCSH cobalamin and folate guidelines	Society guideline (British Committee for Standards in Haematology)	—	—	Consolidated diagnostic algorithm and replacement regimens for cobalamin and folate disorders [devalia2014]
Niafar et al. (2015, Intern Emerg Med), Metformin and B12 meta-analysis	Meta-analysis of randomized and observational studies of metformin and serum B12	—	—	Metformin exposure is associated with reduced serum B12; risk increases with duration and dose [niafar2015]
Green et al. (2017, Nat Rev Dis Primers), Vitamin B12 deficiency	Comprehensive multidisciplinary review	—	—	Authoritative review of B12 biology, deficiency causes, diagnosis, and management; covers all four cobalamin forms and intracellular processing [green2017]
Paul and Selhub (2017, Mol Aspects Med), Excess folate and low B12	Mechanistic and epidemiologic review	—	—	Reviews the interaction between high folate intake and low B12 status, relevant to one-carbon-balanced replacement strategies [paul_selhub2017]
Andrès et al. (2018, J Clin Med), Oral and nasal B12 in GI disorders	Systematic review with pragmatic clinical approach	—	—	Supports oral and nasal B12 routes for B12 deficiency related to GI disorders in most clinical settings [andres2018]
Wolffenbuttel et al. (2019, Mayo Clin Proc Innov Qual Outcomes), Many faces of cobalamin deficiency	Clinical review	—	—	Catalogs heterogeneous clinical presentations of cobalamin deficiency, emphasizing under-recognition in older adults [wolffenbuttel2019]
Kaji et al. (2019, J Neurol Neurosurg Psychiatry), Ultra-high-dose	Long-term phase II/III randomized double-blind placebo-controlled trial of methylcobalamin 25	—	—	Primary endpoint did not differ overall; pre-specified subgroup analysis in patients enrolled within 1 year of

Study	Design	Participants	Duration	Finding
methylcobalamin in ALS (phase II/III)	mg or 50 mg IM twice weekly in adults with ALS			symptom onset suggested benefit [kaji2019]
Kaur et al. (2021, Indian J Pharmacol), Methylcobalamin combinations in diabetic neuropathy	Randomized comparative trial of methylcobalamin, methylcobalamin + pregabalin, and methylcobalamin + duloxetine in adults with diabetic peripheral neuropathy	—	—	Combination regimens produced larger symptom improvements than methylcobalamin alone; methylcobalamin alone produced measurable symptom benefit [kaur2021]
Oki et al. (2022, JAMA Neurology), Ultrahigh-dose methylcobalamin in early-stage ALS (phase III)	Phase III randomized double-blind placebo-controlled trial in adults with ALS within 1 year of symptom onset	130	16 weeks	Methylcobalamin 50 mg IM twice weekly slowed ALSFRS-R decline relative to placebo at 16 weeks (between-group difference 1.97 points; clinically meaningful) [oki2022]
Pratama et al. (2022, Diabetes Metab Syndr), B12 in metformin-treated T2DM	Systematic review of B12 supplementation for metformin-induced deficiency and peripheral neuropathy in T2DM	—	—	Supports routine B12 replacement in metformin-treated adults with documented deficiency or peripheral neuropathy [pratama2022]
Ran et al. (2024, J Diabetes Complications), Disease-modifying therapies for diabetic peripheral neuropathy	Systematic review and meta-analysis of randomized trials of disease-modifying therapies (including methylcobalamin-containing regimens) for diabetic peripheral neuropathy	—	—	Methylcobalamin is among the agents reviewed; pooled effects on symptoms and nerve conduction are heterogeneous across small trials [ran2024]
Deng et al. (2025, Front Endocrinol), Dapagliflozin + methylcobalamin in DPN	Systematic review and meta-analysis of dapagliflozin combined with methylcobalamin in T2DM with peripheral neuropathy	—	—	Pooled analysis suggested improvement in glycemic and neuropathy endpoints with the combination vs methylcobalamin alone in the included trials [deng2025]

Study	Design	Participants	Duration	Finding
Kaji et al. (2026, J Neurol Sci), Ultra-high-dose methylcobalamin ALS open-label extension	Open-label extension of the phase 2/3 randomized controlled study of methylcobalamin in ALS	—	—	Long-term safety data with no new safety signals at extended follow-up; supports the chronic-administration safety profile of ultra-high-dose IM methylcobalamin [kaji2026]

Methylcobalamin (B12) Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Free crystalline cobalamin in any form is absorbed via two pathways. Intrinsic-factor-mediated ileal absorption is saturable at approximately 1.5, 2 µg per dose; passive intestinal absorption accounts for approximately 1% of an oral dose at any dose and is the basis for the efficacy of high-dose oral cyanocobalamin (1,000, 2,000 µg daily) in intrinsic-factor-deficient pernicious anemia [vidal2005, castelli2011]. Sublingual administration produces measurable serum B12 rises comparable to oral at equivalent doses [sharabi2003], although the proportion absorbed via sublingual mucosa vs subsequent oral absorption is debated.

Once in the circulation, cobalamin binds transcobalamin II (holo-TC), the transport protein that delivers B12 to peripheral tissues; haptocorrin binds the larger fraction in plasma but is not a delivery protein. Cellular uptake is receptor-mediated, followed by lysosomal release and cytoplasmic processing through MMACHC (CblC) to a common cob(II)alamin intermediate that is then partitioned into the two coenzyme forms, methylcobalamin in the cytosol and adenosylcobalamin in the mitochondrion [green2017]. The clinical implication is that, in patients without an inborn error of cobalamin metabolism, the upper-axial ligand on the administered cobalamin is converted intracellularly, and the four cobalamin forms are functionally interconvertible.

Hydroxocobalamin has a longer plasma half-life than cyanocobalamin and binds more tightly to plasma proteins, which is the basis for less-frequent dosing intervals with hydroxocobalamin IM B12 replacement and for its dose advantage as the cyanide antidote (5 g IV in Cyanokit). Methylcobalamin plasma half-life has been studied less systematically; pharmacokinetics differ across cobalamin forms in terms of plasma residence and tissue distribution but the cellular conversion to common intermediates means single-dose PK differences do not necessarily predict differences in long-term replacement efficacy.

Pharmacodynamics

Pharmacodynamic endpoints for B12 replacement are restoration of methionine synthase and methylmalonyl-CoA mutase activity, with corresponding normalization of plasma methylmalonic acid and homocysteine and reversal of megaloblastic anemia. Serum B12 normalizes within days to weeks of

replacement; macrocytic anemia resolves over 4, 8 weeks; methylmalonic acid and homocysteine return to normal range over weeks to months [green2017, stabler2013, devalia2014]. Neurologic recovery is slower and may be incomplete in long-standing deficiency.

Pharmacodynamic comparisons of methylcobalamin vs cyanocobalamin vs hydroxocobalamin in non-deficient adults have not been performed at the scale needed to detect modest population-level differences in cognitive, cardiovascular, or peripheral-nerve endpoints. The active-form preference rationale in clinical practice is mechanistic (direct delivery of the methylated coenzyme form, bypass of intracellular cyanide release from cyanocobalamin) rather than population-PD-validated.

↓↑ Comparing Methylcobalamin (B12) Formulations

Cyanocobalamin injection is the standard FDA-approved parenteral B12 product in the United States; oral cyanocobalamin tablets (and OTC supplements at lower doses) are the standard oral form. Cyanocobalamin is the most chemically stable of the four cobalamin forms and is inexpensive. Concerns about the cyanide moiety are theoretical; the dose of cyanide released from a 1,000 µg cyanocobalamin injection is negligible in patients with normal renal and hepatic function and intact cyanide detoxification.

Hydroxocobalamin injection (typically 1,000 µg/mL) is FDA-approved as a longer-acting IM B12 replacement than cyanocobalamin and at 5 g IV (Cyanokit) as the cyanide antidote of choice for cyanide poisoning including smoke inhalation. Hydroxocobalamin binds more tightly to plasma proteins than cyanocobalamin and has a longer plasma half-life, allowing less-frequent dosing schedules.

Methylcobalamin is the active coenzyme form for cytosolic methionine synthase. There is no FDA-approved standalone methylcobalamin drug product in the United States; methylcobalamin is registered as a prescription drug in Japan and several other markets. In the United States it is supplied under 503A compounding as sublingual tablets and sterile injections at custom strengths and excipient profiles [fda503a]. Adenosylcobalamin (the second coenzyme form, used in mitochondrial methylmalonyl-CoA mutase) is also occasionally compounded but is uncommon outside specific metabolic-disease contexts.

The clinical case for compounded methylcobalamin over the FDA-approved cyanocobalamin generic is patient-specific and clinician-directed: excipient sensitivity, documented MTHFR polymorphism with prescriber preference for the methylated form, allergen-free formulation requirements, or specific dose strengths not commercially available [stabler2013]. Compounded methylcobalamin is not bioequivalent to cyanocobalamin or hydroxocobalamin, and clinical-outcome data are not generated for the compounded product itself [green2017; frosst1995].

Methylcobalamin (B12) Storage and Handling

Methylcobalamin is photosensitive; both finished sublingual tablets and sterile injectable solutions are stored protected from light in their original light-resistant containers. Sublingual tablets are typically stored at controlled room temperature (20, 25°C) per the compounding pharmacy's stability data. Sterile injections are typically refrigerated (2, 8°C) with documented stability per USP <797>. Beyond-use dating is assigned per the pharmacy's stability documentation and the relevant USP general chapter requirements [usp_795; usp_797].

Aqueous methylcobalamin solutions undergo photodegradation in ambient light; the corrin ring chromophore (responsible for the deep red color) is the photolabile feature. Light-protected storage is the standard control.

Methylcobalamin (B12) Compounding & Operations

503A compounding

Methylcobalamin is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares sublingual tablets under USP General Chapter <795> for nonsterile pharmaceutical compounding and sterile injectable preparations under USP General Chapter <797> [usp_795; usp_797]. Active pharmaceutical ingredient is sourced from FDA-registered suppliers with documented certificates of analysis. Each batch is documented with gravimetric and analytical verification, beyond-use dating per stability data, and full lot traceability from API source through dispensing.

Sterility and endotoxin testing are performed per the pharmacy's quality management system on sterile injectable batches. Sublingual tablets are tested for content uniformity per USP <795> nonsterile compounding standards [fda503a]. Methylcobalamin's photosensitivity is controlled through light-resistant packaging and light-protected preparation areas.

Pharmacist review

Each prescription for compounded methylcobalamin undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that the FDA-approved cyanocobalamin or hydroxocobalamin product is not appropriate (excipient sensitivity, documented MTHFR polymorphism with prescriber preference for the methylated form, allergen-free formulation requirement, specific dose strength not commercially available, or other documented factor); appropriate concomitant medication review (metformin, proton-pump inhibitors, oral folate); and a prescribed regimen consistent with B12 replacement principles [devalia2014, green2017] [frosst1995].

RonanRx does not fill prescriptions that read as routine substitution of compounded methylcobalamin for the FDA-approved cyanocobalamin generic without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs. The methylcobalamin-form preference is patient-specific and clinician-directed; population-level outcome superiority over cyanocobalamin is not established and is not a basis for routine substitution [fda503a].

Quality and traceability

Active pharmaceutical ingredient is sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, sterility and endotoxin results (for injectables) or content uniformity (for sublingual tablets), and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Sterile compounded methylcobalamin injection is typically a refrigerated product (2, 8°C) protected from light per the pharmacy's stability documentation. Refrigerated transport with temperature monitoring is used between the compounding pharmacy and the patient [usp_797]. Patients are advised to refrigerate the product on arrival, protect it from light, inspect for temperature excursions, and contact the pharmacy if cold-chain integrity is in question. Sublingual methylcobalamin tablets are stored at controlled room temperature in light-resistant packaging and are not a cold-chain product.

Frequently Asked Questions About Methylcobalamin (B12)

What is methylcobalamin and how is it different from cyanocobalamin?

Methylcobalamin is the methylated coenzyme form of vitamin B12 that the body uses inside cells for the methionine synthase reaction [green2017; stabler2013]. Cyanocobalamin is a synthetic, chemically stable B12 form (with a cyano group on the cobalt atom) that is converted to active coenzyme forms inside cells. Cyanocobalamin is the standard inexpensive FDA-approved B12 in the United States; methylcobalamin is the active form supplied under 503A compounding as sublingual tablets or injection.

Is methylcobalamin FDA-approved?

No FDA-approved standalone methylcobalamin drug product is marketed in the United States. Cyanocobalamin injection and tablets are the FDA-approved B12 products. Hydroxocobalamin is FDA-approved as IM B12 replacement and at 5 g IV as the Cyanokit cyanide antidote. Methylcobalamin is approved as a prescription drug in Japan and several other markets; in the United States it is supplied under 503A compounding on a patient-specific prescription [fda503a; green2017].

Why would a doctor prescribe compounded methylcobalamin instead of cyanocobalamin?

Documented reasons include excipient sensitivity to the manufactured cyanocobalamin product, a documented MTHFR C677T polymorphism with prescriber preference for the methylated form, an allergen-free formulation requirement, or a specific dose strength not commercially available. Cost or generic preference does not qualify under section 503A [fda503a; frosst1995].

Is methylcobalamin better than cyanocobalamin?

On a population level, direct head-to-head trials of methylcobalamin vs cyanocobalamin on hard clinical outcomes are limited. For most patients with B12 deficiency, both forms (and hydroxocobalamin) restore serum B12, methylmalonic acid, and homocysteine to normal range and correct megaloblastic anemia [green2017; stabler2013]. The methylcobalamin-preference rationale in patients with documented MTHFR polymorphism or with prescriber preference for the active form is mechanistic and individualized rather than evidence-based at population scale [frosst1995].

What is the MTHFR connection?

MTHFR C677T (rs1801133) is a common polymorphism that produces a thermolabile methylenetetrahydrofolate reductase enzyme with reduced activity [frosst1995]. Homozygotes (TT) have elevated plasma homocysteine and altered folate one-carbon partitioning [paul_selhub2017]. Some clinicians prefer the methylated B12 form for patients with documented MTHFR C677T homozygosity on the rationale that methionine synthase has direct access to methylcobalamin. Randomized comparative outcome trials of methylcobalamin vs cyanocobalamin in MTHFR variant carriers are not available.

Does long-term metformin cause B12 deficiency?

Yes. Long-term metformin reduces ileal absorption of the intrinsic-factor, B12 complex. Pflipsen et al. (2009) reported a 22% prevalence of B12 deficiency in adults with type 2 diabetes, and Niafar et al [pflipsen2009; niafar2015; pratama2022]. (2015) confirmed the association meta-analytically. B12 replacement (any form, cyanocobalamin, methylcobalamin, or hydroxocobalamin) is appropriate when deficiency is documented.

What does the evidence say about methylcobalamin for diabetic neuropathy?

Yaqub, Siddique, and Sulimani (1992) reported a randomized placebo-controlled trial of oral methylcobalamin in diabetic neuropathy with improvement in symptoms and nerve conduction [yaqub1992; ran2024; deng2025]. Kaur et al. (2021) reported a randomized comparative trial of methylcobalamin alone vs methylcobalamin + pregabalin vs methylcobalamin + duloxetine [kaur2021]. The recent meta-analyses by Ran et al. (2024) and Deng et al. (2025) consolidate the diabetic-neuropathy evidence including methylcobalamin-containing regimens. Effects on symptoms are favorable but heterogeneous; methylcobalamin is one option in a multimodal symptom-management approach rather than a disease-modifying standard.

What is the ALS evidence for methylcobalamin?

Kaji et al. (2019) reported a phase II/III randomized trial of ultra-high-dose IM methylcobalamin (25 or 50 mg twice weekly) in ALS; the primary endpoint did not differ overall but the early-treatment subgroup suggested benefit [kaji2019; kaji2026]. Oki et al. (2022) reported the dedicated phase III trial in early-stage ALS (within 1 year of symptom onset): methylcobalamin 50 mg IM twice weekly slowed ALSFRS-R decline at 16 weeks [oki2022]. Kaji et al. (2026) reported the open-label extension safety data. Methylcobalamin is registered for ALS in Japan based on this evidence; it is not FDA-approved for ALS in the United States.

Are sublingual methylcobalamin tablets effective?

Sharabi et al. (2003) reported equivalence of sublingual and oral cyanocobalamin replacement, supporting the sublingual route as a reasonable alternative to oral [sharabi2003; andres2018]. The sublingual route is convenient for patients with food-cobalamin malabsorption or with chronic acid suppression because it bypasses the gastric protein-release step.

Does RonanRx sell compounded methylcobalamin directly to patients?

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

References

1. *[green2017]* Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, Molloy AM, Nexo E, Stabler S, Toh BH, Ueland PM, Yajnik C. *Vitamin B(12) deficiency*. Nature Reviews Disease Primers. 2017. PMID 28660890. (accessed 2026-05-11)
2. *[stabler2013]* Stabler SP. *Clinical practice. Vitamin B12 deficiency*. New England Journal of Medicine. 2013. PMID 23301732. (accessed 2026-05-11)
3. *[reynolds2006]* Reynolds E. *Vitamin B12, folic acid, and the nervous system*. Lancet Neurology. 2006. PMID 17052662. (accessed 2026-05-11)
4. *[andres2004]* Andrès E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, Noblet-Dick M, Maloisel F, Schlienger JL, Blicklé JF. *Vitamin B12 (cobalamin) deficiency in elderly patients*. CMAJ : Canadian Medical Association journal. 2004. PMID 15289425. (accessed 2026-05-11)
5. *[wolffenbuttel2019]* Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, van der Klauw MM. *The Many Faces of Cobalamin (Vitamin B(12)) Deficiency*. Mayo Clinic Proceedings: Innovations, Quality & Outcomes. 2019. PMID 31193945. (accessed 2026-05-11)
6. *[toh1997]* Toh BH, van Driel IR, Gleeson PA. *Pernicious anemia*. New England Journal of Medicine. 1997. PMID 9358143. (accessed 2026-05-11)
7. *[carmel2005]* Carmel R. *Is testing for clinical cobalamin deficiency truly unreliable?*. Blood. 2005. PMID 16033957. (accessed 2026-05-11)

8. *[devalia2014]* Devalia V, Hamilton MS, Molloy AM. *Guidelines for the diagnosis and treatment of cobalamin and folate disorders*. British Journal of Haematology. 2014. PMID 24942828. (accessed 2026-05-11)
9. *[paul_selhub2017]* Paul L, Selhub J. *Interaction between excess folate and low vitamin B12 status*. Molecular Aspects of Medicine. 2017. PMID 27876554. (accessed 2026-05-11)
10. *[frosst1995]* Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, den Heijer M, Kluijtmans LA, van den Heuvel LP, Rozen R. *A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase*. Nature Genetics. 1995. PMID 7647779. (accessed 2026-05-11)
11. *[yaqub1992]* Yaqub BA, Siddique A, Sulimani R. *Effects of methylcobalamin on diabetic neuropathy*. Clinical Neurology and Neurosurgery. 1992. PMID 1324807. (accessed 2026-05-11)
12. *[jalaludin1995]* Jalaludin MA. *Methylcobalamin treatment of Bell's palsy*. Methods and Findings in Experimental and Clinical Pharmacology. 1995. PMID 8749227. (accessed 2026-05-11)
13. *[kaji2019]* Kaji R, Imai T, Iwasaki Y, Okamoto K, Nakagawa M, Ohashi Y, Takase T, Hanada T, Shimizu H, Tashiro K, Kuzuhara S. *Ultra-high-dose methylcobalamin in amyotrophic lateral sclerosis: a long-term phase II/III randomised controlled study*. Journal of Neurology, Neurosurgery, and Psychiatry. 2019. PMID 30636701. (accessed 2026-05-11)
14. *[oki2022]* Oki R, Izumi Y, Fujita K, Miyamoto R, Nodera H, Sato Y, Sakaguchi S, Nokihara H, Kanai K, Tsunemi T, Hattori N, Hatanaka Y, Sonoo M, Atsuta N, Sobue G, Shimizu T, Shibuya K, Ikeda K, Kano O, Nishinaka K, Kojima Y, Oda M, Komai K, Kikuchi H, Kohara N, Urushitani M, Nakayama Y, Ito H, Nagai M. *Efficacy and Safety of Ultrahigh-Dose Methylcobalamin in Early-Stage Amyotrophic Lateral Sclerosis: A Randomized Clinical Trial*. JAMA Neurology. 2022. PMID 35532908. (accessed 2026-05-11)
15. *[kaji2026]* Kaji R, Nishi Y, Ishida T, Takase T, Ueda T, Maeda T, Izumi Y. *Clinical safety of ultra-high-dose methylcobalamin in patients with amyotrophic lateral sclerosis: Open-label extension of a phase 2/3 randomized controlled study*. Journal of the Neurological Sciences. 2026. PMID 41475066. (accessed 2026-05-11)
16. *[sharabi2003]* Sharabi A, Cohen E, Sulkes J, Garty M. *Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route*. British Journal of Clinical Pharmacology. 2003. PMID 14616423. (accessed 2026-05-11)
17. *[vidal2005]* Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A, McDowell I, Papaioannou A. *Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency*. Cochrane Database of Systematic Reviews. 2005. PMID 16034940. (accessed 2026-05-11)
18. *[castelli2011]* Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, Riley MG. *Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study*. Clinical Therapeutics. 2011. PMID 21600388. (accessed 2026-05-11)
19. *[andres2018]* Andrès E, Zulfiqar AA, Serraj K, Vogel T, Kaltenbach G. *Systematic Review and Pragmatic Clinical Approach to Oral and Nasal Vitamin B12 (Cobalamin) Treatment in Patients with Vitamin B12 Deficiency Related to Gastrointestinal Disorders*. Journal of Clinical Medicine. 2018. PMID 30261596. (accessed 2026-05-11)
20. *[niafar2015]* Niafar M, Hai F, Porhomayon J, Nader ND. *The role of metformin on vitamin B12 deficiency: a meta-analysis review*. Internal and Emergency Medicine. 2015. PMID 25502588. (accessed 2026-05-11)
21. *[pflipsen2009]* Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Seaquist D, Topolski R. *The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study*. Journal of the American Board of Family Medicine. 2009. PMID 19734399. (accessed 2026-05-11)

22. *[pratama2022]* Pratama S, Lauren BC, Wisnu W. *The efficacy of vitamin B(12) supplementation for treating vitamin B(12) deficiency and peripheral neuropathy in metformin-treated type 2 diabetes mellitus patients: A systematic review*. Diabetes & Metabolic Syndrome. 2022. PMID 36240684. (accessed 2026-05-11)

23. *[ran2024]* Ran GL, Li YP, Lu LC, Lan SH. *Disease-modifying therapies for diabetic peripheral neuropathy: A systematic review and meta-analysis of randomized controlled trials*. Journal of Diabetes and Its Complications. 2024. PMID 38330524. (accessed 2026-05-11)

24. *[deng2025]* Deng XL, Wu R, Lin XX, Liang JJ, Huang HW. *Dapagliflozin combined with methylcobalamin in the treatment of type 2 diabetes mellitus with peripheral neuropathy: a systematic review and meta-analysis*. Frontiers in Endocrinology. 2025. PMID 40612436. (accessed 2026-05-11)

25. *[kaur2021]* Kaur N, Kishore L, Singh R. *A randomized comparative study of methylcobalamin, methylcobalamin plus pregabalin and methylcobalamin plus duloxetine in patients of painful diabetic neuropathy*. Indian Journal of Pharmacology. 2021. PMID 34854403. (accessed 2026-05-11)

26. *[fda503a]* U.S. Food and Drug Administration. *Compounding and the FDA: Questions and Answers*. FDA. 2024. https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (accessed 2026-05-11)

27. *[usp_795]* United States Pharmacopeia. *USP General Chapter <795> Pharmaceutical Compounding — Nonsterile Preparations*. USP Compounding Compendium. 2023. https://www.usp.org/compounding/general-chapter-795 (accessed 2026-05-11)

28. *[usp_797]* United States Pharmacopeia. *USP General Chapter <797> Pharmaceutical Compounding — Sterile Preparations*. USP Compounding Compendium. 2023. https://www.usp.org/compounding/general-chapter-797 (accessed 2026-05-11)

How to Access Methylcobalamin (B12)

Compounded Methylcobalamin (B12) 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 Methylcobalamin (B12), 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)