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THERAPEUTIC APPLICATIONS OF CITICOLINE AND METHYLCOBALAMINE COMBINATION

***A. B. Pathan, R. C. Doijad, S. S. Baraskar, N. B. Pawar,**
V. D. Maske, and S. L. Gaikwad
Department of Quality Assurance,
Shree Santkrupa College of Pharmacy, Ghogaon, Karad (MS) India

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ABSTRACT:
Combination of citicoline and methylcobalamine is available in market as variable dose combination. It has been approved by DCGI in the year 2010. This combination is generally prescribed for the management of metabolic disordered nerve rejuvenation and nerve regeneration. This combination is chemically and pharmacologically safe and being approved for neurologicaly disorder. Citicoline which is form of vitamin B found in all cell, where as methylcobalamine vitamin B12 is the only B vitamin which is part of mineral, cobalamine contain cobalts, mineral that is known to stimulate RBC formation. Generally brain requires a consistent supply of nutrient to maintain performance efficiency, insufficiency in certain brain nutrient may lead to forgetfulness or momentary memory lapses, this can be avoided by using brain nutrients come to us from B vitamin family and form vital constituent of memory supplements. Now the importance of the combination of citicoline and methylcobalmine known to health care system to boost memory, production of brain energy, sustain cognitive function and motor skill and enhance focus and decision making thought processes. It is being sold as nutraceutical formulation by various manufacturers. This review highlights need for combination of citicoline and methylcobalamine their pharmacological and therapeutic issues and application.

KEY WORDS: Citicoline, Methylcobalamine, nutrient, Cognitive Function.

***Corresponding Author**
Ms. Asma. B. Pathan
Assistant Professor,
Shree Santkrupa College of Pharmacy, Ghogaon,
Karad - 416013 (M.S.) India.
Email- asmapathan9@gmail.com Phone No.: +9158005979. Fax No.: +91-02164257404

INTRODUCTION

Like all functions in the body, the brain also depends on cellular energy. Simply put, the more efficiently brain cells can produce energy, the better the brain functions. As we age, energy productions in the body begin to decline. Energy production declines in the brain could be due to stress, drugs, immoderate alcohol consumption, lack of nutrients, poor circulation, or damage to brain cells due to pollutants. Aging also contributes to a decline in performance mainly due to the cumulative effect of these ravaging damages over a period of time. The brain requires a consistent supply of nutrients to maintain performance efficiency. Scientists now believe that insufficiency in certain brain nutrients may lead to forgetfulness or momentary memory lapses. Two of these important brain nutrients come to us from the B vitamin family and form vital constituents of memory supplements. Neurons or the brain cells found in the central nervous system are different from other cells in the body. Other cells in the body grow old, die and new ones are born to replace old ones. This is not so with neurons. Once neurons die, they are lost for good and can never be replaced. At our birth we are endowed with 10 billion neurons. By the age of 22, your brain starts losing volume. You begin to lose one neuron a second. Cell to cell communication loses efficiency. This may lead to mis-mapping of information or even

loss of information resulting in those "senior moments" so common to the elderly. Aging also impairs membrane functions. Neuronal membranes have unique functions. They are conductors for transmitting nerve impulses.

Citicoline which is a form of the B vitamin choline found in all cells. Citicoline has been extensively studied and proven to benefit brain health. It supports brain functions and even ameliorates some of the cumulative damage that has ravaged the brain over a period of time. It plays a vital function in the formation of cell membranes. The brand Citicoline is known for its purity and consistency in quality. They however can be repaired and citicoline plays a vital role in the repair of neurons. Citicoline supports energy production in the neurons. This in turn supports repair and maintenance of cell membranes, synthesis of brain chemicals, and propagation of electrical impulses—all necessary to support the broader functions of the brain such as memory, motor cognitive functions, thought and decision making processes. Supplementing your diet with memory supplements that contain citicoline is an intelligent choice for those who would like to boost their mental energies and preserve memory and cognitive skills.

Another great ingredient to look for in a memory supplement is Vitamin B12. Vitamin B12 is the only B vitamin which is part mineral. It is called cobalmin and contains cobalt, a mineral that is known to stimulate red blood cell formation. One of the important roles of red blood cells is the transport of oxygen to various parts of the body. A deficiency in B12 leads to a deficiency in red blood cells and results in less oxygen supply to the entire body. Twenty percent of the body's oxygen supply is required by the brain. And a lack of oxygen in the brain can starve neurons to death, leading to brain atrophy or shrinking of the brain which happens as we age.B12 also helps to regulate the level of homocysteine (amino acid) in the body. Studies show that higher levels of homocysteines in the body are associated with a decline in memory and impaired cognitive abilities. B12 also helps in the maintenance and functions of neurons and is known to have neuron-protective properties. Generally, Myelin is made up of cholesterol, phosphatidyl choline complex. Myelin is the insulating layer which, along with fatty acids, surrounds nerve fibres. This protects nerves just like the insulation arround electrical cables. In B12 deficiency, toxic 15-17 coal atom fatty acids have a demyelinating effect on nerves, and electrical impulse transmission is disturbed. B12 is a vitamin required for blood formation and rapidly growing tissues. B12 is recognized as a factor in the synthesis of myelin. Methylcobalamin production requires cobalamin and is the cobalamin found in the central nervous system (CNS) and brain where it transports methyl groups (-CH3) to proteins in the myelin.[38] It is for these reasons that B12 deficiency leads to anaemia (blood disorders include macrocytos and pernicious anaemia) and neurological disorders (Alzheimer's disease and suspected amalgam related disorders).

There are, as with many diseases, usually more than one factor which may be involved with causation. Given that the former disorders are rare, even in vegans who have low B12 intakes, what is more concerning is the potential for neurological disorders that may be subclinical. This occurs because it is possible to have a deficiency of B12 in the CNS even when blood levels of B12 are "normal", or what is called non-anaemic deficiencies. These occur for meat eaters with huge B12 intakes as well as for vegans. So laying the blame for neurological problems on veganism or indeed any alleged B12 intake deficiency is not always accurate, since increased B12 dietary intake will evidently, not always work. In these serious cases B12 is usually injected since dietary availability of B12 can be as low as 1% of the total ingested for mega B12 doses, and some patients do not convert dietary B12 to the methylcobalamin required for normal neurological activity so well.[36,37]

STRUCTURE

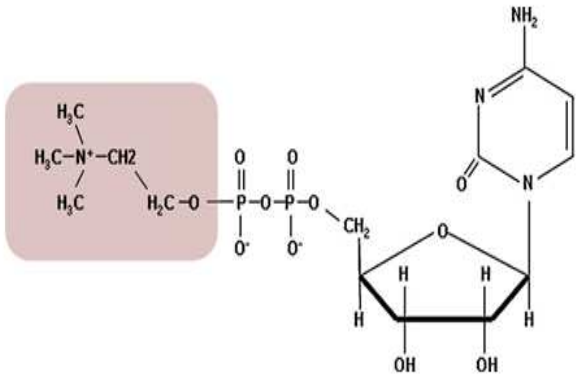

Fig. 1: Structure of Citicoline

Citicoline (CDP-choline, cytidine diphosphate choline, cytidine 5_-diphosphocholine,) is a nucleotide composed of ribose, pyrophosphate, cytosine and choline. It is organized in two moieties, cytidine and choline, that are linked by a diphosphate bridge (Fig. 1). It is supplied as a freebase, as a dietary supplement in the United States, and as a sodium salt in Europe (cytidine 5_-(trihydrogen diphosphate) [2-

(trimethylammonio)ethyl] ester inner salt, C14H26N4O11P2). It is a water-soluble compound (90-percent bioavailability) which is, after ingestion hydrolyzed in the small intestine and absorbed as choline and cytidine. Following absorption, choline and cytidine are re-phosphorylated and citicoline is synthesized from cytidine triphosphate and choline monophosphate by cytidine triphosphate-phosphocholine cytidylyltransferase (PCCT).[1]

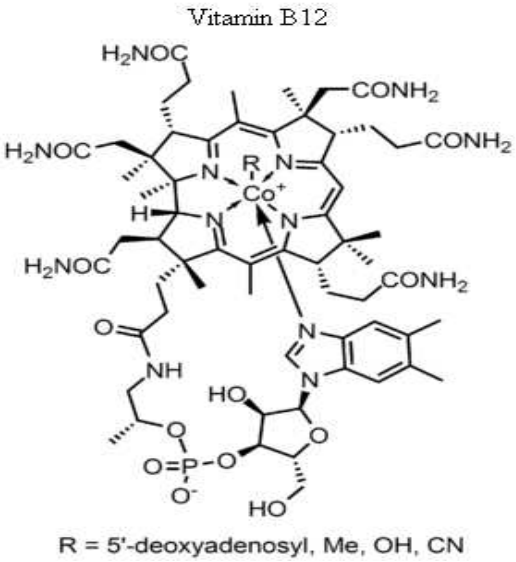

Fig 2: Structure of Methylcobalamine

Vitamin B_{12} is a collection of cobalt and corrin ring molecules which are defined by their particular vitamin function in the body. All of the substrate cobalt-corrin molecules from which B_{12} is made must be synthesized by bacteria. However, after this synthesis is complete, the body has a limited power to convert any form of B_{12} to another, by means of enzymatically removing certain prosthetic chemical groups from the cobalt atom. The various forms (vitamers) of B_{12} are all deeply red colored, due to the color of the cobalt-corrin complex. B_{12} is the most chemically complex of all the vitamins. The structure of B_{12} is based on a corrin ring, which is similar to the porphyrin ring found in heme, chlorophyll, and cytochrome. The central metal ion is cobalt. Four of the six coordination sites are provided by the corrin ring, and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the center of reactivity, is variable, being a cyano group (-CN), a hydroxyl group (-OH), a methyl group (-CH_3) or a 5'-deoxyadenosyl group (here the C5' atom of the deoxyribose forms the covalent bond with Co), respectively, to yield the four B_{12} forms mentioned above. Historically, the covalent C-Co bond is one of first examples of carbon-metal bonds to be discovered in biology. The hydrogenases and, by necessity, enzymes associated with cobalt utilization, involve metal-carbon bonds.[2]

BIOCHEMISTRY

Grouped with the B vitamins, choline is a trimethylated nitrogenous base that enters three major metabolic pathways: (1) phospholipid synthesis via phosphorylcholine; (2) acetylcholine synthesis; and (3) oxidation to betaine, which serves as a methyl donor. Endogenously, formation of citicoline from choline is the rate-limiting step in the synthesis of phosphatidylcholine, a key membrane phospholipid.[3] Cytidine, a major component of RNA, undergoes cytoplasmic conversion to cytidine triphosphate (CTP). In the citicoline metabolic pathway, choline is phosphorylated by the enzyme choline kinase; the resulting phosphorylcholine combines with CTP to form citicoline.[4] Citicoline then combines with diacylglycerol (DAG), forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction.[5] Exogenous citicoline, hydrolyzed in the small intestine and readily absorbed as choline and cytidine, enters the various biosynthetic pathways that utilize citicoline as an intermediate. Citicoline thus has a sparing effect on systemic choline reserves, as well as inhibiting the breakdown of membrane phospholipids.

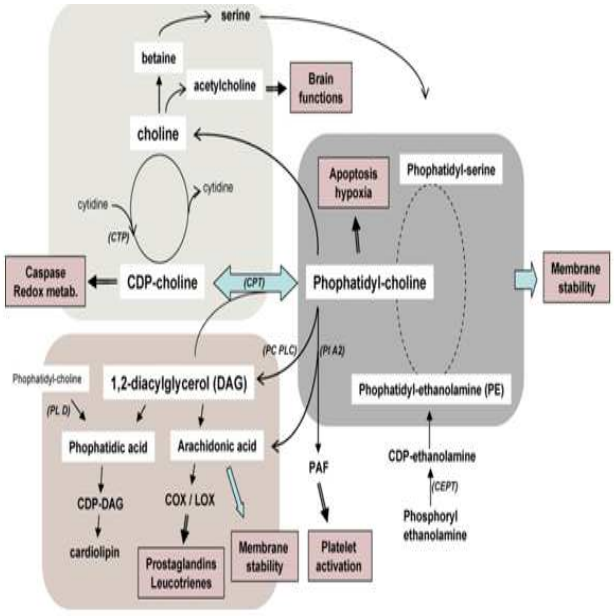

Fig 3: Synthesis of Citicoline

Methylcobalamin is the active form of vitamin B12 that acts as a cofactor for methionine synthase in the

conversion of homocysteine to methionine, thus lowering blood levels of homocysteine. Methylcobalamin acts as a methyl donor and participates in the synthesis of SAM-e (S-adenosylmethionine), a nutrient that has powerful mood elevating properties.[22]

PHARMACOKINETICS

Citicoline is a water-soluble compound with greater than 90-percent bioavailability. Pharmacokinetic studies on healthy adults have shown oral doses of citicoline are rapidly absorbed, with less than one percent excreted in feces. Plasma levels peak in a biphasic manner, at one hour after ingestion followed by a second larger peak at 24 hours post-dosing. Citicoline is metabolized in the gut wall and liver. The byproducts of exogenous citicoline formed by hydrolysis in the intestinal wall are choline and cytidine. Following absorption, choline and cytidine are dispersed throughout the body, enter systemic circulation for utilization in various biosynthetic pathways, and cross the blood-brain barrier for re-synthesis into citicoline in the brain.[6] Pharmacokinetic studies using C citicoline show citicoline elimination occurs mainly via respiratory C and urinary excretion, in two phases mirroring the biphasic plasma peaks. The initial peak in plasma concentration is followed by a sharp decline, which then slows over the next 4-10 hours. In the second phase, an initially rapid decline after the 24-hour plasma peak is similarly followed by a slower elimination rate. The elimination half-life is 56 hours for C and 71 hours for urinary excretion.[7]

Methylcobalamin is the neurologically active form of vitamin B12 and occurs as a water-soluble vitamin in the body. It is a cofactor in the enzyme methionine synthase, which functions to transfer methyl groups for the regeneration of methionine from homocysteine.[38] In anaemia, it increases erythrocyte production by promoting nucleic acid synthesis in the bone marrow and by promoting maturation and division of erythrocytes.

Evidence indicates methylcobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B12. Experiments have demonstrated similar absorption of methylcobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin. Human urinary excretion of methylcobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention. It is readily absorbed in distal half of the ileum, Peak plasma concentrations after 3 hr (oral); 0.9 hr (IM); 3 min (IV). Its Protein binding is very high to specific transcobalamins plasma proteins binding of hydroxocobalamin is slightly higher than cyanocobalamin. Its metabolism occurs majorly in hepatic cells. Its half-life is approximately 3 hrs to 6 days (400 days in the liver) and excretion is through renal system.[8]

METABOLISM

Endogenous citicoline serves as an intermediate in the biosynthesis of phospholipids, including phosphatidylcholine, the primary phospholipid in cell membranes.[9] Cytidine a major component of RNA, undergoes cytoplasmic conversion to cytidine triphosphate (CTP). In the citicoline metabolic pathway, choline is phosphorylated by the enzyme choline kinase: the resulting phosphorylcholine combines with CTP to form citicoline.[10] Citicoline then combines with diacylglycerol (DAG), forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction.

The optimal absorption of dietary methylcobalamine requires the formation of a complex between dietary cobalamins and R-proteins, and the secretion, by the stomach parietal cells, of intrinsic factor. The cobalamin-R-protein complex is digested by pancreatic enzymes in the small intestine, and the released cobalamin molecule binds with intrinsic factor and is absorbed in the distal ileum. Cobalamin is then detached from intrinsic factor in the enterocyte cells of the small intestine, and is bound to transcobalamin II for transport into tissues. [11]

MECHANISM OF ACTION

Citicoline acts by various mechanisms as cerebral activators which are listed below:

a. Phospholipid Precursor: Evidence of citicoline's role as a phosphatidylcholine precursor has been found in animal studies.[12]

b. Neuronal Membrane Repair: Citicoline has been investigated as a therapy for stroke patients. Three mechanisms are postulated: (1) repair of the neuronal membrane via increased synthesis of phosphatidylcholine; (2) repair of damaged cholinergic neurons via potentiation of acetylcholine production; and (3) reduction of free fatty acid buildup at the site of stroke-induced nerve damage. [13,24]

c. Effect on beta-Amyloid: Evidence has surfaced that citicoline counteracts the deposition of beta-amyloid, a neurotoxic protein believed to play a central role in the pathophysiology of Alzheimer's disease (AD).[14, 15]

d. Effect on Neurotransmitters

Evidence of citicoline's ability to enhance norepinephrine release in humans was found in a study showing citicoline raised urinary levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite. Norepinephrine increased in the cerebral cortex and hypothalamus, dopamine increased in the corpus striatum, and serotonin increased in the cerebral cortex, striatum, and hypothalamus.[16,27,28]

Methylcobalamin such as Vitamin B_{12} normally plays a significant role in the metabolism of every cell of the body, especially affecting the DNA synthesis and regulation but also fatty acid synthesis and energy production. However, many (though not all) of the effects of functions of B_{12} can be replaced by sufficient quantities of folic acid (vitamin B_9), since B_{12} is used to regenerate folate in the body. Most vitamin B_{12} deficiency symptoms are actually folate deficiency symptoms, since they include all the effects of pernicious anemia and megaloblastosis, which are due to poor synthesis of DNA when the body does not have a proper supply of folic acid for the production of thymine. When sufficient folic acid is available, all known B_{12} related deficiency syndromes normalize, save those narrowly connected with the vitamin B_{12}-dependent enzymes Methylmalonyl Coenzyme A mutase, and 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), also known as methionine synthase; and the buildup of their respective substrates (methylmalonic acid, MMA) and homocysteine.

Coenzyme B_{12}'s reactive C-Co bond participates in three main types of enzyme-catalyzed reactions[17,18]

1. **Isomerases**. Rearrangements in which a hydrogen atom is directly transferred between two adjacent atoms with concomitant exchange of the second substituent, X, which may be a carbon atom with substituents, an oxygen atom of an alcohol, or an amine. These use the adoB_{12} (adenosylcobalamin) form of the vitamin.
2. **Methyltransferases**. Methyl ($-CH_3$) group transfers between two molecules. These use MeB_{12} (methylcobalamin) form of the vitamin.
3. **Dehalogenases**. Reactions in which a halogen atom is removed from an organic molecule. Enzymes in this class have not been identified in humans.

In humans, two major coenzyme B_{12}-dependent enzyme families corresponding to the first two reaction types are known. These are typified by the following two enzymes:

1. MUT is an isomerase which uses the AdoB_{12} form and reaction type 1 to catalyze a carbon skeleton rearrangement (the X group is -COSCoA). MUT's reaction converts MMl-Co to Su-CoA, an important step in the extraction of energy from proteins and fats.[19] The MUT function cannot be affected by folate supplementation, which is necessary for myelin synthesis and certain other functions of the central nervous system. Other functions of B_{12} related to DNA synthesis related to MTR dysfunction can often be corrected with supplementation with the vitamin folic acid, but not the elevated levels of homocysteine, which is normally converted to methionine by MTR.
2. MTR, also known as methionine synthase, is a methyltransferase enzyme, which uses the MeB_{12} and reaction type 2 to catalyze the conversion of the amino acid homocysteine (Hcy) back into methionine (Met) . Increased homocysteine can also be caused by a folic acid deficiency, since B_{12} helps to regenerate the tetrahydrofolate (THF) active form of folic acid. Without B_{12}, folate is trapped as 5-methyl-folate, from which THF cannot be recovered unless a MTR process reacts the 5-methyl-folate with homocysteine to produce methionine and THF, thus decreasing the need for fresh sources of THF from the diet. THF may be produced in the conversion of homocysteine to methionine, or may be obtained in the diet. It is converted by a non-B_{12}-dependent process to 5,10-methylene-THF, which is involved in the synthesis of thymine. Reduced availability of 5,10-methylene-THF results in problems with DNA synthesis, and ultimately in ineffective production cells with rapid turnover, in particular blood cells, and also intestinal wall cells which are responsible for absorption. The best-known "function" of B_{12} (that which is involved with DNA synthesis, cell-division, and anemia) is actually a facultative function which is mediated by B_{12}-conservation of an active form of folate which is needed for efficient DNA production.[20] Other cobalamin-requiring methyltransferase enzymes are also known in bacteria, such as Me-H4-MPT, coenzyme M methyl transferase.

THERAPEUTIC APPLICATION OF COMBINATION OF CITICOLINE AND METHYLCOBALAMINE

Combination of methylcobalamin and citicoline could be the boon for the management for various cognitive disorders. The combination enters into the cerebrospinal fluid of the brain easily because it can cross the blood-brain barrier. The major indication of the combination could be:

- Metabolic Disorders

- Nerve Rejuvenation
- Nerve Regeneration and Alertness.
- Diabetic Neuropathy
- Glaucoma
- Diabetic Gastropathy
- Memory Loss
- Brain Injury
- Anorexia

Nutritional building blocks for healthy brain function. This combination is a physician formulated, science-based brain-health supplement designed to supply the essential vitamins, antioxidants and nutrients necessary to assist the body in supporting healthy memory, mood and motor functions. It nutritionally supports healthy brain oxygenation, blood flow, immune system defense, and cell membrane structure. In addition, it also nutritionally supports cell-to-cell communication which is crucial to healthy cognitive function.

The brain controls everything we do, see, say, hear, touch, taste, feel and think...all at the same time, Mental clarity, Memory capability, Cell-to-cell communication, Healthy blood flow, Brain oxygenation, Cell membrane structure and Immune system function etc.

The brain is the command center of the body. The brain has about 100 billion neurons that fire messages across trillions of microscopic gaps each moment of your life. It has more than 10 billion interlinked cells. It sends messages to, and receives stimulation from, all parts of the body and the brain operates while you're sleeping or awake. So, it's no wonder the brain is probably the most nutritionally demanding organ in the body.

Memory loss is not inevitable. Many people believe that poor memory is a natural consequence of aging. However, if that were true, then why do we all know senior citizens who can still think as clearly as many younger people? And why are there senior citizens that are totally capable of living happy, healthy, independent lives? The answer is simple...significant memory loss is not necessarily a fundamental part of aging.

It keeps your brain functioning at its optimum level. Strong evidence suggests that those who take the most proactive stance on healthy nutrition typically enjoy greater physical and mental wellness. And therefore, many complementary alternative medical practitioners believe that supplement intervention with memory-specific nutrients; plus a healthy lifestyle, annual check-ups and regular physical and mental activities may support mental sharpness, speed, and flexibility well into the senior years.

Whereas, Citicoline is a naturally occurring nontoxic and well-tolerated drug[33,34] that is an essential intermediate for the synthesis of phosphatidylcholine, a major constituent of the gray matter of brain tissue.[26] Citicoline promotes brain metabolism by enhancing the synthesis of acetylcholine and restoring phospholipids content in the brain. Citicoline is a used in pharmacotherapy of brain insufficiency and some other neurological disorders, such as stroke, brain trauma, and Parkinson's disease. It can also cross blood-brain barrier and treats brain related disorders. It improves memory loss, concentration, learning ability, alertness, brain injury, Alzheimer's disease, headache, dizziness, and tinnitus, improves cognitive functions, glaucoma, Parkinson's disease, Vascular Dementia.[31,32] 500 mg per day might be the optimum citicoline dose and it can go up to 2,000 mg.[29,30] It was concluded that citicoline modestly improves memory and behavioral outcomes. Both the salts separately prescribed by physicians, cardiologists, dialectologists, neurologists and general physicians.

Methylcobalamin is the active form of vitamin B12. It can easily enter into the cerebrospinal fluid of the brain. It is therapeutically used for the treatment of nerve degeneration and to treat metabolic induced disorders such diabetic neuropathy, diabetic gastropathy, glaucoma, male impotency, arthritis, hyperhomocysteinemia, sleep disturbances, arrhythmia, anorexia and anemia. Usual dose starts from 500 mcg and goes up to 6,000 mcg.[21]

MARKETED FORMULATIONS:

Tablet Formulation	Content	Manufacturer
Prexaron -M (SR)	Citicolin(1000mg) + Mecobalamine(1500mg)	Intas Pharma
Citimac - M	Citicolin(500mg) + Mecobalamine(750mcg)	Mecleods Pharma
Nervijen – T	Citicolin(500mg) + Mecobalamine(750mcg)	Jenburkt Pharma
Strocit-M (FC)	Citicolin(500mg) + Mecobalamine(750mcg)	Sun Pharma

CONCLUSION:

Memory impairment and enhancement of cognitive function of brain is a part of treatment of various disorders associated with elderly patients or patients with neurological disorders at any age due to stroke and related shocks. Neutraceuticals are effective ways of treating such conditions. Various drugs are identified and established as therapeutic agents for treatment of cognitive disorders. Effective therapy can be set forth if rationale combinations of such agents are being design, characterized for their pharmacological, biochemical and physical compatibility and developed into suitable

formulation. Neutraceutical combinations are coming into the market as boost for health care system to prevent early degeneration of neurons, memory loss and brain related aging.

Citicoline and methylcobalamine is one of such combination which has been proved pharmacologically, biochemically and physically compatible. It has been developed into tablet formulation which is available into market. This combination has therapeutic applications in Metabolic Disorders, Nerve Rejuvenation, Nerve Regeneration and Alertness, Diabetic Neuropathy, Glaucoma, Diabetic Gastropathy, Memory Loss, Brain Injury and Anorexia.

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