10 October, 2007

Company Announcement
Visit to Australia by Leading Bioeffective® A Researcher

The Directors of Solagran Limited are pleased to announce that one Russia’s most experienced clinical researchers into the use of Bioeffective® A will be visiting Australia in November for a series of seminars with Australian health practitioners, and for discussions in relation to forthcoming clinical trials.

In July this year, a decision was taken to begin the process of engaging with local clinicians and the Australian medical research community in relation to the science and the use of Bioeffectives.

Despite more than 75 years research in Russia and well over 50 successful clinical trials with different Bioeffectives, their efficacy and the science that underpins them is virtually unknown in Australia. The fact that they are natural complexes with very low side effects, whose multi-faceted efficacy does not rely just on one or a small number of active ingredients, means that understanding their mechanism of action in the body is extremely difficult. It demands a deep and comprehensive understanding of their nature and composition – an understanding which goes well beyond that required for a conventional, single molecule pharmaceutical.

Solagran understands Bioeffective® A with its many components as well as any conventional pharmaceutical company understand its single molecule substances. As far as science allows us to determine, Bioeffective® A contains nearly 800 individual components, including different forms of chlorophyll and its derivatives; carotenoids, including beta carotene and Provitamin A; Vitamin E; Vitamin K; phytosterols (mainly β-sitosterol); polyprenols; squalene; minerals; sodium salts of fatty, resin, dibasic, oxo- and oxy- acids; essential oils and many other substances. It should be thought of as one natural active ingredient with a very balanced composition and not an amalgam of many others.

In the words of one leading Russian researcher commenting on a recent bioavailability and pharmacokinetics study demonstrating the speed with which Bioeffective® A entered the blood stream and is then distributed to the spleen, bone marrow, brain, liver and lungs:

“As a powerful antioxidant, among many other things, Bioeffective® A enhances the immune system, reduces oxidative stress, eliminates heavy metals and normalises pathological changes to cells. It also acts as a powerful anti-microbial and anti-fungal. Every patient is different and in each case the body exactly draws what it needs from Bioeffective® A.”

V.G. Bespalov DSc (Med)
N.N. Petrov Institute of Oncology
Bridging this gap in knowledge and understanding in Australia is only possible by presenting the work of Russian researchers and by communicating the experiences of Russian clinicians.

Since August, Solagran has been bringing leading Russian medical research scientists and clinicians to Australia. The first to come were Professor Anatoly Zhebrun and Dr Natalia Roschina from the Pasteur Institute. Professor Zhebrun had recently completed a series of sophisticated *in vitro* trials using cultures from human biopsies to understand the potential of *Bioeffective® A* to inhibit the growth and reproduction of *Helicobacter pylori*.

Since then, Dr Nina Golovkina has visited Australia. Dr Golovkina is the Head of the Department of Psychosomatic Illnesses at the Skvortsova-Stepanova Psychiatric Hospital. This Department conducted clinical trials involving the use of *Ropren* in the treatment of Alzheimer’s patients in 2005, and also in the treatment of heroin addicted chronic alcoholics in 2006. Her department also recently supervised a third series of trials using *Bioeffective® A* to treat heroin addicted chronic alcoholics.

In November, Dr Vladimir Bespalov DSc (Med), the Head of the Cancer Chemoprophylaxis Group within the N.N. Petrov Institute of Oncology, will be visiting both Australia and New Zealand. Soon after that, Dr Tamara Nikitina, Solagran’s St Petersburg-based clinical trials co-ordinator, will visit. Solagran is also in negotiations to bring the Vice Chancellor of Postgraduate Medical Academy in St Petersburg to Australia.

Dr Bespalov is a respected oncologist with some 230 publications in Russian and international scientific journals. He is also the author of 10 books and monographs. He has extensive experience in conducting clinical trials, and many years experience working with *Bioeffectives* in the prevention and treatment of both stomach and breast cancer.

Much of his research has focussed on the use of *Bioeffective® A*, as well as *Algiclam* and *Mammoclam*.

At the *Gastro 2006* Gastroenterology Symposium / Conference in St Petersburg in May 2006, he presented a paper entitled *Dietary Prophylaxis of Stomach Cancer*. This paper is related to the use of *Bioeffectives* in the treatment of atrophic gastritis – a precancerous condition of the stomach. The paper is available from the conference proceedings and a translation of the abstract is attached.

Also attached is a paper that Dr Bespalov wrote in conjunction with his predecessor as Head of the Cancer Chemoprophylaxis Group at the Institute of Oncology. This paper reviews and summarises the results of recent trials conducted in Russia with *Bioeffective® A*.

It is important to appreciate that this paper covers only the more recent trials with *Bioeffective® A*. At the time that Solagran submitted its application to have *Bioeffective® A* approved for use in products listed on the on the Australian Register of Therapeutic Goods (ARTG), under the name Conifer Green Needle Complex (CGNC), there had been a total of 49 human clinical trials conducted with *Bioeffective® A* in Russia.
These comprised:

- 36 oral ingestion trials involving a total of 3,630 people with ages ranging from 7 to 84 years, and
- 13 topical use trials involving a total of 2,079 participants ranging in age from 19 to 70 years.

No side effects from the use of Bioeffective® A were evident from any of these trials, although there were 6 cases of individual intolerance encountered when it was applied topically in concentrations well above that required for therapeutic efficacy.

Since CGNC was approved for inclusion in products listed on the ARTG, Solagran has conducted additional human clinical trials with Bioeffective® A, including the chronic alcoholics trial referred to above.

While in Australia, Dr Bespalov will progress negotiations in relation to:

- A series of phased multi-centre clinical trials to be conducted by the Pasteur Institute with the participation of Dr Bespalov. These trials will be aimed at achieving full pharmaceutical registration in Europe for Bioeffective® A in the prevention and treatment of H. pylori infection and associated conditions (including H. pylori infections in the oral cavity), and
- Clinical trials to be conducted at the Institute of Oncology involving the use of Bioeffective® B to treat prostate cancer.

Peter Stedwell
Company Secretary
On behalf of the Board of Directors of Solagran Limited

Attachments

1. Letter from Dr Bespalov dated 8 October, 2007 (in Russian and English)
В компанию «Солагран»

Уважаемый президент компании «Солагран»
д-р Вагиф Султанов!

Я с благодарностью принял Ваше предложение посетить Мельбурн, и, в частности, Вашу компанию с целью расширения дальнейших совместных исследований в области Биоэффективов.

Также, в результате ранее проведенных переговоров, планирую встретиться с врачами, naturопатами и различными группами специалистов для того, чтобы поделиться моим многолетним опытом исследования биологически активных веществ из хвой сосны и ели, а также морских водорослей. Одним из особенно интересных продуктов является хлорофилло-каротиновая паста, на основе которой получен Биоэффектив А, свойства которого, а также медицинское применение, очень хорошо изучены мною и моими коллегами.

Наиболее благоприятное время, когда я могу посетить Вас, с начала ноября до начала 20-х чисел этого же месяца 2007 года.

Буду рад нашей встрече в Австралии.
Заранее благодарю,

Старший научный сотрудник,
руководитель группы химико-профилактики рака
ФГУ НИИ онкологии им. Н.Н. Петрова Росмедтехнологий,
доктор медицинских наук,
врач-онколог, врач восстановительной медицины

В.Г. Беспалов
No.3/0 of 08/10/2007

To:  
Solagran Limited  
Chairman  
Dr Vagif Soultanov

Dear Dr Soultanov,

I am grateful for your offer to visit Melbourne, and particularly your company, in order to extend our collaboration in research of Bioeffectives.

Also, as the result of the earlier discussions, I am planning to meet medical practitioners, naturopaths and various groups of medical specialists to share my many years of experience in research of biologically active substances from pine and spruce needles as well as from seaweeds. One of the most interesting products is coniferous chlorophyll-carotene paste, which became a basis for Bioeffective A. The properties and medical applications of this material have been thoroughly studied by my colleagues and me.

The most convenient time for me to visit would be from beginning to around early 20’s of November of 2007.

I look forward to our meeting in Australia.  
Thank you.

Senior Scientist  
Head of Cancer Chemoprophylaxis Group  
Federal State Enterprise, N.N. Petrov Scientific-Research Institute of Oncology of the Russian Medical Technologies  
Dr of Medical Sciences  
Specialist in oncology and rehabilitation medicine

Bespalov V.G. [signed]
Dietary Prophylaxis of Stomach Cancer

Bespalov V.G.

N.N. Petrov Scientific Research Institute of Oncology, St Petersburg
Russia

Aim of research: to evaluate possibility of chemotherapy of stomach cancer using medications containing anticarcinogenic compounds.

Materials and methods 166 volunteers from a group of patients with a risk of development of stomach cancer (with atrophic gastritis) were selected for the clinical trials. The patients were randomised. The patients were treated with three biologically active nutritional additives (BANA): BANA 1, containing polyunsaturated fatty acids of omega-3 type, chlorophyll, iodine; BANA 2, containing phytosterols, chlorophyll, vitamin E and carotenoids; and BANA 3, containing beta-carotene, vitamin E and C, garlic powder. The test-substances were administered at the dose of 2-6 tablets per day for 6 months. The control group of patients remained under supervision, with one group receiving no treatment and the other receiving a placebo. Effects of the treatment were evaluated on the basis of clinical and fibrogastroscopic examination, measurement of pH and pepsin level in the gastric juice, histological and cytological analysis of biopsies of the mucous membrane of the stomach. Helicobacter pylori infection was determined using urease test and cytological analysis of smears/prints.

Experimental results During histological analysis, all patients were identified with atrophy of the mucous membrane of the stomach. Some of the patients had stomach polyps and H.pylori infection. BANA 1, BANA 2 and BANA 3 relieved the symptoms of dyspepsia and endoscopic symptoms of chronic gastritis, restored the functional activity of the stomach. BANA 2 and BANA 3 suppressed H.pylori infection; BANA 1 caused regression of intestinal metaplasia and displasia; BANA 3 inhibited intestinal metaplasia. A positive effect of the BANA 1 therapy was registered in 87% of the patients; BANA 2 - 81%; BANA 3 - 85%, which significantly exceeded the placebo effect by 25-30%.

Conclusions The medications containing anti-carcinogenic compounds normalise pathological changes in patients with atrophic gastritis and can be useful for dietary prophylaxis of stomach cancer.
CLINICAL USE OF CONIFER GREEN NEEDLE COMPLEX
A REVIEW OF MEDICAL APPLICATIONS

Prepared by:
V.G. Bespalov, Dr. Med. Sci.,
Clinical Oncologist, Senior Scientist,
CANCER CHEMOPROPHYLAXIS GROUP

Reviewed by:
Professor V.A. Alexandrov, Dr. Med. Sci.
Head,
CANCER CHEMOPROPHYLAXIS GROUP

St-Petersburg, 2006
INTRODUCTION

This review presents data on Conifer Green Needle Complex (CGNC) - also known as Bioeffective® A - a natural biologically active substance obtained from green conifer needles.

The major active components of CGNC are chlorophyll derivatives, carotenoids, vitamins E and K, phytosterols, polyprenols, squalene and sodium salts of resin acids. This document covers mechanisms of action and provides an overview of therapeutic and prophylactic properties of these biologically active components.

The review presents the results of studies of CGNC and CGNC-based products as used in various fields of medicine.

INDICATIONS

CGNC has proven antimicrobial, immunostimulating, antioxidant, hematogenic, tissue regenerative, anti-atherosclerotic and anticarcinogenic properties.

Internally, CGNC is indicated for prevention and treatment of infectious diseases such as influenza and other acute respiratory viral infections (ARVI), tuberculosis and viral hepatitis. It is also recommended for preventing or inhibiting progression of atherosclerosis, reducing the risk of oncological disorders, normalising hematogenesis in anaemic cases, treating toxic damage to bone marrow and as an adjuvant in treating chronic diseases of the lungs and of the GI tract.

Topical use of CGNC is indicated for treatment of skin and mucosa damage and periodontal tissue pathology.

COMPOSITION

Conifer Green Needle Complex is obtained by processing green conifer needles using the method originally developed by F.T. Solodky. The method consists of extracting bioactive compounds from ground conifer needles using an organic solvent, isolation of lipids from the extract and basification of the obtained product. The resultant product is CGNC [Nekrasova V.B. et al, 2000, Roschin V.I., 2000].

This unique complex contains a wide range of biologically active compounds [Roschin V.I., 2000]. The chemical composition of CGNC is shown in Table 1. This table also includes recommended daily intake levels (RDI), listed in the State Sanitary-Epidemiological Standard of the Russian Federation, for nutritional and biologically active compounds found in CGNC [RDI's 2004].

### Table 1

<table>
<thead>
<tr>
<th>Component</th>
<th>Content in CGNC</th>
<th>RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chlorophyllin and other chlorophyll derivatives</td>
<td>400-1600 mg/dl</td>
<td>100 µg</td>
</tr>
<tr>
<td>β-Carotene and other carotenoids</td>
<td>20-120 mg/dl</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vitamin E (α-tocopherol and its acetate)</td>
<td>30-50 mg/dl</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vitamin K group</td>
<td>1.2-2 mg/dl</td>
<td>120 µg</td>
</tr>
<tr>
<td>Phytosterols (mainly β-sitosterol)</td>
<td>1.5-2.9 %</td>
<td>340 mg</td>
</tr>
<tr>
<td>Polyprenols</td>
<td>0.46-1.2 %</td>
<td>-</td>
</tr>
<tr>
<td>Squalene</td>
<td>0.14-0.16 %</td>
<td>400 mg</td>
</tr>
<tr>
<td>Minerals</td>
<td>5-7 %</td>
<td>5 g*</td>
</tr>
<tr>
<td>Sodium salts of fatty, resin, dibasic, oxo- and oxyacids</td>
<td>44-60 %</td>
<td>500 mg**</td>
</tr>
<tr>
<td>Waxes</td>
<td>5-8 %</td>
<td>-</td>
</tr>
<tr>
<td>Essential oils</td>
<td>1-1.2 %</td>
<td>-</td>
</tr>
<tr>
<td>Water</td>
<td>up to 100 %</td>
<td>-</td>
</tr>
</tbody>
</table>

* total for all mineral compounds  
** total for group of organic acids
As Table 1 shows, CGNC contains a range of important, concentrated nutritive and biologically active compounds, providing consumers with levels close to the recommended daily intake from ingestion of a relatively small amount of the extract. The major active ingredients of CGNC are chlorophyll derivatives, carotenoids, vitamin E, vitamin K, phytosterols, polyphenols, squalene, sodium salts of resin acids (balsamic compounds) and essential oils. The last two components are responsible for phytoncidal activity of green conifer needles (phytoncides are volatile plant-produced antimicrobials).

**Chlorophyll** derivatives have an established spectrum of biological activity. They are known to have antioxidant and antimicrobial activity. They stimulate hematogenesis and immune response and facilitate the healing of ulcers, wounds and burns [Moiseyeva M.V., Mikhailescu G.A., 2000]. They also have antimitogenic, anticarcinogenic and antiinflammatory properties [Chernomorsky S. et al, 1999], and can protect DNA from damage by carcinogens and other toxins [Egner P.A. et al., 2003].

**Carotenoids** have antioxidant and immunomodulating activity. They affect cellular signalling of the redox system; inhibit oncogenic expression, activity of ornithinedecarboxylase, adenylate- and guanylate-cyclase; modulate cytochrome P450 enzymes; inhibit arachidonic acid metabolism; prevent chromosomal instability; retard proliferation and induce cellular differentiation and apoptosis. Beta-carotene and several other carotenoids are metabolised into vitamin A [Elliott R., 2005]. Epidemiological and experimental studies confirmed the ability of carotenoids to prevent development of tumours of various localisations, atherosclerosis and associated cardiovascular diseases and cataracts [Tapiero H. et al, 2004].

**Vitamin E** performs several functions in the body, one of the most important of which is that of an antioxidant. It is required for maintaining stability of cellular membranes. Vitamin E participates in protein biosynthesis, processes of cellular division and tissue respiration. It reduces risk of vascular thrombosis, affects the hormonal balance and immune response, regulates cellular signalling and transcription processes and induces apoptosis [Brigelius-Flohe R. et al., 2002]. Epidemiological and experimental studies also showed protective action of vitamin E in such disorders as atherosclerosis, certain types of cancer, diabetes, chronic inflammation, cataracts and Alzheimer’s Disease [Brigelius-Flohe R. et al., 2002, Dutta A, Dutta S.K., 2003].

**Vitamin K** includes a series of compounds from the naphthoquinone group, the most frequently found are vitamin K1 (phyloquinone) and vitamin K2 (menaquinone). Vitamin K participates in synthesis of coagulating factors and therefore regulates blood coagulation, increases resistance of vessel walls to damage, prevents vascular calcification, regulates bone cumulation and resorption of calcium, participates in peristalsis [Vermeer C. et al., 2004]. Increased intake of various forms of vitamin K is associated with a reduction in risk of ischemic heart disease [Erkkila A.T. et al., 2005, Geleijnse J.M. et al., 2004]. In addition to the listed anti-atherosclerotic mechanisms, vitamin K acts as a cofactor in activation of anti-atherogenic proteins [Berkner K.L. et al., 2004]. Vitamin K also suppresses tyrosinekinases activity and expression of oncogenes Myc and Fos, participates in apoptosis, cellular growth, transmission and phagocytosis. These factors contribute to its anticarcinogenic and antitumour effects [Berkner K.L. et al., 2004, Lamson D.W, Plaza S.M., 2003]. Experimental, epidemiological and clinical studies demonstrated that vitamin K prevents development of osteoporosis [Iwamoto J. et al., 2004].

**Phytosterols** are sterols of plant origin which are structurally similar to cholesterol. They possess antiatherosclerotic, anticarcinogenic, antioxidant and immunostimulating activity [de Jong A. et al., 2003]. Phytosterols usually come from nutritional sources, and in the body, the highest concentration of β-sitosterol and campesterol is in the blood [Li J.H. et al., 2001]. Epidemiological studies have proven that intake of phytosterols with food reduces the risk of ischemic heart disease by 20-25%. These findings, beginning in early 1990s, have
contributed to the growing popularity of functional nutrition products enriched with phytosterols in economically developed countries [Gylling H., Miettinen T.A., 2005].

Mechanisms of anti-atherosclerotic action of phytosterols are related to their ability to inhibit absorption of cholesterol via the GI tract, reduce cholesterol and low density lipoprotein levels in blood [de Jong J.H. et al., 2003, Gylling H., Miettinen T.A., 2005]. Epidemiological studies showed that increased intake of phytosterols was associated with a reduction in risk of cancer of the large intestine, prostate, mammary glands [Awad A.B., Fink C.S., 2000], and of the stomach [De Stefani E. et al., 2000] and lungs [Mendilaharsu M. et al., 1998].

The mechanisms of anticarcinogenic action of phytosterols are related to their effect on the structure of cellular membranes and regulation of cellular signalling; their ability to inhibit tumour growth and to induce apoptosis; to stimulate immune response and normalise cholesterol metabolism [Awad A.B., Fink C.S., 2000].

Some clinical studies showed that phytosterols have the capacity to reduce symptoms of urological pathology, to improve urination as well as quality of life for patients with benign prostatic hyperplasia [Coleman C.I. et al., 2002].

**Polyprenols** and their 2,3-dihydro derivatives (dolichols) - long-chain alcohols composed of residual isoprenes – act as natural bioregulators and are found in small quantities in various plant and animal tissues [Rezanka T., Votruba J., 2001]. Polyprenols are present in plants, whereas dolichols are found in animals. Functions of polyprenols and dolichols are linked with their involvement in transport of hydrophilic molecular fragments through cell membranes during synthesis of polysaccharides, glycoproteins and other biopolymers. Ingested polyprenols are metabolised by the liver into active dolichols [Chojnacki T., Dallner G.J., 1983]. Live conifer needles are one of the richest and most widely available sources for extraction of polyprenols [Kazimierczak B. et al., 1997]. Interest in polyprenols and dolichols is associated with their wide range of demonstrated biological activity, lack of side effects and extremely low toxicity.

Polyprenols stimulate the immune system, cellular reparation and spermatogenesis, and have antistress, adaptogenic, antiulcerogenic and wound-healing activity [Roschin V.I., 2000]. Dolichols have antioxidant activity and protect cell membranes from peroxidation [Bergamini E. et al., 2004]. Experiments on mice demonstrated that polyprenols have antiviral activity, in particular, against influenza viruses [Safatov A.S. et al., 2005]. It has been established, that dolichol levels in liver tumour cells are reduced in comparison with healthy hepatic cells [Eggens I., Elmberger P.G., 1990].

**Squalene**, an isoprenoid from the group of polyphenyl compounds, is an intermediate metabolite in cholesterol synthesis. It has antioxidant, immunostimulating, hypolipidemic, cholesterol reducing, anticarcinogenic and antiinflammatory activity [Kelly G.S., 1999].

Experimental and clinical studies demonstrated that squalene protects skin cells from peroxidation, participates in detoxification from xenobiotics, stimulates cellular and non-specific immune response, and reduces levels of cholesterol and triglycerides in the blood [Kelly G.S., 1999].

Epidemiological studies showed that intake of squalene mixed, for example, with olive oil was associated with a reduction in risk of oncological and cardiovascular disease [Owen R.W. et al., 2004]. Experimental rodent studies using induced carcinogenesis model showed that squalene inhibited carcinogenesis of the large intestine, lungs and skin. Mechanisms of anticarcinogenic action of squalene may be related to its ability to inhibit activation of oncogene Ras, modulation of oncogenic activation and its antioxidant properties [Smith T.J., 2000]. Squalene also possesses antimicrobial activity, in particular, in relation to tuberculosis mycobacteria [Jimenez A. et al., 2005].
Green conifer needles contain a plethora of substances with phytoncidal activity. Currently, phytoncides are defined as plant produced biologically active compounds which kill or inhibit growth and reproduction of bacteria, fungi, protozoa, and viruses. The chemical nature of phytoncides varies [Sokolov S.Ya., 2000]. Salts of resin acids (balsamic compounds) and essential oils present in CGNC can be considered to be members of the phytoncides group found in green conifer needles.

Thus, the biologically active compounds contained in CGNC impart it with a wide spectrum of therapeutic-prophylactic activity. The main properties of CGNC are listed in Table 2.

### Table 2
Therapeutic and Prophylactic Properties of CGNC

<table>
<thead>
<tr>
<th>Property</th>
<th>CGNC Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial</td>
<td>Chlorophyll, polyprenols, squalene, salts of resin acids, essential oils</td>
</tr>
<tr>
<td>Immunostimulating</td>
<td>Chlorophyll, carotenoids, vitamin E, phytosterols, polyprenols, squalene</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Chlorophyll, carotenoids, vitamin E, phytosterols, polyprenols, squalene</td>
</tr>
<tr>
<td>Hematogenic</td>
<td>Chlorophyll, carotenoids, vitamin E</td>
</tr>
<tr>
<td>Tissue Regenerative</td>
<td>Chlorophyll, vitamin E, polyprenols</td>
</tr>
<tr>
<td>Anti-atherosclerotic</td>
<td>Carotenoids, vitamin E, vitamin K, phytosterols, squalene</td>
</tr>
<tr>
<td>Anticarcinogenic</td>
<td>Chlorophyll, carotenoids, vitamin E, vitamin K, phytosterols, squalene</td>
</tr>
</tbody>
</table>

Due to the compositional complexity of CGNC, summation and synergism of effects of these biologically active compounds can take place.

### PRODUCTS AND TRIALS

Two products based on CGNC have been developed and registered as Biologically Active Nutritional Additives (BANA) in Russia. Product 1 is a 0.67g coated (0.64g uncoated) tablet with 100mg of CGNC as the active ingredient along with the excipients – starch, MCC and calcium stearate. Product 2 is a coated 0.65g (0.63g uncoated) tablet containing: 108mg of CGNC with excipients – starch, MCC and calcium stearate.

A CGNC-based toothpaste (Product 3), also containing chlorophyll derivatives, was also developed and sold in Russia.

CGNC and CGNC-based products have been studied in comprehensive preclinical and clinical trials conducted at various medical centres throughout Russia. CGNC was studied at the St-Petersburg S.M. Kirov Military Medical Academy and at the St-Petersburg Scientific Research Institute of Radiation Hygiene.

For treatment of suppurating wounds, CGNC administered to patients internally at doses of 0.5-0.75 g., in capsules, 3 times per day during pre- and post-surgical period, improved bronchial drainage, increased blood haemoglobin count and reduced inflammation at the surgical wound site.

Internal administration of CGNC at doses of 3-4 g per day reduced cholesterol and lipoproteins blood content in patients with atherosclerosis. CGNC prevented development of experimental atherosclerosis in rabbits.

Topical application of CGNC ointment (on bandages) to granulating wounds had anaesthetic, wound-healing and deodorising effects and stimulated wound edge epithelisation. External application of CGNC salve with Diethone in experiments and clinical trials showed burn healing and radioprotective activity.
External application of 30-50% solution of CGNC in patients had beneficial effect in treatment of burns, slow-healing wounds and ulcers. When used as the active ingredient in a douche, CGNC showed efficacy in treatment of colpitis, vulvovaginitis, and cervical erosion [Nekrasova V.B. et al., 2000].

**Anticarcinogenic Activity**

In preclinical trials, anticarcinogenic activity of CGNC was investigated at the N.N. Petrov Scientific Research Institute of Oncology (St-Petersburg), using 5 models of chemically induced carcinogenesis in rodents. CGNC was administered to the animals for an extended period of time together with water, at the concentration of 2 g/l. CGNC effectively inhibited carcinogenesis of the mammary gland, large intestine and multi-organ carcinogenesis induced by N-methyl-N-nitrosourea in rats, as well as carcinogenesis of skin induced by benzpyrene in mice. The results obtained allowed for drawing a conclusion about the general nature of anticarcinogenic activity of CGNC, which inhibited development of induced tumours differing in localisation and histogenesis. Anticarcinogenic effects were registered during administration of CGNC, both over the entire period of carcinogenesis and when administered only during the carcinogenesis promotion / progression stage [Bespalov V.G. et al., 2000].

Anticarcinogenic activity of Product 1 and its effect on lipid metabolism were investigated in preclinical trials at the N.N. Petrov Scientific Research Institute of Oncology (St-Petersburg). Tumours were induced in rodents by chemical carcinogens. This CGNC product was mixed with animal feed on a daily basis at the dose of 20 tablets per 1 kg of feed, over the duration of either 6 or 10 months. Product 1 effectively inhibited multi-organ carcinogenesis induced by N-methyl-N-nitrosourea in rats and carcinogenesis of the lungs induced by urethane in mice. Product 1 also normalised lipid metabolism in rats, which was evidenced by a reduction in total cholesterol and triglycerides content in blood [Bespalov V.G. et al., 2000].

The N.N. Petrov Scientific Research Institute of Oncology conducted a study of leucoprotective activity of Product 2 on 30 patients with systemic or generalised malignant tumours, who developed leucopenia as a result of chemotherapy. The basic chemotherapy, identical during the first (control) and subsequent cycles, showed moderately expressed myelotoxicity. Product 2 was prescribed internally at doses of 2 tablets 3 times per day, 30 minutes before food. Treatment with Product 2 was initiated on secondary hospitalisation - in order to continue cytostatic therapy - and continued throughout the entire second course of chemotherapy, as well as after its completion, until leucocyte count was re-established to optimal levels. Evaluation of this CGNC product as a leukogenesis protector was based on the results of analysing the leucocyte and granulocyte levels in peripheral blood. Here, Product 2 showed expressed leucoprotective activity. Following the treatment cycle with Product 2, reduction in leucocyte and granulocyte count in peripheral blood was significantly less than after the control cycle, correspondingly by 29% and 41.9% [Bespalov V.G., Nekrasova V.B., 2004].

**Oral Health**

Clinical trials of the Product 3 (toothpaste) were conducted at the S.M. Kirov Military Medical Academy (St-Petersburg). The trials involved 34 patients with pathological changes to periodontal tissue. The participants included teenagers, adult men and women, and pregnant women. Long term prophylactic use of Product 3 enabled maintenance of good oral hygiene, reduction in gum bleeding and noted deodorising and whitening effect [Zhukova L.V., 2003].
Acute Respiratory Infections

A trial of prophylactic activity of Product 2 against influenza and other acute respiratory viral infections (ARVI) in children was conducted at the Research Institute of Influenza at the Russian Academy of Medical Sciences (St-Petersburg). This trial included 227 children aged 2 - 16, from four centres: two St-Petersburg orphanages (No. 1 and No. 10), Kirovsky region boarding-school No.60, and Krasnoselsky region kindergarten No.38.

Product 2 was prescribed to 74 children at the dose of 1 tablet, 2 times per day, over two 3-week courses, with a 1-month interval in between. The control group included 153 children. All children were monitored over 3 months after completion of treatment with Product 2. The prophylactic activity of Product 2 was evaluated according to two parameters: rate and incidence of children’s illness and severity and duration of clinical symptoms of ARVI in the compared groups.

Two coefficients were utilized: an efficacy index (EI), expressed as illness rate in the Product 2 group vs. the control, and the epidemic efficacy index (EEI), expressed as a percentage of participants in the test group protected from illness.

In the group of children treated with Product 2, the incidence of ARVI was significantly lower than in the control group: EI = 2.14; EEI = 53.3%.

Duration of ARVI symptoms in children from the treatment group was decreased and complications occurred much less frequently in comparison with the control group (p<0.05). Thus, this trial provided confirmation for the prophylactic efficacy of Product 2 against influenza and other ARVIs [Osidak, L.V. et al., 2004].

Clinical trials of Product 1, used as a preventative for influenza and other ARVIs, were conducted at the State Scientific Research Institute of Influenza at the Russian Academy of Medical Sciences (St-Petersburg). Forty one male patients aged 45 and older - former Chernobyl rescue workers and Special Forces veterans were selected for the trials. Product 1 was prescribed at the dose of 1 tablet, 3 times per day, over 2 months. The control group included 24 males who did not receive Product 1.

The frequency of incidence of ARVI over the Product 1 treatment course, and for 2 months following discontinuation of treatment in the experimental group was 1.9 x lower than in the control group (p>0.05).

In the subgroup of patients with chronic damage to the respiratory tract, who also frequently contracted ARVIs, EI of Product 1 was improved: 2.6 vs. 4 for the control (p<0.05). This finding enabled the investigators to conclude that Product 1 has prophylactic efficacy in reducing the risk of contracting influenza and other ARVIs, and may be used by at risk patients, especially individuals with chronic damage to the respiratory tract who are prone to ARVIs [Osidak L.V. et al., 2000].

Detox Activity / Heavy Metals Elimination

At the Scientific Research Institute of Influenza at the Russian Academy of Medical Sciences (St-Petersburg), clinical trials were conducted on 66 pregnant women, in order to: a.) study the capacity of Product 1 to prevent influenza and other ARVIs, and b.) to reduce heavy metal content in the body. Product 1 was prescribed at the dose of 1 tablet, 3 times per day, over 2 months. The women who received Product 1 had ARVI incidence 2x less that in the control group (18.2% and 36.4% correspondingly).
Product 1 showed hemostimulating activity in relation to haemoglobin and erythrocyte counts. The percentage of pregnant women showing improvement in these markers was respectively 2.3x and 2.9x higher than for the control group. As a result of treatment with this CGNC product, there was a reduction in endogenous toxicity markers and improvement in T-cell immunity parameters recorded for the women in the experimental group, which was significantly higher than the changes recorded for the control group.

Normalisation of mercury content in blood was registered in 45.4% of patients taking Product 1, vs. only 14.3% in the control group. The investigators concluded that Product 1 has a wide range of beneficial properties facilitating health improvement. They confirmed this CGNC based product supports prophylactic efficacy against ARVI and detox activity in relation to heavy metal accumulation [Karpova L.S., 2004].

The St-Petersburg Scientific Research Institute of Tuberculosis and Pulmonology and the Department of Tuberculosis at the St-Petersburg Medical Academy for Postgraduate Studies conducted clinical trials of Product 2 in healthcare workers in contact with TB infected individuals.

Forty clinically healthy women aged 24 – 75, employed at the Frunze Regional St-Petersburg TB Treatment Centre No.17 were selected for the trials. Product 2 was prescribed at the dose of 2 tablets, 3 times per day, over 1 month.

Product 2 was shown to normalise peripheral blood: to increase hemoglobin and erythrocyte counts in cases where baseline values were low; to reduce monocytes in individuals with normal red blood indices; and to increase monocyte levels in patients with initially lowered haemoglobin and erythrocytes levels.

Product 2 has a beneficial effect on tuberculin sensitivity: enabling transition from negative test reaction to positive or indeterminate, and from hyperergic to normoergic. The researchers concluded that this CGNC product can be indicated as an adaptogenic for healthcare workers in contact with TB-infected patients for normalising blood work parameters, reducing sensitivity to TB mycobacteria, and enhancing immune status [Tyarasova K.G. et al., 2001].

At the Republican Centre for Protection of Families, Mothers and Children at the Tatarstan Republic Ministry of Health (Kazan), Product 1 was used as an adjuvant in combined medical-ecological rehabilitation of children with chronic gastrointestinal disorders. The trials monitored 239 children aged 10 – 15 and this CGNC supplement was prescribed at the dose of 1 tablet, 2 times per day, over 2 weeks. The intervention increased efficacy of the rehabilitation, facilitated elimination of heavy metals (lead and chromium), and cumulation of essential microelements (zinc) in the body [Malscev S.V. et al., 1999].

Adaptogenic Properties

Kazan Republican Infectious Diseases Hospital No.1 trialled CGNC Product 1 as an adjuvant in treatment programs of 22 patients with chronic viral hepatitis. It was prescribed at the dose of 1 tablet, 3 times per day, over 1 month. Addition of Product 1 to standard therapy was shown to lead to faster restoration of liver function, diminishment of anaemia symptoms, and a reduction in the severity of side effects caused by interferon therapy. The product also showed adaptogenic activity and positively affected the function of the GI tract in patients with chronic viral hepatitis [Bulatova N.A., 2000].

At the Kazan Republican Infectious Diseases Hospital No.1 and at the Municipal Centre for Diagnostics and Treatment of Intestinal Dysbacteriosis, CGNC Product 2 was used as an adjuvant in treating intestinal dysbacteriosis in 22 patients aged 35 - 65, diagnosed with chronic prostatitis. It was prescribed at the dose of 1 tablet, 3 times per day, over 1 month.
Product 2 facilitated restoration of beneficial bifidobacteria count and adequate colibacillus; normalised functioning of the GI tract and prevented recurrence of chronic prostatitis [Bulatova N.A., Bulatov D.A., 2004].

Antioxidant / Cholesterol Management / Heart Health

At the St Petersburg State Scientific Research Institute of Cardiology at the Russian Ministry of Health, CGNC Product 1 was trialled in 27 patients with ischemic heart disease and hypertonic disease with disorders of lipid metabolism. The dose was 2 tablets, 2 times per day, with duration of treatment ranging from 1 - 3 months.

Product 1 helped normalise markers of lipid metabolism and reduce the rate of lipid peroxidation in 19 patients (70.3%). It also demonstrated moderate hypocholesteremic and hypotriglyceridemic activity, which was evidenced as a reduction in levels of total cholesterol, β-cholesterol, pre-β-cholesterol, triglycerides and in the atherogenic coefficient, with concurrent increase of α-cholesterol count. The investigators concluded that Product 1 is beneficial for patients with cardiovascular disease, as it assists in correction of moderate disorders of lipid metabolism [Shevchenko I.A. et al., 2000].

Preclinical trial of Product 1 investigating postradiation changes in animals was conducted at the St-Petersburg Scientific Research Institute of Radiation Hygiene at the Russian Ministry of Healthcare. Adult female rats were subjected to one-time total X-ray dose of 2.5 gray (Gy). Product 1 was administered daily, at 2 g/l of drinking water, ad libitum over 3 months.

Over the postradiation period, reduction in animals’ body weight and disruption in hematosis were registered. In comparison, the animals treated with Product 1 showed no weight loss during the earlier phase and gained weight more actively than the irradiated control animals. The product also reduced the severity of hematological dysfunctions during the acute period, and facilitated in full recovery of hematogenic parameters over the extended postradiation period. Product 1 had a positive effect on all blood elements: erythrocytes, granulocytes, and lymphocytes. The researchers concluded that this CGNC product reduces the severity of symptoms of acute radiation exposure, aids in mitigating damage to the blood system and accelerates recovery of irradiated animals [Ivanov E.V., Ponomareva T.V., 1999].

The Scientific Research Institute of Pulmonology at the I.P. Pavlov Medical University, St-Petersburg, conducted a trial on 18 patients diagnosed with occupational lung diseases including pneumoconiosis and chronic obstructive lung disease. Product 1 was prescribed at the dose of 1 tablet, 3 times per day, over 3 months. Treatment with this CGNC product contributed to improved pulmonary gas exchange, reduced the load on the right ventricle of the heart, reduced neutrophil and lymphocyte counts in bronchoalveolar lavage fluid and increased antioxidant activity in blood plasma. The researchers concluded that Product 1 is an efficacious adjuvant in the treatment of patients with chronic pulmonary pathology [Danilov L.N. et al., 1999].

Gastrointestinal Health

Clinical trials of Product 1 were conducted on 50 patients with chronic atrophic gastritis, considered by many specialists to be a precancerous disorder of the stomach, at the N.N. Petrov State Scientific Research Institute of Oncology at the Russian Ministry of Health (St-Petersburg). The experimental group included 26 patients who received Product 1 at the dose of 2 tablets, 3 times per day, over 6 months. The control group of 24 patients did not receive this treatment.

In comparison with control, Product 1 led to a statistically significant reduction in dyspepsia symptoms and in endoscopic markers of chronic gastritis. Product 1 also suppressed
Following 6 months of monitoring, no significant improvement in the above parameters was noted in control patients. Moreover, in several cases, there was a noted aggravation, resultant from progression of chronic gastritis. The investigators concluded that Product 1 may be used effectively for reducing the risk of developing stomach cancer [Bespalov V.G., 2004].

All the clinics undertaking investigations of CGNC and CGNC-based products (Product 1, Product 2 and Product 3-toothpaste), reported that the products were well tolerated by all the patients. While there were several cases of individual intolerance, there were no adverse drug reactions or significant side effects registered over the course of the trials. The main results of clinical studies of CGNC and CGNC-based products are presented in Table 3.

### Table 3

**Results of Clinical Trials of CGNC and CGNC-Based Products**

<table>
<thead>
<tr>
<th>Clinical Effect</th>
<th>CGNC Dose, Route of Administration and Course</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in rate of ARVI in children and teenagers, reduction in severity of</td>
<td>0.2 g/d, 3 week course internal</td>
<td>Osidak L.V. et al., 2004</td>
</tr>
<tr>
<td>clinical symptoms of infection and reduction in number of complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of rate of ARVI in Chernobyl rescue workers and veterans special</td>
<td>0.3 g/d, 2 month course internal</td>
<td>Osidak L.V. et al., 2000</td>
</tr>
<tr>
<td>forces</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of ARVI rate, hemostimulating, immunostimulating and detoxifying</td>
<td>0.3 g/d, 2 month course internal</td>
<td>Karpova L.S., 2004</td>
</tr>
<tr>
<td>activity in pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalisation of hematogenesis, reduction of sensitivity to TB mycobacteria</td>
<td>0.6 g/d, 1 month course internal</td>
<td>Tyarasova K.G. et al., 2001</td>
</tr>
<tr>
<td>in healthcare workers in contact with TB-infected patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faster recovery of liver function in patients with chronic viral hepatitis</td>
<td>0.3 g/d, 1 month course</td>
<td>Bulatova N.A., 2000</td>
</tr>
<tr>
<td>Reestablishment of normal microflora in patients with intestinal dysbiosis</td>
<td>0.3 g/d, 1 month course</td>
<td>Bulatova N.A., Bulatov D.A., 2004</td>
</tr>
<tr>
<td>Reduction in cholesterol and lipoprotein blood levels in patients with</td>
<td>3-4 g/d, internal</td>
<td>Nekrasova V.B. et al., 2000</td>
</tr>
<tr>
<td>atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in cholesterol and triglyceride levels in patients with heart</td>
<td>0.4 g/d, internal 1-3 month course</td>
<td>Shevchenko I.A. et al., 2000</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
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<tr>
<td>Regression of pathological symptoms, suppression of H. pylori infection,</td>
<td>0.6 g/d, 6 month course internal</td>
<td>Bespalov V.G., 2004</td>
</tr>
<tr>
<td>improvement of functional activity of the stomach in patients with atrophic</td>
<td></td>
<td></td>
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<tr>
<td>gastritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase of efficacy of rehabilitation, elimination of heavy metals in</td>
<td>0.2 g/d, 2 week course</td>
<td>Malscev S.V. et al., 1999</td>
</tr>
<tr>
<td>children with chronic diseases of GI tract organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakening of leucocytopenia and granulocytopenia in oncological patients</td>
<td>0.6 g/d, adjuvant to chemotherapy</td>
<td>Bespalov V.G., Nekrasova V.B., 2004</td>
</tr>
<tr>
<td>undertaking cytostatic chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>Improvement of bronchial drainage function and reduced inflammation in patients</td>
<td>1.5-2.25 g/d, internal</td>
<td>Nekrasova V.B. et al., 2000</td>
</tr>
<tr>
<td>with purulent pulmonary disease</td>
<td></td>
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<tr>
<td>Improvement of pulmonary gas exchange, reduction of load on the right heart</td>
<td>0.3 g/d, 3 month course</td>
<td>Danilov L.N. et al., 1999</td>
</tr>
<tr>
<td>ventricle in patients with chronic pulmonary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaesthetic, healing, and deodorising activity in patients with wounds</td>
<td>Topical, as ointment</td>
<td>Nekrasova V.B. et al., 2000</td>
</tr>
<tr>
<td>Reduction in gum bleeding; noted deodorising, and whitening effects in</td>
<td>In toothpaste formulations</td>
<td>Zhukova L.V., 2003</td>
</tr>
<tr>
<td>patients with periodontal disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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CONCLUSIONS AND THERAPEUTIC INDICATIONS

1. CGNC is obtained from green conifer needles using the technology originally developed by F.T. Solodky. The active principles of CGNC include chlorophyll derivatives, carotenoids, vitamins E and K, phytosterols, polyprenols, squalene, and a complex of phytoncidal compounds contained in green conifer needles.

2. CGNC has proven antimicrobial, immunostimulating, antioxidant, hematogenic, regeneration-stimulating, anti-atherosclerotic, and anticarcinogenic properties.

3. CGNC is recommended for increasing non-specific immune response and as an additional source of dietary chlorophyll, carotenoids, vitamin E and phytosterols.

4. CGNC and CGNC-based products were successfully tested in clinical trials at leading Russian hospitals, specializing in different fields of medicine. These trials served as the basis for delineating the list of therapeutic indications and for concurring the prescribing guidelines.

5. CGNC is recommended for prevention, and as an adjuvant in the treatment of infectious diseases. CGNC may be used for prevention of influenza and other ARVI’s. CGNC is indicated for improving immune status in healthcare workers exposed to TB carriers, as well as an adjuvant in the treatment of chronic viral hepatitis, helicobacteriosis and other infections. CGNC is also indicated as an adjuvant in treatment of intestinal dysbiosis.

6. CGNC is indicated for patients with cardiovascular disease, for correction of moderate disorders of lipid metabolism.

7. CGNC is indicated for reducing the risk of developing oncological disorders, in particular, for patients with atrophic gastritis, considered a precancerous disorder of the stomach.

8. CGNC is recommended for normalisation of hematogenesis: to increase hemoglobin and erythrocyte counts, for protecting leucocyte production after toxic exposure, for example, for cancer chemotherapy patients.

9. CGNC is indicated as an adjuvant in the treatment of chronic pulmonary disease and chronic GI tract disorders.

10. The recommended CGNC dose for internal use for adults and children 12 and older is 0.3-0.6 g per day. The standard course is 1-3 months, which may be extended to 6 months or longer. With chronic diseases, CGNC is indicated after basic therapy, as an adjuvant in the recovery / convalescence / rehabilitation treatment program.

11. CGNC can be applied topically to the skin or mucosa for acceleration of wound healing, and as an active ingredient in toothpaste formulations for prevention and treatment of periodontal disorders.

12. CGNC is a safe substance, and in clinical use it has not led to any adverse drug reactions or significant side effects. CGNC is contraindicated in rare cases of individual intolerance.
References:


