RonanRx
PERSONALIZED MEDICINE

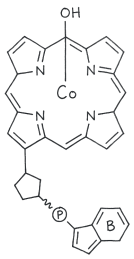
CLINICAL MONOGRAPH · ENERGY & NUTRITIONAL

Hydroxocobalamin

Long-acting B12 form prescribed in select clinical contexts

Hydroxocobalamin is a form of vitamin B12. It is the form your body actually circulates in blood and stores in the liver, and it converts inside cells into the two active coenzyme forms (methylcobalamin and adenosylcobalamin). It has been used clinically since the 1960s, first to treat pernicious anemia and later in two very different settings: vitamin B12 deficiency injections and emergency treatment of cyanide poisoning [carmel2008; stabler2013; adams1965].

In the US, the only FDA-approved hydroxocobalamin product is Cyanokit, a 5 g intravenous kit approved in 2006 for known or suspected cyanide poisoning. There is no FDA-approved standalone hydroxocobalamin injection for routine B12 deficiency in the US (cyanocobalamin is the manufactured generic) [fda_label_cyanokit]. When a clinician needs hydroxocobalamin for a patient, for example because the patient does not tolerate cyanocobalamin, has tobacco-related optic-nerve disease, or has been exposed to chronic low-dose cyanide, it is prepared by a compounding pharmacy under 503A on a patient-specific prescription.



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

Hydroxocobalamin is the cobalt(III) hydroxyl form of vitamin B12. In the bloodstream it binds transcobalamin II and is delivered to cells, where intracellular processing converts it to the two active coenzyme forms, methylcobalamin (cytosolic, methionine synthase cofactor) and 5'-deoxyadenosylcobalamin (mitochondrial, methylmalonyl-CoA mutase cofactor). Parenteral hydroxocobalamin exhibits substantially greater tissue retention than parenteral cyanocobalamin: classical retention studies using radio-labeled cobalamin demonstrated approximately 30% retention of an injected hydroxocobalamin dose at 1 week vs approximately 8% for cyanocobalamin, attributable to higher plasma protein binding and slower urinary excretion of the hydroxyl form [boddy1968, adams1965, tudhope1967] [fda_label_cyanokit].

Cyanokit (hydroxocobalamin 5 g for injection) is FDA-approved (December 2006) for known or suspected cyanide poisoning [fda_label_cyanokit]. Hydroxocobalamin chelates cyanide ion with high affinity through ligand exchange at the cobalt center, forming non-toxic cyanocobalamin that is renally excreted [freeman1996]. The prospective clinical series by Borron and colleagues [borron2007prospective] in 69 adult smoke inhalation victims with measured cyanide levels documented 50% survival overall (and 67% survival in patients without cardiac arrest at presentation) following 5, 15 g IV hydroxocobalamin, supporting the regulatory approval [burnes2017; shapeton2019]. Pharmacokinetic data in smoke-inhalation victims [houeto1996] and healthy volunteers [uhl2006safety, uhl2008bp] characterize the dose-related plasma cobalamin(III) exposure, the transient and clinically modest blood-pressure rise mediated by nitric-oxide scavenging, and the cutaneous, urinary, and serum chromogenic discoloration that interferes with several spectrophotometric and co-oximetric laboratory assays [borron2007cohb, ranjitkar2015, carlsson2011].

Compounded 503A use is principally for patient-specific vitamin B12 deficiency replacement when cyanocobalamin is not appropriate, patients with documented intolerance to cyanocobalamin, patients with chronic low-grade cyanide exposure (tobacco-amblyopia, cassava-associated tropical ataxic neuropathy, Leber hereditary optic neuropathy carriers) where the cyano- group is undesirable, and patients who prefer the non-cyano natural form on documented grounds [stabler2013] [carmel2008; carelli2002sadun]. Off-label intravenous high-dose hydroxocobalamin (typically 5 g IV) has been studied as a rescue treatment for refractory vasoplegic syndrome after cardiopulmonary bypass and as a vasopressor adjunct in distributive shock states; this off-label use is supported primarily by case reports, case series, a porcine LPS-shock RCT [bebarta2019lps], and a 2024 systematic review and meta-analysis [cadd2024] comparing hydroxocobalamin with methylene blue [roderique2014]. The proposed mechanism is inhibition and scavenging of nitric oxide, cobalamins are direct inhibitors of nitric oxide synthase [weinberg2009] [leighton1979].

Why Personalized Hydroxocobalamin

Cyanokit's 5 gram IV dose was calibrated for a single emergency, acute cyanide poisoning in an adult, given once by paramedics or in a hospital. That regimen was never meant to address the everyday reasons a person actually needs B12. It does not account for how deep your deficiency runs, whether your gut still absorbs cobalamin at all (pernicious anemia, prior gastric surgery, long-term PPI or metformin use), how fast your kidneys clear the cobalt-(III) complex, whether you have an optic-nerve context like tobacco amblyopia or an LHON carrier state where the cyanide-trapping form matters, or whether you simply do not tolerate the cyanocobalamin generic that dominates the US outpatient market.

That gap is the work a compounding pharmacy does. The molecule is the same cobalamin reviewed by the FDA for Cyanokit. What we change is everything around it: strength outside the commercial 5 gram vial, IM or subcutaneous route instead of IV, a loading schedule sized to how depleted the patient is on labs, a maintenance cadence that fits how long their tissues actually retain the dose, and a preservative-free or excipient-stripped formulation when the prescriber documents a sensitivity. The prescription is written for one named patient by a prescriber who has seen their chart, not chosen from a shelf.

This is the older arrangement, the one that pre-dates mass manufacturing. A prescriber writes for a named patient. A pharmacist prepares that prescription. Modern state licensure, pharmacist review, and the recall path keep it honest.

Quick Facts About Hydroxocobalamin

Category: Vitamin B12 (cobalamin), hydroxyl-cobalt(III) form

Active ingredient: Hydroxocobalamin, a naturally occurring cobalamin in which the upper axial ligand on cobalt(III) is a hydroxyl group; exchanges for cyanide to form cyanocobalamin in vivo

FDA-approved branded form: Cyanokit (hydroxocobalamin 5 g for injection, IV), FDA-approved December 2006 for known or suspected cyanide poisoning

Routes (compounded): Intramuscular or subcutaneous injection on patient-specific prescriptions; intravenous administration is reserved for the manufactured Cyanokit indication

Evidence posture: Cyanokit is FDA-approved for cyanide poisoning on the basis of a prospective clinical series in smoke inhalation [borron2007prospective] and supporting volunteer PK and safety data [uhl2006safety, houeto1996]. Compounded IM/SC hydroxocobalamin for B12 deficiency draws on a long

observational literature comparing cobalamin forms [adams1965, boddy1968, tudhope1967, carmel2008, stabler2013].

FDA-approval status: Manufactured Cyanokit (5 g IV for cyanide poisoning) is FDA-approved. Compounded IM/SC hydroxocobalamin preparations are not FDA-approved.

Compounded under: 503A, patient-specific prescription only. In the US there is no commercially-marketed standalone IM/SC hydroxocobalamin product for vitamin B12 deficiency; the cyanocobalamin generic dominates that market.

Common compounded strengths: Typically 1 mg/mL or 5 mg/mL sterile preservative-free or preservative-containing solutions for intramuscular or subcutaneous injection

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Hydroxocobalamin 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 Hydroxocobalamin?

Hydroxocobalamin is a naturally occurring form of vitamin B12 (cobalamin) in which the cobalt(III) atom at the center of the corrin ring is coordinated by a hydroxyl group in its upper axial position. It is the cobalamin form predominantly circulating bound to transcobalamin II in human plasma and stored in the liver, and is interconverted in vivo with the two coenzyme forms, methylcobalamin and 5'-deoxyadenosylcobalamin.

Hydroxocobalamin was characterized in the 1950s and entered clinical use in the 1960s, principally as an injectable treatment for pernicious anemia and other vitamin B12 deficiency states. In the 1980s and 1990s a parallel role developed in France for use as a cyanide antidote in fire-victim smoke-inhalation cases [borron1996review, houeto1996, thompson2012]; this work led to FDA approval of Cyanokit (Meridian Medical Technologies / Mylan) at 5 g IV for known or suspected cyanide poisoning in December 2006 [fda_label_cyanokit, borron2007prospective].

In US clinical pharmacies, the only commercially marketed hydroxocobalamin product is Cyanokit, a 5 g lyophilized powder for reconstitution and intravenous infusion. There is no FDA-approved standalone manufactured IM or SC hydroxocobalamin injection in the US for routine vitamin B12 deficiency replacement; the manufactured B12 generic market is dominated by cyanocobalamin 1000 µg/mL. When a prescriber writes for hydroxocobalamin in concentrations and routes appropriate for outpatient B12 replacement (typically 1 mg/mL or 5 mg/mL for IM or SC injection), the preparation is dispensed by a 503A compounding pharmacy on a patient-specific prescription [fda503a, usp_797].

How Hydroxocobalamin Works

Hydroxocobalamin is the hydroxyl-cobalt(III) form of vitamin B12. After parenteral administration it binds plasma transcobalamin II and is delivered to tissues, where it enters cells through the transcobalamin-receptor pathway. Intracellularly it is reduced and processed into the two coenzymatically active forms: cytosolic methylcobalamin, which serves as the methyl-group donor cofactor for methionine synthase in homocysteine remethylation, and mitochondrial 5'-deoxyadenosylcobalamin, which serves as the cofactor for methylmalonyl-CoA mutase in propionate metabolism [carmel2008, stabler2013].

Relative to cyanocobalamin, hydroxocobalamin exhibits higher plasma protein binding, slower urinary excretion, and greater tissue retention. Classical comparative retention studies using radio-labeled cobalamin showed that approximately 30% of an injected hydroxocobalamin dose was retained at 1 week vs approximately 8% for an equivalent cyanocobalamin dose [boddy1968, adams1965]. Clinically, this supports less frequent dosing intervals for hydroxocobalamin in B12-deficiency replacement, and supports its use in chronic cyanide-exposure states where the hydroxyl-cobalt(III) ligand exchange capacity is therapeutically useful [shapeton2019; cadd2024].

In cyanide poisoning, hydroxocobalamin acts as a direct, stoichiometric chelator. Free cyanide displaces the hydroxyl ligand at the cobalt(III) center to form cyanocobalamin, a non-toxic complex that is renally excreted. Each 5 g IV dose of Cyanokit binds approximately 100 mg of cyanide [fda_label_cyanokit, shepherd2008, thompson2012]. In vasodilatory shock states, hydroxocobalamin additionally scavenges nitric oxide and directly inhibits constitutive and inducible nitric oxide synthase isoforms [weinberg2009], a mechanism proposed to underlie its off-label hemodynamic effect in vasoplegic syndrome and distributive shock [roderique2014; burnes2017].

Biological Role of Hydroxocobalamin

Vitamin B12 is one of the eight B-complex vitamins and is required as a cofactor by two enzymes in mammalian metabolism: methionine synthase (cytosol; remethylates homocysteine to methionine using methylcobalamin) and methylmalonyl-CoA mutase (mitochondrion; isomerizes methylmalonyl-CoA to succinyl-CoA using adenosylcobalamin). Loss of either function produces measurable biochemical derangements (elevated homocysteine; elevated methylmalonic acid), and chronic deficiency produces macrocytic megaloblastic anemia and a characteristic neurological syndrome including peripheral neuropathy and subacute combined degeneration of the spinal cord [carmel2008, stabler2013].

Among the four pharmaceutically encountered cobalamins, hydroxocobalamin is the form most closely matched to physiological B12 transport: it is the form that circulates bound to transcobalamin II and is the form that the liver stores. Cyanocobalamin is a synthetic storage-stable form that the body must first convert to the active coenzymes by removing the cyano group; methylcobalamin and adenosylcobalamin are the two intracellular coenzymatically active forms. From a strictly physiological perspective, hydroxocobalamin is the natural form [freeman1996]. Whether that physiological match translates into clinically meaningful differences from cyanocobalamin in routine B12 replacement remains a long-standing debate, with the strongest evidence for hydroxocobalamin's advantages being its substantially greater tissue retention after parenteral dosing [adams1965; boddy1968; tudhope1967].

Detailed Mechanism of Hydroxocobalamin

The four cobalamins encountered in clinical pharmacy, cyanocobalamin, hydroxocobalamin, methylcobalamin, and adenosylcobalamin, differ in the identity of the upper axial ligand on the cobalt(III) atom of the corrin ring. Cyanocobalamin (cyano- ligand) is a synthetic, storage-stable form; hydroxocobalamin (hydroxyl ligand) is the form predominantly circulating in plasma; methylcobalamin and adenosylcobalamin are the two intracellular coenzyme forms. After parenteral hydroxocobalamin administration, the hydroxyl-cobalt(III) form binds rapidly to plasma transcobalamin II (haptocorrin and intrinsic factor are not relevant to parenteral cobalamin disposition) and is delivered to tissues by the transcobalamin-receptor pathway. Intracellular reduction to cobalt(II) and (I) and ligand exchange yield methyl- and adenosyl-cobalamin, the active coenzyme forms [carmel2008, stabler2013].

Pharmacokinetic comparisons with cyanocobalamin published over six decades consistently demonstrate that hydroxocobalamin has substantially higher tissue retention. The Adams and Kennedy (1965) study in pernicious anemia subjects [adams1965] documented markedly lower urinary excretion of hydroxocobalamin vs cyanocobalamin in the 48 hours after parenteral dosing, and the Boddy and colleagues (1968) Lancet retention study [boddy1968] reported 1-week whole-body retention of approximately 30% for hydroxocobalamin vs approximately 8% for cyanocobalamin. The Tudhope and

colleagues (1967) clinical trial in pernicious anemia [tudhope1967] confirmed that hydroxocobalamin produced higher and more sustained serum B12 levels than equimolar cyanocobalamin, and supported the European convention of less frequent dosing intervals for hydroxocobalamin replacement.

In healthy volunteers, single-dose IV hydroxocobalamin pharmacokinetics have been characterized by Uhl and colleagues (2006) [uhl2006safety] across the dose range used clinically for cyanide poisoning. After 5 or 10 g IV, total cobalamins-(III) plasma concentrations peak at the end of infusion and decline biexponentially with a terminal half-life of approximately 26, 31 hours. Approximately 50, 60% of an administered dose is recovered unchanged in urine over 72 hours; the remainder is bound to plasma proteins and slowly redistributed. The Uhl and colleagues (2008) blood-pressure substudy [uhl2008bp] demonstrated a transient, dose-related rise in systolic and diastolic blood pressure correlated to plasma cobalamins-(III) concentrations, consistent with nitric-oxide scavenging.

In cyanide poisoning, hydroxocobalamin binds free cyanide stoichiometrically via ligand exchange at the cobalt(III) center, forming cyanocobalamin. Each 5 g of hydroxocobalamin binds approximately 100 mg of cyanide [thompson2012, shepherd2008]. The resulting cyanocobalamin complex is non-toxic and renally excreted [houeto1996, fda_label_cyanokit]. Hydroxocobalamin is, in mechanism, a chelator, unlike the alternative methemoglobin-inducer (amyl nitrite / sodium nitrite) component of the older Lilly cyanide antidote kit, it does not depend on inducing methemoglobinemia and is therefore preferred for cyanide poisoning in smoke-inhalation victims where additional impairment of oxygen carrying capacity is undesirable [borron2007prospective, shepherd2008, thompson2012].

In vasodilatory shock, hydroxocobalamin scavenges nitric oxide and directly inhibits nitric oxide synthase. Weinberg and colleagues (2009) [weinberg2009] characterized cobalamins and cobinamides as direct inhibitors of all three NOS isoforms (neuronal, endothelial, and inducible). This mechanism is proposed to underlie the rise in mean arterial pressure documented after 5 g IV hydroxocobalamin in refractory vasoplegic syndrome after cardiopulmonary bypass [roderique2014, burnes2017, shapeton2019] and in distributive shock from sepsis [bebarta2019lps]. A 2024 systematic review and meta-analysis [cadd2024] comparing hydroxocobalamin with methylene blue across pooled vasoplegic-shock cohorts after cardiopulmonary bypass reported comparable hemodynamic effects with a differing adverse-event profile.

Hydroxocobalamin Research History

Cobalamins were isolated and structurally characterized in the late 1940s, and the four major pharmaceutically encountered cobalamins (cyano-, hydroxo-, methyl-, and adenosyl-) were chemically distinguished through the 1950s. Hydroxocobalamin entered clinical use in the 1960s, first as a parenteral treatment for pernicious anemia. The Adams and Kennedy (1965) study [adams1965] and the Boddy and colleagues (1968) Lancet retention study [boddy1968] established its substantially greater tissue retention than cyanocobalamin. The Tudhope and colleagues (1967) clinical trial in pernicious anemia [tudhope1967]

established higher and more sustained serum B12 levels with hydroxocobalamin than equimolar cyanocobalamin [freeman1996].

From the 1970s into the 1990s, hydroxocobalamin was investigated as the active treatment for tobacco-alcohol amblyopia and for the Cuban epidemic optic and peripheral neuropathy [leighton1979; sadun1998; carelli2002sadun]. Mechanistic interest centered on chronic low-grade cyanide exposure (from tobacco smoke and from incompletely processed cassava in the Cuban context) and on the differential capacity of hydroxocobalamin, but not cyanocobalamin, to chelate environmental cyanide.

A parallel acute-toxicology indication developed in France through the 1980s and 1990s, motivated by smoke-inhalation deaths in structure fires. Houeto and colleagues (1996) [houeto1996] characterized pharmacokinetics of high-dose IV hydroxocobalamin in fire-victim smoke-inhalation cases. Borron, Baud, and colleagues conducted the prospective clinical series [borron2007prospective] of 69 adult smoke-inhalation victims with measured cyanide levels treated with 5, 15 g IV hydroxocobalamin, reporting 50% overall survival and 67% survival in patients without cardiac arrest at presentation. This evidence, together with the volunteer safety and PK data of Uhl and colleagues [uhl2006safety, uhl2008bp], supported FDA approval of Cyanokit (5 g hydroxocobalamin IV) in December 2006 for known or suspected cyanide poisoning [fda_label_cyanokit].

Through the 2010s and into the 2020s, off-label use of high-dose IV hydroxocobalamin for refractory vasoplegic syndrome after cardiopulmonary bypass emerged through a sequence of case reports [roderique2014, burnes2017] and was reviewed by Shapeton and colleagues (2019) [shapeton2019]. Cadd and colleagues (2024) [cadd2024] published a systematic review and meta-analysis comparing hydroxocobalamin with methylene blue for vasoplegic shock following cardiopulmonary bypass, the most rigorous comparative evidence to date in this indication. A swine LPS-induced distributive shock RCT [bebarta2019lps] supported the mechanistic rationale of NOS inhibition and NO scavenging characterized at the molecular level by Weinberg and colleagues (2009) [weinberg2009]. Laboratory-interference investigations [borron2007cohb, carlsson2011, ranjitkar2015] characterized the chromogenic interference of high plasma hydroxocobalamin concentrations on common spectrophotometric and co-oximetric assays.

Hydroxocobalamin Timeline

- **1965** • Adams and Kennedy (J Lab Clin Med), excretion and retention after parenteral hydroxocobalamin in anemic and non-anemic subjects [adams1965]
- **1967** • Tudhope, Swan, and Spray (Br J Haematol), clinical trial in pernicious anemia comparing cyanocobalamin, hydroxocobalamin, and cyanocobalamin-zinc tannate [tudhope1967]
- **1968** • Boddy, King, Mervyn, Macleod, Adams (Lancet), whole-body retention of cyanocobalamin, hydroxocobalamin, and coenzyme B12 after parenteral administration [boddy1968]

1979 • Leighton, Bhargava, Shail (Doc Ophthalmol), tobacco amblyopia treatment effect on the electroretinogram, characterizing hydroxocobalamin's role in chronic cyanide-mediated optic neuropathy [leighton1979]

1996 • Borron and Baud (Arh Hig Rada Toksikol), narrative review of acute cyanide poisoning clinical spectrum, diagnosis, and treatment [borron1996review]

1996 • Houeto, Borron, Sandouk, Imbert, Levillain, Baud (J Toxicol Clin Toxicol), pharmacokinetics of hydroxocobalamin in smoke-inhalation victims [houeto1996]

1996 • Freeman (J R Soc Med), letter comparing clinical preference for hydroxocobalamin vs cyanocobalamin in B12 replacement [freeman1996]

1998 • Sadun (Trans Am Ophthalmol Soc), acquired mitochondrial impairment as a cause of optic nerve disease, with hydroxocobalamin among proposed interventions for cyanide-related optic neuropathies [sadun1998]

2002 • Carelli, Ross-Cisneros, Sadun (Neurochem Int), optic nerve degeneration and mitochondrial dysfunction in genetic and acquired optic neuropathies (Leber hereditary optic neuropathy framework) [carelli2002sadun]

2004 • Fortin, Ruttiman, Domanski, Kowalski (JEMS), hydroxocobalamin for smoke-inhalation-associated cyanide poisoning in pre-hospital fire-victim care [fortin2004]

2006 • Uhl, Nolting, Golor, Rost, Kovar (Clin Toxicol), safety of hydroxocobalamin in healthy volunteers in a randomized placebo-controlled study; supported the Cyanokit safety package [uhl2006safety]

2006 • FDA approves Cyanokit (hydroxocobalamin 5 g for injection) for known or suspected cyanide poisoning (December 15, 2006) [fda_label_cyanokit]

2007 • Borron, Baud, Barriot, Imbert, Bismuth (Ann Emerg Med), prospective clinical series of hydroxocobalamin for acute cyanide poisoning in 69 adult smoke-inhalation victims with measured cyanide levels; landmark Cyanokit evidence base [borron2007prospective]

2007 • Borron, Uhl, Nolting, Hostalek (Ann Emerg Med, letter), interference of hydroxocobalamin with carboxyhemoglobin co-oximetry measurements should not limit clinical use [borron2007cohb]

2008 • Uhl, Nolting, Gallemann, Hecht, Kovar (Clin Toxicol), randomized blood-pressure substudy after IV hydroxocobalamin in healthy volunteers; transient dose-related BP rise correlated with plasma cobalamins-(III) concentration [uhl2008bp]

2008 • Carmel (Blood), How I treat cobalamin (vitamin B12) deficiency: contemporary clinical practice review [carmel2008]

2008 • Shepherd and Velez (Ann Pharmacother), narrative review of hydroxocobalamin in acute cyanide poisoning [shepherd2008]

2009 • Weinberg, Chen, Jiang, Beasley, Salerno, Ghosh (Free Radic Biol Med), cobalamins and cobinamides are direct inhibitors of nitric oxide synthase; mechanistic foundation for hydroxocobalamin's vasoplegia indication [weinberg2009]

2011 • Carlsson, Hansen, Hilsted, Malm, Ødum, Szecsi (Scand J Clin Lab Invest), characterization of hydroxocobalamin chromogenic interference on nine commonly used chemistry and co-oximetry instruments [carlsson2011]

2012 • Thompson and Marrs (Clin Toxicol), comprehensive review of hydroxocobalamin in cyanide poisoning [thompson2012]

2013 • Stabler (NEJM, Clinical Practice), vitamin B12 deficiency: contemporary review of evaluation and treatment [stabler2013]

2014 • Roderique, VanDyck, Holman, Tang, Chui, Spiess (Ann Thorac Surg), first case report of high-dose hydroxocobalamin for vasoplegic syndrome after cardiopulmonary bypass [roderique2014]

2015 • Ranjitkar and Greene (Clin Chim Acta), therapeutic hydroxocobalamin concentrations interfere with several spectrophotometric assays on Beckman Coulter DxC and AU680 analyzers [ranjitkar2015]

2017 • Burnes, Boettcher, Woehlck, Zundel, Iqbal, Pagel (J Cardiothorac Vasc Anesth), hydroxocobalamin as rescue treatment for refractory vasoplegic syndrome after prolonged cardiopulmonary bypass [burnes2017]

2019 • Shapeton, Mahmood, Ortoleva (J Cardiothorac Vasc Anesth), review of hydroxocobalamin for the treatment of vasoplegia and considerations for use [shapeton2019]

2019 • Bebarta, Garrett, Maddry, Arana, Boudreau, Castaneda, Dixon, Tanen (Clin Exp Pharmacol Physiol), prospective randomized trial of IV hydroxocobalamin vs noradrenaline or saline for LPS-induced hypotension in a swine model [bebarta2019lps]

2021 • Datt, Wadhhwa, Sharma, Virmani, Minhas, Malik (J Card Surg), systematic review of vasoplegic syndrome after cardiovascular surgery, including hydroxocobalamin in the therapeutic algorithm [datt2021]

2024 • Cadd, Watson, Kilpatrick, Hardy, Gallop, Gerard, Cabaret (J Cardiothorac Vasc Anesth), systematic review and meta-analysis comparing hydroxocobalamin and methylene blue for vasoplegic shock following cardiopulmonary bypass [cadd2024]

Clinical Contexts for Hydroxocobalamin

Known or suspected cyanide poisoning FDA APPROVED

FDA-approved indication for manufactured Cyanokit (hydroxocobalamin 5 g IV).

Cyanokit (hydroxocobalamin 5 g IV, repeatable to a total of 10 g) is FDA-approved (December 2006) for the treatment of known or suspected cyanide poisoning [fda_label_cyanokit]. The pivotal evidence is the prospective open-label clinical series by Borron and colleagues [borron2007prospective] in 69 adult smoke-inhalation victims with measured pre-treatment cyanide levels: 50% overall survival, and 67% survival in patients without cardiac arrest at presentation, with 32 of 39 survivors having a favorable neurological outcome [borron1996review; houeto1996]. The supporting volunteer PK and safety package [uhl2006safety] and supporting reviews [shepherd2008] further characterize the dose-response, the transient blood-pressure rise, and the chromogenic laboratory interference. Hydroxocobalamin is the preferred cyanide antidote in smoke-inhalation cases because it does not require induction of methemoglobinemia (unlike the older Lilly sodium nitrite + sodium thiosulfate kit) and so does not further impair oxygen carrying capacity in patients with concurrent carbon monoxide poisoning [uhl2008bp; thompson2012].

Branded product: Cyanokit (hydroxocobalamin 5 g for injection, Meridian Medical Technologies / Mylan / Viatris)

Vitamin B12 deficiency (pernicious anemia and other malabsorption etiologies) WELL STUDIED

Well-studied use, particularly in European practice; compounded 503A in the US given the absence of a manufactured standalone IM/SC product.

Hydroxocobalamin is established for parenteral treatment of vitamin B12 deficiency from pernicious anemia, dietary insufficiency, ileal resection, or other causes of malabsorption. Comparative studies versus cyanocobalamin demonstrate substantially higher tissue retention (~30% vs ~8% at 1 week after parenteral dose) [boddy1968, adams1965] and higher, more sustained serum B12 levels [tudhope1967]. In British and European practice, hydroxocobalamin is the standard parenteral B12 replacement and is administered IM at approximately 1 mg every 2, 3 months for maintenance after deficiency correction [carmel2008, freeman1996] [stabler2013]. In US practice, cyanocobalamin 1000 µg/mL is the dominant manufactured generic; hydroxocobalamin for outpatient IM/SC B12 replacement is dispensed via 503A compounding on patient-specific prescriptions.

Tobacco-alcohol amblyopia (toxic optic neuropathy) WELL STUDIED

Well-studied use; supported by mechanistic and clinical evidence for chronic cyanide exposure-mediated optic neuropathy.

Tobacco-alcohol amblyopia is a toxic optic neuropathy historically attributed to chronic low-grade cyanide exposure from tobacco smoke in the context of poor nutrition or alcohol-related B12 deficiency. Hydroxocobalamin has been preferred over cyanocobalamin in this setting because the cyano- group is undesirable in a chronic cyanide-exposure context. The Leighton and colleagues (1979) study [leighton1979] documented electroretinographic effects of treatment. The mechanistic framework of acquired mitochondrial optic neuropathies including the Cuban epidemic optic neuropathy was developed by Sadun and colleagues [sadun1998, carelli2002sadun]; Freeman (1996) [freeman1996] articulated the clinical preference for hydroxocobalamin over cyanocobalamin in B12 replacement in such patients.

Leber hereditary optic neuropathy (LHON), supportive treatment context WELL STUDIED

Well-studied conceptual framework; not a specific FDA-approved indication. Treatment paradigms emphasize avoidance of cyanide-containing cobalamin and supportive supplementation.

LHON is a maternally-inherited mitochondrial optic neuropathy in which inherited Complex I dysfunction renders the retinal ganglion cell pathway susceptible to additional mitochondrial stressors, including chronic cyanide exposure from tobacco. The Carelli, Ross-Cisneros, and Sadun (2002) review [carelli2002sadun] and the Sadun (1998) review [sadun1998] frame the genetic and acquired optic neuropathies in this mitochondrial-dysfunction paradigm and discuss why cyanocobalamin (which delivers a cyanide group on conversion to active cobalamins) is conceptually undesirable in LHON carriers exposed to tobacco. Hydroxocobalamin is the conceptually preferred B12 form when supplementation is given. No randomized trial has demonstrated that hydroxocobalamin alters LHON outcomes.

Refractory vasoplegic syndrome after cardiopulmonary bypass WELL STUDIED

Off-label use supported by case reports, case series, and a 2024 systematic review and meta-analysis comparing hydroxocobalamin with methylene blue.

High-dose IV hydroxocobalamin (typically 5 g IV) has been used as a rescue treatment for refractory vasoplegic syndrome after cardiopulmonary bypass when escalating vasopressors and methylene blue do not adequately restore mean arterial pressure [datt2021]. The first case report was Roderique and colleagues (2014) [roderique2014]; additional case reports include Burnes and colleagues (2017) [burnes2017]. Shapeton, Mahmood, and Ortoleva (2019) [shapeton2019] reviewed the accumulated literature and considerations for use. The Cadd and colleagues (2024) systematic review and meta-analysis [cadd2024] of hydroxocobalamin versus methylene blue for vasoplegic shock following cardiopulmonary bypass found comparable hemodynamic effects with a differing adverse-event profile. The mechanistic basis is direct inhibition of nitric oxide synthase by cobalamins and cobinamides [weinberg2009] and scavenging of free nitric oxide.

Distributive shock from sepsis (vasopressor adjunct) EMERGING

Off-label use; emerging evidence from preclinical models and small case series. Phase III evidence is not available.

Beyond cardiopulmonary-bypass-associated vasoplegia, hydroxocobalamin has been investigated as a vasopressor adjunct in distributive shock states from sepsis. Bebarta and colleagues (2019) [bebarta2019lps] conducted a prospective randomized trial in a swine LPS-induced hypotension model comparing IV hydroxocobalamin with noradrenaline and saline; hydroxocobalamin raised mean arterial pressure relative to saline. Human evidence is limited to case reports and small series; randomized clinical trial evidence in human sepsis is not available. Mechanism is shared with the vasoplegia indication: cobalamins are direct inhibitors of nitric oxide synthase [weinberg2009] [datt2021].

Reversal of nitrate or nitroprusside-induced vasodilation EMERGING

Off-label; mechanistic rationale and limited case-report evidence.

Nitrate-induced and sodium-nitroprusside-induced vasodilation are mediated by nitric oxide signaling, and the same NO scavenging and NOS inhibition mechanisms that motivate hydroxocobalamin use in vasoplegia also support its theoretical use in nitrate-mediated vasodilation reversal [shapeton2019]. Clinical evidence is limited to case reports and small case series; high-quality randomized evidence is not available. The mechanistic underpinning is the Weinberg (2009) characterization of cobalamins as direct NOS inhibitors [weinberg2009].

Off-Label Uses of Hydroxocobalamin

Refractory vasoplegic syndrome after cardiopulmonary bypass WELL STUDIED

Off-label; supported by case reports, case series, narrative reviews, and a 2024 systematic review and meta-analysis comparing hydroxocobalamin and methylene blue.

Off-label IV hydroxocobalamin 5 g as a rescue treatment for refractory vasoplegic syndrome after cardiopulmonary bypass [roderique2014; burnes2017; shapeton2019]. Phase III randomized evidence is not available; the strongest comparative evidence to date is the Cadd 2024 systematic review and meta-analysis vs methylene blue [cadd2024].

Distributive shock from sepsis (vasopressor adjunct) EMERGING

Off-label; emerging from preclinical LPS-shock models and small clinical series.

Off-label IV hydroxocobalamin as a vasopressor adjunct in sepsis-related distributive shock, supported principally by a swine LPS-shock RCT [bebarta2019lps] and mechanistic data on NOS inhibition [weinberg2009].

Long-term B12 supplementation in patients who prefer the non-cyano form on principle

EMERGING

Off-label preference-based use; the practical clinical question is whether the prescriber's patient-specific clinical rationale justifies 503A compounding when cyanocobalamin manufactured product is available.

Some patients and prescribers prefer the non-cyano natural form of vitamin B12 on principle, for example, chronic smokers, individuals with mitochondrial-disease family histories, or patients who simply prefer the physiological form [carmel2008]. RonanRx fills compounded hydroxocobalamin prescriptions only when the prescriber documents a patient-specific clinical rationale that the manufactured cyanocobalamin product cannot meet (intolerance, optic neuropathy, chronic cyanide exposure context, etc.), not on the basis of preference alone, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy] [freeman1996].

FDA-Approved Uses of Hydroxocobalamin

Brand	Indication	Year	Route
Cyanokit	Treatment of known or suspected cyanide poisoning in adults and pediatric patients	2006	Intravenous infusion (5 g over 15 minutes; repeatable to a total of 10 g based on severity and clinical response)

Cyanokit (hydroxocobalamin 5 g for injection) was approved by the FDA on December 15, 2006 for the treatment of known or suspected cyanide poisoning [borron2007prospective]. It is supplied as a lyophilized powder in a single-use vial, reconstituted with 200 mL of normal saline and administered as an IV infusion over 15 minutes. The labeled adult dose is 5 g IV; a second 5 g dose may be administered based on clinical severity and response, to a total dose of 10 g. The labeled pediatric dose is 70 mg/kg up to 5 g per dose [fda_label_cyanokit].

Cyanokit is the only FDA-approved hydroxocobalamin product in the US. There is no FDA-approved manufactured standalone IM/SC hydroxocobalamin product for routine vitamin B12 deficiency replacement, despite hydroxocobalamin's established use in this context outside the US (notably in British and European practice) [carmel2008, freeman1996] [borron2007prospective].

Compounded Hydroxocobalamin (503A)

RonanRx dispenses compounded hydroxocobalamin under 503A only on patient-specific prescriptions written by licensed prescribers for identified patients with a documented clinical reason that the manufactured product is not appropriate [tudhope1967]. Because Cyanokit is the only manufactured hydroxocobalamin product in the US, and it is a 5 g IV cyanide-antidote kit, not an outpatient B12 replacement product, the compounded preparations addressed here (typically 1 mg/mL or 5 mg/mL sterile

injectable solutions for IM or SC administration) are not 'copies' of any commercially available outpatient product [adams1965; boddy1968]. There is no manufactured competitor for the compounded preparation in routine outpatient B12 replacement, optic-neuropathy, or chronic cyanide-exposure contexts [fda_label_cyanokit, fda503a] [carmel2008].

Typical documented patient-specific clinical rationales include: (1) intolerance to or adverse reaction with cyanocobalamin (the dominant manufactured B12 generic in the US); (2) tobacco-related toxic optic neuropathy or amblyopia, where the cyano- group is undesirable in a chronic cyanide-exposure context [leighton1979, freeman1996]; (3) Leber hereditary optic neuropathy carriers or family histories of mitochondrial optic neuropathy [carelli2002sadun, sadun1998]; (4) chronic dietary cyanide exposure (e.g., cassava-associated tropical ataxic neuropathy); (5) excipient sensitivity to a component of the manufactured cyanocobalamin product; or (6) a documented prescriber preference for the physiological non-cyano form based on the substantially greater tissue retention demonstrated for hydroxocobalamin in comparative cobalamin retention studies.

Compounded hydroxocobalamin preparations are not bioequivalent to Cyanokit and are not intended for IV use in cyanide poisoning. They are prepared at concentrations and in volumes appropriate to IM or SC administration on a per-prescription basis. Compounded preparations may differ from any reference product in concentration, excipient profile, and container closure; PK and tolerability data published for manufactured Cyanokit IV use do not transfer to outpatient IM/SC compounded use without separate stability and tolerability assessment [adams1965].

Pharmacovigilance signals relevant to all compounded sterile injectables apply, including sterility-related events, dosing errors, and excipient or container-closure interactions [fda_essentially_a_copy]. RonanRx pharmacist review at dispensing is documented per the pharmacy's quality management system.

Hydroxocobalamin Formulations and Routes

Form	Concentration	Description
Sterile intramuscular or subcutaneous injection (compounded)	Typically 1 mg/mL or 5 mg/mL; volume per dose per the prescriber's order	Sterile preservative-free or preservative-containing solution prepared under USP <797> standards for sterile compounding on a patient-specific prescription. Container closure, excipient profile, and concentration are documented per batch and matched to the patient's clinical profile.
Manufactured Cyanokit lyophilized powder for IV infusion (reference product)	5 g hydroxocobalamin per single-use vial; reconstituted to 25 mg/mL in 200 mL normal saline	Cyanokit is the FDA-approved manufactured product, a 5 g lyophilized powder kit for reconstitution and IV infusion in known or suspected cyanide poisoning. It is not intended for outpatient IM/SC B12 replacement.

Routes used in published literature: intramuscular, subcutaneous, intravenous.

Hydroxocobalamin Dosing

Route	Population	Range	Duration	Study type
Intravenous	Adults with known or suspected cyanide poisoning (Cyanokit labeled regimen)	5 g IV infused over 15 minutes; a second 5 g dose may be administered based on clinical severity and response, to a maximum total of 10 g	Single or repeated dose per labeled regimen	FDA-approved labeled regimen
Intravenous	Pediatric patients with known or suspected cyanide poisoning (Cyanokit labeled regimen)	70 mg/kg up to a maximum single dose of 5 g; repeatable based on clinical severity and response	Single or repeated dose per labeled regimen	FDA-approved labeled regimen
Intramuscular	Adults with documented vitamin B12 deficiency (compounded, European-pattern replacement dosing)	1 mg IM at induction (commonly every other day or every 3 days for the first 1, 2 weeks for severe deficiency or neurological involvement), then 1 mg IM every 2, 3 months for maintenance	Maintenance is generally lifelong in pernicious anemia and other malabsorptive etiologies	Observational and consensus practice; comparative retention studies underpin the less frequent maintenance interval
Intramuscular	Adults with tobacco-alcohol amblyopia or chronic cyanide-exposure optic neuropathy (compounded)	1 mg IM weekly to monthly, individualized to clinical response; concurrent smoking-cessation counseling and nutritional repletion	Months to indefinite based on clinical response	Observational and case-series evidence
Intravenous	Adults with refractory vasoplegic syndrome after cardiopulmonary bypass (off-label, manufactured Cyanokit)	5 g IV over approximately 15 minutes, with a second 5 g dose reported in some refractory cases	Single or repeated dose per institutional practice	Case reports, case series, and a 2024 systematic review and meta-analysis vs methylene blue

Doctor-prescribed and titrated. The Cyanokit IV cyanide-antidote regimen and the IM/SC outpatient B12 replacement regimens are clinically distinct and should not be conflated. The IV 5 g cyanide-antidote dose is one to two orders of magnitude larger than any single outpatient B12 replacement dose. Compounded IM/SC preparations are typically dispensed at 1 mg/mL or 5 mg/mL for milligram-quantity dosing per injection [fda_label_cyanokit].

European pernicious-anemia replacement practice (1 mg IM every 2, 3 months for maintenance) [carmel2008] reflects hydroxocobalamin's substantially greater tissue retention than cyanocobalamin [adams1965, boddy1968, tudhope1967] [fda_label_cyanokit]. US practice with cyanocobalamin typically uses monthly maintenance doses. Maintenance interval should be individualized to serum B12, methylmalonic acid, homocysteine, and clinical response [stabler2013].

Hydroxocobalamin Safety

Hydroxocobalamin has a benign safety profile at vitamin-replacement doses; the safety considerations that dominate the literature are concentrated at the high IV antidote doses used in cyanide poisoning. The volunteer safety package by Uhl and colleagues (2006) [5] in 70 healthy adults receiving placebo or 2.5, 5, 7.5, 10, or 15 g IV hydroxocobalamin reported pinkish-red discoloration of skin, sclera, and mucous membranes (uniform); red discoloration of urine (uniform, with duration proportional to dose); transient dose-related rise in systolic and diastolic blood pressure peaking at the end of infusion; and a low rate of self-limited gastrointestinal, headache, and injection-site events. The blood-pressure substudy by Uhl and colleagues (2008) [6] characterized the BP rise as correlated to plasma cobalamins-(III) concentrations, consistent with nitric-oxide scavenging.

Hypersensitivity reactions to hydroxocobalamin (anaphylactoid, urticarial, or facial flushing) have been reported and are listed in the Cyanokit label [1]. Acute kidney injury and oxalate nephropathy have been reported in case series after high-dose IV use; baseline and follow-up renal function monitoring is appropriate after Cyanokit administration. Chromogenic interference is clinically important: high plasma hydroxocobalamin concentrations interfere with several spectrophotometric chemistry assays (creatinine, AST, bilirubin, magnesium, iron) and co-oximetric measurements (carboxyhemoglobin, methemoglobin) for hours after dosing [4][27][28]. Cyanokit-administered patients should be flagged for clinical laboratories for the duration of detectable plasma cobalamins-(III) discoloration.

At vitamin-replacement IM/SC doses (typically 1 mg per injection), adverse events are uncommon and mild. The most frequent are injection-site reactions, transient mild flushing, and rare hypersensitivity. Compounded preparations should be assessed individually for excipient profile and sterility assurance.

Compounded sterile injectable preparations carry the general 503A pharmacovigilance considerations applicable to any compounded sterile injectable [29]: sterility, dose-strength accuracy, container-closure integrity, and beyond-use dating. RonanRx pharmacist review at dispensing is documented per the pharmacy's quality management system.

Contraindications

Hydroxocobalamin is contraindicated in patients with known serious hypersensitivity to hydroxocobalamin or to cyanocobalamin (cross-reactivity has been reported) or to any component of the formulation [1]. There are no other absolute contraindications for the cyanide-antidote indication; the risk-benefit calculation in known or suspected acute cyanide poisoning generally favors treatment in the absence of demonstrated hypersensitivity.

For outpatient compounded IM/SC use in vitamin B12 replacement, the principal practical contraindication is documented prior hypersensitivity. Caution applies in patients with active acute kidney injury when administering high doses, given the renal route of cobalamin elimination and case reports of oxalate nephropathy after high-dose IV use [1].

Drug interactions

Hydroxocobalamin does not undergo cytochrome P450 metabolism and is not expected to participate in CYP-mediated drug-drug interactions. The principal clinically relevant interaction is laboratory-assay interference: high plasma hydroxocobalamin concentrations (after Cyanokit IV administration) chromogenically interfere with several spectrophotometric chemistry assays and with co-oximetric carboxyhemoglobin and methemoglobin measurement [4][27][28] [1]. Clinical laboratories should be notified after Cyanokit administration; alternative analytic methods (CO-oximetry, GC-MS, ion-selective electrode) may need to be substituted for the duration of detectable plasma cobalamins-(III) discoloration.

Concurrent administration of hydroxocobalamin with sodium thiosulfate (the second component of the older Lilly cyanide antidote kit) is not contraindicated but is not in the Cyanokit label; if administered, sodium thiosulfate should be infused through a separate IV line to avoid chemical interaction in the line [1]. Concurrent use with nitrate vasodilators or nitroprusside is mechanistically opposed (hydroxocobalamin scavenges nitric oxide); clinical management should account for this interaction [20].

Adverse events

In the Uhl 2006 volunteer safety study [5] (N = 70 healthy adults), the most common adverse events with IV hydroxocobalamin 2.5, 15 g were: reversible pinkish-red discoloration of skin, sclera, and mucous membranes (essentially uniform, duration proportional to dose); red discoloration of urine (essentially uniform, duration proportional to dose, up to several weeks at the highest doses); transient dose-related rise in systolic and diastolic blood pressure; mild self-limited gastrointestinal symptoms (nausea, headache); and injection-site reactions. The Uhl 2008 BP substudy [6] characterized the hypertensive effect as correlated to plasma cobalamins-(III) concentrations.

In the Borron 2007 prospective clinical series [2] in 69 smoke-inhalation cyanide-poisoning patients, hydroxocobalamin 5, 15 g IV was associated with the same chromogenic effects on skin, mucous membranes, and urine, plus the transient hypertensive effect; no anaphylactoid events were reported. Post-

marketing reports filed with the Cyanokit label include hypersensitivity reactions (urticaria, facial flushing, anaphylactoid reactions) and rare cases of acute kidney injury and oxalate nephropathy [1].

Chromogenic interference is clinically important. Hydroxocobalamin's intense red color produces interference on multiple spectrophotometric chemistry assays, creatinine, AST, bilirubin, magnesium, iron, and on co-oximetric measurement of carboxyhemoglobin and methemoglobin [42728]. The interference can persist for hours to days at the high IV antidote doses and is rare at outpatient IM/SC vitamin-replacement doses.

At outpatient compounded IM/SC doses, adverse events are uncommon and generally limited to injection-site reactions, transient mild flushing, and rare hypersensitivity. Compounded sterile injectable pharmacovigilance considerations apply, including sterility-related events and dose-strength errors [29].

Monitoring Hydroxocobalamin Therapy

Baseline assessment for outpatient B12 replacement should include serum B12, methylmalonic acid, homocysteine, complete blood count with indices and peripheral smear, and clinical assessment for neurological involvement. Renal function and a focused medication history (proton-pump inhibitors, metformin, other interactions) round out the baseline workup. Pregnancy status should be confirmed and dose timing reviewed where relevant.

On therapy: serum B12 and clinical response at 1, 3 months; repeat methylmalonic acid and homocysteine where biochemical confirmation of deficiency was used at baseline [carmel2008; stabler2013]. Hematological parameters should normalize within 6, 8 weeks of replacement initiation; neurological recovery may take months. For the Cyanokit indication, monitoring includes hemodynamics (blood pressure, mean arterial pressure), oxygen saturation (with awareness that pulse oximetry and co-oximetric measurements may be artifactually altered), renal function, and the chromogenic interference period [fda_label_cyanokit; borron2007cohb; carlsson2011].

Hydroxocobalamin in Special Populations

Hydroxocobalamin Evidence Quality

Evidence supporting the FDA-approved Cyanokit indication for cyanide poisoning is moderate-to-strong for a rare acute toxicological emergency. The pivotal clinical evidence is the prospective open-label series by Borron and colleagues (2007) in 69 adult smoke-inhalation victims with measured pre-treatment cyanide levels, with 50% overall survival and 67% survival in patients without cardiac arrest at presentation [borron2007prospective]. This is supplemented by the volunteer PK and safety package [uhl2006safety, uhl2008bp], pharmacokinetic data in fire-victim cases [houeto1996], and the narrative review and meta-

summary literature [borron1996review, shepherd2008, thompson2012]. Randomized comparative trials versus the older Lilly nitrite-thiosulfate cyanide antidote kit have not been conducted and are not ethically feasible.

Evidence supporting outpatient B12 replacement with hydroxocobalamin is well-established but largely observational: classical retention studies [adams1965, boddy1968], a comparative clinical trial in pernicious anemia [tudhope1967], and consensus practice reviews [carmel2008, freeman1996, stabler2013] establish hydroxocobalamin's pharmacokinetic and clinical adequacy relative to cyanocobalamin. The principal pharmacokinetic finding, substantially greater tissue retention than cyanocobalamin (~30% vs ~8% at 1 week), is consistent across studies and underpins European-practice extended maintenance dosing intervals.

Evidence supporting off-label use in refractory vasoplegic syndrome after cardiopulmonary bypass is dominated by case reports and case series [roderique2014, burnes2017] aggregated in narrative reviews [shapeton2019, datt2021] and one 2024 systematic review and meta-analysis comparing hydroxocobalamin and methylene blue [cadd2024]. The mechanistic basis (cobalamins inhibit NOS isoforms; cobalamins scavenge NO) is well characterized [weinberg2009]. Phase III randomized comparative evidence in human vasoplegia is not available; the strongest comparative evidence to date is the Cadd 2024 systematic review and meta-analysis [cadd2024]. Evidence for distributive shock from sepsis is limited to mechanistic and preclinical data including a swine LPS-shock RCT [bebarta2019lps] and case reports.

Major Hydroxocobalamin Clinical Studies

Study	Design	Participants	Duration	Finding
Borron et al. (2007, Ann Emerg Med), Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation	Open-label prospective clinical series of adult smoke-inhalation victims with measured pre-treatment blood cyanide levels, treated with 5, 15 g IV hydroxocobalamin	69	Pre-hospital and inpatient through hospital discharge	Overall survival 50% (34/69); survival 67% in patients without cardiac arrest at presentation; 32 of 39 survivors had a favorable neurological outcome. The pivotal evidence supporting FDA approval of Cyanokit [borron2007prospective].
Uhl et al. (2006, Clin Toxicol), Safety of hydroxocobalamin in healthy volunteers	Randomized, placebo-controlled, single-dose study of IV hydroxocobalamin 2.5, 5, 7.5, 10, or 15 g vs placebo in healthy adult volunteers	70	Single-dose with 4-week follow-up	Reversible pinkish-red discoloration of skin, sclera, and urine (uniform; duration proportional to dose); transient dose-related rise in blood pressure; low rate of self-limited GI and injection-site events; no serious adverse events.

Study	Design	Participants	Duration	Finding
				Supported the Cyanokit safety package [uhl2006safety].
Uhl et al. (2008, Clin Toxicol), Blood pressure substudy	Randomized blood-pressure substudy assessing the relationship between plasma cobalamins-(III) concentrations and BP changes after IV hydroxocobalamin in healthy volunteers	—	—	Transient dose-related rise in systolic and diastolic blood pressure correlated to plasma cobalamins-(III) concentration; consistent with nitric-oxide scavenging as the mechanism [uhl2008bp]
Houeto et al. (1996, J Toxicol Clin Toxicol), PK in smoke inhalation victims	Pharmacokinetic study of IV hydroxocobalamin in adult smoke-inhalation fire-victim cases	—	—	Characterized plasma cobalamins-(III) concentration-time profile and urinary recovery after high-dose IV hydroxocobalamin in cyanide-poisoning conditions; informed the dose selection for the Borron 2007 prospective series and the Cyanokit label [houeto1996]
Adams and Kennedy (1965, J Lab Clin Med), Excretion and retention	Comparative excretion and retention study of parenteral hydroxocobalamin in pernicious-anemia subjects and non-anemic controls	—	—	Markedly lower urinary excretion of hydroxocobalamin vs cyanocobalamin in the 48 hours after parenteral dosing; supports greater tissue retention for the hydroxyl form [adams1965]
Boddy et al. (1968, Lancet), Whole-body retention	Comparative whole-body retention study of radio-labeled cyanocobalamin, hydroxocobalamin, and coenzyme B12 after parenteral administration	—	—	Approximately 30% of an injected hydroxocobalamin dose retained at 1 week vs approximately 8% for cyanocobalamin; foundational evidence for the pharmacokinetic superiority of hydroxocobalamin in B12 replacement [boddy1968]
Tudhope, Swan, and Spray (1967, Br J Haematol), Clinical	Clinical comparison trial of cyanocobalamin,	—	—	Higher and more sustained serum B12 levels with hydroxocobalamin than

Study	Design	Participants	Duration	Finding
trial in pernicious anemia	hydroxocobalamin, and cyanocobalamin-zinc tannate in patients with pernicious anemia			equimolar cyanocobalamin; supports the European-practice longer maintenance interval for hydroxocobalamin [tudhope1967]
Carmel (2008, Blood), How I treat cobalamin (vitamin B12) deficiency	Narrative clinical practice review of contemporary evaluation and treatment of cobalamin deficiency	—	—	Established the contemporary clinical-practice framework for B12 deficiency evaluation and replacement, including comparative roles of hydroxocobalamin and cyanocobalamin [carmel2008]
Stabler (2013, NEJM), Vitamin B12 deficiency (Clinical Practice)	Clinical Practice review article	—	—	Contemporary review of evaluation and treatment of vitamin B12 deficiency, addressing the choice of cobalamin form for replacement [stabler2013]
Weinberg et al. (2009, Free Radic Biol Med), Cobalamins inhibit NOS	In vitro biochemical study of cobalamins and cobinamides as inhibitors of nitric oxide synthase isoforms	—	—	Cobalamins (including hydroxocobalamin) and cobinamides directly inhibit neuronal, endothelial, and inducible NOS isoforms; mechanistic foundation for hydroxocobalamin's vasoplegia and distributive-shock indications [weinberg2009]
Roderique et al. (2014, Ann Thorac Surg), First vasoplegia case report	Case report	—	—	First reported use of high-dose IV hydroxocobalamin (5 g) for refractory vasoplegic syndrome after cardiopulmonary bypass; rapid hemodynamic improvement [roderique2014]
Burnes et al. (2017, J Cardiothorac Vasc Anesth), Vasoplegia case report	Case report	—	—	Hydroxocobalamin 5 g IV as rescue treatment for refractory vasoplegic syndrome after prolonged cardiopulmonary bypass; restored mean arterial pressure and allowed

Study	Design	Participants	Duration	Finding
				vasopressor de-escalation [burnes2017]
Bebarta et al. (2019, Clin Exp Pharmacol Physiol), Swine LPS-shock RCT	Prospective randomized trial of IV hydroxocobalamin vs noradrenaline vs saline in a swine LPS-induced distributive-shock model	—	—	Hydroxocobalamin raised mean arterial pressure relative to saline in LPS-induced hypotension; preclinical support for vasopressor-adjunct use in distributive shock [bebarta2019lps]
Cadd et al. (2024, J Cardiothorac Vasc Anesth), Systematic review and meta-analysis	Systematic review and meta-analysis of hydroxocobalamin vs methylene blue for vasoplegic shock following cardiopulmonary bypass	—	—	Comparable hemodynamic effects across pooled cohorts with a differing adverse-event profile; the most rigorous comparative evidence to date in this off-label indication [cadd2024]
Carlsson et al. (2011, Scand J Clin Lab Invest), Assay interference	Evaluation of hydroxocobalamin chromogenic interference across nine commonly used chemistry and co-oximetry analyzers	—	—	Therapeutic-range plasma hydroxocobalamin produces clinically significant interference on multiple spectrophotometric assays and on co-oximetric measurement of carboxyhemoglobin and methemoglobin [carlsson2011]
Ranjitkar and Greene (2015, Clin Chim Acta), DxC/AU680 interference	Analytic evaluation of hydroxocobalamin interference on Beckman Coulter DxC and AU680 chemistry analyzers	—	—	Therapeutic hydroxocobalamin concentrations interfere with several spectrophotometric assays on these specific analyzers; supports the case for laboratory notification after Cyanokit administration [ranjitkar2015]
Thompson and Marrs (2012, Clin Toxicol), Cyanide poisoning review	Comprehensive narrative review	—	—	Reviewed the chemistry, pharmacology, pharmacokinetics, clinical evidence, and operational role of hydroxocobalamin in cyanide poisoning; consolidated the

Study	Design	Participants	Duration	Finding
				evidence supporting Cyanokit [thompson2012]
Shepherd and Velez (2008, Ann Pharmacother), Role of hydroxocobalamin	Narrative review	—	—	Reviewed the role of hydroxocobalamin in acute cyanide poisoning, including comparative considerations vs the older Lilly nitrite-thiosulfate kit and operational use in pre-hospital and emergency-department settings [shepherd2008]
Shapeton et al. (2019, J Cardiothorac Vasc Anesth), Vasoplegia review	Narrative review	—	—	Reviewed the off-label use of hydroxocobalamin in vasoplegic syndrome, mechanistic basis, dosing considerations, and adverse-event profile [shapeton2019]

Hydroxocobalamin Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Hydroxocobalamin is administered parenterally (IV in the cyanide-antidote indication; IM or SC in outpatient B12 replacement). After IV administration, hydroxocobalamin binds rapidly and extensively to plasma transcobalamin II, albumin, and other plasma proteins [tudhope1967]. Total cobalamins-(III) plasma concentrations peak at the end of infusion. The terminal elimination half-life is approximately 26, 31 hours after a 5 g IV dose in healthy volunteers [uhl2006safety]. Approximately 50, 60% of an administered dose is recovered unchanged in urine over 72 hours; the remainder is slowly redistributed and excreted over weeks.

Compared with cyanocobalamin at equimolar parenteral doses, hydroxocobalamin shows substantially higher tissue retention: approximately 30% of an injected dose is retained at 1 week vs approximately 8% for cyanocobalamin [boddy1968, adams1965] [tudhope1967]. This difference reflects higher plasma protein binding for the hydroxyl form and slower urinary excretion; it is the pharmacokinetic basis for the longer maintenance dosing intervals used for hydroxocobalamin in B12 replacement [houeto1996].

After IM or SC administration in outpatient B12 replacement (typical doses 1 mg per injection), absorption is essentially complete and the elimination kinetics parallel those after IV administration at the lower dose range [tudhope1967]. Compounded preparations may differ from any reference product in concentration,

excipient profile, and container closure; the manufactured Cyanokit IV PK data should not be assumed to translate without separate evaluation.

Pharmacodynamics

In B12 replacement, the pharmacodynamic endpoints are correction of macrocytic anemia, normalization of methylmalonic acid and homocysteine, and resolution of neurological signs and symptoms. Hematological response is typically observable within 1, 2 weeks and complete by 6, 8 weeks; neurological recovery is slower.

In the cyanide-antidote indication, the pharmacodynamic endpoint is reversal of cellular asphyxiation from cyanide-mediated cytochrome-c oxidase inhibition. Surrogate measurements include lactate clearance, mean arterial pressure stabilization, mental-status recovery, and (in retrospect) measured fall in blood cyanide level [borron2007prospective, houeto1996]. In the off-label vasoplegia indication, the pharmacodynamic endpoint is increase in mean arterial pressure and reduction in vasopressor requirement [roderique2014, burnes2017, cadd2024]; the mechanistic substrate is direct NOS inhibition and NO scavenging [weinberg2009].

↓↑ Comparing Hydroxocobalamin Formulations

The manufactured product is Cyanokit (Meridian Medical Technologies / Mylan / Viatris), a 5 g lyophilized powder for reconstitution and IV infusion in cyanide poisoning. It is not intended for outpatient IM/SC B12 replacement. There is no FDA-approved manufactured standalone IM or SC hydroxocobalamin product in the US [fda_label_cyanokit].

Compounded sterile injectable hydroxocobalamin preparations (typically 1 mg/mL or 5 mg/mL for IM or SC use) are dispensed by 503A pharmacies on patient-specific prescriptions. They vary in concentration, excipient profile (preservative-containing vs preservative-free), and container closure. They are not bioequivalent to Cyanokit and are not intended for cyanide-antidote IV use; clinicians and patients should anticipate that local PK and tolerability may differ from manufactured-product data when switching or initiating therapy. The principal alternative manufactured cobalamin product in the US is cyanocobalamin (multiple manufactured generic IM/SC injection products) [carmel2008, freeman1996] [fda_label_cyanokit].

🌡 Hydroxocobalamin Storage and Handling

Manufactured Cyanokit is stored at controlled room temperature (15, 30°C / 59, 86°F) per labeling, protected from light. Reconstituted Cyanokit should be used within 6 hours per the label. Compounded sterile injectable hydroxocobalamin is stored per the pharmacy's stability data and beyond-use date

assignment under USP <797>; refrigerated storage with light protection is typical for multi-dose preparations, given hydroxocobalamin's known photo-instability [usp_797].

Hydroxocobalamin is light-sensitive and should be stored in light-protective amber or opaque container closures [fda_label_cyanokit].

Hydroxocobalamin Compounding & Operations

503A compounding

Compounded hydroxocobalamin is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares sterile injectable preparations 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 [fda503a; usp_797; usp_795]. For any nonsterile preparative steps the corresponding USP General Chapter <795> applies; however, the finished injectable product is governed by <797> in full.

Beyond-use dating, ingredient identity verification, sterility assurance, light-protection during storage, and stability assessment follow USP <797> requirements. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from active pharmaceutical ingredient lot through dispensing.

Pharmacist review

Each prescription for compounded hydroxocobalamin undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that the manufactured cyanocobalamin product (the dominant manufactured B12 generic in the US for outpatient IM/SC use) is not appropriate, typically intolerance, optic-nerve-disease context (tobacco amblyopia, LHON carrier), chronic cyanide-exposure context, excipient sensitivity, or a documented prescriber rationale based on the comparative tissue-retention advantage of hydroxocobalamin; absence of contraindications (prior hypersensitivity to hydroxocobalamin or cyanocobalamin) [fda_label_cyanokit]; appropriate concomitant medication review; and a prescribed regimen consistent with established hydroxocobalamin replacement practice [carmel2008] [adams1965].

RonanRx does not fill prescriptions for compounded hydroxocobalamin as a routine substitution for cyanocobalamin without a documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy] [boddy1968; tudhope1967]. Compounded sterile injectable pharmacovigilance considerations apply across the supply chain, and the pharmacist's review documents that the patient's prescription does not present sterility, dose-strength, container-closure, or excipient red flags.

Quality and traceability

Active pharmaceutical ingredients are 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 test result, endotoxin test result, light-protection during storage, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Compounded sterile injectable hydroxocobalamin is typically refrigerated and protected from light through the supply chain. Refrigerated transport with temperature monitoring is used between the compounding pharmacy and the patient [usp_797]. Patients are advised to refrigerate and light-protect the product on arrival, to inspect for temperature excursions, and to contact the pharmacy if cold-chain integrity is in question. Manufactured Cyanokit is stored at controlled room temperature per its label and is not a cold-chain product [fda_label_cyanokit].

Frequently Asked Questions About Hydroxocobalamin

Is compounded hydroxocobalamin the same as Cyanokit?

No. Cyanokit is the FDA-approved manufactured hydroxocobalamin product, a 5 g lyophilized powder kit for intravenous infusion in cyanide poisoning [fda_label_cyanokit]. Compounded hydroxocobalamin is pharmacy-prepared on a patient-specific prescription, typically at 1 mg/mL or 5 mg/mL for intramuscular or subcutaneous outpatient use in vitamin B12 replacement or related contexts. Compounded drugs are not FDA-approved and are not bioequivalent to Cyanokit [fda503a].

Why would a clinician choose hydroxocobalamin over cyanocobalamin?

Hydroxocobalamin is the physiological circulating form of vitamin B12 and has substantially greater tissue retention than cyanocobalamin after parenteral dosing, approximately 30% retention at 1 week vs approximately 8% for cyanocobalamin in classical comparative studies [boddy1968; adams1965; carmel2008]. Clinical reasons to prefer hydroxocobalamin include intolerance to cyanocobalamin, tobacco-related toxic optic neuropathy where the cyano- group is undesirable, family history or carrier status for Leber hereditary optic neuropathy, chronic dietary cyanide exposure, and excipient sensitivity to the manufactured cyanocobalamin product [tudhope1967; freeman1996; leighton1979].

Is hydroxocobalamin used for anything other than B12 replacement?

Yes. The FDA-approved indication is cyanide poisoning, where Cyanokit (5 g IV) acts as a stoichiometric chelator forming non-toxic cyanocobalamin [fda_label_cyanokit; borron2007prospective]. Off-label uses include rescue treatment of refractory vasoplegic syndrome after cardiopulmonary bypass and vasopressor-

adjunct treatment of distributive shock from sepsis; both off-label uses rest on the mechanistic basis that cobalamins directly inhibit nitric oxide synthase [roderique2014; cadd2024; weinberg2009].

Why is there no over-the-counter IM hydroxocobalamin generic in the US?

In the US, the manufactured outpatient B12 injection market is dominated by cyanocobalamin generic products. The only FDA-approved hydroxocobalamin product is Cyanokit, which is an emergency 5 g IV cyanide-antidote kit and not intended for outpatient B12 replacement [fda_label_cyanokit]. Patients who need outpatient IM or SC hydroxocobalamin therefore obtain it via 503A compounding pharmacies on patient-specific prescriptions [carmel2008].

What are the side effects of hydroxocobalamin?

At outpatient IM/SC B12-replacement doses, side effects are uncommon and mild, injection-site reactions, transient flushing, and rare hypersensitivity [carlsson2011; ranjitkar2015]. At the high IV antidote doses used in cyanide poisoning, reversible pinkish-red discoloration of skin, sclera, and urine is essentially uniform; transient mild blood-pressure elevation occurs; and chromogenic interference with several spectrophotometric chemistry assays and with co-oximetric carboxyhemoglobin and methemoglobin measurement is clinically important and persists for hours to days [uhl2006safety; uhl2008bp; borron2007cohb].

Does RonanRx sell compounded hydroxocobalamin directly to patients?

No. Compounded hydroxocobalamin requires a patient-specific prescription written by a licensed clinician for an identified patient with a documented clinical reason that a manufactured 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 Hydroxocobalamin

Compounded Hydroxocobalamin 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 Hydroxocobalamin, 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)