

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

ADDITION TO THE EXPERT'S REPORT FOR HERBAL REMEDIE

VARUMIN[®] - 1

The request of preparing the ADDITION TO THE EXPERT'S REPORT for herbal remedy **VARUMIN[®] - 1** 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[®] - 1**, 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[®] - 1.**

1.0 FORM AND COMPOSITION

Form: solution for oral administration

Composition:

100 ml solution contains:

- Water extract from herbal drugs* 99.50 g
- Aloes dry extract 0.30 g
- Methylparahydroksy benzoate..... 0.18 g
- Propylparahydroksy benzoate 0.02 g

*100 ml water extract from herbal drags contains:

- Viscum album 1.00 g
- Propolis 0.80 g

2.0 GENERAL INFORMATION FOR THE PRODUCT

Varumin[®] 1 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.

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 states which are characterized with lessen immunity and bad general condition.

Aloe

Aloe is juice made from the 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, pointed on the top and on the edge spines leaves and the flowers are carried in a large candelabra-like flower-head. It grows in semi desert regions in South and East Africa. It is used for producing of the Aloe capensis (Gorunovik 2001; WHO 1999).

Aloe barbadensis Mill. (Synonym Aloe vera L.)

It is lower herb Mediterranean native. It is cultivated in South America, on Anthill islands in west India. It is used for producing Kirasao or Barbados aloe (Aloe curassavica) (Gorunovik 2001; WHO 1999).

Composition: (Gorunovik 2001; WHO 1999).

Drug contains follow ingredients:

- Antranoids; 25-40% barbaloin, a mixture from two diastoisomer 10-glikozilantrons: aloin A and B.
Aloin A and B are substances in which beta-D-glucose is bond with C-glycoside connection to C-atom on the position C(10).
The aloi content 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).
- Aloinozid A and B, isomer 11-O-alpha-ramnozid of aloin A and B.
This substances are characterized by alfa-L-ramnose is glycoside connected to the primary alcohol hidroksi-metil group, on the position C(3).
- Free aloe-emedin to 1%.
- Aloezin hromons derivate, in form of A and B.
Two commercial forms of aloe contain these compounds, 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 B (only in Aloe capensis).
- 7-hidroksialoin A and B (only in Aloe curassavica).
- Aetheroleum oil, resins in traces,
- 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. Eur II it is made by herb extraction with acetone. According to the specification of some other pharmacopoeias the drug is made with extraction with hot water, and clear extract is evaporated to dry.

Aloes dry extract is in yellow pieces or yellow powder, although with out odor, and much bitter taste.

The extract contains bigger quantities of aloin and other constituents of the drug, except resins, which results with bigger drug activity.

Viscum album

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

Propolis

Propolis is natural product from bees. It is waxy substance with yellow-green to dark or dark-red color. By using of the different solutions and distilling with water it is confirmed that propolis contained wax up to 30 %, mechanical impurities 20%, 40-60 % resin, and balsam, 5-10 % essential oil, 5-15 % tannins, pollen and other. But in the chemical way this terms are undefined, and only proved basic component in propolis are flavonoids which are present more that 25%.

In his composition are also following flavonoids: chrisin, galanin, tektochrisin, akacetin, kvercetin and others.

It also contains mineral matters, esters of the fat acids, high alcohols, 10-15 % carbohydrates, free fat acids, vitamins and other. (Gorunovic 2001).

3.0. PHARMACODINAMIC ACTIONS

According to the pharmacodinamic actions of the components of the product and the product Varumin 1 itself, which are detailed presented in the Expert Report for Varumin 1 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, aloes 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 aloes 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 aloes 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 metotaxate 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; Hulsen 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. Propolis

The propolis has bacteriostatic, bactericide and fungicide action. Antibacterial materials which are present in the propolis are termostabile. Gram positive bacteria are more sensitive to propolis than gram-negative bacteria. The researches on the antimicrobial activity of ethanol extract shown that propolis have influence on *Bacillus cereus*, *staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida Albicans*. The antimicrobial activity of propolis on absolute value is considerable lower than in antibiotic activity, but in less than grade other antibacterial products; propolis antibacterial action on the *staphylococcus* is similar with the sulfonamide action.

Antibacterial activity of the propolis mostly is a result on the flavonoide action, and in lower rate on the other constituents. The flavonoide – akacetin who is contained in the propolis decreases the inflammation and enlarge the resistance if the capillary barrier. Propolis has wide use in dentist practice, otorinolaringology, and gastroenterology and in some skin diseases. Propolis also has anesthetic action, and trific-granulic effect which lower the pain and stimuli the wound and erosion healing (Grunovik, Lukic-Farmakognosy 2001).

4. 0. TOXICOLOGICAL RESEARCH

The data for the toxicological characteristics of the components of the product Varumin-1 are detailed presented in the Expert's Report 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-1.

This data are submitted in the Annex 1.

5.0. CLINICAL EFFICACY

5.1. Aloe

The aloes 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 aloes 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 aloes 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 aloes efficacy for internal use as laxative. The results from these clinical studies with no doubt confirmed the therapeutically efficacy and tolerance of aloes products in treatment of constipacy. In some of these studies aloes 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 aloes 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 hart diseases. It was registrated the lowering of the total lipids level, total serum cholesterol, serum triglycerides, lowering the glicemy 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, hart 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).

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.

7.0. EFFECTS OF THE PRODUCT USE

Varumin 1 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 chronicle diseases, malignant diseases, anemia and other states that are characterized with lessen 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 soupsoon 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 (Khron 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 lose of potassium and to assignee the effect of cardiac glycosides and antiarytmic drugs.

Parallel use of the aloe preparations with tiazide 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.

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.

Steatorrea 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-1 has been registered in R. Macedonia, there was no application for undesired effects of the use of Varumin-1 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[®] 1 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.

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 50 ml solution for oral use.

12.0 CONCLUSION

Varumin[®] 1 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[®] 1 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 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.

Varumin[®] 1 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 1 has been registered in R. Macedonia, there was no application for undesired effects of use of Varumin 1 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 1 – 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[®] - 1, a product of the firm Inter-evrogeneks, Novo Selo, Republic Macedonia and it has been adopted.

Director
Prof. d-r Stojmir Petrov

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 stimulative 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).