

Complete Prescribing Information

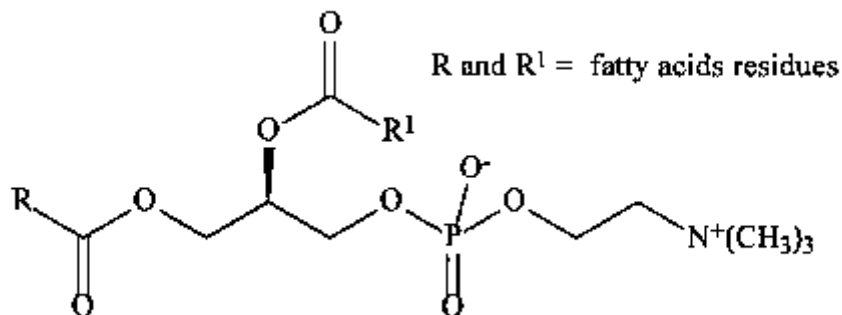
DESCRIPTION

3-sn-Phosphatidylcholine (EPL Nattermann) 250 mg.

Lipostabil (Phosphatidylcholine) the 'German' registered trade name of 'Essentiale 303', consists of essential phospholipids from soya that are specially formulated for intravenous administration. Phospholipids are extremely important components of cell membranes. The integrity of the cell membrane is critical to the proper functioning of the cell. As the cell ages the phospholipid composition of the membrane changes and the cell's functions deteriorate and it loses its normal shape and elasticity. Eventually the cell dies and is destroyed by the immune system. Damage to the cell membrane, and thereby aging, is thought to be mediated by the actions of highly reactive chemicals referred to as free radicals. The damage caused by free radicals must be repaired in order to preserve normal cell function, and in order to do so, the cells need an abundant supply of the essential phospholipids phosphatidylcholine and deoxycholic acid. Lipostabil Phosphatidylcholine contains these important phospholipids and other essential nutrients that allow cells to repair damage and restore youthful function.

Phosphatidylcholine is a phospholipid that is a major constituent of cell membranes.

Phosphatidylcholine is also known as 1, 2-diacyl-:ussn:ue-glycero-3-phosphocholine, PtdCho and lecithin. It is represented by the following chemical structure:



Phosphatidylcholine

Lecithin is usually used as synonym for phosphatidylcholine, a phospholipid which is the major component of a phosphatide fraction which may be isolated from either egg yolk, or soy beans. It is commercially available in high purity as a food supplement and for medical uses.

Lecithin is regarded as a well tolerated and non-toxic emulsifier. It is approved by the United States Food and Drug Administration for human consumption with the status "Generally

Recognized As Safe". It is an integral part of cell membranes, and can be totally metabolised.

Lecithin is used commercially for anything requiring a natural emulsifier and/or lubricant, from pharmaceuticals to protective coverings. For example, lecithin is the emulsifier that keeps chocolate and cocoa butter in a confectionery bar from separating.

The term lecithin itself has different meanings when used in chemistry and biochemistry than when used commercially. Chemically, lecithin is phosphatidylcholine. Commercially, it refers to a natural mixture of neutral and polar lipids. Phosphatidylcholine, which is a polar lipid, is present in commercial lecithin in concentrations of 20 to 90%. Most of the commercial lecithin products contain about 20% phosphatidylcholine.

Lecithins containing phosphatidylcholine are produced from vegetable, animal and microbial sources, but mainly from vegetable sources. Soybean, sunflower and rapeseed are the major plant sources of commercial lecithin. Soybean is the most common source. Plant lecithins are considered to be GRAS (generally regarded as safe). Egg yolk lecithin is not a major source of lecithin in nutritional supplements. Eggs themselves naturally contain from 68 to 72% phosphatidylcholine, while soya contains from 20 to 22% phosphatidylcholine.

The fatty acid makeup of phosphatidylcholine from plant and animal sources differ. Saturated fatty acids, such as palmitic and stearic, make up 19 to 24% of soya lecithin; the monounsaturated oleic acid contributes 9 to 11%; linoleic acid provides 56 to 60%; and alpha-linolenic acid makes up 6 to 9%. In egg yolk lecithin, the saturated fatty acids, palmitic and stearic, make up 41 to 46% of egg lecithin, oleic acid 35 to 38%, linoleic acid 15 to 18% and alpha-linolenic 0 to 1%. Soya lecithin is clearly richer in polyunsaturated fatty acids than egg lecithin. Unsaturated fatty acids are mainly bound to the second or middle carbon of glycerol.

Choline comprises about 15% of the weight of phosphatidylcholine.

ACTIONS AND PHARMACOLOGY

MECHANISM OF ACTION

Phosphatidylcholine's role in the maintenance of cell-membrane integrity is vital to all of the basic biological processes. These are: information flow that occurs within cells from DNA to RNA to proteins; the formation of cellular energy and intracellular communication or signal transduction. Phosphatidylcholine, particularly phosphatidylcholine rich in polyunsaturated fatty acids, has a marked fluidizing effect on cellular membranes. Decreased cell-membrane fluidization and breakdown of cell-membrane integrity, as well as impairment of cell-membrane repair mechanisms, are associated with a number of disorders, including liver disease, neurological diseases, various cancers and cell death.

PHARMACOKINETICS

Phosphatidylcholine is absorbed into the mucosal cells of the small intestine, mainly in the duodenum and upper jejunum, following some digestion by the pancreatic enzyme phospholipase, producing lysophosphatidylcholine (lysolecithin). Reacylation of lysolecithin takes place in the intestinal mucosal cells, reforming phosphatidylcholine, which is then transported by the lymphatics in the form of chylomicrons to the blood. Phosphatidylcholine is transported in the blood in various lipoprotein particles, including very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL); it is then distributed to the various tissues of the body. Some phosphatidylcholine is incorporated into cell membranes.

Phosphatidylcholine is also metabolized to choline, fatty acids and glycerol. The fatty acids and glycerol either get oxidized to produce energy or become involved in lipogenesis. Choline is a precursor of acetylcholine. Serum choline levels peak between 2 to 6 hours after oral intake.

Common uses

Hepatic steatosis due to alcohol and metabolic disorders (diabetes, lipidoproteic hypernutrition, obesity and hyponutrition). Adjuvant in the treatment of intoxications from toxic agents and some kinds of drugs (antitubercotics; anti-psychotics; anti-epileptics; immunosuppressants). Very useful in the non-toxic treatment of lipid disorders such as hyperlipidemias and Hypercholesterolemia. European steroid users often use this product in an effort to maintain optimum hepatic function. It has been used very extensively in Europe and now in the US as a non-toxic supplement for weight reduction, particularly when associated with gross obesity and high serum lipid and Cholesterol levels, with very good results. This may be an effective way to combat a few of the toxic effects of anabolic steroids. It is used for protecting the liver.

RESEARCH SUMMARY

As a hepatoprotective

Clinical studies have demonstrated that choline is essential for normal liver function. Phosphatidylcholine is a better delivery form and is also more tolerable than choline. But, in addition, research has shown that phosphatidylcholine, independent of its choline content, has striking hepatoprotective effects. In two animal studies using baboons fed diets high in alcohol, some supplemented with a soy-derived polyunsaturated lecithin (60% phosphatidylcholine) and some unsupplemented, both fibrosis and cirrhosis were largely prevented in the phosphatidylcholine group. Most of the unsupplemented animals in these studies, which continued for up to eight years, developed fibrosis or cirrhosis.

Because these researchers had previously found that choline, equal in amounts contained in the phosphatidylcholine-rich lecithin they subsequently used, had no comparable protective effects on the liver, they concluded that the polyunsaturated phospholipids themselves may have been

responsible for the benefits observed.

In vitro studies have shown that these phospholipids increase hepatic collagenase activity and may thus help prevent fibrosis and cirrhosis by encouraging collagen breakdown. Several other mechanisms under investigation may also contribute.

Others have reported similarly encouraging results in animal models. Clearly, human trials are warranted.

In addition, phosphatidylcholine has demonstrated other protective effects in non-alcoholic liver disorders, including protection against various other toxic substances. Its benefits in viral hepatitis were reported some years ago by several different research groups in Europe and elsewhere. In one of these studies, individuals suffering from hepatitis type A and B were given 1.8 grams of phosphatidylcholine daily. Compared with unsupplemented controls, the phosphatidylcholine group enjoyed quicker recoveries, fewer relapses and quicker normalization of liver function tests.

Researchers in Great Britain treated chronic active hepatitis C patients with 3 grams daily of phosphatidylcholine in double-blind fashion. The phosphatidylcholine patients had significantly reduced symptoms, compared with controls. All histologic evidence of the disease disappeared in some cases. These researchers, like others, have hypothesized that phosphatidylcholine's possible antiviral effects are related to the supplement's apparent ability to increase cellular membrane fluidity and repair the membranes of liver cells.

Detoxification:

The health of the membrane is synonymous with the health of the entire organism. Toxins have an affinity for fatty acids; they literally take up residence in the lipid environment and in so doing, weaken and disrupt. The probable result is early apoptosis, premature death of the cell. Generally, normal mitosis provides for new cellular growth to maintain the health of the body, i.e. the previous discussion on photo receptors. However, toxicity's affinity for lipids can easily redistribute toxins and diseased toxic lipids into the new growth. In a healthy state with adequate glutathione and ascorbate to bind the toxins before they take up new residence, the body can keep the bad guys under control. However, if defenses are weak, toxins can continually be redistributed and eventually hide in the CNS and bone where the regeneration process is at a slower pace. The goal of detoxification is to 1) encourage regrowth with a renewed effort at the correct balancing of the essential nutrients, with the exchange of high energy lipids (PUPA and HUP A) to fuel regeneration and the eventual detoxification process; and 2) at the correct time, the inclusion of the toxin removal specialists, ascorbate, chlorella, and if possible IV glutathione.

Detoxification of neurotoxins requires that the cell membrane is nourished with balanced essential fatty acids (4:1, plus HUFAs) and supportive phospholipids. Phosphatidylcholine (PC) is the most abundant phospholipid of the cell membrane and protects the liver, with its 33,000 square meters

of membrane, against toxicity and infection. The liver plays a pivotal role in detoxification but due to its fatty acid content and the lipid soluble characteristics of neurotoxins, lipid based interventions are required to impact toxic burdens. Once the liver has been damaged it can no longer metabolize fats normally. Pools of lipids are then deposited within hepatocytes throughout the liver. Beta oxidation of fatty acids is suppressed impairing detoxification and prostaglandin production. Extensive research with PC has revealed that it protects the liver against damage from alcohol, pharmaceuticals, environmental pollutants, xenobiotics and infection due to viral, bacterial and fungal manifestations (Lieber 1994a, 1994b, 1995, 2001a, 2001b).

Hypercholesterolemia and Atherosclerosis:

Phosphatidylcholine increases the solubility of cholesterol and thereby decreases its ability to induce atherosclerosis. Phosphatidylcholine also aids in lowering cholesterol levels, removing cholesterol from tissue deposits, and inhibiting platelet aggregation. (Brook, JG, Linn, S, and Aviram, M. *Biochem Med Metabol Biol.* 35;31-39, 1986.) Here some of the beneficial effects may be attributable to the high content of linoleic acid in phosphatidylcholine.

The phospholipid preparation Lipostabil has been researched for use in the treatment of high cholesterol levels and atherosclerosis. In several trials evaluating this 70% phosphatidylcholine content lecithin product from Germany, total serum cholesterol and triglyceride levels dropped significantly and HDL cholesterol levels improved using dosage ranging from 1.5 g once daily to 3.5 g three times per day. (Lipostabil. Natterman International GMBH, 1990; Wojcicki, J, et al. *Phytotherapy Res.* 9;597-599, 1995)

A high-concentration phosphatidylcholine preparation, marketed in Germany under the trade name "Essentiale", has produced clinical results consistent enough to gain authorization from the BGA, the German equivalent of the FDA. This form contains 90% phosphatidylcholine, with 50% of the molecule having linoleic acid, the essential fatty acid, bound at the proper position; i.e., the first and second carbon of the glycerol molecule. Using this preparation the standard dosage recommendation is 350 mg three times per day with meals. (Essentiale, Natterman International GMBH, 1989.)

Phosphatidylcholine has been used to lower serum cholesterol levels, based on the premise that lecithin cholesterol acyltransferase (LCAT) activity has an important role in the removal of cholesterol from tissues. A few studies have shown reduction in serum cholesterol with phosphatidylcholine intake. The results were quite modest, and most studies have shown significant cholesterol-lowering activity across the membrane. Similarly, PPC is incorporated in blood lipoproteins such as cholesterol, leading to lipid-lowering properties. In one Russian clinical trial, the supplement lowered total and LDL ("bad") cholesterol by about 15%, decreased triglyceride levels by 32%, and raised levels of "good" HDL cholesterol by 10%.

Phosphatidylcholine and weight reduction

Experts point out that simply losing weight often will result in a significant reduction of excess fat in the liver. But they add that it is best to lose weight slowly—at a rate of no more than 1 to 2 pounds a week—because rapid weight loss has been shown to exacerbate a fatty liver condition, causing inflammation and even resulting in liver failure. Phosphatidylcholine does both, assists the body to lose weight without side effects yet protects the liver from fatty change dystrophy! Doctors say that NAFLD (non alcoholic fatty liver disease) can probably be largely prevented and even eliminated in the future by encouraging the adoption of healthy eating habits and more-active lifestyles. For those who already have nonalcoholic fatty liver disease, encouraging discoveries show that the use of natural products may potentially alter the course of this serious consequence of aging and unhealthy lifestyles.

The treatment with phosphatidylcholine in the context of injection lipolysis (fat dissolving injections).

Phosphatidylcholine is a phospholipid found in the cell membrane (membrane phospholipid), a chemical that is involved in cell structure and intra- and intercellular metabolism. Apart from the sphingolipids, phosphatidylcholine is the most important essential phospholipid (EPL) of mammals and is a major component of the cell membranes in the human body. Furthermore, it has an important function for intra- and intercellular metabolism.

It has primarily been used clinically for intravenous treatment of fat embolism, for lowering cholesterol levels and as a liverprotective substance.

For some years now, phosphatidylcholine has also been used for subcutaneous treatments of circumscribed fat deposits at eyelids, abdominal folds, flanks, upper and lower limbs and other body areas; and the clinical results have been excellent.

Phosphatidylcholine exerts an important influence on the regulation of lipid homeostasis by producing essential components of lipoproteins..

It activates L-CAT (lecithin-cholesterol acyltransferase) which in turn initiates the transportation of excess cholesterol found in the tissue, to the liver and their transformation into bile acids.

In the lungs, phosphatidylcholine is active as a surfactant preventing the alveolar breakdown at the end of the expiration. As from the 35th week of pregnancy, a mix consisting of 90% phosphatidylcholine and 10% proteins (surfactant proteins SP-A and surfactant proteins D) is produced in the pneumocytes in the course of the foetal lung development. This spreads like a film on the alveolar surface and can be detected in bronchial secretion and amniotic fluid. It facilitates the development of the collapsed alveoli of the newborn and forms a part of the protection and self-cleaning mechanism of the bronchial system. In case of a surfactant deficiency syndrome, it is – in addition to other measures - set into the bronchial system.

Also in connection with the body's inflammatory process, phosphatidylcholine fulfils important physiological tasks, namely by means of the biosynthesis of prostaglandins, leukotrienes and thromboxanes of the arachidonic acid. Phospholipase-A2 releases arachidonic acid from the membrane lipids. Through the action of cyclooxygenase, it is turned into prostaglandin H₂, the precursor of all physiological prostaglandins and thromboxanes. Due to cyclooxygenase inhibition, phosphatidyl has a prostaglandin-antagonistic effect. Phosphatidylcholine is hydrolyzed in the fatty tissue by phospholipase D and produces apolar phosphoric acid and polar cholines. Cholines have lipotropic properties and work as emulsifiers; and are components of the phospholipids. At the end of the 80s, phosphatidylcholine was used for infiltration in xanhelasmata, and this with satisfactory success. In the 90s, some physicians in Brazil started with subcutaneous injections into fat deposits under the eyelids, in the abdomen, hip and flanks. The results of these treatments of localised adiposities to improve body contours were outstanding.

Scientific research of the lipolysis mechanism of phosphatidylcholine on to human adipocytes revealed that phosphatidylcholine penetrates the adipocytes and is then, due to the impact of phospholipase D, hydrolyzed to phosphoric acid and choline. Cholines act as emulsifiers, and phosphoric acid triggers the activation of protein kinase C (PKC). The latter has the effect that lipolytic lipases – assisted by HSL (hormone sensitive lipases) hydrolyze triglycerides to become fatty acids and glycerine. With the help of lipoproteins – e.g. phosphatidylcholine is the major component of HDL - these are now transported to the liver and eliminated as bile acids.

Lipostabil® is the tradename for an injectable preparation of phosphatidylcholine manufactured by Aventis. It is approved for cardiological (to reduce cholesterol) use in some countries in Europe, though not including the United Kingdom.

Essentiale 303, Flabjab™, Lipomelt™, Lipodissolve, Fat-Away & Lipostabil® are all marketing names used to promote the latest “flab-busting” treatment that is finding it's way into an increasing number of UK aesthetic clinics.

Where is the evidence?

According to a clinical paper published in October 2003 in the Journal of Drugs in Dermatology: Phosphatidylcholine in the treatment of localized fat.

The only large clinical trial that we could find was the study mentioned above involving 213 patients, published in the Journal of Drugs and Dermatology in October 2003.

Volunteers received phosphatidylcholine injections in several different areas of localized fat deposits, (thighs, hips, abdomen, flanks and/or the chin region of the face). The patients were submitted to 1 to 5 treatment sessions with an average interval of 15 days between each session. At each treatment session, digital photographs were taken of the patient's front view, back view, and profile, according to the area to be treated. In some patients the thickness of the fatty pad was measured with a specific ruler. Various laboratory tests were also carried out on the volunteers

during the treatment with phosphatidylcholine.

Clinical results showed that phosphatidylcholine was effective in reducing the fatty pads in the treated areas, with few side effects. From the authors' point of view, they stated that the off-label use of phosphatidylcholine in the treatment of fatty pads and small areas of localized fat is safe, low cost, and effective. They also stated that, as with any other medications, it needs wide investigation for new treatment uses and long-term studies, so that the recommended dose and safe application technique can be standardized

The Syndrome X Connection

Because abdominal obesity, insulin resistance, and elevated triglyceride levels all appear to be strongly linked to NAFLD, some researchers advocate classifying NAFLD as an additional feature of the cluster of abnormalities called metabolic syndrome (or Syndrome X).⁴¹ Syndrome X is characterized by the National Institutes of Health as having at least three of the following health concerns: abdominal obesity; high triglyceride levels (150 mg/dL or higher); low HDL ("good") cholesterol levels (less than 50 for women and less than 40 for men); moderately elevated or high blood pressure (130/85 or higher); and moderately elevated or high blood sugar levels (a fasting glucose of 110 or higher).

According to the American Medical Association, one in five American adults, or about 47 million, are afflicted with the syndrome, which can more than double one's risk of heart attack, stroke, and diabetes. One study of people with NAFLD found that 88% of those with nonalcoholic steatohepatitis had metabolic syndrome, compared to 55% of patients with simple fatty liver. The researchers concluded that the presence of the syndrome increased the risk of a person with benign fatty liver disease progressing to nonalcoholic steatohepatitis.

No cure and no single specific treatment are available for metabolic syndrome; today doctors can only treat the various conditions—such as obesity, hypertension, high cholesterol, and diabetes—that are components of the disease. Even more important than the fact that a person is obese is where excess fat is stored on the body. Research has shown that people who carry excess weight around their middle (abdomen or waist) are most prone to developing insulin resistance. And recent studies have revealed that the majority of people with nonalcoholic fatty liver disease have central (abdominal) obesity. Phosphatidylcholine, should be an essential part of any sensible weight reduction programme, when weight reduction is large and side effects are to be kept to the bare minimum. For any weight reduction regime to be permanent it is strongly advised for drug therapy to be combined with diet (calorie) reduction and a regular exercise programme.

Phosphatidylcholine and the mind

Lecithin is known as phosphatidylcholine, although lecithin is also a term loosely applied to describe a combination of phosphatidylcholine with other phospholipids. Most people normally ingest 3 to 6 grams of lecithin a day through eggs, soy, and meats. Vegetables, fruits and grains

contain very little lecithin.

Phosphatidylcholine is the most abundant phospholipid component in all cells. phosphatidylcholine levels in brain cell membranes decline with age.

Several studies have been done with phosphatidylcholine to investigate its effects on memory. The results of the studies have not been consistent. Some have shown positive responses (Sorgatz 1987, Ladd, 1993), while others showed no difference in memory or learning after lecithin administration (Gillin 1980). Phosphatidylcholine may help some with tardive dyskinesia, a neurological disorder characterized by defective cholinergic nerve activity. Both supplemental choline and phosphatidylcholine were found to reduce the muscular hyperactivity of this disorder by about 50% in some studies. However, one significant trial did not see a beneficial effect.

There is some very preliminary evidence that phosphatidylcholine may help control manic symptoms in some.

Alzheimer's Disease:

Choline supplementation increases the accumulation of acetylcholine within the brain in normal patients so many researchers hypothesized that phosphatidylcholine supplementation would benefit Alzheimer patients. Some research has indicated that increasing acetylcholine content in the brain through supplemental choline might result in improved memory. However, clinical trials using phosphatidylcholine have not produced significant benefits. Studies revealed inconsistent improvements in memory from choline supplementation in both normal and Alzheimer's patients. Nevertheless, criticisms of these studies and their interpretations have been raised on the grounds that sample size was too small, the dosage of phosphatidylcholine used was too low, and the studies themselves were poorly designed. (Rosenberg, G and Davis, KL. Am J Clin Nutr. 36; 709-720, 1982; Levy, R, et al. Lancet 1;474-476,1982; Sitaram, N, et al. Life Sci 22; 1555-1560, 1978.)

Alzheimer's disease is characterized by a decrease in cholinergic transmission, but the basic defect in cholinergic transmission in Alzheimer's disease relates to impaired activity of the enzyme acetylcholine transferase, not to a deficiency of choline. Acetylcholine transferase combines choline with an acetyl molecule to form acetylcholine. However, since increased levels of choline do not necessarily increase the activity of this critical enzyme, phosphatidylcholine supplementation will probably not prove efficacious in the majority of patients with Alzheimer's disease.

In a patient with mild to moderate dementia, the use of a high-quality phosphatidylcholine preparation at a dosage level of 15 to 25 g/day may be beneficial. (Murray, M. p. 140, 1996.)

In cancer prophylaxis

Recently it has been suggested that phosphatidylcholine might eventually have some therapeutic role in some cancers. There is no evidence of this to date, but animal studies indicate that

deficiencies in choline and phosphatidylcholine may disrupt cell membrane signal transduction in ways that could lead to various cancers. There is ample evidence that liver cancer is promoted in various animals by choline-deficient diets, and it has been shown that excess choline can protect against liver cancer in a mouse model.

PRECAUTIONS

Those with malabsorption problems may develop diarrhea or steatorrhea when using phosphatidylcholine supplements. Those with the antiphospholipid-antibody syndrome should exercise caution in the use

Contraindications

Known hypersensitivity to any of the ingredients. To be used only under medical advice or in hospitals. Due to the benzylic alcohol content, the product is not suitable for children under 2 years.

Those with malabsorption problems may develop diarrhea or steatorrhea when using phosphatidylcholine supplements. Those with the antiphospholipid-antibody syndrome should exercise caution in the use of phosphatidylcholine supplements.

Dosage

By i.v injection: carefully inject by slow i.v. injection (duration of injection 3-4min). It is suggested to dilute with patient's own blood with a 1:1 ratio. Do not mix any other substance or electrolytic solution into the same syringe. Recommended dosage is 1-2 amps daily. It can be increased according to doctor's advice, to 3-4 amps daily. It is possible to inject 2 amps at the same time, with the same syringe, always very slowly. By phleboclysis: the amps content must be diluted only in glucidic solutions (such as glucose or levulose). The solution must be clear for the whole duration of phleboclysis. In acid environments, some fine flocculation episodes could occur. For the same reason electrolytic solutions cannot be used for dilution. The final solution Ph should be close to 7.5. The suggested dosage is 4-8 amps daily in 250-1000ml sugary solution. It can be increased according to doctor's advice, to 12-16 amps daily, especially in the total parenteral nutrition. Tolerability can be increased, by adjustment of phleboclysis speed in those patients particularly sensitive from a neurovegetative point of view. If phleboclysis injections are not given daily, intravenous injections are suggested between intervals. Parenteral treatment should be completed, as soon as possible, by oral treatment with Essentiale forte caps. • Using lecithin, the most common form of choline supplementation, with 90 percent phosphatidylcholine, the dosage (three times daily with meals) is:

- 350-500 mg t.i.d. for the treatment of liver disorders;
- 500-900 mg t.i.d. for lowering cholesterol;
- 5,000-10,000 mg q.d. for the treatment of Alzheimer's disease and bipolar depression.

* For Lipodissolve treatment please refer previous section for details
(Murray, M. p. 141,

ADVERSE REACTIONS

No major side effects have been reported. Mild side effects have been noted occasionally such as nausea, diarrhea and increased salivation in some. This holds for all forms of phosphatidylcholine.

INTERACTIONS

There are no known interactions.

OVERDOSAGE

There are no reports of overdose.

LITERATURE

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