MTHFR SUPPORT AUSTRALIA
TECHNICAL MANUAL
Patients with MTHFR and methylation issues require a unique approach. The standard products on the market may not be suitable for those with specific issues and therefore a more targeted programme is required.

The ability to split your B vitamins is desirable as each patient will have a different need and this allows you to tailor to the individual patient.

What is methylation?

Methylation or one carbon metabolism is a network of interrelated biochemical pathways for reduction or oxidation and transfer to other compounds. This allows the transfer of a methyl group (one carbon and three hydrogen atoms) onto amino acids, proteins, enzymes and DNA in every cell and tissue of the body. This regulates healing, produces energy, genetic expression of DNA, synthesises neurotransmitters, liver detoxification, immunity and hormonal clearance. So disturbances in this methylation pathway can have significant and widespread effects on many body systems.

The key pathways are the folate pathway (of which the MTHFR gene is a crucial final step), the methionine pathway which plays a major role in methyl group metabolism as it allows the recycling of homocysteine back to methionine and elimination via the CBS (Cystathione beta synthase pathway). The methionine synthase enzyme contains a cobalamin cofactor which ensures that with the help of Vitamin B12 the methyl group is transferred to homocysteine. Methionine, which is regenerated from homocysteine is then converted to S-adenosylmethionine (AdoMET). AdoMet then donates the methyl group it obtained from 5-MTHF to over 80 biological methylation reactions, including the methylation of DNA, RNA, proteins, lipids and lipoproteins. The key methyltransferases are the enzyme groups that benefit from this donation of methyl’s by AdoMET.

What is MTHFR?

MTHFR is a gene, which produces the MTHFR (methylene tetrahydrofolate reductase) enzyme and is considered a key enzyme in one-carbon metabolism, because it catalyses the irreversible conversion of 5,10-methylene THF to 5-methyl tetrahydrofolate. 5-MTHF is our active folate that is then used in the methylation cycle.
What happens if MTHFR activity is reduced?

1. 5-MTHF levels go down
2. Transmethylation cycle slows
3. All tissues except liver and kidney show effects of decreased methylation which leads to:
   - Decreased neurotransmitter production
   - Deficiency in glutathione
4. BHMT becomes depleted in choline which causes:

http://www.aacc.org/publications/cln/2011/january/Pages/FolateMetabolismFigure.aspx
homocysteine levels to rise
methylation in the liver and kidneys decrease
phosphatidylcholine production drops causing cell membrane and myelin instability

This may then have affects for the following conditions:

- Diabetes
- Cancer
- Pulmonary embolisms
- Cleft palate
- Spina Bifida
- Autism
- Parkinson’s Disease
- Neural tube defects
- Cardiovascular disease – atherosclerosis, elevated cholesterol, hypertension, fat metabolism issues
- Immune deficiency
- ADD/ADHD
- MS
- Alzheimer’s
- Anxiety
- Schizophrenia
- Bipolar
- Allergies
- Chemical sensitivity
- Congenital Heart defects
- Fibromyalgia
- Chronic fatigue syndrome
- Depression
- Alcoholism
- Addictive behaviours
- Insomnia
- Downs syndrome
- Autism
- Chronic viral infection
- Thyroid dysfunction
- Neuropathy
- Recurrent miscarriage
- Infertility

References


4. Homocysteine and Risk of Ischemic Heart Disease and Stroke A Meta-analysis

Starter B

Dietary Supplement
TGA Approved.

Contains 60 capsules
Product order code: STARTER B

Starter B. STEP 1 IN METHYLATION SUPPORT

This is the first step in methylation support. Provides initial support for people with the MTHFR gene mutation to aid, assist or help support as a cofactor for key enzymes in the methylation Cycle.
This product does not contain B12 or folate which allows you to supplement with different forms of B12 and folate as indicated.

DIRECTIONS FOR USE:
Take 1 capsule after breakfast. Start with Starter B for two weeks before introducing your B12. Then wait another week before introducing your folate.

OTHER INGREDIENTS:
Vegetable Cellulose, water, ascorbyl palmitate.

FREE OF:
gluten, soy, corn, egg, dairy, GMO, fish, shellfish, nuts or prebiotics.
Vegan/Vegetarian friendly

<table>
<thead>
<tr>
<th>Each capsule contains:</th>
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<tbody>
<tr>
<td>B5, Pantothenic acid</td>
<td>180 mg</td>
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<tr>
<td>(as Calcium pantothenate)</td>
<td></td>
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<tr>
<td>B3, Niacin (Nicotinamide)</td>
<td>130 mg</td>
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<tr>
<td>B1, Thiamine (as Thiamine hydrochloride)</td>
<td>50 mg</td>
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<tr>
<td>B2, Riboflavin sodium phosphate (Riboflavin 5 phosphate)</td>
<td>25 mg</td>
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<tr>
<td>B6, Pyridoxine (as Pyridoxal 5 phosphate)</td>
<td>15 mg</td>
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<tr>
<td>Biotin</td>
<td>500 mcg</td>
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**Starter B & Methylation Support**

**Specific Indication:** Step 1 in methylation support. Initial support for people with the MTHFR gene mutation to aid, assist in or help support as a cofactor for key enzymes in the methylation cycle (Figure 1).

**Pharmaceutical Effects:** Starter B contains six B vitamins without Vitamin B12 or folate.

**Clinical Benefits:** The B vitamins all act as cofactors in the methylation cycle to support critical enzymes integral to the pathway.

Thiamin (B1) and Pyridoxine (B6) are confirmed by human clinical trials to work together to cause a decrease in DNA glycation.\(^1\,^3\) Human studies show that the effect of Thiamin decreasing DNA glycation results in higher levels of methylation.\(^2,^3\)

Riboflavin (B2) acts as a cofactor for folate and so increases methylation. It is the limiting nutrient for pyridoxine folate and B12 metabolism.\(^2,^3,^4\) It can also assist niacin in reducing excessive DNA methylation.\(^2\) It is the cofactor for the MTHFR gene.

Niacin (nicotinamide, B3) and its derivative nicotinamide are dietary precursors of nicotinamide adenine dinucleotide (NAD). NAD functions in oxidation-reduction (redox) reactions and non-redox reactions.\(^11\) NAD is an important cofactor for MTRR (methionine synthase reductase) enzyme.
Pantothenic acid (B5) is confirmed by human clinical trials to improve the nutritional and metabolic status of the genome including DNA methylation,\textsuperscript{16,17} particularly for mental health in adults and psychology in children.\textsuperscript{18,19,20}

Pyridoxine (B6) is confirmed by human clinical trials to increase DNA methylation levels and work together with riboflavin, folate, and B12.\textsuperscript{21,22} Deficiency of Pyridoxine in animals results in reduction of DNA methylation.\textsuperscript{23,24} B6 is an important cofactor for the CBS pathway.

Biotin (B7) is confirmed by human clinical trials to be related to folate in its DNA methylation functions.\textsuperscript{16,25} It works with other vitamins, such as pantothenic acid, riboflavin, niacin, pyridoxine, folate and B12, to play essential roles in maintaining mitochondrial functions including DNA methylation.\textsuperscript{2}

All doses are safe according to the Australian RDI and the U. S. DRI.

References


21 Pirouzpanah S, Taleban FA, Mehdipour P, Atri M. Association of folate and other one-carbon related nutrients with hypermethylation status and expression of RARB, BRCA1, and RASSF1A genes in breast cancer patients. Journal of molecular medicine (Berlin, Germany), August 2015, 93(8), 917-34. PubMed PMID: 25805039


Hydroxy B12

Hydroxocobalamin B12–2,000mcg Chewable Tablet.

STEP 2 IN METHYLATION SUPPORT
Hydroxocobalamin B12.

CONTAINS 60 CHEWABLE TABLETS
PRODUCT CODE: HYROXYB

Hydroxy B12 is the precursor to your active B vitamins Adenosylcobalamin (Mitochondrial B12 that may support energy) and methylcobalamin (neurological B12 that may support neurological function).
If you are unsure if you can tolerate methyl or if you need to support adenosylcobalamin levels then start with this formula.

This support is ideal for people with SNP’s that affect B12 production such as: TCN 1, TCN 2, TCN 3, MUT, MMAB, MTR, MTRR, FUT 2
Hydroxocobalamin is 4 x better than Cyanocobalamin in raising serum cobalamin Levels.

DIRECTIONS FOR USE:
Adults chew ¼ tablet daily for the first week, then increase to ½ tablet for the next week and continue thereafter until you are chewing ½-1 tablet daily. Children chew ¼ - ½ tablet daily.
Do not introduce methyl’s until your B12 is introduced for at least 1 - 2 weeks.
Chewable B12 allows the B12 to be broken down and absorbed through the mucosal membrane that lines your mouth. This means that it gets into the bloodstream without having to go through the gastrointestinal tract. Ideal for those with GIT disturbances.
Chewable tablets are perfect for children that cannot swallow capsules.

OTHER INGREDIENTS:
Xylitol granular, dicalcium phosphate, microcrystalline cellulose, ascorbyl palmitate, magnesium stearate, natural red cherry flavour, silica

FREE OF:
gluten, soy, egg, dairy, GMO, fish, shellfish or nuts.
Vegan - Vegetarian friendly
Hydroxocobalamin & Methylation Support

**Specific Indication**: Step 2 in methylation support.

**Pharmaceutical Effects**: Precursor to Active B12’s – methylcobalamin & adenosylcobalamin

**Clinical Benefits**:
- Provides a stable and naturally occurring form of Vitamin B12
- Converts to both methylcobalamin and adenosylcobalamin.
- May support the methylation cycle without causing side effects
  Particularly important for those with adenosylcobalamin SNP’s – MMAB, MUT
- Chewable form for better absorption
- Easily taken by children

Hydroxocobalamin is a naturally occurring form of Vitamin B12. It is a precursor molecule for methylcobalamin and adenosylcobalamin. In the human body, hydroxocobalamin is converted to cobalamin that is readily absorbed in the gut. One of the important functions of hydroxocobalamin in the body is conversion of homocysteine into the essential amino acid methionine\(^2\). It is also required for proper functioning in of the nervous system and energy generation for cellular activities.

**Role of Hydroxocobalamin as a Cofactor**

The cobalamin or Vitamin B12 is one of the essential nutrients required for integral functions. It usually works with folate to carry out chromosomal replication and DNA synthesis in myeloid cells and bone marrow. Similarly, its role is also well established in maintaining the integrity and stability of the myelin sheath on nerve cells\(^4\). Vitamin B12 deficiency directly impacts the nerve cells impairing cognitive and psychological capabilities. It also coverts methymalonic acid to another compound namely succinate. Succinate further helps in linking carbohydrate and lipid metabolism in the body for energy generation\(^5\). In the cytosol, due to methylation processes hydroxocobalamin is converted into methylcobalamin. But in many instances, the reduction reaction in the presence of ATP results in the generation of adenosylcobalamin.

**Prescription as a Therapeutic Agent**

Hydroxocobalamin has shown high affinity for the cyanide molecule and reacts with any cyanide molecules by pulling them out of the mitochondria. The reaction of cyanide and hydroxocobalamin results in production of cyanocobalamin which can easily be excreted through urine resulting in detoxification.
One very important function of hydroxocobalamin is its role as a scavenger of nitric oxide and its derivatives. Many studies have indicated that hydroxocobalamin is in fact the only form of Vitamin B12 that reduces the cellular toxicity of nitric oxide by neutralizing its damage and toxicity of cellular functions.

The core atom of hydroxocobalamin, Cobalt (III) interacts with nitric oxide neutralising the toxicity. Nitric acid functions as a muscle regulator but due to a number of circumstances increases in levels leads to discomfort and swelling in the neural cells. In one study, the utilization of hydroxocobalamin was seen to significantly reduce the occurrence, frequency and severity of migraines.

References:


Methyl B12

Methylcobalamin – Methyl B12 – Chewable Tablet.

Methyl B12.
CONTAINS 60 CHEWABLE TABLETS
PRODUCT CODE: METHYB12

Methylcobalamin is the active B12 that may assist in the support of neurological function. This support is ideal for people with SNP’s that affect B12 production such as: TCN 1, TCN 2, TCN 3, MUT. MMAB, MTR, MTRR, FUT 2
B12 deficiency may reduce DNA methylation and will affect the use of your methyl groups. Your active folate cannot be utilised efficiently if B12 levels are low.

DIRECTIONS FOR USE:
Adults chew ¼ tablet daily for the first week, then increase to ½ tablet for the next week and continue thereafter until you are chewing ½-1 tablet daily.
Children chew ¼ - ½ tablet daily.
Do not introduce methyl's until your B12 is introduced for at least 2 weeks.
Chewable B12 allows the B12 to be broken down and absorbed through the mucosal membrane that lines your mouth. This means that it gets into the bloodstream without having to go through the gastrointestinal tract. Ideal for those with GIT disturbances.
Chewable tablets are perfect for children that cannot swallow capsules.

Each Tablet Contains:
Mecobalamin, Methyl B12
(Co-methylcobalamin) 2 mg (2000 mcg)

OTHER INGREDIENTS:
Xylitol granular, dicalcium phosphate, microcrystalline cellulose, ascorbyl palmitate, magnesium stearate, natural red cherry flavour, silica

FREE OF:
gluten, soy, egg, dairy, GMO, fish, shellfish or nuts.
Vegetarian - Vegan friendly
Methylcobalamin & Methylation Support

**Specific Indication:** Step 2 in methylation support.

**Pharmaceutical Effects:** Active B12

**Clinical Benefits:**
- Critical coenzyme required for methylation through methionine Synthase\(^4\)
- Plays an important role in developing cognitive ability by regulating the myelin sheath and basic structure of nerve cells
- Only cobalamin compound that regulates the sleep wake cycle.
- Is directly utilised by enzymes that are dependent on Vitamin B12 for their functioning i.e.: methionine synthase.\(^4\)
- Chewable form for better absorption
- Easily taken by children

Methylcobalamin also referred to as MeB12 and MeCbl is another compound of the cobalamin family. It is one of the naturally occurring coenzyme forms of cobalamin found in the human body.\(^1\)\(^3\)

Hydroxocobalamin is metabolised into adenosylcobalamin and methylcobalamin. According to estimates, almost 80% of cobalamin present in body is in the form of methylcobalamin.

**Important Functions of Methylcobalamin**

Plays an important role in developing cognitive ability by regulating the myelin sheath and basic structure of nerve cells.

Only cobalamin compound that regulates the sleep wake cycle. It improves the overall quality of sleep and helps in developing nerve cells by maintaining the circadian rhythms. Due to its deficiency, the sleep wake cycle is greatly disturbed leading to symptoms such as agitation, anxiety, restlessness and distress.

Methylcobalamin is one of the coenzymes that is directly utilized by enzymes which are dependent on vitamin B12 for their functioning. Methionine synthase specifically utilises methylcobalamin as a cofactor in their reactions\(^4\).

Acetyl-CoA is one of the basic compounds required by a number of organisms to produce complex organic derivatives for different reactions and pathways. A reduced level of methylcobalamin can prompt subacute spinal cord degeneration and megaloblastic iron deficiency\(^4\).

**Analgesic Effect of Methyl Cobalamin**
a. Neuropathic Pain in Diabetic Neuropathy

One of the important clinical benefits of methylcobalamin is inhibiting pain connected with diabetic neuropathy. The neuropathic pain has been described as burning and aching irritation which increases the sensitivity of the skin. The clinical trials have indicated that methylcobalamin may reduce the occurrence and frequency of neuropathic pain associated with diabetes. The oral use of methylcobalamin reduces intensity of pain by improving overall velocity of nerve impulses and conduction. The studies have observed the reduction in overall pain scale score in neuropathic pain after consumption of methyl cobalamin. After four weeks of injectable methylcobalamin, 73% reduction in pain symptoms were observed through Likert-type pain intensity scale. The researchers identified improved sensory and motor nerve impulses and velocity through consumption of methylcobalamin indicating its significant role as analgesic.

b. Neuralgia

The action of methylcobalamin has also been reported to ease pain associated with different neuralgia. Considerable reduction in pain values was observed in trigeminal neuralgia, facial neuralgia, sub-acute herpetic neuralgia and glossopharyngeal neuralgia. Intravenous injection of methylcobalamin greatly reduces the symptoms of pain in trigeminal neuralgia. It not only reduces the pain symptoms but may also improves quality of life. It may also improve the velocity of nerve conduction thus acting as an analgesic in many neuropathies.

References


Total B-Methyl

Total B with methyl

Dietary Supplement
TGA Approved.

CONTAINS: 60 CAPSULES
PRODUCT CODE: TOTALBM

Total B with methyl.
Multi B support with methyl folate and methyl B12. May support and assist methylation reactions.

DIRECTIONS FOR USE:
Take 1 capsule after breakfast. Stop your starter B when you introduce this multi. You may continue with your B12 if your B12 levels need supporting.

OTHER INGREDIENTS:
Vegetable Cellulose, water, ascorbyl palmitate.

FREE OF:
gluten, soy, corn, egg, dairy, GMO, fish, shellfish or nuts
Vegan - Vegetarian friendly

WARNINGS:
Tamper evident: use only if bottle is sealed.
if pregnant, consult your health-care practitioner before using this product
Store below 25°C in a cool dry place.

SERVING SIZE:
one capsule.

Each capsule contains:
B5, Pantothenic acid (as Calcium pantothenate) 180 mg
B3, Niacin (Nicotinamide) 130 mg
B1, Thiamine (as Thiamine hydrochloride) 50 mg
Biotin 500 mcg
B2, Riboflavin sodium phosphate (Riboflavin 5 phosphate) 25 mg
B6, Pyridoxine (as Pyridoxal 5 phosphate) 15 mg
Folate, (as Lepromelofolic acid/L-5-MTHF) 400 mcg
Mecobalamin, Methyl B12 (Co-methylcobalamin) 400 mcg

WARNING:
Some people may have an adverse reaction to methyls. Headaches and muscle aches and pains may happen for 3-4 days. This is normal and should disappear. If your anxiety levels increase or mood decreases, immediately stop this product and take niacin. See niacin product for details. It is important for you to purchase the niacin at the same time as this product to ensure you have it on hand.
Total B (methyl) & Methylation Support

**Specific Indication:** Step 3 in methylation support. Multi B with active methyl folate and methyl B12 support and assist in methylation reactions (Figure 1).

**Pharmaceutical Effects:** Total B contains eight B vitamins with methylcobalamin and methylfolate.

**Clinical Benefits:**
- Supports critical enzymes in the methylation cycle
- Contains Metafolin form of L-5MTHF for superior absorption and stability
- Low excipients
- Vegan and vegetarian friendly
- No corn, soy, gluten, dairy, egg, GMO

Thiamin (B1) and Pyridoxine (B6) are confirmed by human clinical trials to work together to decrease DNA glycation,\(^1\)\(^-\)\(^3\) which increases higher levels of methylation.\(^4\)\(^,\)\(^5\)

Riboflavin (B2) enhances the effect of low-dose folate by increasing methylation reactions of other vitamins such as pyridoxine, folate and B12.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\)

Niacin (nicotinamide, B3) and its derivative nicotinamide are dietary precursors of nicotinamide adenine dinucleotide (NAD). NAD functions in oxidation-reduction (redox) reactions and non redox reactions.\(^11\)

NAD is an important cofactor for MTRR (methionine synthase reductase) enzyme.

Pantothenic acid (B5) is confirmed to improve DNA methylation,\(^15\)\(^,\)\(^16\) particularly for mental health.\(^17\)\(^,\)\(^18\)\(^,\)\(^19\)
Pyridoxine (B6) increases DNA methylation levels and works together with riboflavin, folate, and B12. Deficiency causes reduced DNA methylation.

Biotin (B7) is related to folate in its DNA methylation functions. It works with other vitamins on mitochondrial functions and DNA methylation.

Folate (L-5-MTHF) increases genome and other DNA methylation in healthy patients.

Oral folate will not cause excessive DNA methylation. The folate effect of increasing DNA methylation can reduce homocysteine levels. 5-MTHF, works faster, more efficient, is safer, crosses the blood brain barrier and does not mask a Vitamin B12 deficiency.

Methylcobalamin (Methyl B12) maintains a desirably high degree of genome DNA methylation. B12 deficiency can reduce genome DNA methylation in the body up to 2 folds. It works with folate to reduce homocysteine level.

Metafolin (L (6S)-5-MTHF) is a calcium. As a crystalline type I form it has solid stability, is soluble in water.

All doses are safe according to the Australian RDI and the U. S. DRI.
References


38Wallin,H;Kuznesof,PM. Calcium L-5-Methyltetrahydrofolate (L-5-MTHF-CA). Chemical and Technical Assessment 65th JEFCA.


Niacin 50mg

Niacin (As Nicotinamide)

Purchase this product when you take methyls. This provides an immediate antidote to methyl symptoms ie: rash, mood decrease, elevated anxiety, headache, muscle aches and pain, brain fog, diarrhoea, palpitations.

Dietary Supplement
TGA Approved.

60 Tablets: 50mg Niacin
Order Code: NIAVIN50

Niacin – helps to reduce methylation reactions and side effects.
if you have been taking methyls and experience any of the following then take Niacin to remove these symptoms: Headaches, muscle aches and pains, irritability, palpitations, rash, anxiety, decrease in mood.

DIRECTIONS FOR USE:
Take 1 tablet every hour until you feel your symptoms improve. This may be required for up to 24 hours. Once you feel back to normal stop your niacin and see your practitioner.
NB: it is normal for some people to get a niacin flush. This is a feeling of prickling on the skin, heat and flushing. Do not panic if this happens. It feels awful but will do you no harm.

OTHER INGREDIENTS:
dicalcium phosphate, microcrystalline cellulose, magnesium stearate, croscarmellose sodium, silica

FREE OF:
gluten, soy, corn, egg, dairy, GMO, fish, shellfish or nuts or prebiotics
Vegan - Vegetarian friendly
B3 – Niacin (Nicotinamide) and Excessive Methylation Inhibition

**Specific Indication:** Assists in the reduction of excessive DNA methylation reactions.

Excessive methyl side effects may include:

- Increased anxiety
- Decrease in mood
- Headaches or migraines
- Muscle aches and pains
- Rash
- Nausea
- Acne
- insomnia

**Pharmaceutical Effects:** The randomized and single blinded clinical trial conducted by Premkumar et al. from India in 2008 confirmed that 50 mg niacin (nicotinamide) intake daily can reduce excessive DNA methylation in human patients effectively. No patient drop off or adverse effects were reported.

**Clinical Benefits:**

- Reduces methylation reactions
- Eases side effects within hours
- No gluten, soy, corn, egg, dairy, GMO, fish, shellfish, nuts or prebiotics
- Vegan and vegetarian friendly

Another five clinical studies from Japan, China and the U.S. support the evidence that niacin (nicotinamide) can reduce DNA methylation significantly in healthy humans, and humans with diseases. In addition, the five studies in humans support the evidence that 50 to 100 milligram niacin (nicotinamide) oral intake daily can effectively reduce excessive DNA methylation levels.
Warning: Any niacin may cause flushing. Flushing is caused by the activation of phospholipase A2, an enzyme that stimulates the production of specific lipids called prostanoids. These molecules can induce the dilation of blood vessels in the skin and trigger a flushing response. This flushing is not dangerous and is no reason for alarm.

References

http://www.nature.com/nchembio/journal/v9/n5/full/nchembio.1234.html?message-global=remove


