

# Prescribing Information

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PhosChol

100% pure Polyenylphosphatidylcholine

Softgel Capsules and Liquid Concentrate

# PhosChol Prescribing Information

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(Polyenylphosphatidylcholine)  
Softgel Capsules and Liquid Concentrate

### Product Description

**PhosChol®** (PPC) is purified polyenylphosphatidylcholine (PPC) and an oral therapy for use as a membrane therapeutic. With its special ingredient **1,2-dilinoleoylphosphatidylcholine** (–up to 52%) PPC is theoretically of importance in all those diseases in which damaged membrane structures, reduced phospholipid levels and/or decreased membrane fluidity are present. This is a hypothesis which is supported by experimental and clinical investigations on various membrane-associated disorders and illnesses.

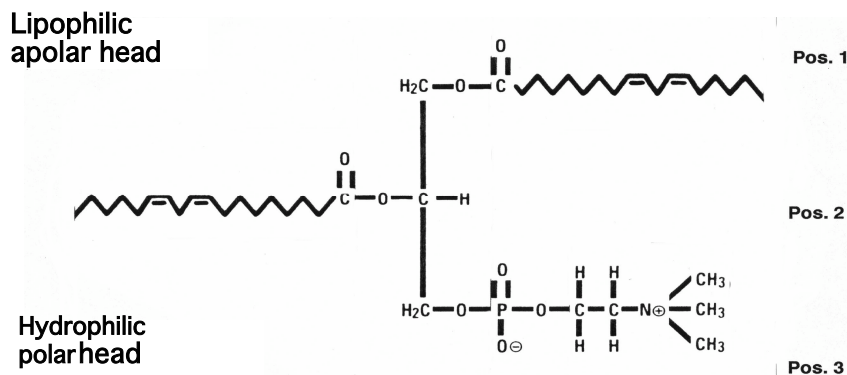
### The predominant molecule in the PPC-substance has in both positions a linoleic acid.

This is the most important difference between PPC on one side and all other phospholipids on the other side! At the same time this fact is responsible for the therapeutic advantages of the PPC compared to other phospholipids or lecithins.



**The quantitatively and qualitatively dominating molecule in PhosChol is 1,2-dilinoleoylphosphatidylcholine (DLPC) with linoleic acid bound in c1- and c2-position of the molecule**

*This is the most important difference between PPC and the typical phospholipids such as triple lecithin and raw lecithin! Additionally, this difference is the main reason for the therapeutic advantages of PPC over the other phospholipids.*



### Composition

**PhosChol** contains: Highly purified Essential Phospholipids (EPL) or Polyunsaturated Phosphatidylcholine / Polyenylphosphatidylcholine (PPC) (active principle: diglyceride esters of cholinephosphoric acid of natural origin, with excess of unsaturated fatty acids, predominantly linoleic acid [approximately 70%] with 1,2- dilinoleoylphosphatidylcholine [(DLPC) up to 52%], linolenic acid and oleic acid).

### Indications

Acute and chronic hepatitis; cirrhosis; toxic liver damages, fatty degeneration of the liver of any origin; prophylaxis of gallstone formation; radiation syndrome; dyslipoproteinemia (increased VLDL- and LDL-cholesterol, decreased HDL-cholesterol, and hypertriglyceridemia); atherosclerosis; coronary, cerebral, and peripheral circulatory disturbances; angina pectoris; condition following myocardial infarction, and apoplexy; hypertension due to sclerosis; vascular diseases, especially in diabetes mellitus; nephritic syndrome.

### Membrane Therapeutic

Pharmacological investigations, a broad range of clinical trials, and other available data on PPC and its different modes of action, demonstrate that PPC acts primarily through its influence on membranes. As membrane changes and damages occur in many disorders, PPC's therapeutic approach in man is a physiological and holistic one.

The possibilities of application reside in the kind and severity of membrane damage and in the influence on membrane fluidity and thus on membrane-dependent metabolic processes by the incorporation of the special molecule **1,2-dilinoleoylphosphatidylcholine**. In addition, the PPC membrane pool for the endogenous metabolism is increased.

From this we can infer that PPC can be applied (in general as adjuvant medication) in membrane-associated damages and diseases, and, in specific cases, to enhance membrane-related physiological processes.

### Chemistry

The term polyenylphosphatidylcholine indicates the highly purified extract of the semen of *Glycine max* (Linne Merrill) with a standardized content of 94% (3-sn-phosphatidyl) choline in the oral preparations.

The (3-sn-phosphatidyl) choline purified to 94% presents no other phospholipids, only 3% of other lipids, and 3% of oil.

The term "essential" phospholipids results from the characteristic fatty acid composition of the soya bean phospholipids, which is distinguished by its particularly high content of polyunsaturated fatty acids, predominantly linoleic acid (approximately 70% ), linolenic acid and oleic acid.

The detailed composition of the polyenylphosphatidylcholine molecule is :

### Composition of Polyenylphosphatidylcholine (PPC) from Soybean

<b>Polyenylphosphatidylcholine (PC)</b>	<b>94-96%</b>
- <b>dilinoleoyl (18:2-18:2) PC (DLPC)</b>	<b>40-52%</b>
- <b>palmitoyl-linoleoyl (16:0-18:2) PC (PLPC)</b>	<b>23-24%</b>
- <b>oleoyl-linoleoyl (18:1-18:2) PC (OLPC)</b>	<b>12-13%</b>
- <b>linolenoyl-linoleoyl (18:3-18:2) PC (LLPC)</b>	<b>6-7%</b>
- <b>stearoyl-linoleoyl (18:0-18:2) PC (SLPC)</b>	<b>6%</b>
- <b>palmitoyl-oleoyl (16:0-18:1) PC (POPC)</b>	<b>3-4%</b>
- <b>stearoyl-arachidonoyl (18:0-20:4) PC (SAPC)</b>	<b>1-2%</b>

Lieber CS et al: *Gastroenterology* 1994; 106: 152-159

Up to 52% of these molecules consist of 1,2 dilinoleoylphosphatidylcholine, its main active component:

The atomic formula of polyenylphosphatidylcholine is: C<sub>44</sub>H<sub>80</sub>N<sub>08</sub>P x H<sub>20</sub>, the molecular weight: 800.

Typical analytical data of the phosphatidylcholine molecules are:

Phosphorus content: 3.8 %

Choline content: 14.9 %

Fatty acid content: 69.0 %

And the following molecular proportions:

Phosphorus: choline = 1.00

Fatty acids: choline = 2.02

Fatty acids: phosphorus = 2.00

PPC is a colorless or slightly yellow compound with wax-like consistency and a nut-like taste.

**Standard Composition Analysis - Results Per 100 Grams****PhosChol – Lot # 2200260**

Moisture	7.69%
Ash	3.21 grams
Protein (N x 6.25)	9.64 grams
Fat	70.66 grams
Saturated	5.6 grams
Polyunsaturated	16.1 grams
Monounsaturated	48.9 grams
Cholesterol	<0.1 grams
Total Dietary Fiber	0%
Total Carbohydrates	8.80 grams
Calories	710.0
Calories from Fat	635.9
Sodium	19 ppm
Calcium	<5 ppm
Potassium	0.07%
Iron	<5 ppm
Phosphorus	1.2%
Thiamin	<0.04 milligrams
Riboflavin	<0.04 milligrams
Niacin	<0.2 milligrams
Vitamin A	less than 50 IU/100 grams
Vitamin C	Less than 0.5 milligrams
Folic Acid	0.0887 milligrams/lb.
Vitamin B12	<0.002 milligrams/lbs.
Vitamin D	<30.0 IU/100 grams
Vitamin E	796 IU/lb.

### Active Principle and Indications

Studies on the active principle of PPC as well as pharmacological and clinical trials are available on the following disturbances and diseases related to membrane damages:

- In liver diseases the hepatocyte structures are always damaged, for example by viruses, organic solvents, alcohol, medicaments, drugs or too much fatty food. As a consequence, membrane fluidity and permeability are disturbed, membrane-dependent metabolic processes are impaired as well as membrane-associated enzyme activities. Immunological and receptor properties may be changed. This may considerably inhibit liver metabolism.
- In hyperlipoproteinemia, with or without atherosclerosis, various pathomechanisms, such as lipid peroxidation, decrease of lipid-metabolizing enzyme activity and modification of lipoprotein structure and function interact and provoke a rise in serum cholesterol and triglyceride levels and a subsequent accumulation of fat in the peripheral tissue, avoiding the receptor-mediated uptake of cholesterol. As it is relatively lowered, serum HDL takes up and transports less cholesterol from the periphery back to the liver.
- One of the hemorrheological disturbances is an elevated cholesterol/phospholipid ratio in the membranes of platelets and red blood cells (RBC) with concomitant changes in membrane function. This leads to an increased tendency of platelets and RBC to aggregate, which in turn influences blood flow properties and microcirculation.
- In neurological diseases the reduction of choline, a precursor to the neurotransmitter acetylcholine, the deficiency in unsaturated fatty acids, or increased rigidity of neuronal membranes may influence metabolic processes and functions of the nerves.
- In gastrointestinal inflammation the mucosa quality, membrane structures, membrane-dependent immunological reactions and the local prostaglandin synthesis are altered.
- In lung diseases, such as infant or adult acute respiratory distress syndrome, the fatal outcome of the disease is triggered by a phospholipid deficiency in the pulmonary alveoli (surfactant).
- In kidney diseases a phospholipid deficiency in the membranes is present, involving impaired excretion and reduced prostaglandin synthesis.

- In the multifactorial picture of gestosis, disorders of the lipid metabolism and lipid peroxidation, as well as impaired liver and kidney function, can be observed.
- In skin diseases, such as psoriasis, the pathological mechanisms seem to be favoured, among others, by alterations of cell structures and of the fatty acid and phospholipid composition.
- Aging patients are often faced with a combination of age-linked physiological changes and diseases, e.g. degenerative liver damage or atherosclerotic changes of the vascular wall associated with other degenerative or not degenerative diseases.

All these very different diseases may have comparable membrane disorders in common. With PPC, such disorders may be positively influenced, eliminated or even improved beyond normal due to the high content in polyunsaturated fatty acids. For example:

- 1) HDL particles enriched with PPC are able to take up more cholesterol from LDL and tissues. More cholesterol can be transported back to the liver. This action on the reverse cholesterol transport is unique. All other lipid-lowering agents reduce either the cholesterol absorption in the body, or the cholesterol synthesis in the liver and its distribution to the periphery. These substances, however, do not physiologically mobilize the cholesterol already present in the periphery.
- 2) The stimulation of lipolytic enzymes, such as lipoprotein lipase and hepatic triglyceride lipase, favors the breakdown of triglyceride-rich lipoproteins.
- 3) The cholesterol/phospholipid ratio in membranes, platelets and red blood cells decreases and membrane function is improved. Aggregability and blood viscosity decrease, microcirculation and the lifespan of the mentioned blood corpuscles increase.
- 4) Peroxidative reactions are reduced, damaged hepatocyte membrane structures restored, membrane fluidity and function stabilized, immunomodulation and cell protection improved, and membrane-associated liver functions enhanced.
- 5) With the normalization of the cholesterol/phospholipid ratio, the bile is also stabilized.
- 6) The substitution with polyunsaturated fatty acids and choline may have a cytoprotective effect in the brain and activate neuronal processes.

## Liver Disease

Experimental and clinical results support the assumption that the therapeutic application of PPC has protective and even curative and regenerative effects on the biological membranes of sinus endothelial cells and hepatocytes.

The cytoprotective effect of PPC has been corroborated in 13 in vitro and in 117 in vivo experiments, in which 31 different models with 8 different animal species were used. Types of intoxication which are known to play a role in the etiology of liver disease have mostly been applied: chemical substances, medicaments, alcohol, cholestasis, immunological phenomena, exposure to radiation, etc.

The hepatoprotective effects of PPC have been confirmed as compared to the controls and were the more pronounced the earlier PPC was administered:

- 1) Structures of membranes were normal or largely normalized;
- 2) Fatty infiltrations and hepatocyte necrosis could be diminished or even eliminated;
- 3) Corresponding data were found for lipid peroxidation, transaminase and cholinesterase activity, and for serum lipids; liver cell metabolism increased;
- 4) The increase of RNA and protein synthesis and of the liver cell glycogen content indicated a stimulation of the liver cells;
- 5) Reduced collagen production, collagen/DNA ratio and liver hydroxyproline indicated a reduced formation of connective tissue.

Through May 2004, 127 open, 46 single-blind and 19 double-blind clinical trials with a total of 12,197 patients were carried out. 137 of these studies were based on 3 groups of criteria, 43 on 4 groups and 5 on 5 groups of criteria (including electron microscopy). 48 studies including histological controls were performed. 17 studies were even done on newborns and children.

The dosage of PPC ranged from 525 mg to 2700 mg/day when administered orally. The duration of treatment lasted from some weeks to up to 30 months. The main liver indications were: **acute hepatitis, chronic hepatitis, fatty liver, toxic liver damage, and cirrhosis of the liver.**

**The clinical findings, showing the efficacy of PPC, can be summarized generally as follows:**

- 1) Accelerated improvement or normalization of subjective complaints, clinical findings and several biochemical values.
- 2) Improved histological result as compared to the control groups.
- 3) Shortened hospitalization duration.

Two pharmacological, 11 open and 1 double-blind trials have shown the effectiveness of PPC in hepatotoxicity of anti-TB agents, which is the only representative clinical model of liver damage to assess effectiveness of a liver therapeutic in intoxication.

### **Renal Disorders**

Eight pharmacological and 23 clinical studies give a first impression of PPC and its influence on renal disorders.

The range of commonly observed effects includes a significant rise of creatinine, urea and sodium clearances, correction of lipid metabolism disorders, disappearance of proteinuria and hypoalbuminemia, and a decrease of lysolecithin excretion. Signs of intoxication could be particularly improved in nephrotic forms. The main effects of PPC are the stabilization of renal cell membranes and a positive influence on cytoprotective prostaglandins.

### **Gestosis**

A total of 684 patients in 13 studies received as adjuvant treatment 250-1000 mg of PPC intravenously and/or 1.8 g PPC orally per day.

In these patients suffering from early or late gestosis, the subjective symptoms, such as hyperemesis gravidarum, clearly improved or disappeared. This positive effect was also seen with respect to accompanying disturbances, such as lipid peroxidation, renal disorders, pathological liver function and hyperlipidemia.

### **Hyperlipoproteinemia/Atherosclerosis**

To date, the influence of "essential" phospholipids on the lipid metabolism has been studied in 14 in vitro and 95 pharmacological investigations, in which PPC was applied in different models or diets in 11 different animal species by the intravenous, oral, subcutaneous, intracardial or intraperitoneal route, prophylactically, simultaneously or curatively.

The results of these studies, reflecting the effects of PPC in lipid metabolic disturbances, can be summarized as follows:

- 1) Increase of polyunsaturated fatty acids in cholesterol esters, phospholipids, triglycerides and lipoproteins, in serum and aorta.
- 2) Influence on enzyme activities in serum and aorta, such as on LCAT, HTGL, LPL, ACAT and phospholipase.
- 3) Lowering effect on serum lipid values.

- 4) Influence on lipoprotein structure and cholesterol content, especially on HDL-C/LDL-C ratio.
- 5) Antiatherogenic effect in prophylactic and therapeutic use.
- 6) Decrease of (lipid) peroxidation and platelet aggregation together with improved hemorrheology.

Through the end of 1989, 205 clinical trials with a total of 7606 patients were carried out, 12 of them double-blind, and 53 controlled (save fat embolism).

In the mean, PPC reduced total serum cholesterol by -8 to -30%, LDL cholesterol by -10 and -31%, triglycerides by -12 and -58%, and it increased HDL cholesterol by +10 to +45%.

In a pilot study in 15 patients with hyperlipoproteinemia and high-cholesterol plaques, signs of reduced growth rate of minor plaques and a reduction of the size of larger high-cholesterol plaques were found.

Eleven studies demonstrated the influence of PPC on the erythrocyte morphology including improved cholesterol/phospholipid ratio in membranes, filterability and flexibility of red blood cells, erythrocyte aggregation, blood viscosity and capillary blood flow.

In 20 studies it was shown that platelet membrane composition improved, and that platelet susceptibility to ADP, PAF or collagen, and the thromboxane/6-keto-PGF1 \_ ratio of thrombocytes were normalized.

According to some authors, injected PPC micelles or liposomes simulate HDL function and improve reverse cholesterol transport.

### **Gastrointestinal Inflammation**

The following experiments, among others, were carried out:

- Whole-body autoradiographs of rats after an oral dose of radioactively labelled 1,2-dilinoleoylphosphatidylcholine, visualizing the high PPC concentration in the gastric and intestinal mucosa even 24 hours after administration.
- Mucosal PGE2 synthesis and release experimentally reduced by indomethacin application reincreased significantly after 60 and 120 minutes of simultaneous PPC administration.

Correspondingly, NSAID-induced gastric mucosal damage was reduced or prevented in experimental studies, when PPC was applied concomitantly.

Similar results were found in orientating clinical trials in gastroduodenal damage, especially due to NSAIDs, which, however, were dose-related.

These findings underline the significance of the surface-action of phospholipids for the hydrophobic properties of the gastrointestinal surface.

### **Neurology**

Fourteen experimental studies have shown that:

As PPC is taken up to a small amount intact into the brain, endogenous phospholipid synthesis is stimulated - positive effects, such as raised choline content in the brain, improved cerebrovascular circulation and cerebral enzyme antioxidant system, and favourable actions on the dendritic material have been demonstrated.

35 clinical investigations with 1,968 patients and 3 in 31 volunteers have also given clinical evidence of some positive effects in certain diseases, such as involuntional dementias and multiple sclerosis. Improvements of subjective well-being, such as headache, dizziness, memory, concentration, endurance, irritability, insomnia, angina attacks, and walking time have been reported. However, final conclusions cannot yet be drawn as neither the exact PPC dose to be applied in different neurological diseases is known nor is the classification of the diseases with their sub-types clear enough.

### **Lung Surfactant**

3 experimental and 8 clinical studies demonstrate that the therapeutic possibilities of PPC in this indication field consist first of all in the prophylactic substitution of phosphatidylcholine molecules in the decisive pregnancy weeks to support the formation of surfactant in the unborn child. Another possibility is the compensation of membrane damages, e.g. in the presence of inflammatory processes in the lung, or in atherosclerotically changed blood flow properties and erythrocyte flexibility.

### **Psoriasis**

Thirteen studies with a total of 915 patients treated from 1 month to up to several years demonstrated the value of PPC as an adjuvant therapeutic application in this condition. The positive effect is probably based on the correction of lipid values in the skin, primarily of fatty acid levels.

## Geriatrics

In geriatrics, where age-related physiological changes in the organism are often combined with specific diseases, the membrane therapeutic PPC may prove to be useful. The effects described so far for various indications can be summarized as follows: enhanced memory performance of the aging brain, promotion of gastrointestinal function by mucosa restoration, activation of the liver metabolism and detoxication, activation of renal function, influence on the lipid metabolism and on atherosclerosis by cholesterol mobilization, improvement of the coronary, peripheral and cerebral blood flow and, finally, correction of the increased cholesterol/phospholipid ratio in cellular membranes in general.

Since multimorbidity is often present in old age and the elderly usually have to take different drugs, it is essential that geriatric disorders be treated with a preparation that does not provoke additional side-effects or which even alleviates the adverse reactions of the accompanying medication. "Essential" phospholipids are a phytotherapeutic product without noteworthy side-effects even in long-term application, and without contraindications.

## Pharmacokinetics

The phospholipids reaching the organism by the way of PPC differ from endogenous phosphatidylcholines by their fatty acid pattern. 1,2-dilinoleoylphosphatidylcholine, the main active ingredient in PPC, is usually not present in the body. Therefore, in pharmacokinetic investigations radioactively labelled 1,2-dilinoleoylphosphatidylcholine was used, which can be obtained by synthetic or semisynthetic ways. In order to find an answer to the questions of distribution and excretion, different isotopes ( $^{32}\text{P}$ ,  $^3\text{H}$ ,  $^{14}\text{C}$ ) and sometimes multiple labels, at various molecular components were applied.

## Pharmacokinetics in Man

The results of pharmacokinetic studies in man using  $^3\text{H}/^{14}\text{C}$ -labelled PPC agree largely with the data derived from animal experiments. Here again, the **rate of absorption was found to be greater than 90%**.

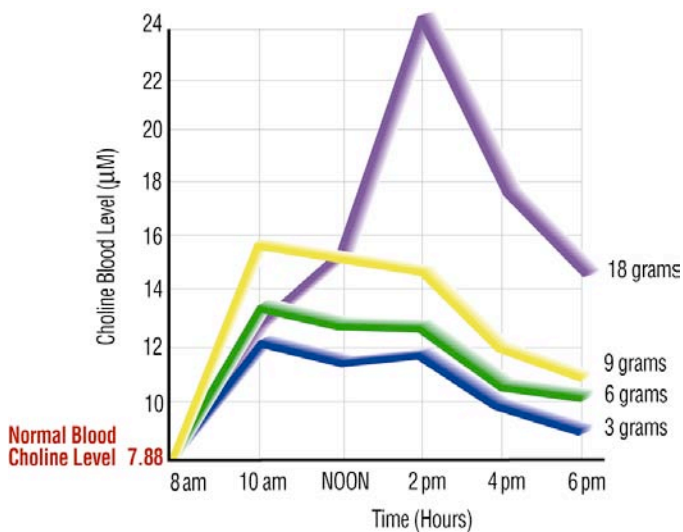
In man the maximum concentration in blood reached 6 hours after oral administration of the  $^{14}\text{C}$ -labelled substance was about 20 % of the administered dose and thus approximately four times that measured in rats and monkeys.

Examination of lipoproteins revealed that the specific activity of polyenylphosphatidylcholine in HDL was 2 to 6 times higher than in apo-B-containing lipoproteins, and up to 20 times that of red blood cells or total blood. Thus, in man, PPC is also preferentially incorporated into the HDL fraction.

According to Zierenberg et al. "essential" phospholipids are exchanged for phospholipids of membranes and lipoproteins.

After intravenous administration and a quick initial decrease in total plasma lipids (redistribution into other lipid fractions in plasma), the concentrations decreased slowly with an elimination half-life of 59 days indicating largely catabolic reactions. The pharmacokinetic studies in animals and in man show that upon parenteral administration of PPC the radioactivity may be detected practically in the liver and there especially in the membranes. After oral application it amounts to about 50% of the applied compound. **PPC is incorporated in toto.**

Studies have shown that as little as 3 grams of PhosChol® per day can effectively raise blood choline levels by 50%, and 9 grams a day can double it.



### Absorption in Animal Experiments

**The absorption rate determined by D. LeKim and E. Graf following oral administration of radiolabelled PPC to rats was greater than 90%.**

This confirms the results of J. M. Fox et al. who found that PPC is almost completely taken up from the intestinal lumen within 24 hours. S. Parthasarathy et al. also obtained concordant results. Almost 100% of the administered dose of PPC is hydrolysed to 1-acyl-lysophosphatidylcholine during absorption. Of this, about 50% is reacylated to intact PPC in the intestinal mucosa.

This finding is important insofar as studies by M. Whyte et al. indicate that, in mammals, free unsaturated fatty acids given orally are not effective in changing the fatty acid moieties of endogenous phosphatidylcholine so as to produce molecules containing polyunsaturated fatty acids in the 1- and 2- positions. **In mammalian systems phosphatidylcholine is esterified preferentially with a saturated fatty acid in the 1-position.**

### Distribution in Animal Experiments

PPC enters the liver via the lymph and the blood pathways. In the liver, it is partly taken up by cell membranes and subcellular membrane fractions. In the blood, phospholipid fractions of the lipoproteins exchange with PPC, the latter being taken up preferentially by the high-density lipoproteins (HDL).

Studies in rats and mice given PPC i.v. showed that approximately 80% of the injected dose was eliminated from plasma after 15 minutes, approximately 92% after 75 minutes and approximately 100% after 10 hours.

After a single oral dose (350 mg/kg b.w.) of 3H/14C-labelled PPC in rats, maximum concentration of radioactivity in the liver reached 24.5% after 24 hours of application and slowly declined to 4% within 8 days. Significant quantities of radioactivity were found in the striped muscles: 5.8% of the dose after the first 6 hours, an increase of up to 25% being observed within the first 8 days of dosing. Lower amounts of radioactivity were distributed in the kidneys, the lung and the myocard: 2.7%, 0.9% and 0.3% respectively of the administered dose within 24 hours. Following single oral administration of labelled PPC, radioactivity was detected in the plasma only for 48 hours. After 96 hours approximately 22%, and after 8 days up to 54% were absorbed from the cells.

After a 5-day repeated oral administration of 3H/14C-labelled PPC to rats, significant concentrations of the 14C- radiolabel were detected in the liver (18.6%), the depot fat (7.0%), the striped muscles (31.4%) and the bones (5.6%).

Lower concentrations of C-radioactivity were located in the lungs, kidneys, testes, gastrointestinal tract, blood and plasma. Six hours after the 5th administration of labelled PPC 22.9% of the dose were accumulated in the liver. This value declined to 2.3% after 16 hours. <sup>14</sup>C-radioactivity in the striped muscles rose to 36.9% within 4-day. Little radioactivity was measured in the bones and the depot fat: a maximum of 4.7% and 5.6% resp. of the dose 24 hours after the 5th application. Kidneys and adrenals presented 1.3% and 1.7% resp. of <sup>14</sup>C after 6 hours. The <sup>14</sup>C- radiolabel in the blood showed a fairly homogeneous distribution in blood cells and plasma throughout the 4-day dosing.

Eight days after the 5th dosing up to 65% of the total radioactivity were concentrated in the blood. After another 8 days already 76% of the <sup>14</sup>C- radiolabel was detected in the cells .

Similar results were also obtained in rhesus monkeys after single and repeated dosing of <sup>3</sup>H/<sup>14</sup>C-labelled PPC: 6 hours after the last repeated administration of the radiolabel 11% of the PPC dose was detected in the liver, 7% in the depot fat and 16-20% in the striped muscles. After 17 days the values in the liver and depot fat declined to 1.78 and 4.5% resp. to the applied dose, whereas the concentration in the striped muscles remained fairly constant. Six hours after the last dosing, the <sup>14</sup>C-radiolabel in blood was mainly located in the plasma: 74-75% of the dose. After 17 days the values declined to 46 and 28% respectively.

Whole-body autoradiographs taken after oral administration of 1,2- <sup>3</sup>H-dilinoleoyl-3-sn-phosphatidyl- <sup>14</sup>C-choline to Wistar rats, showed principally the following results: 6 hours after a single dose of labelled PPC, radioactivity was mainly located in the liver, kidneys and the intestinal mucosa. Low concentrations were found in the secretory glands, the lymph nodes and the gut contents. 12 hours after application the distribution of radioactivity was somewhat more homogeneous, major concentrations, however, still being present in the liver, kidneys and the intestinal mucosa. A similar distribution was detected after 24 hours, low activity still being found in addition in the bone marrow, lungs, spleen, epidermis, testes and the secretory glands. 48 hours after application of the labelled PPC, the substance was completely distributed, major concentrations being located in the liver and the gastrointestinal tract. In addition, considerable amounts were still found in the kidneys, epidermis, testes and the secretory glands (salivary, thymus and thyroid glands). There were signs of a general distribution in the striped muscles. After 96 hours the concentrations of radioactivity had sharply declined without specifically accumulating in one of the mentioned organs. Only low amounts of radioactivity, distributed homogeneously, could be detected after 8 days. Slight local accumulations were found in the intestinal mucosa, epidermis, testes and the seminal vesicles. A similar distribution pattern was described after repeated PPC application, low

concentrations still being present additionally in the brain, spinal marrow and in the striped muscles.

To put the available results of investigations on the uptake of the intact molecule into the brain into more concrete terms, it can be said that less than 1% of an orally or intravenously applied dose is found in the brain. The autoradiographs show no special affinity for neurons.

Analytic examinations of the incorporated PPC radiolabel by means of cell fractionation of the liver homogenate after 6 hours of oral application of 3H/14C-PPC clearly showed that the radioactivity was concentrated to a quantitatively high degree in the membrane-containing fractions, the distribution being ubiquitous in all liver cell fractions. This result is in accordance with former investigations on the i.v. application of PPC.

Hydrolysis by phospholipase A2 showed that 6 hours after application of the radiolabel, the phosphatidylcholine isolated from the liver still contained 96% of the labelled fatty acids in the 1-position, whereas there were only 4% in the 2-position. Moreover, the determination of the expired CO<sub>2</sub> after oral application of differently labelled 14C/3H-dilinoleoyl-phosphatidylcholines showed that a high concentration of the 14C-radioactivity was present only when the fatty acid in the 2-position of the phosphatidylcholine molecule was labelled with 14C.

Renal excretion after a single dose in the first 5 days is 17.4% of the administered dose in rats and 17.7% in rhesus monkeys. After a single dose about 15% of the radioactivity is expired in rats and rhesus monkeys with the breathing air, a finding which may be attributed to degradation of fatty acids during absorption of phosphatidylcholine. As the excretion in the feces is low with 3-8% of the dose in the first 5-7 days in rats, a considerable part of the PPC must be subjected to a vast enterohepatic circulation.

## **Toxicology**

The following gives a short survey of the most significant studies on the toxicology and teratology of PPC after mainly oral or intravenous application.

### **Acute Toxicity**

Acute toxicity in single administration of PPC has been tested in the mouse, the rat and the rabbit in oral (p.o.), subcutaneous (s.c.), intravenous (i.v.) and intraperitoneal (i.p.) applications.

For reasons of volume, obviously, no higher doses could be applied. As no animal died within the 7-day follow-up period, it can be affirmed that the highest

tolerable dose, as used in the mentioned species and application forms, corresponds to the given doses or is even higher. From the clinical viewpoint, only sporadically slight symptoms were observed, mostly none at all. Only in subcutaneous application, the section showed sporadically rests of substance at the site of application.

Under the aforementioned trial conditions, PPC has to be judged as practically non-toxic for the mouse, the rat, and the rabbit.

In acute toxicity studies with PPC 5 ml ampoules for intravenous application (1 ml contains 50 mg of PPC and 23 mg of deoxycholic acid), the LD50 was found to be as follows:

### **Toxicity in Repeated Administration**

Neither in subchronic nor in chronic toxicity tests were observed any reactions of intolerance when daily oral doses of up to 3,750 mg/kg b.w. were applied to rats, or up to 2,500 mg/kg b.w. to dogs.

In investigations with the PPC ampoules on rabbits and dogs after 4-week application the "no-effect" dose was found to be 1.2 ml or 0.6 ml/kg b.w. for the dog and 0.6 ml/kg b.w. for the rabbit.

13 weeks of application in dogs showed a "no-effect" dose between 0.3 and 0.9 ml/kg b.w. for local tolerance and more than 0.9 ml/kg b.w. for systemic compatibility. The topic and systemic tolerance in rhesus monkeys ranged from 0.3 to 0.6 ml/kg b.w..

### **Teratogenicity and Embryotoxicity of PPC**

No toxic effects of PPC on pregnant rats or fetuses were observed either when doses of up to 1,000 mg/kg b.w. were administered to rats or up to 500 mg/kg b.w. to rabbits.

Similar results were found when using Essentiale or Lipostabil ampoules in doses of up to 1.2 ml/kg b.w. in rats or rabbits.

### **Perinatal and Postnatal Toxicity, Fertility and Reproductive Performance**

Perinatal and postnatal development of rats is not influenced by oral PPC doses of up to 3,750 mg/kg b.w./day. When the substance was applied until the end of the third lactation week all parameters were found to be within the normal histological range.

Male rats received PPC 10 weeks and female animals 2 weeks before the beginning of the test. Oral doses of 150, 750 and 3,750 mg/kg b.w. were applied per day. Even with the highest dose, no effect of PPC on male and female fertility, nor on the reproductive performance was observed. An increase in dominant lethals could not be found.

The Liquid ampoules neither influenced the fertility nor the reproductive performance of the rats.

### **Mutagenic and Carcinogenic Potential**

In-vitro investigations with Salmonella and yeast strains, and with a human cell line, and in-vivo test systems such as the urinary assay (intraperitoneal) and the host-mediated assay (subcutaneous), did not yield any mutagenic potential.

According to a statement of the German Cancer Research Centre, Heidelberg, **PPC does not belong to a class of substances suspected of carcinogenicity**. Also in the analysis of the FDA report on lecithins it is explicitly said that there is "no significant incidence of tumor formation" and "no evidence of carcinogenicity". The GRAS-Report (Generally Recognized As Safe) ordered by the FDA even refers to findings according to which carcinogen-induced tumours in mice are rather inhibited by simultaneous lecithin administration. As a consequence of these results, studies on carcinogenicity have not been performed.

### **Safety Pharmacology and Pharmacodynamic Effects of PPC**

In 1976 an extensive publication appeared on the pharmacology, particularly on general safety pharmacology, of the hitherto obtained experimental results.

The pharmacological properties of PPC were tested in a series of trials into rodents. The animals were kept under standard conditions. They were fed an appropriate pelleted food according to the species. In most cases PPC was given in the form of a max. 10% suspension in aqua dest., freshly prepared every day, at doses of 10 to 5000 mg/kg by the oral route. The volume was usually 10 ml/kg b.w., in exceptional cases up to 50 ml/kg.

In-vitro and ex-vivo trials were carried out to study the influence of PPC on heart function of guinea-pigs, and on the hemolytic index in sheep and human erythrocytes.

**In these general screening tests, it was demonstrated that PPC, even at high doses, has no effects on the central or peripheral nervous system.** Neither analgetic, spasmolytic, or spasm-influencing effects, nor any effects

inhibiting coordination or reflexes were found. Neither were antiphlogistic nor locally anaesthetising effects observed.

**No influences on renal function** or on heart function or circulation were seen, no sympatholytic effects were reported. Only extremely high doses produced an inhibition of capillary permeability. With lower doses, in contrast, was observed a marked dose-related broncholytic effect of PPC in histamine asthma of the guinea-pig. In several species a slightly choleric action was seen. Reduction of free and total cholesterol, and of the total lipid and triglyceride levels was found.

**In the general pharmacological screening, no toxic effects of the PPC substance were observed.**

### Tolerance of PPC

From the toxicological investigations, from safety pharmacology, and from the general pharmacodynamic effects of PPC it is evident that this extract is safe and non-toxic. It is easy to believe this fact since PPC corresponds with endogenous phospholipids and differs only by its polyunsaturated fatty acids in the 1-position of the phosphatidylcholine molecules.

There is no risk that oxygen autoxidizes the polyunsaturated fatty acids during storage after the manufacturing process: G.-Sh. Wu et al. showed that 1 Mol  $\alpha$ -tocopherol is enough to efficiently protect 2,000-20,000 Mol linoleic acid from oxidation with atmospheric oxygen. To substitute the naturally present vitamin E, which is lost during manufacturing, 0.3%  $\alpha$ -tocopherol are added to the PPC during the production process. This quantity guarantees sufficient protection of the unsaturated fatty acids in the phospholipids.

The "essential" phospholipids (PPC) were marketed for the first time under the name of "Essentiale" in 1952. Meanwhile, it has been further purified, different galenic forms were brought into the market, and it has been registered in 54 countries.

### Oral Application of PPC

Data on the tolerance of daily doses of 700-2700 mg PPC are available from 1,705 patients who participated in 39 clinical studies on lipid metabolism disorders.

Only undesired drug reactions affecting the gastrointestinal tract have been reported. In 20 out of 1504 patients undergoing PPC therapy, and in 5 of 201 placebo-treated patients, complaints such as slight, unspecific gastric disorders, soft stool and diarrhea were observed. In one case, only the investigational medication had to be interrupted because of diarrhea. The incidence of side-effects in these clinical studies was 1.3%.

Abnormal values with respect to hematology, blood chemistry and urine analysis, or interactions with other substances have not been reported.

Besides the undesired drug reactions recorded in clinical studies, 7 spontaneous records were made in Germany between 1978 and 1989, 2 about stomach complaints and 2 about allergic reactions. Three records about arrhythmias are from prior to 1988, when the formulation of PPC still contained etophylline.

With the very slight gastrointestinal complaints the intolerance might also be attributable to the gelatine contained in the capsule mass.

**According to a rough estimation, a total of 225 million daily doses of PPC were sold in Germany between 1954 and 1989.**

**No manifestations of intoxication or overdosing have been reported. There are neither contraindications nor precautions to be observed in the administration of the preparation.** From the animal experiments on fertility and reproduction as well as from the hitherto obtained clinical results no restrictions for the application during pregnancy and lactation can be inferred.

### Dosage

The majority of the existing clinical studies with PPC were carried out with daily doses of 1.5 g to 3 g orally, and 500 mg to 2.0 g intravenously. In isolated cases higher doses were applied (up to 45g orally), especially on the basis of deliberation such that

- insufficient quantities of the phospholipid substance will pass the blood brain barrier;
- the major part of the applied material will be captured by other tissues or organs before reaching the target site.

No dose-finding studies are available which would indicate the optimum dose in a specific indication field under consideration of factors such as body weight, sex, age, activity, and duration of the disease etc.

Neither can such studies be expected because of the complicated nature of indications like liver disease, neurologic diseases or disorders of the lipid metabolism, including atherosclerosis.

The mere fact that a large variety of liver diseases exist reflects the necessity of individual dosing:

- this indication field covers conditions ranging from simple disorders of liver function to hepatic coma and liver cell carcinoma;
- it may be of viral, toxic, metabolic, autoimmune or other origin;
- it is often associated with biliary, hemorrhologic or other accompanying diseases;
- and - let alone mixed forms - pure hepatoses, such as fatty liver, fibrosis or cholestasis have to be distinguished.

Under the consideration that PPC as a membrane therapeutic favors the regeneration of the liver (to stick to our example) we could take the regenerative potential of the organ as a basis for the dose; this attempt, however, will fail so long as no adequate variable will have been found.

**Neither help us with experimental data since a range of different doses of PPC yielded beneficial results.** Individual studies with increasing dose ranges are available, which, as a general trend, describe a better therapeutic success with higher doses. From these results, however, definitive dose schedules for humans cannot be deduced .

Conversely, J.F. Flood et al. stated in their publication that the dose-effect relation of cholinergic substances is similar to an inverted U-curve. For PPC this would mean an optimum dose effect. One or the other clinical studies suggests such a phenomenon, but is insufficient, however, to give evidence of this presumption.

Knowing about this dilemma, PPC doses will be oriented in the future along the clinical experiences collected by doctors and along the results obtained so far in trials. Evaluating the existing experimental and clinical studies, the optimum dose range amounts to 1.5 to 3.0 g orally (possibly even up to 4.5 g).

PhosChol has a PPC content of 900mg per softgel capsule, and 3000mg per teaspoon in the liquid concentrate.

### **Recommended Dosage and Administration**

The recommended daily dose is 2-3 grams (2-3 capsules or 1 tsp. liquid concentrate) once daily. To be administered during meals, with a little liquid if required.

### **Presentation**

PhosChol 900 softgel capsules are available in 30, 100, and 300 count bottles. Each capsule contains 900mg of purified PPC. PhosChol Liquid Concentrate is available in 8 oz. And 16 oz. bottles. Each tsp. is approximately 3000mg of purified PPC.



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