

DEPARTMENT OF PRECLINICAL AND CLINICAL
PHARMACOLOGY AND TOXICOLOGY
MEDICAL FACULTY, SKOPJE
REPUBLIC OF MACEDONIA

ADDITION TO THE EXPERT'S REPORT FOR HERBAL REMEDIE

VARUMIN[®] - 2

The request of preparing the ADDITION TO THE EXPERT'S REPORT for herbal remedy VARUMIN[®] - 2 was submitted by **Inter-evrogeneks, Novo Selo, Republic Macedonia.**

On the base of decision of the Expert collegiums of the Department of Preclinical and clinical Pharmacology and toxicology at Medical Faculty in Skopje, I was chosen to make an ADDITION TO EXPERT'S REPORT for herbal remedy VARUMIN[®] - 2, submitted by **Inter-evrogeneks, Novo Selo, Republic Macedonia.**

After the study of the submitted documentation to me and other relevant information I suggest to the Expert collegiums of the department to accept this text like ADDITION TO THE EXPERT'S REPORT for herbal remedy VARUMIN[®] - 2.

1.0 FORM AND COMPOSITION

Form: solution for oral administration

Composition:

100 ml solution contains:

- Water extract of herbal drugs* 99.00 g
- Aloes dry extract..... 0.80 g
- Methylparahydroksy benzoate..... 0.18 g
- Prophyilparahydroksy benzoate 0.02 g

*100 ml water extract of herbal drags is prepared from:

- Inulae Radix 1.60 g
- Visci Herba 1.20 g
- Cornus Cortex 0.60 g
- Calendulae Flos..... 1.00 g,
- Milefolii Herba 0.40 g
- Cynodon Rhizoma 1.50 g
- Hyperici Herba 1.40 g
- Aqua purificataad 100

2.0 GENERAL INFORMATION FOR THE PRODUCT

Varumin 2 is herbal remedy (solution for oral administration), which in his composition contains water extract from herbal drugs and aloe dry extract, which are in fact their main active components of the herbal remedy.

VARUMIN[®]2 in combination with VARUMIN[®] 1 is assigned for improving the general state of the organism when exhausted, for increasing the power of resistance, like adjoin therapy to the standard therapy in various acute and chronic illnesses, malignant diseases, anemia and in other positions which are characterized with lessen immunity and bad general condition.

Aloe

Aloe is dry juice made from leaves of different types of aloe, Liliaceae. For preparing the dry extract the different types of Aloe is used, the most used are Aloe Ferox Mill. and Aloe Barbadosis Mill.

Aloe Ferox Mill.

It is many years succulent herb, 2-3 meters high with big, fat, and succulent, on the top pointed and on the edge/margin toothed leaves and upstanding flower stem. It grows in semi desert regions in south and east Africa. It is used for producing of the Aloe capensis (Goruno-vik 2001; WHO 1999).

Aloe Barbadosis Mill.

It is a lower herb from Mediterranean origin. It grows in South America, in Anthill islands in west India. It is used for producing so called Kirasao or Barbados aloe (*Aloe curassavica*) (Gorunovik 2001; WHO 1999).

Composition: (Gorunovik 2001; WHO 1999).

Drug contains follow ingredients:

- Antranoids; 25-40 % barbaloin, which is a mixture of two diastoisomer 10-glikozilantrons; aloins A and B.
Aloins A and B are substances in which beta-D-glucose is bond with C-glycoside connection to C-atom on the position C (10).
Content of the aloin ware in wide ranges, due to the herb type and origin. *Aloe curassavica* contains min 28 %, and *Aloe capensis* min 18 % hidroksiantracen derivate, calculated as dry aloin (Ph. Eur III).
- Aloinozids A and B, isomer 11-O-alfa-ramnozid of aloins A and B.
This substances are characterized by alfa-L-ramnose, who is glycoside connected to the primary alcohol hydroxyl-methyl group, on the position C (3).
- Free aloe-emodin to 1%.
- Aloezin hormone derivate, in forms of A and B.
The two commercial forms of aloe contain these substances, but in different proportions: aloezin A is present in the two types of aloe in the same quantity; the concentrations of aloezin B are significant bigger in *Aloe capensis*.
- Bitter ingredient- aloenin.
- 5-hidroksialoin A and 5-hidroksialoin B (only in *Aloe capensis*).
- 7-hidroksialoin A and 7-hidroksialoin B (only in *Aloe curassavica*).
- Essential oil in trace, resins,
- 1-2 % mineral matter.

Extractum aloes siccum (aloes dry extract) (Gorunovik 2001; WHO 1999).

Aloes dry extract is purified form of the drug. According to the specifications of the Ph. Jug. II it is made by extraction of the herb with acetone. According to the specification of some other pharmacopoeias, it is made with extraction with hot water, and clear extract is evaporated to dry.

Aloes dry extract is in yellow pieces or powder with yellow color, without odor, and much bitter taste.

Contains bigger quantities of aloin and other constituents of the drug, except resin, which results with bigger activity.

Radix inulae

Inulae helenium is cabbage herb, high up to 2 meters. Drug contains root and rhizome. The composition of the drug is; 44% inulin, terpenoids (sitosterols, stigmasterol and fridelin), aetheroleum oil (1-4%) which main compounds are sesquiterpene lactones including and alantrolacton, isoalantrolacton and dihydroalantrolacton, allantoin acid and azulene, resin and other (Tucakov 1999, Gorunovic 2001).

Viscum album

Viscum album (European mistletoe) is parasite in shape of bush grow on apple tree, pear-tree, oak tree. Active ingredients are: alkaloid viskotoksin, inositol, flavones heterosides, wax, mucous, lecithin, holin and other ingredients (Gorunovic 2001).

Hyperici herba (Hypericum perforatum - St. John's worth)

St. John's worth is many years herb, which grows on higher places in Europe, North Africa and East Asia. St. John's worth is traditionally known and used medical herb, which are use to cure many diseases. From the herb is collected the above land part Hyperici herba thus flowers and short branches (25 cm length).

Hyperici herba contain: 0.04-0.3 5% hypericin and similar materials (pseudohypericin, isohypericin, protohypericin and other); 6.5-15 % catechyn-type tanins and condensate-type proanthocyanidins (catechin, epicatechin, leucocyanidin); 2-5 % flavonoides main hyperozides (0.5-2%), rutin (0.3-1.6%), kvercetin (0.3%), isokvercetin (0.30); kvercetin and kempherol; biflanoides (near 0,26% biapigenin); floroglucinol derivates (up to 4 % hyperforin); fenolic acid (cafeic, chlorogenic, ferulic); sterols (sitosterol); vitamins C and A; ksantons (to 10 ppm) and holing, (Bruneton 1995; ESCOP 1997; Leung and Foster 1996; Newal 1996; Wichtl 1994).

Millefolii herba (Achillea millefolium, Yarrow)

From the herb the upper part is collected, 25 cm long millefolii herba or only the flowers with out flower branches millefolii flowers. Upper parts and flowers contain Vitamin K, essential oil which contain azulene, bitter matter achillein, organic acids, resins, inulin, gums, proteins and other not exam materials. From the essential oils beside azulene there is and d- α -pinene, 1-limonene, 1-borneol, bornilacetate and other borneol esters, tujon, 1-kamfor, aldehyds, cineol, izovaleic acid, salicylic acid, sesquiterpene alcohols, 20 % hamazulene, sterols and tannins (PDR for Herbal Medicines 2002; Gorunovic 2001).

Flores calendulae

Calendula flowers contain essential oil (0.2-0.3 %) with dominant content of sesquiterpene, triterpene saponins (2-10%); saponosides A-F, triterpene alcohols, diols, triols, flavonoids, polysaccharides, coumarins, bitter matter and other (Joanne Barnes 2002; Tucakov 1999; Gorunovic 2001).

Rhizoma cynodon dactylon

Cynodon dactylon (Bermuda grass) is one of the most spreading weed. Fast in multiplying and have stamina rhizomes. The rhizome is used. Herb is not yet well exam. It contains asparagines, amilym, minerals and other. It is part of some diuretic teas. (Tucakov 1999).

Cortex cornus mas (Corn. Cherry dogwood)

Cortex cornus mas (Corn. Cherry dogwood) is short three, 5-8 m high. Fresh and dried fruits are used, also rare the bark is used. The fruits contain tannins, organic acids, pectin, sugars and mucous matters, the bark contains and resins. Fruits and bark have convenient action on intestinal membrane, and they are used in treatment of various digestive disorders. (Tucakov 1999).

3.0. PHARMACODINAMIC ACTIONS

According to the pharmacodinamic actions of the components of the product and the product Varumin 2 itself, which are detailed presented in the expert report for Varumin 2 issued from the Instity of Preclinical and Clinical Pharmacology and toxicology at his First registration in R. Macedonia. In the period after the registration of the product, there are no relevant data published which will have influence on the pharmacodinamic properties of the product.

3.1. Aloe

Aloes extracts has wide spectra of pharmacodinamic actions, which now days find big use in the traditional and homeopathic medicine, also in the scientific medicine, also in the cosmetics and in the food industry (WHO 1999; PDR for Herbal Medicines 2002; Joanne Barnes 2002).

In vitro and In vivo examinations

Laxative action: Aloes laxative activity depends on antranoid glycoside content. Glycosides are metabolized with the glycosidase in the intestinal flora to active antrons. Aloes laxative action is a result of the increased of the motility of the large intestine, try the inhibition of the Na⁺/K⁺ pump and chloride ions channels. The increasing of the secretion of the liquids is result of the stimulation of the mucosa and chloride ions secretion.

Aloes laxative effect is examined on the rats. Nine hors after the per os administration, aloe induct diarrhea of 5g/kg (at 20% of the rats) and 20 g/kg (at 100% of the rats. Pretreatment of the rats with NO-sintetaze inhibitor (L-arginine) in the dose of 20 g/kg intra peritoneal, significant increase the aloe induced diarrhea. These results have suggested that endogen NO changes the aloes diarrheic effect (Izzo 1999; Joanne Barnes 2002; PDR for Herbal Medicines 2002; WHO 1999).

Anti inflammation action: The inhibitor effect of the 5 types of aloe water extract, including the Aloe ferox, Aloe barbadensis and Aloe pulvis (Japanese Pharmacopoeia) on

the histamine release from the peritoneal fat cells in the rats, is induced with antigen was In vitro tested. All tested aloes extracts have inhibitor action on the histamine release, which have dose depend character, but aloe ferox extracts, aloes powder and aloe barbadensis have shown the strongest inhibition on the histamine release. (IC₅₀ 0.16, 0.07 and 0.02 mcg/ml) (Yamamoto 1993; Joanne Barnes 2002; PDR for Herbal Medicines 2002).

Action on the alcohol content in the body: In vivo studies have shown that aloes water extracts increased and accelerated the ethanol oxidation. The oral administration of the aloin (300 mg/kg) on rats 12 hours before ethanol administration (3g/kg) results in significant decreasing (40%) of the blood alcohol concentration. Pretreatment with intraperitoneal administrated aloe-emodin 2 hours before the administration of the alcohol also has significant decreasing in blood alcohol concentration; this means that aloin is metabolized in the body to aloe-emodin which has influence on the alcohol metabolism in the body. (Joanne Barnes 2002; Chung 1996; Shin 1997).

Antineoplastic action: For aloe-emodin (ethanol extract from aloe) has some anti tumor activity. In the experimental studies has been shown that emodin supreme tyrosine kinase activity in cancer cells which have too large expression of HER2 (Joanne Barnes 2002).

Hypoglycemic action: The aloe extract has hypoglycemic action. The hypoglycemic action of the aloes extract is shown and documented in experimental studies performed at aloxan-diabetic mouses and diabetic rats (Ghannam 1986; Al-Avadi 1985, 1987; Joanne Barnes 2002).

Antibacterial and antiviral action: In the In vitro studies has shown that the aloe-barbaloidin component has antimicrobial and antiviral action on Mycobacterium tuberculosis and Bacillus subtilis (minimal inhibitor concentration from 0.125 mg/ml and 0.25 mg/ml).

Pharmacodynamic aloe's effects on the local application

A lot of number of in vitro and In vivo studies have been shown that aloe extracts have stimulation activity on the grow of the fibroblasts and epithelia cells and induct response similar as lecithin in immune cells which are involved in reparation processes of the skin wounds. At the skin cells culture, aloe treatment has stimulated the cell grow and lead to the faster healing on the provoked wounds lesions. According to the immune system cells, aloes studies have shown that aloe stimulated the lymphocyte blastogenesis and induce agglutination of the human periphery blood erythrocytes (PDR For herbal Medicines 2002).

3.2. Viscum album

Pharmacodynamic studies with the extracts of Viscum album mostly are focused on the cytotoxic and immunostimulative action of the plant.

Cytotoxic activity: The cytotoxic activity was investigated In vivo and In vitro, with the extract from Viscum album, Iscador, with single glycoprotein fractions (lecithin, viskotoxin) and alkaloid fractions.

The *Viscum album* extract has shown significant antitumor action on the tumor models in mice, at Luis carcinoma on the lungs, colon 38 adenocarcinoma and C3H adenocarcinoma on the breast 16/C.

In some studies the sensibility of the *Viscum album* extract activity are shown at acute lymphoblast leukemia which is resistant to metotrexate and citarabin. The anti tumors action is based on the amino acids, present in the *Viscum album*, ability to keep on the cell differentiation (Khwaja 1980, 1986; Evans 1973; Konopa 1980; Hulsén 1987; Joanne Barnes 2002; PDR for Herbal Medicines 2002).

Immune stimulate action: In vivo, the immune stimulate action in mice (the humoral and cell immunity) was proved for the *Viscum Album* extract, Iscador and for polysaccharide fractions isolated from the plant, thru the prolonged and decreased the induced hypersensitive reactions. This immune stimulate action is presumption that probably is result on the stimulation of the monofagocit system and is depend upon the frequentation and quantity of the aplicated extract (Bloksma 1982; Joanne Barnes 2002; PDR for Herbal Medicines 2002).

Agglutination activity: agglutination activity is documented for Iscador and for lecithin fraction on the *Viscum album* extract. For the lecithin it is documented that it is bounded to large number of cells, like erythrocytes, lymphocytes, leucocytes, macrophages, and glycoprotein and plasma proteins.

For the *Viscum album* lecithin it is proved that it prevents the viscotoxine and allergen-induced release of histamine in human leucocytes. (Luther 1974, 1977; 1973; Ziska 1978; Franz 1981; Joanne Barnes 2002).

Anti hypertensive action: Antihypertensive action of the *Viscum album* is documented for the extract, also for the great number of his single components. The right mechanism of this anti hypertensive action is not known yet, but it is presumed that is result on the inhibitor activity on the excitability on the vasomotor centre in medulla oblongata. (Petkov 1979; Joanne Barnes 2002).

3.3.Hyperici herba

The medical activity of the St. John's is known from long ago, and it was used for external and internal purpose.

For internal use known is St. John's tea for regulation of stomach and intestine work, as excellent appetitive and stomachic. The St. John's essential oil was used against intestinal parasites, and fenolic substances present in St. John's have strong antibacterial action. Also it is used for liver diseases and urinary tract.

The oldest, and the most known St. John's wort therapeutic actions are antidepressive, antinarcotics, and anti anksiolitic, and he is used in therapy on neuralgias, anxiety, neuroses, depression and other neurological and psychiatric disease.

In many In vitro studies his antidepressive action is confirmed from much number of authors with using the products that contain St. John's wort. Although the EU Commission has been categorized St. John's wort as MAO inhibitor (on the base of the In vitro studies), In vivo researches suggested that that St. John's wort has weak Mao-inhibiting action, based on the presence of hiperforine, flavonoide aglikans and kvercetine, and less on hypericin. These components have anksiolitic, action thru inhibition of the type A monoamine oxidizes.

St. John's wort is used for alleviation of the insomnia, epilepsies, enuresis nocturne, also for regulation of the menstrual period.

3.4. Radix inulae

The Inula extract and his main constituents (alanolacton, isoalanilacton and other sesqui terpenolactones) have many pharmacodinamic actions; the most important are antiphlogistic, antibiotic, antihelminthic, antifungal and expectorant actions.

Antibacterial and antihelminthic action are result on the presence of sesquiterpen lactones, and expectorant and antiseptic action is based on the essential oil presence. (PDR For herbal Medicines 2002).

In the researches made in mice the sedative effect from Inula infuse was shown. For the alantolactone was proven his anti hypertensive, hypoglycemic (in big doses) and hypoglycemic action (in small doses) on the experimental animals.

For the sesquiterpen lactones isolated from Helenium microcephalum his anti tumor action was proven (Joanne Barnes 2002).

3.5. Millefolii herba

Yarrow is one of the most popular and the most used traditional medicinal herb, also for external and internal use. His healing action was known from long ago, from the time of ancient Greeks and Romans.

Yarrow is not poison, do not make dependence and can be use for every day use for improving of the organs za varenje. It has mild antiseptic and anti-inflammatory action. The yarrow extract has shown an anti-inflammatory action on animal paw models on rats and mice, on edema instigated with yeast, histamine, karagenin and prostaglandin. Yarrow water extract has diuretic action. Dose of 300-600 mg/kg lower the spontaneous motor activity in rats and inhibits the convulsions inducted with pentile tetrasole. On isolated rabbit intestine, the yarrow flavonoide fraction has spasmolitic action, and sesquiterpen lactones fraction has antipyretic and antihypertensive action. (PDR for Herbal Medicines 2002, Joanne Barnes 2002).

3.6. Callendulae flos (Callendula flower)

Calendula flower has many pharmacodinamic actions; the most significant are spasmolitic, mild diaphoretic, and anti-inflammatory, anti chemoragical, tissue granulation stimulative and antiseptic action. Although the efficacy of the calendula flower products is well examined and documented, the natural active materials are not complete defined. The essential oil and flavonoids have antibacterial and antifungal action. Anti-inflammatory action is based on the free and esterificated triterpene alcohols. Traditionally calendula flower is used for treatment of gastric and duodenal ulcers, amenorrhea, anal egcema, proctitis, limfadenom, inflammatory skin lassies (loccaly) and conjunctivitis.

4. 0. TOXICOLOGICAL RESEARCH

The data for the toxicological characteristics of the components of the product Varumin-2 are detailed presented in the Expert's Report for Varumin-2 issued from the Department of Preclinical and clinical Pharmacology and toxicology at Medical Faculty in Skopje, on his first registration in the R. Macedonia. In the period after the registration of the

product, there are no relevant data published which will have significant influence on the toxicological characteristics of the components of the Varumin-2.

This data are submitted in the Annex 1.

5.0. CLINICAL EFFICACY

5.1. Aloe

The aloe extracts are used in traditional medicine with centuries. At the beginning of their use they have been used external, for fastening of the wounds healing and burns, on dermal ulcers and for prevention of the secondary infections of the damaged skin. Also the aloe extract and juice for many years are used as raw materials in cosmetic, especially for hand and face creams, lotions and etc.

For internal use the aloe products were used for treatment on constipation, cough, wounds, ulcers, diabetes, malignant diseases, headache, arthritis, immune deficit and in many other diseases. But until these days the only well documented and supported with relevant clinical studies is aloe efficacy for internal use as laxative. The results from these clinical studies with no doubt confirmed the therapeutically efficacy and tolerance of aloe products in treatment of constipation. In some of these studies aloe products are used as monotherapy, but in the bigger cases part of them are used in combination with aloe and some other laxative.

In some smaller studies the aloe effect on wounds healing, (given orally) was investigated from different etiology (cuts, abrasions, minor burns and other). There was no enough relevant data for aloe efficacy, use orally, on the treatment on these diseases.

In one study with 5 000 patients, the positive effects of aloe use are registered in decreasing of the risk factors in patients with heart diseases. It was registered the lowering of the total lipids level, total serum cholesterol, serum triglycerides, lowering the glycemie at diabetic patients and increasing the level of HDL lipoproteins. But for confirmation of this data it is necessary of additional well controlled clinical studies (Joanne Barnes 2002; PDR for Herbal Medicines 2002; WHO 1999).

5.2. *Viscum album*

In some human studies the extract from *Viscum album* is applied on human with breast carcinoma, cervix, colon, rectum and stomach. After the systematic control of the controlled clinical studies performed with extract from *Viscum Album* in treatment of malignant diseases, 11 studies are identified. In 10 of them there are positive results in the relation with the controlled group (the best in the patients with colon carcinoma), but it must be mentioned that the most of them are performed with poor methodological quality; they are not performed on the base of the modern clinical pharmacology. Only one study is performed with high methodological quality, but there are no registered differences between the tested and controlled group.

Viscum album has mild anti hypertensive action, heart depressive action and sedative action, and was used in severe small studies or isolated at some patients with high blood pressure, arteriosclerosis, tachycardia, headache on hypertension, chorea and hysteria, positive results were shown, but they have more empirical meaning. (Joanne Barnes 2002; PDR for Herbal Medicines 2002; WHO 1999).

5.3. *Radix inulae*

In some studies positive data have been shown with the use of alantolactones from *Inula helenium* as antihelmintic. Also positive results are shown in use of *Inula racemosa* in prevention of ST-depression and inversion of T-wave at the patients with ischemic heart diseases and patients with documented angina pectoris (Joanne Barnes 2002).

5.4. *Hyperici herba*

The efficiency of the St. John's worth as medical herb is known from the ancient period, from where are the first data for this herb use in traditional Greek medicine, original documented from Hippocrates. From that time until today St. John's worth continuously is used and have significant place in traditional medicine in treatment of different neurological and psychiatric diseases, also and for treatment of gastrointestinal diseases, skin diseases and injures and other. But in the last few years his efficacy was scientifically approved in many clinical studies which are performed on the principles of modern clinical pharmacology, performed as random, controlled and double blind researches.

From 1979 year there are performed around 30 controlled clinical studies with St. John's worth extract, with thousand of patients with mild to severe depressive symptoms. Most of the studies are performed on the period of time of 28-42 days with daily dose from 900 mg standardized extract to 0.3 % Hypericin (Jarsin[®]). Until 1997 year there are at least 15 studies in which are used methanol St. John's worth extract, (LI 160) and 12 controlled studies on 4 products which contains ethanol St. John's worth extract, (Schultz 1998). All these studies confirmed the antidepressive action of the St. John's worth extract, at human (Bombardelli and Morazzoni 1995; Linde 1996; Reuter 1998; Upton 1997).

The contents and mechanism of the St. John's worth, antidepressive action are examined by many authors, with citation of many possible mechanisms (Bombardelli and Morazzoni 1995; Reuter 1995; 1998; Rasmussem 1998). But the latest randomized, double blind, placebo controlled, multicentric studies performed at 147 man and woman patients with mild to severe depression suggested that hiperforine can be primary active constituents and play active role in antidepressive St. John's worth action. Lowering the depressive symptoms was significant lower than placebo group at the patient which were taking extract with 5 % hiperforin, but the group of the patients with 0.5 % hiperforin no significant improvement was observed (Laakmann 1998a; 1998b). Also the results from other clinical and experimental studies have confirmed the tests that St. John's antidepressive action is based on the hiperforine presence (Chatterjee 1998; Bhattacharya 1998; Schulz 1998).

6.0. USE

6.1. Aloe Ferox Mill. (Capensis)

PDR[®] For Herbal Medicines 2002

Indications approved by "Commission E"

- constipation

Use in the traditional medicine (Europe)

In traditional medicine it is used for treatment of constipation, for stool softening at anal fissures, after the recto-anal surges.

Homeopathic use

Treatment of gastrointestinal diseases, hemorrhoids and constipation.

Chinese medicine

Treatment of fungal diseases.

India medicine

Stomach tumors, constipation, colic, skin diseases, amenorrhea, and skin infections.

6.2. Viscum Album

PDR[®] For Herbal Medicines 2002

Indications approved by "Commission E"

- rheumatism
- adjuvant therapy in tumors

Use in the traditional medicine

For treatment of degenerative inflammation diseases of the knuckle, palliative treatment of the malignant diseases. In treatment of mild hypertension and for arteriosclerosis prophylaxis.

Homeopathic use

Treatment of dizziness, high blood pressure, heart arrhythmia and degenerative knuckle diseases.

Chinese medicine

Treatment of knuckle diseases, tendon and muscle, lumbago, vaginal bleeding during the pregnancy and galactia.

6.3. Hyperici herba

PDR[®] For Herbal Medicines 2002

Indications approved by "Commission E"

- anxiety
- depressive situations
- skin inflammatory diseases
- wounds and burns

Use in the traditional medicine

Internal use: treatment of bronchitis, asthma, gall-bladder diseases, gastritis, diarrhea, dyspepsia, podagra, rheumatism, enuresis nocturna.

External use: neuralgia, wounds and burns, skin infections and other.

Homeopathic use

Treatment of periphery and central injuries of the central neuron system, asthma and cerebral vascular calcification.

Chinese medicine

St. John's wort gargle solution is used for local treatment of tonsillitis.
For external use as lotion for dermatose treatment.

7.0. EFFECTS OF THE PRODUCT USE

Varumin 2 is herbal remedy for improving of the general state of the body if exhausted, for increasing of the resistance, like adjuvant in standard therapy of acute and chronic diseases, malignant diseases, anemia and other states that are characterized with lessened immunity and bad general state.

8.0. DOSE AND WAY OF USE

VARUMIN[®] 1 is assigned for oral combine use with product VARUMIN[®]2 as on the scheme:

VARUMIN[®]1: at the beginning of the therapy, drink the whole amount (50 ml) of VARUMIN[®]1. After 6 hours begin to take VARUMIN[®] 2.

VARUMIN[®]2: to take 4 times a day, one soup spoon before meal.

9.0. PRECAUTION OF THE PRODUCT USE

(Joanne Barnes 2002; PDR for Herbal Medicines 2002; WHO 1999).

VARUMIN[®] 1 must not be used at:

- Persons extremely sensitive to some of the components of the preparation;
- Children under than 10 years
- Persons with intestinal obstruction;
- Persons with inflammatory intestinal illnesses (Chron disease, ulcer colit);
- Inflammatory of the appendix (appendicitis) and stomach-ache with enigmatic etiology;
- During pregnancy,

9.2. Interactions

Long term use of aloe preparations together with cardiac glycosides and anti-arrhythmic drugs can take to excessive loss of potassium and to assignee the effect of cardiac glycosides and antiarrhythmic drugs.

Parallel use of the aloe preparations with thiazide diuretics and corticosteroids increases the possibility of potassium deficient.

Drugs that contain *Viscum album* can stress the effect of the cardiac glycosides, anti-hypertensive, anti-depressives and anti-coagulants.

Patients who use at the same time selective inhibitors of the reuptake of the serotonin (exam. sertraline) and preparations based on St John's wort the increasing of the level of

serotonin is registered. All the knowledge suggested that St John's have affection on the hepatic cytochrom P450 system, by enlarging of the activity of the isoenzyme CYP3A4, worth may reduce the activity of some medicaments which are used at the same time known as the replacements of that enzyme, like no sedative antihistamines, oral contraceptives, amprenavire, some antiretroviral medicaments, antiepileptic, Cablocators, cyclosporine, some chemotherapeutics, macrolitic, antibiotics and certain antifungal medicaments.

9.3. The measures of precaution and warning

Prolonged use of preparations that contain aloe can provoke:

- hypersensitive reactions which manifest themselves with papular dermatitis and eczematous formations;
- losing of electrolytes (especially potassium), which can result in hyperaldosteronism, inhibition of the intestinal motility and stressing the activity of the cardio active medicaments;
- gastrointestinal difficulties, heart arrhythmia and nephropathies (in rare circumstances);
- albuminuria and chematuria

9.4. Adverse effects

Stomach-ache and spasms can appear in application even if one dose of preparations that contain aloe. Chronicle use of laxatives (like the extract of aloe) can provoke electrolytic misbalance (hypo potassium and hypocalcaemia), metabolite acidosis, and malabsorbtion; lose in weight, albuminurija and chematuria. Weakness and orthostatic hypotension can be expected in aged patients, after long-term of use of extracts of aloe.

Steatorea and gastroenteropathy with hypoalbuminemia are registered at some patients on aloe therapy. Malanotics pigmentation on the colon mucosa (pseudomelanosis coli) is registered at patients who take antrahinon laxatives for long period of time. This pigmentation is from reversible character and is withdrawn after 4-12 months after the interruption of the therapy.

In the period after the product Varumin 2 has been registered in R. Macedonia, there was no application for undesired effects of use of Varumin 2 to the National centre for ensuing of the unexpected effects of the drugs and herbal remedies of R. Macedonia, that speak about the safety and security of the same for the mentioned field of indications.

10.0 RATIONALITY OF THE COMBINATION

Varumin[®] 2 is herbal remedy (solution for oral administration), which in his composition contains water extract from herbal drugs and aloes dry extract, which are the main active components of the herbal remedy. In the sufficient literature there is lots of information which lead to the wide applications of these compounds in traditional and homeopathic, also in scientific medicine.

In the elaborated literature there are no data about the possible interactions or incompatibilities between the composing components of the product.

11.0 PACKAGING

-Glass bottle with 200 ml solution for oral use.

12.0 CONCLUSION

Varumin[®] 2 is herbal remedy (solution for oral administration), which in his composition contains water extract from herbal drugs; aloes dry extract and propolis, which are the main active components of the herbal remedy.

Varumin[®] 2 is herbal remedy which in combination with Varumin 2 is assigned for improving of the general state of the body if exhausted, for increasing of the resistance, like adjuvant in standard therapy of acute and chronicle diseases, malignant diseases, anemia and other states that are characterized with lessen immunity and bad general state. In the sufficient literature for the active compounds of the herbal remedy there are many data which lead to the wide applications of these compounds in traditional and homeopathic, also in scientific medicine. The active ingredients of the product have laxative, anti-inflammatory, anti-microbe, immune-stimulative, detoxificative, citotoxic, diuretic, anti-depressive and other actions. These pharmacodinamic characteristics of the some compounds of the Varumin 2 justified the purposed field of action.

Varumin[®] 2 has marketing authorization and is used in R. Macedonia as herbal remedy 3 years, in which period there are many positive experiences from his use.

In the period after the product Varumin 2 has been registered in R. Macedonia, there was no application for undesired effects of use of Varumin 2 to the National centre for ensuing of the unexpected effects of the drugs and herbal remedies of R. Macedonia, that speak about the safety and security of the same for the mentioned field of indications.

On the base of the above mentioned in these Addition to the Expert report, I consider that Varumin 2 – product of the firm Inter-evrogeneks, Novo Selo, R. Macedonia, fulfilled the conditions on his composition and characteristics, directed for the herbal remedies of that kind and be registered in R. Macedonia as herbal remedy.

The Expert report is made by

Prof. d-r Stojmir Petrov

The Expert collegiums of the Department of Preclinical and clinical Pharmacology and toxicology, on his meeting on the 09.01.2006, make an overview on the text of the ADDITION OF THE EXPERT'S REPORT for herbal remedy VARUMIN[®] - 2, a product of the firm Inter-evrogeneks, Novo Selo, Republic Macedonia and it has been adopted.

Director
Prof. d-r Stojmir Petrov

LITERATURE:

ANNEX 1

4. 0. TOXICOLOGICAL RESEARCH

4.1. Aloe

Aloes extracts are strong purgatives which can provoke stomach pain and gastrointestinal irritation, and their administration can result with nephritis, bloody diarrhea and hemorrhagic nephritis. Similar with other purgatives, the prolonged use of this extracts can provoke water diarrhea with excessive lose of liquids and electrolytes (especially Potassium), muscle weakness and loose of the weight.

Administration of the aloes dry extract in dose of 50 mg/kg/day in the period of 12 weeks in mice, results with hard pathological disorders, although is registered increasing of the concentration of sorbitol dehydrogenase, which can point at possible hepatic damages. (Joanne Barnes 2002; PDR for Herbal Medicines 2002).

4.2. Viscum album

Toxicological researches on animals are documented for lecithin, viscotoxine and tiramine.

Intravenous application of viscotoxine on cats in dose of 35 mcg/kg leads to heart negative inotropic effect, bradycardion and hypotension. LD₅₀ for viscotoxin in mice after peritoneal application is 0.7 mg/kg. LD₅₀ for lecithin who inhibits the protein synthesis in mice is 80 mcg/kg. Tiramin from Viscum Album has shown a stimulate action on uterus in animals' studies and that is why Viscum Album extracts are not allowed for use in pregnancy (Joanne Barnes 2002; PDR for Herbal Medicines 2002).

4.3. *Hyperici herba*

In the available literature there are no data for acute toxicity, toxicity after several time administration, reproductive toxicity and teratogen potential of the *Hypericum perforatum*.

On the base of the available literature, the flavonoides from the St' Johns extract, are the components for whom there are data for possible mutagen effect. According to the In vitro data on the bacterial cultures (Ames test on *S. typhimurium* types: TA 1535, TA 1538, TA 97, TA 98, TA 100 and TA 102) kvercetine (present in the St. John' extract) which generate spot (point) mutation on the cultures TA 97, TA 98, TA 100 and TA 102. At the same time, the action of the falconoid was stressed with addition of S9 microsomal fraction of rat liver (Czeczot 1990). In contrary to this, kvercetin did not manifest carcinogen potential after chronically application at rodents in the period of 12 months. This is explained with the fast and complete metabolism of kvercetin on the influence of the enzyme katechol-ortho-mathyl transverase (COMT) in vivo. (Formica 1995). But, it must be mentioned the In vitro and In vivo researches made with standard ethanol-water extract of St. John' wort which manifest that St. John' wort has no genotoxic action (Okpanyi 1990).

4.4. *Millefolii herba*

Yarrow is no toxic herb. The toxicological researches have shown that LD₅₀ (subcutaneous) for rats is 16,86 g/kg, and for mice (oral) is 3,65 g/kg. For comparison, ED₂₅ for anti-inflammatory action is 0,43 g/kg. In the period of pregnancy and lactation his use must be avoid due his abortive action and can have effect on the menstrual period. Yarrow can provoke allergic reactions at the sensitive persons.

4.5. *Flores Calendulae (Marigold flower)*

The LD₅₀ value for the marigold water extract at mice is 375 mg/kg, respectively LD₁₀₀ is 580 mg/kg (interperitoneal). After chronic administration at mice, there are no registered signs for toxicological effects from marigold water extract.