

Vitamin B12 Lozenges



As methylcobalamin, a highly bioavailable form of B12

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Vitamin B12 Lozenges are a great tasting, high dose vitamin B12 product. Each berry flavored lozenge contains 5000 mcg methylcobalamin, a highly bioavailable form of B12. Methylcobalamin is naturally present in foods, and can be readily converted to the active intracellular forms of B12, such as methylcobalamin, adenosylcobalamin, glutathionylcobalamin, and possibly other physiologically active B12 forms. B12 lozenges are formulated to support healthy levels of vitamin B12.

The Lozenge Advantage

This product is designed to deliver B12 through the mucous membranes in order to bypass the need for intrinsic factor (IF), a protein produced in the stomach known to be needed for one route of GI absorption of B12. It uses a lozenge delivery system, allowing for two routes of absorption for B12: 1) directly through the oral mucosa, and 2) bound by haptocorrin (binding protein secreted in saliva) and carried to the GI tract where it may be absorbed by passive diffusion.

Absorption Routes and Rates of Supplemental B12 Absorption

It is commonly accepted that vitamin B12 is absorbed and transported across cellular plasma membranes in the terminal ileum by two alternate mechanisms:

(i) Endocytosis of B12 bound to gastric IF. This route has limited efficiency due to IF saturation at around 2 mcg per meal, and it is severely impaired in various conditions.

(ii) Passive diffusion directly into the intestinal cell by mass action of very high doses of B12. One study evaluated absorption rates of B12 (as cyanocobalamin) when given at escalating doses.¹¹⁶ The results revealed absorption rates of approximately 50% for doses up to 0.5 mcg, 20% for doses around 1 mcg, and only 1-1.2% for doses around 500 mcg. By extrapolation, approximately 10-12 mcg may be absorbed from a total of 1000 mcg B12 ingested at one time. Since the natural form of B12, methylcobalamin, is more bioavailable, it may have higher absorption rates than cyanocobalamin, but as of yet these rates have not been determined.

Supplementation with B12 May Be Beneficial For:*

- **Nervous system related impairments:** brain and nerve function, conditions where the need for myelin repair is increased, such as during chemotherapy (for cancer, arthritis, lupus) or any condition involving neurological autoimmunity. Many of these conditions may involve poor cognition, dementia, dizziness, postural hypotension, tinnitus, neuropathy, or hyporeflexia.
- **Impaired healing of oral or GI mucosa:** canker sores, various inflammatory conditions of the gut, or during treatment with NSAIDs or chemotherapy. Gastric mucosal damage causes B12 malabsorption, thus creating a vicious cycle of worsening B12 status and the health of all mucosal membranes.²³
- **Low white blood cells:** which impairs immunity.
- **Low platelet count:** which impairs healing.
- **Anemia, and/or macrocytic red blood cells:** (high mean corpuscular volume), impaired circulation and oxygen supply.
- **Elevated homocysteine:** associated with increased risk of birth defects, cardiovascular disease and Alzheimer's. It is also an indicator of systemically impaired capacity for methylation, which is involved in neurotransmitter synthesis and clearance, hormone methylation and genetic expression through DNA methylation. Some of these conditions may involve depression, anxiety, mania, poor appetite, loss of taste, and a higher risk of cancer.
- **Conditions that involve impairment of energy production and/or low oxygen supply to cells:** may include generalized fatigue, anemia, heart failure, respiratory disease, and shortness of breath.
- **Poor sleep quality:** B12 may be involved in normalization of circadian rhythm.¹⁰⁵
- **Impotence, incontinence**
- **Infertility or high risk of miscarriage or birth defects (5X higher for spina bifida) and poor cognitive and motor development of the fetus or infant,** due to mother's B12 deficiency during pregnancy and breastfeeding.

Mechanisms of Action of B12

B12 is in high demand by cells with high turnover rate, such as epithelial cells in skin, oral and GI mucosa. B12 is instrumental to new DNA synthesis needed for optimal cell replication and differentiation. Pregnancy is an especially demanding condition where healthy cell division and differentiation is needed for adequate fetal development.

B12 supports energy production from branched chain amino acids, odd-chain fatty acids and cholesterol by providing the mitochondrial enzyme cofactor adenosylcobalamin. Buildup of odd-chain fatty acids may cause demyelination.

B12 supports the immune response to various infectious agents (oral or systemic). Adequate B12 status is required for the proper proliferation of immune cells.

B12 has been shown to alleviate certain aspects of the autoimmune response, which has been implicated in canker sore outbreaks. B12 supplementation has been shown to alleviate the severity of canker sores^{25,26,57,59,66,73,115} and various autoimmune diseases such as atopic dermatitis⁹² and rheumatoid arthritis.⁸⁷ B12 was shown to have a balancing effect on the immune response by down-regulating inflammatory processes mediated by inducible nitric oxide synthase (iNOS).

B12 was shown to reduce toxicity of heavy metals such as mercury. Heavy metal toxicity may contribute to various pathologies of the nervous system or autoimmune response by binding to body proteins, which dysregulates immune tolerance.⁹⁵

Conditions Associated with B12 Deficiency

There are many conditions where a B12 deficiency acts as an etiological or aggravating factor. Many of these have been shown to improve with adequate B12 supplementation (very high doses such as 0.5 mg, 1 mg or more). It is often necessary to optimize the status of many other synergistic nutrients in order to support the reversal of these conditions. Folate is one of the most important cofactors that helps realize the benefits of optimizing B12 status. Other B vitamins, essential minerals, and fatty acids may also have crucial effects in allowing B12 benefits to be maximized, thus the need to supplement with multivitamin, multimineral and essential fatty acid formulas should always be evaluated. (Consider using Trifolamin™ lozenges [3000 mcg B12 plus 680 mcg DFE] for those who may benefit from additional folate along with B12.)

B12 Deficiencies

There are many causes of B12 deficiency, a far more common occurrence, one that is most likely far more common than many practitioners may realize. Vitamin B12 is found only in animal foods, in a wide range of meat and dairy products. Thus, vegetarians and vegans should be tested for B12 deficiency and should supplement vitamin B12 daily. Keep in mind that a serum deficiency may not show up for quite some time. Functional markers, such as the methylmalonic acid (MMA) test, is a preferred method of determining functional B12 status in individuals.

Common Causes of Functional B12 Deficiency

a. Inadequate dietary intake of B12. Vitamin B12 is readily available only in animal products, primarily dairy, meat, and eggs,⁶⁴ making vegetarians and vegans at highest risk for deficiency. Many vegan sources of B12, such as fermented spirulina or brewer's yeast, may include a high proportion of B12 analogues with no B12 activity in human physiology.^{186,187} Also, as much as 33% of vitamin B12 may be lost due to heating, which is commonly used with animal-derived foods.¹⁵³

b. Malabsorption of B12 from food. This becomes more prevalent with aging, especially after the age of 50.¹⁵⁰

B12 malabsorption may be caused by any of the following^{117,132}:

b.1. Inadequate stomach acidity. Hydrochloric acid (HCl) releases B12 from food proteins, which is a prerequisite for its binding to haptocorrin and then to intrinsic factor (IF), which carries it during GI absorption.⁶³ However, the metabolism of B12 found in nutritional supplements does not require optimal HCl levels.

Insufficient stomach acidity may be due to:

- Suboptimal HCl production, which may be the result of conditions such as atrophic gastritis or H. Pylori infection. Atrophy of the gastric mucosa is more prevalent in the elderly⁶² and those infected with *H. Pylori* (*H. Pylori* has a 30%-40% incidence in the US and 70% in developing countries.¹⁶⁵)
- Pharmaceutical drugs that neutralize HCl or reduce HCl production
- Nutritional supplements containing calcium carbonate

b.2. Inadequate pancreatic protease production, which cleaves B12 from haptocorrin and transfers it to IF

b.3. Impaired production of IF. This may be due to congenital IF deficiency, atrophic gastritis or autoimmune conditions that cause antibodies to gastric parietal cells or IF (also referred to as pernicious anemia). Other potential causes include gastric surgeries (gastric bypass), gastric ulcers or cancer.

b.4. GI disorders: ulcerative colitis, celiac disease and other gastro-pathologies due to GI inflammation/infections; treatment with antibiotics or chemotherapy.⁶⁶

b.5. Pharmaceutical drug side-effects. Metformin interferes with B12 absorption.⁶⁵

b.6. Poor B12 binding to transcobalamin (a B12 transport protein in the blood), due to genetic polymorphisms

c. Poor intracellular metabolism of B12. Various genetic polymorphisms may result in poor release of cobalamin from the lysosome or poor conversion of cobalamin to the active forms of B12. Glutathione-S transferase is involved in this step.

Special Features of the B12 Form of Methylcobalamin Found in Vitamin B12 Lozenges

(a more detailed explanation is found in "Position Paper on Vitamin B12 Forms," available upon request from Designs for Health)

The form of B12 found in Vitamin B12 Lozenges is naturally occurring, and commonly found in animal foods as well as in some fermented vegetarian foods. This B12 form is highly bioavailable, most likely because it is bioidentical to the methylcobalamin form occurring in human physiology.^{116, 173} Specifically, methylcobalamin (MeCbl) is more bioavailable than the cyanocobalamin form found in many supplements and used for food fortification.^{143, 186} Cyanocobalamin is not a naturally occurring molecule and some individuals have genetic difficulties breaking down its bond to enable activation in the body. One study that compared its bioavailability with MeCbl showed that it had 3X higher excretion in the urine and much less retention in the liver.¹⁴³ In addition, the hydrolysis of this compound produces small amounts of cyanide. Historically, cyanocobalamin was the most common form of supplemental B12 and presented stability advantages in solution for B12 injections and in fortified foods. Today, however, there is no reason to use this form since other bioidentical forms of B12 are available and stable.

Vitamin B12's metabolic conversions are illustrated in Fig.1. Methylcobalamin delivered orally by B12 lozenges converts first to a cobalamin intermediate and then to the two main intracellular active forms of B12: methylcobalamin and adenosylcobalamin (AdCbl). It is important to note that the methyl ligand provided by oral methylcobalamin is cleaved upon cell entry and is not utilized as such during further metabolic activations. It may be that the physiological rationale for this is to even the playing field by making the synthesis of B12's active forms independent of the form of B12 ingested.

The amounts of MeCbl and AdCbl synthesized from methylcobalamin are dictated by cellular conditions and sometimes influenced by genetic polymorphisms. Genetics can affect the activity of enzymes involved in B12 metabolism, absorption and/or binding to blood transport proteins. However, there are no genetic data available at this time that point to specific advantages of any particular form of B12. **Thus, it is impossible to predict whether any particular individual will respond better to any one of the three natural, commercially available forms of B12, namely, methylcobalamin, hydroxycobalamin or adenosylcobalamin.**

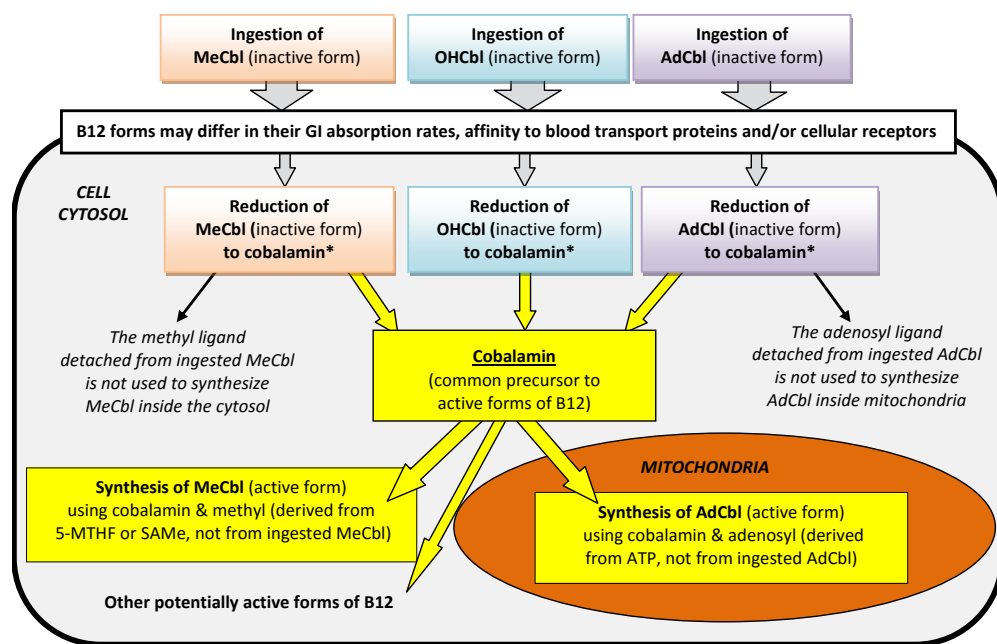
If there is no satisfactory clinical response to methylcobalamin supplementation due to unknown factors, Designs for Health offers Trifolamin™, an alternative B12 formula **which includes all three forms of B12 mentioned above, in equal amounts, for maximal clinical efficacy to possibly overcome various genetic polymorphisms or clinical conditions involving B12 metabolism and related pathways.**

Clearing up Misconceptions about B12

1. It is a misconception that the methyl groups from supplemental MeCbl participate in intracellular methylation reactions, thus affecting the cellular levels of SAMe (universal methyl donor). In contrast, studies have shown that only 5-MTHF or SAMe can provide methyl groups that bind to cobalamin and form MeCbl inside the cytosol.^{173, 183} In a subsequent reaction, MeCbl donates its methyl group to homocysteine, while being reduced at the same time back to cobalamin. Then the cycle repeats itself where cobalamin proceeds to pick up another methyl group from 5-MTHF or SAMe, and so on. Studies show that these reactions are not influenced by the methyl groups included with ingested MeCbl. The only other methyl group providers for the homocysteine methylation pathways are betaine and choline. As a result of this misconception, another invalid concept has been promoted stating that supplementing with hydroxycobalamin (OHCbl) versus MeCbl may result in lower intracellular levels of SAMe. This has been disproven by research reviewed in detail in the "Position Paper on Vitamin B12 Forms."

2. Similarly, there is a misconception that the adenosyl group from supplemental AdCbl is used in the synthesis of intra-mitochondrial AdCbl or the synthesis of SAMe, thus making supplemental AdCbl more suited than methylcobalamin or hydroxycobalamin for those with genetic impairment of AdCbl or SAMe synthesis. This was disproven by research that looked at individuals with methylmalonic aciduria who have a severe genetic impairment of synthesizing AdCbl and could not be helped by AdCbl supplementation or any other form of B12. Research shows that the adenosyl ligand is synthesized from ATP inside mitochondria, while the adenosyl ligands brought in by supplemental AdCbl are not utilized as such.^{131,133,168} The only approach that may help individuals with such polymorphisms would be to supplement with higher doses of B12 (such as with methylcobalamin or with all three forms of B12, as offered by DFH's Trifolamin™) to hopefully "push" some of these pathways by mass action in hopes of producing more of the metabolites needed.

Fig. 1 Genetic SNPs may affect various steps in B12 absorption, blood transport and/or conversions to intracellular active forms of B12. (adapted from references 133, 142, 168, 200)



*B12 is converted to cobalamin at different rates among B12 forms and using enzymes specialized for their particular ligand

Advantages of Vitamin B12 from Supplements vs. Food¹⁶²

- **High doses (>1000 mcg) of B12** can be incorporated in supplements at levels approximately 100X higher than even those found in healthy/Paleo diets at 10-20 mcg B12/day. A US survey found an average intake of B12 of 5.3 mcg/day from food alone and 24.4 mcg/day from food + B12 fortified food + B12 supplements.
- **Circumvent the deficiency of IF** and push B12 absorption through the GI border and oral mucosa by diffusion at rates of 1-1.2%. Absorption by IF may be saturated at around 1-2 mcg per meal.
- **Supplemental B12 forms are not protein-bound**, thus they bypass the need for HCl and proteolytic enzymes, which are typically required to separate B12 from food proteins.
- **B12 deficiency may take a long time to be corrected without high dose supplementation.** Body stores of B12 (mostly in the liver) have been estimated at 2500 mcg. Thus, a patient who is very depleted in B12 may need approximately 50 Vitamin B12 lozenges to support a significant repletion (assuming that 10-12 mcg are absorbed from 1 mg B12). The amount of B12 derived from most multivitamins and fortified foods is often inadequate, as they contain much less than 1000 mcg of B12 per dose and are often in the cyanocobalamin form, which may only be 70-80% bioavailable for some individuals, but not bioavailable at all for those with of genetics-related difficulty cleaving the cyano ligand.

Supplement Facts

Serving Size 1 lozenge

Amount Per Serving	% Daily Value	
Vitamin B-12 (as Methylcobalamin)	5000 mcg	208,333%

Other Ingredients: Mannitol, modified cellulose, natural berry flavor, vegetable stearate, citric acid, luo han guo extract (fruit).

RDA of B12 May Not Support Optimal Health

The generally accepted guidelines set by the Institute of Medicine (IOM) through the **RDA tables recommend an intake of 2.4 mcg of vitamin B12 per day** for adults under 50 years old. The recommended B12 RDAs for pregnant and nursing women are 2.5 mcg and 2.6 mcg, respectively.¹⁵⁰ For individuals over 50 years of age, the RDA for B12 is 150-200 mcg. This dose, which is much higher than the regular RDA for the younger population, is justified by the fact that 10-30% of older individuals may absorb B12 poorly, whether from natural foods, fortified foods or supplements.¹⁵⁰ However, malabsorption may obviously happen for younger individuals as well due to various conditions described earlier. One study showed that 4-7 mcg of B12 are needed to optimize the B12 status markers homocysteine and methylmalonic acid,¹⁸⁴ which is proof with one line of evidence that the RDA for B12 is suboptimal.

Researcher M. Fenech has published a number of studies proposing new criteria for optimal intake of certain vitamins, including folate and B12.^{77, 144, 145, 158} He found that a level of B12 intake above 7 mcg/day is optimal, as long as serum levels of B12 are also maintained above 406 ng/ml. His research shows that meeting these goals correlates with the lowest level of chromosomal damage found in lymphocytes and probably other cells.¹⁴⁵ In addition, adequate folate status is needed to support healthy DNA replication because the metabolic pathways of B12 and folate are interrelated in supporting this physiological function.

Prominent Paleo diet researcher Loren Cordain provided a novel frame of reference for optimization of macro- and micronutrient intakes. Cordain has published an analysis of a sample Paleolithic-type diet implemented with readily available modern foods.¹⁴⁶ He estimated that the average B12 content of a 2200 Kcal Paleolithic-type diet was 17.6 mcg/day, while that of folates was 891 mcg/day. Consequently, we propose here that an optimal intake of vitamin B12 may be at least as high as the average evolutionary intake of vitamin B12 to which humans have adapted for millions of years, which is approximately 17.6 mcg/day, and which also meets and exceeds recommendations based on Fenech's criteria of 7mcg/day. In addition, for individuals who may absorb as little as 1% of the ingested B12 dose, the recommendation needs to be approximately 100X higher, which is approximately 1760 mcg B12.

Recommended Use:

- Dissolve one lozenge slowly in mouth and swallow per day, or as directed by your health care practitioner.
- Best taken after a meal. The B12 portion carried to the GI tract needs to be released from the haptocorrin transport protein by proteases, which are typically secreted in the GI tract in response to food.

For a list of references cited in this document, please visit:

<https://www.designsforhealth.com/techsheet-references/vitamin-b12-lozenges-references.pdf>

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Health care practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

To contact Designs for Health, please call us at (860) 623-6314, or visit us on the web at www.designsforhealth.com.