



**GENERAL INFORMATION ABOUT dsRNA LARIFAN
AND LARIFAN PRODUCTS**

Non-clinical and clinical studies

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SHORT CHARACTERISTICS of dsRNA LARIFAN

An original active substance - Larifan was developed at the Latvian Academy of Sciences and at present is produced at "Larifans" Ltd. Larifan is a double-stranded RNA (dsRNA) of natural origin obtained from bacteriophage-infected E.coli cells. It is heterogeneous population of dsRNA molecules with mean molecular mass of about 500 kDa and average length of RNA - 750 nt/p. Larifan (dsRNA) has been developed as a new poly-functional and wide-spectrum medical drug for viral and oncologic diseases.

Larifan possesses multiple biological activities like interferon-inducing, immunomodulating, antiviral, antitumoral and antimutagenic properties. These activities are as result of the action of induced endogenous interferon or may be provoked directly by the dsRNA molecule as well.

Some drug forms such as ointment and injection form are being produced for human use. The injection drug form is registered in the Drug Register of Latvia (2004) and in the appropriate authorities of Georgia (2010), Azerbaijan (2011) and Turkmenistan (2015), the drug form of the ointment (0,05%) was in the Drug Register of Latvia (1994 – 2004), drug form of Suppositories 4.0 mg is in the process of clinical trial. The product line is developed in which the dsRNA as active substance is included. Some cosmetic Larifan-containing products –lip balm, tooth paste, ointment (0,025%) and consumer goods– spray, suppositories (0.5, 1.0 or 1.5 mg/supp) and pessaries are being developed and produced. Currently the gel form, patches and candies are in the process of development.

In Larifan-containing cosmetic and consumer goods the active substance is included in subtherapeutic doses, which are not sufficient for healing activities but ensure mobilization of the body's natural defenses, providing anti-virus protection and immunomodulatory effects.

Larifan's clinical efficacy has been studied in different clinics and institutes of Latvia and the former USSR since the 80-ties of the last century.

In human clinics Larifan is employed as an immunomodulator with antiviral and antitumoral activities. Its therapeutic antiviral effect has been demonstrated in the treatment of herpes (in Russian, Ukrainian, Latvian clinics), papilloma, respiratory and other virus infections. Larifan's advantage when compared with chemical antiviral preparations is its broad antiviral spectrum and absence of immunosuppressive properties. Because of its interferoninducing ability Larifan possesses a theoretically universal antiviral spectrum. Immunomodulating activities are responsible for correction of the immunodeficiency, which is characteristic for many viral infections. When compared with exogenous interferons Larifan-induced endogenous interferon should be considered as a more physiological one and thus having less side effects. The endogenous interferon is supposed to be more stable, with more prolonged action and better distribution in the organism.

Regarding antitumoral potential there is enough evidence to consider Larifan as a perspective drug for malignant diseases. Its ability to possess both antitumoral and immunomodulating properties at the same time is of special value for oncology. In oncology Larifan is applied in combined biotherapy schedules aimed to change surface antigens of malignant cells and activate immunocompetent effector cells as well.

The research results obtained in recent years has shown that Larifan not only induces interferons, but also a lot of other cytokines and chemokines.

Larifan`s interferon inducing activity is observed both in humans and different kinds of animals, such as monkeys, calves, sheep, rabbits and small rodents. The level of induced interferon and formation dynamics depend on the medicament administration form.

In human blood serum interferon can be found after 10 hours following Larifan administration in the form of rectal suppositories; after subcutaneous and intramuscular injection the maximal titres were detected after 6 to 10 hours, and already after 2 hours after aerosol administration. Human eye conjunctiva swab taken 4 hours after Larifan ointment application has demonstrated a substantial interferon titre increase. Larifan as well as interferon can be considered to be a universal antiviral medicament, as it interrupts virus replication in stages, which are common for all viruses.

Larifan antiviral effects are demonstrated both in vitro and in vivo. During animal experiments and in tissue cultures, Larifan inhibits virus reproduction and infection process for herpes, flue, tick-borne encephalitis, encephalomyocarditis, Semiliki, Sindbis, Venezuelan encephalitis, Aujeski, rabies and other viral infection cases. Inhibitory Larifan effect on experimental clamydia infection in mice has also been demonstrated.

Antitumor effects have been observed in different experimental tumor models – Moloney sarcoma, Rauscher leukemia, lymphatic leucosis NK/Ly, sarcoma S-37, Lewis carcinoma 3LL, melanoma B-16 and others. Larifan suppresses the formation of primary tumor, prolongs survival time and in some models (Lewis carcinoma, melanoma B-16) markedly inhibits the formation and development of metastases.

Immunomodulating activities have been observed at local and parenteral application. When applied locally, it causes local lymphocytoses as well as an increase in NK cells. After parenteral administration Larifan stimulates macrophage phagocytic activity, acts as immunoadjuvant, activates NK cells, increases the amount of total and active T-cells and particularly some of their subpopulations, activates HLAexpression, modifies structure of tumor cell surface antigens. Ex vivo studies show, that Larifan activates dendritic cells (DC) and promotes their differentiation, including formation of plasmacitodic cells.

Within the body ribonucleic acids are subjected to ribonucleases (RN-ases) action. RNases commonly found in nature easily break up single-stranded RNA and to lower extent also dsRNA. However specifically dsRNA are broken only byRN-ase III. RN-ase III is specific for primates and is not found in lower animals. Therefore the fate of dsRNAin animals and humans is substantially different. RN-ase III existing in the human body in few minutes time breaks up dsRNA into oligonucleotides which are not distinguishable from the usual body metabolites. It was found that unshielded free dsRNAmolecule after contact with human serum in few minutes is broken into low molecular fragments and loses interferon-inducing activity. Low molecular weight compounds do not have biological activity typical for dsRNA molecule and they are not different from the usual body metabolites.

Preclinical investigations have shown that Larifan does not exhibit carcinogenic, mutagenic, local irritating and allergic properties.

Mutagenic investigations demonstrated that Larifan does not exhibit mutagenic properties. However, special investigations revealed that Larifan may decrease mutagenic activity of another antitumor medicament (Fotrin) and therefore has some antimutagenic activity.

Preclinical data of standard investigations about pharmacological safety, repeated dose toxicity and possible carcinogenicity did not reveal any special risks for humans.

The method of manufacturing dsRNA is patented.

THE ACCUMULATED DATA ON THE NONCLINICAL STUDIES OF LARIFAN ACTIVE SUBSTANCE - dsRNA (integrated overview)

The preparation made in the Latvian Institute of Microbiology - larifan is a double-stranded ribonucleic acid (dsRNA) of a natural origin, which is isolated from the *Escherichia coli* cells, infected with bacteriophage. It induces interferon, causes antiviral, immunomodulatory and antitumoral effect. dsRNA is heterogeneous by molecular length, with sedimentation constant approximately 6,3S, which corresponds to the molecular mass of approximately $3.5 - 5.0 \cdot 10^5$ Da.

Preclinical studies of dsRNA preparation – Larifan performed at various research institutions, namely, at:

- 1) Institute of Virology. D.I.Ivanovskogo Academy of Medical Sciences of the USSR
- 2) Institute of Microbiology. A.Kirhenshteyna Latvian Academy of Sciences,
- 3) the Riga Institute of Medicine, in the Department of Immunology Research Laboratory of Applied Pharmacology and Toxicology.
- 4) the Riga Institute of Medicine, in the Department of Pharmacology and Toxicology Research Laboratory of Applied Pharmacology and Toxicology
- 5) Research Institute of Oncology. NN Petrov St. Petersburg
- 6) Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR

The research results are presented by performers in the attached reports and articles (mostly in Russian).

See reference in accordance with the report or article number in the content list

PHARMACOLOGY

Specific pharmacological activity

Report Nr 1

Articles Nr.Nr.42,43,31, 32, 5-11, 14-30, 35, 39, 40.

Specific pharmacological activity has been researched in the leading scientific institutes –at the Institute of Virology of Academy of Medical Sciences in Moscow and at the Institute of Microbiology of Latvian Academy of Sciences.

Pleiotropic biological activity has been stated for larifan, such as the ability to induce interferon, cause antiviral, immunomodulatory, antitumorous and antimutagenic effects. Larifan's interferoinducing activity has been observed experimentally with animals of various species – mice, rabbits, calves, monkeys.

Larifan, likewise as interferon, is an universal antiviral preparation, because it interrupts viral replication in stages common for all viruses. Larifan's antiviral effect is shown both *in vitro* and *in vivo*. *In vitro* systems is proven its ability to inhibit the reproduction of *Sindbis*, mice encephalomyocarditis, Venezuelan horse encephalomyelitis and other viruses, decreasing the viral outcome by 5 lg.

In experimental animals larifan demonstrates prophylactic effect in the cases of tick encephalitis, mice encephalomyocarditis, *Semliki*, *Aujeski*, rabies, flu and other viral infections. Therapeutic effect has been observed in rabies and encephalomyocarditis infections. The inhibitory effect of larifan has been shown in the experimental chlamydia infection in mice.

Larifan caused „early” interferon production, with the maximum after 4-8 hours. Effect is dose dependent and it was observed in different animal species.

Larifan's antitumoral effect has been shown on many experimental tumour models – *Moloni* sarcoma, Rauscher's leukemia, *NK/Ly* lymphoma, chemically induced with methylcholantrene, urethane a.o., *Ca Lewis carcinoma 3LL*, *tumor MX-17*, *Ehrlich ascites carcinoma*, *melanoma B-16*. Larifan inhibits the development of primary tumor and the number and time of appearance of metastases. Discovered the ability of the drug to inhibit the metastatic process in a concomitant immunity, ie, drastically slow down the development of metastases that are characteristic in the postoperative period.

Larifan's immunomodulatory action was shown both by local application and systemic use. Locally applied larifan causes local lymphocytosis and *NK* cell number growth. Larifan injections activate macrophages, stimulates its phagocytic activity, strengthens *NK* activity, increases the number of active T-cells, induces T-ly cytotoxic activity, acts as an adjuvant when used together with specific vaccines, lowers the late hypersensitivity. There are indications of regulation of the expression of several genes that play a role in the anti-tumor immunity. Simultaneously Larifan acts on the effector cells, increasing the expression of HLA, activating CD8 + lymphocytes, and thus increasing potency of cell immunoreactivity . Applications such as before surgery, and before a course of radiation or chemotherapy, this drug can make a significant contribution to reducing the toxic effects arising as a result of application of the classical treatment, as well as the delay in tumor metastasis.

Trials on general pharmacological qualities

Report Nr 5

Studies on general pharmacological qualities were run at the Pharmacology laboratory of Riga Institute of Medicine in 1986.

Effect on cardiovascular system

Investigations on rats were performed using indirect method, namely using USA equipment *ITT* for indirect arterial blood pressure measurements for rats. Effect on cardiovascular system was determined on white rats, administering larifan intravenously (in tail vein – dosages 5mg/kg, 10 mg/kg and 15 mg/kg) and subcutaneously (dosage 50 mg/kg). Larifan dosage 5 mg/kg caused a slight lowering of the arterial pressure, but

dosage 15 mg/kg lowered pressure by 30 – 45 %. Pressure normalized after 60 min. Also when administered subcutaneously, larifan (50 mg/kg) caused a slight lowering of the arterial pressure (mostly diastolic pressure), which set in after 1 – 2 hours and normalized after 4 hours. Larifan dosage of 15 mg/kg intravenously slowed the function of the heart, without affecting breathing frequency. These changes were abolished after 2 hours.

Larifan's effect on blood pressure, breathing and acetylcholine reaction was proven also in investigations on cats, administering the preparation intravenously with dosages ranging from 0,1 mg/kg to 2 mg/kg. Slight, short-term blood pressure lowering was stated after dosage of 2 mg/kg. Breathing and acetylcholine reaction did not change in these conditions.

Effect on central nervous system

Effect on CNS was tested in investigations on white mice, administering larifan subcutaneously with dosages 3 mg/kg (which is 1/10 of LD₅₀) and 0,5 mg/kg (which is the optimal interferoninducing dosage). The mice received larifan 30 minutes or 4 hours before preparations affecting the functions of CNS. Results showed that larifan:

- does not affect coordination and muscle tone
- does not affect body temperature
- does not show analgesic effect
- does not change cramp clonic phase onset time
- dosage of 3 mg/kg prolongs cramp tonic phase onset time
- does not affect hexenal narcosis length, but both tested dosages intensifies barbital-natrium narcosis and shortens its latent period

Effect on endocrine system

Rabbits and dogs, what were used for the trials of chronic toxicity, were used for the evaluation of larifans effect on thyroid, suprarenal gland, reproductive glands, thymus. Macroscopic inspection has not stated visible changes, morphological investigations have not shown deviances from the normal gland histological structure.

Pyrogenicity examination.

Larifan's pyrogenicity has been tested in trials on rabbits, administering the preparation intravenously with dosage 0,2 mg/kg and 0,06 mg/kg. In both doses larifan turned out as pyrogenic. It is a feature immanent for double stranded structure. It is known from literature, that synthetic dsRNA preparation - poli I . poli C also is pyrogenic, while single strands (poli I or poli C) do not show pyrogenicity (Lindsay H.L., Trown P.W. et al. Nature, 1969, V 223, 717 - 18).

Anti inflammatory action

Anti inflammatory action has been tested in experiments with white mice, who had inflammation and oedema caused by administration of formalin into food. Larifan, administered i/p with a dosage /10 of LD₅₀ simultaneously with formalin or 30 minutes before it, slightly inhibits forming of oedema on foot (when evaluated 4 hours after applying of the irritant). Direct inflammatory action of larifan is not observed.

PHARMACOKINETICS

Article Nr 44

Ribonucleic acids are subjected to the effect of ribonucleases (RN-ases) in the organism. The naturally widespread RN-ases easily split single stranded RNA and can slightly affect also the dsRNA. However, it's only the RN-ase III which splits specifically dsRNA. RNA-ase III is characteristic to primates, but is not found in the organisms of lower animals. Herewith the fate of dsRNA in the organisms of animals and humans is different and there is no basis on which to make pharmacokinetical investigations on animals.

In the few minutes the RN-ase III found in the human organism splits the dsRNA to oligonucleotides, which can't be differentiated from the regular metabolites of the organism. There is data in literature about the fate of synthetic compounds (similar to the structures of dsRNA) – poli I . poli C in human material, which verify the aforementioned. (Nordlund J.J., Wolff S.M., Levy H.B.. Proc. Soc. Exp. Biol. Med. 1970, V 133., Nr.2, 439-444; Torelli U., Ferrari St., Gadoni R., Ferrari S. Experientia, 1976., V 32., 285-287.).

Working on the subject of the probable protection of the larifan's molecule in the human organism by processing with poli-L lysine it was found that unprotected molecules lost their activity completely after 4 hours contact with serum while protected ones retains their biological features. The studies were performed at the St.Petersburg's institute of Nuclear physics together with Latvian Institute of Microbiology.

There are literature data on other natural dsRNS product distribution in the body of mice.

Using radiolabelled product it was found that the highest levels were in the blood serum, as long as in the liver, spleen and brain radiolabel was significantly lower.

After 24 hours, only the radioactivity trace could be detected.

(Mayer V., Stanček D., Doskočil J. Acta virol., 1976,V 20.Nr.2 p.169.)

Toxicology studies

Toxicological trials were made at the Riga Institute of Medicine in 1986.

Acute toxicity. (Single-dose Toxicity) Report Nr 2 Article Nr.35

Larifan's acute toxicity was researched in experiments with mice, rats and rabbits.

White noninbred mice, after intravenous injection of preparation had a LD₅₀ of 3,0 mg/kg, after intraperitoneal administration – 8,0 mg/kg, after subcutaneous administration - 20 - 30 mg/kg.

Rats weighing 120 - 170 g after intraperitoneal larifan administration had a LD₅₀ of 140 mg/kg.

Rabbits – after subcutaneous larifan administration of a dosage of 10 or 20 mg/kg, the next day the animals are sedentary, apathic; behaviour goes back to normal in the second or third day. Consequently, the LD₅₀ in rabbits is greater than 20 mg/kg.

Research on acute toxicity shows differences in the sensitivity against larifan of various rodents – rats are 17 times more resistant towards a lethal dosage than mice (species' sensitivity coefficient is 17).

The LD₅₀ parameters show a rather high toxicity for larifan, but since its biological activity is also high, the established toxicity must be taken in context with its therapeutical effectivity, respectively, by analogy with synthesized preparations, a so-called therapeutical index (TI) must be defined. TI shows the relation between minimal toxic dosage (MTD) and minimal effective dosage (MED). Minimal toxic dosage, which is LD₅₀ : 4 in this case is 8 mg/kg : 4 = 2 mg/kg. The minimal effective dosage in this specific case is determined by assuming the smallest larifan dosage, which induces interferon for mice (i.e. 0,1 mg/kg). Consequently MDT: MED is 2: 0,1 = 20. Interferon inductors, for which the TI surpasses 16,

are considered highly active [39]. Preparations with an index to 4 and to 8 are respectively weakly active and active.

Repeat- dose toxicity

Reports Nr,Nr 3,4

Rabbits had larifan administered subcutaneously in three dosages. Minimal dosage was selected from the calculations that the therapeutic dosage for human would be 10mg, the second and the third dosage surpasses the first by three and six times. Animals received the preparation each day for the period of 30 days.

It was established that the administration of larifan did not affect the animal behaviour and physical sense, there were no local changes in the area of administration, short-term body temperature elevation was recorded. Rabbits gained weight normally. No changes in blood count were recorded, save gradual growth of the number of eosinophil leukocytes. Biochemical indicators in blood (alkaline phosphatase, AsAt, AlAt, general protein, albumins, globulins, bilirubin, cholesterol, sublimate proven) did not show any change from control, except the lowering of sugar levels. Electrocardiogram showed no changes. Histological investigations at the end of the experiment showed no changes in any of the examined organs (heart, kidneys, suprarenal glands, liver, spleen, brain, cerebellum, reproductive glands, urinary bladder, urethra, thyroid, thymus, small and large intestine, trachea, oesophagus, lungs, skin in the area of administration).

Dogs received larifan subcutaneously in two dosages. The smallest dosage (0,15 mg/kg) was chosen as respective to the dosage provided for humans (guided by the calculation that the therapeutic dosage for humans would be 10 mg), the second – 6,5 times greater (1 mg/kg). Animals received the preparation each day for one month.

For dogs who received the greater dosage, change in their behaviour and physical sense were recorded at the beginning of the experiment, but normalized in the last weeks. One of the animals from this group fell after two weeks. In the first weeks animals dropped behind in weight, but later on the weight was restored. Administration of larifan did not affect biochemical indicators in blood (alkaline phosphatase, AsAt, AlAt, leftover nitrogen, general protein, protein fractions, protrombin index) and urine (pH, sugar, protein, nitrites, ketones, bilirubin, urobilinogen, masked blood). No change in the mass of the internal organs and mass coefficient of dogs due to the administration of larifan was recorded, except for the kidney mass coefficient, which was greater in comparison with control.

Histological investigation showed different degrees of change in internal organs. One of three animals, who received the smallest dosage, showed change in lungs, of the like which are registered in the case of lobular bronchopneumonia and interstitial pneumonia. Serious change was found in dogs, who received larifan in dosage of 1 mg/kg. All dogs were recorded of having liver hemorrhages, one of them (the one who fell after the first two weeks) was found several necrotic nests with dissolved nucleus. All of the animals of this group had heightened liver hepatocyte cytoplasm vacuolization, as well as granular and oleaginous dystrophy. Kidneys show visible hemorrhage in the kidney channels and around them, spleen shows interfollicular tissue hyperaemia, oedema and leukocyte infiltration. The rest of the organs (heart, lymph nodes, small intestine, urinary bladder, uterus, ovaries, testicles, suprarenal glands, thyroid, pancreas) showed no pathological change.

Dogs, who usually are used as one of the animal species to evaluate chronic toxicity, in the specific case proved to be ineligible. In literature there is described a special investigation (Phillips B.M., Hartnagel R.E. et al. Toxicol. Appl. Pharmacol., 1971, V 18, 220 - 230) about double stranded RNS (synthetic preparation poli I . poli C) comparative toxicity in rodents and dogs. It is recorded that dogs are especially sensitive against preparation of this kind. The dosages used in the investigation(0,2 un 2 mg/kg), length of the administration period (42 days) as well as the observed clinical picture and histological change in organs are similar to those, which were observed while evaluating larifan. Smallest of the dosages after 42 day every-day administration was declared as well-

bearable and authors made the conclusion, that the observed phenomena is not a obstacle for the administration of the preparation on humans after carefully selecting the acceptable dosage.

Chronic toxicity was evaluated in trials also with white mice, administering them larifan s/c once a day for the period of 3 days in the dosages of 0,07 mg/kg, 2,5 and 3,0 mg/kg (1/10 LD50), 4,2 and 5,8 mg/kg (LD5). Hyperaemia and infiltrates were not established in the area of administration. Hematological indicators – Hb, erythrocytes, leukocytes and leukocytary formula did not show any deviances from the physiological norm in any of the trial groups. The weight of animals and their internal organs (liver, kidney, spleen, heart) did not differ in control and trial groups.

Local irritant action trials.

Report Nr. 9.

Irritant effect on eye mucous membrane was evaluated on rabbits. 0,5% larifan was administered in the conjunctive sack once did not cause irritation of the mucous membrane, 1% solution showed light irritation, 4% solution caused heavy irritation, which disappears only after 48 hours.

Larifan's effect on muscular tissue in the area of administration was evaluated on guinea pigs. After eight 0,1% solution administrations histological muscular tissue investigation showed no pathological deviances. Parenchymatous organ histological trials show no change.

Rabbits had larifan of various dosages (0,07 – 2 mg/kg) injected subcutaneously 3 times and were observed for local irritation. Change on skin in the area of administration were not observed, the histological tissue trial showed no deviances from the norm.

Studies on allergic properties.

Report Nr. 10.

Guinea pigs had larifan's sensibilizing dosage (25 mkg, 50 mkg or 100 mkg) administered intracutaneously in the ear. Sensibilization was evaluated after 12 days. The determinant dosage was administered intracutaneously in the side of the guinea pig. Early type allergic reaction, which is evaluated after 60 min after the administration of the determinant dosage, was negative for the guinea pigs. Late type reaction, which is evaluated after 6-8 hours also showed to be negative. Late type sensibilization reaction (after 24 – 48 h) also was not observed. Specific leukocyte agglomeration reaction, showed intensity of 2 magnitudes (dosage of 50 and 100 mg), which is regarded as weak sensibilization.

As a result, in the specific trial conditions there was not observed neither early, nor late type allergic reaction, but with greater dosages there was observed the leukocyte agglomeration reaction, which indicates that there is a chance of forming an early type allergic reaction, for example, urticaria. Therefore people with a predisposition to allergic reaction should use the preparation with caution.

Cumulative properties trials.

Report Nr. 8.

Cumulative action trials were made in investigations on white mice. Preparation was administered s/c for 28 days, heightening the dosage every 4 days from 0,1 LD50 to 1,22 LD50. In total, the animals received larifan in the dosage of 328 – 393 mg/kg. Signs of intoxication, which showed as falling behind on weight, started on day 13, i.e. when animals had received 1,88 LD50. Animal fall started with day 16 (males) and day 20 (females), when the total dosage reached respectively 3,24 and 5,24 LD50.

Calculated cumulation LD50 is 245 mg/kg for males, 215 mg/kg for females.

Cumulation coefficient, which is LD50 in cumulative: LD50 acute is 8,17 (males) and 8,6 (female). Changes in blood count (lowering of Hb, lymphocyte count lowering) show relatively late, i.e. when animal falling has already begun.

Overdosage therapy experimental substantiation.

Report Nr. 7.

Investigation was made on mice, administering larifan of dosage that corresponds to LD50. Mice received (before or after larifan being administered) dimedrol (10 mg/kg), corazol (10 mg/kg) or ephedrine (1 mg/kg). Larifan was administered i/v together with preparations or s/c and the preparation 2 hours after. It was observed, that with prophylactic intents (administering together with larifan) the most effective is ephedrine, but the so-called therapeutical action is the most visible with dimedrol, which lowers the falling of animals by half.

Hence in the case of overdose it is advised to use antihistamine remedy and in the case of hypotension – ephedrine.

Mutagenous properties trials.

Report Nr. 13.

Article Nr.4.

Mutagenecity trials were made in the Riga Medical institute in the year 1985 under the supervision of professor A. Žilēvica.

Mice medulla cells show no chromosomal damage after $\frac{1}{2}$ LD₅₀, namely 4 mg/kg larifan dosage administered intraperitoneally to 2 months old mice. Trials were made after Ford and Hammerton method. Exposition was 6, 24 and 48 hours, each group had 5-6 animals, in each group 300 metaphases were analyzed. Control was used – animals, that did not receive the investigated preparation. Aberrations of chromosomes were not observed.

In investigations with human lymphocyte cultures a dosage of 4 mg/kg was used. In each group 300 metaphases were analyzed. No mutations were observed.

Larifan's effect on gene mutations and dominant lethal mutation possible induction was investigated in the *Salmonella typhimurium* microorganism test. Stems that allow to observe mutations (the basis of which are the change of basis in the DNA molecule) were used, as well as stems, that show mutations that originate from the offset of genetic code reading. None of the cultures showed any gene mutations.

Dominant lethal mutations, that cause first generation posterity ruin in the embryonal stage, were investigated on mice, by administering larifan of dosage of 4 mg/kg i/p on mice males. Results show, that preparation had no effect on spermatocytes neither pre-, nor postmeiotic spermatogenesis stage, in result of which no ruin of embryo was observed. Therefore, larifan does not cause dominant lethal mutations.

Complex investigation, using 4 different tests, show that larifan does not have any mutagenous properties.

Cancerogenicity trials.

Report Nr. 6.

Cancerogenicity trials were made under the order of USSR Virusology institute (taskwork N.70/89). Trials were made in the Scientifically-investigative St.Petersburg Oncological institute.

Trials were made with white rats and white mice. Maximally bearable dosage, which were determined in the subchronic experiment by s/c administration: 3 mg/kg and dosages which are close to the human therapeutical dosage – 0,3 mg/kg. Preparation was

administrated for a period of 24 months, once a week. The first group received a dosage of 0,3 mg/kg, the second – 3,0 mg/kg and the third group – control group.

Morphological diagnostics and statistic processing was made in accordance to the International Cancer investigation agency's guidelines.

Evaluation was made after several according to the guidelines criteria: general survival, frequency of tumours.

No difference was observed in the frequency and structure of the tumours in different investigated groups, namely it was not dependant from the dosage.

Trial results show that larifan does not possess any cancerogenous properties.

Embryotoxic and teratogenous action trials.

Article Nr.1.

Trials were made in the Latvian organic synthesis institute (OSI), in accordance to the USSR 1972. methodic indications.

Trials were made on rats, which in the time of gravidity from the first to the 17th day received the preparation s/c in dosage of 20 mg/kg (which several hundred times exceeds the average therapeutical human dosage). Under the effect of larifan, the diminishing of the count of live embryos, their mortality, mostly in the preimplantation period, was observed. Evaluation the embryos macroscopically, anomalies in the fetus' development was not observed. The frequency of the ruin of embryos indicates that larifan is a weak embriotrope substance, hence larifan injections should not be recommended for pregnant women.

CONCLUSIONS

Standard pre-clinical studies of dsRNA preparation shows no adverse effects on the cardiovascular system, central nervous system the endocrine system and also it has no carcinogenic properties.

Study of repeated dose toxicity revealed no specific toxicity to certain organs

Study of mutagenic properties shows that the dsRNA does not cause chromosome, gene and dominant lethal mutations.

The cumulation of clinically recommended dosages is not possible.

dsRNA can be considered as weak potential embryotropic substance and therefore Larifan injection form is not recommended for pregnant women.

Protective effect of Larifan is observed in various experimental viral infections and tumor models

Thereby data obtained on the dsRNA in preclinical studies of standard pharmacological safety, toxicity of repeated doses, genotoxicity, carcinogenicity and effects on reproduction do not indicate a risk for humans except that injection form it is not recommended for pregnant women

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CLINICAL STUDIES of THREE LARIFAN DOSAGE FORMS

Clinical trials were carried out with three Larifan dosage forms - injection, ointment 0.05% and suppositories 4 mg

Injection and ointment studied from 1985 to 1999, according to the requirements of that time in the USSR territory.

Larifan suppositories clinical efficacy studied in 2001 to 2003 according to the Latvian State Agency of Medicines requirements. This study has not been completed

As the basis for registration of Larifan injection form served the results obtained in multicenter clinical trial during the years 1987 -1999. With ointment clinical studies was started on 1985.

Clinical trial of injection and ointment forms was organized and coordinated by the Institute of Microbiology of the Academy of Sciences of the Latvian SSR

Studies conducted in 8 different health institutions in the territory of the former USSR and in Latvia.

Medical institutions where studies were carried out, were the leading ones by Pharmacological Committee of clinical trials. Practical observations accumulated over a period of last 20 years.

The results, obtained in these studies, are summarized in table form (see following tables)

For the other products containing Larifan have been accumulated clinical observations, mainly from family doctors.

SUMMARY DATA ON THE CLINICAL EFFICACY OF LARIFAN INJECTION FORM

OVERVIEW TABLE OF CLINICAL STUDIES

The name of the medical institution	Time of the study	Diagnoses	The number of patients
Department of skin diseases of 1 st Moscow Medical Institute	1989	Generalized herpes infection	25
Department of Dermatology of the Kiev Institute of Postgraduate Medical	1989	Severe recurrent herpes infection	17
Clinical Hospital "Gaijezers" and the Institute of Neurology of the Stradins University Hospital.	1997	Viral infections of the neural system:	40
State Center of Tuberculosis and Lung Diseases	1990	Metastatic exudative pleuritis	20
Department of Ophthalmology of the Medical Academy of Latvia	1997	Herpes simplex ceratoconjunctivitis	12
Latvian Cancer Center	1987	Trial of the tolerability and harmlessness	75
Cabinet immunotherapy of cancer consultative clinic of the Stradins University Hospital.	1987 - 1999	Secondary immunodeficiency of different origin, particularly oncopathology	155
State Center for Family Health	1996 - 1999	Different pathologies (STD of viral etiology, chlamydia a.o.)	188

SUMMARY OF CLINICAL DATA

References	Indications Studied	Dosage range, posology and dosage form	Patient characteristics	Study design	Main results	Side effects	Conclusions
<i>Generalized herpes infection</i>							
Reports on clinical trials of the 1st Moscow Medical Institute, 1989	Generalized herpes infection with fever, increased body temperature, weakness, fatigue, headache, regional lymphadenopathy, ganglionitis, ganglionic radiculoneuritis,	Injection form, 10 mg administered s/c, the course - 4 doses with the three-day intervals.	25 patients (11 men and 14 women). Age range 25 to 52 years. Duration of the disease before treatment: in 9 patients 6 months - 3 years, in 13 3 - 10 years, in 3 more than 10 years. Localization of the process: genital herpes, gluteus, face or disseminated herpes. In 3 patients the herpetic process was continuous, in others relapses repeat one to two times a month	administration schedule - 4 doses with the three-day intervals. Examinations: the duration of the present relapse, severity of symptoms, the duration of remission, the severity of the next relapse, the frequency of relapses. Clinical and biochemical analyzes as well as control of interferon in blood sera were performed	Therapeutic effect was observed in 23 patients, two patients had no effect. Further development of the process stops after the first injection, normalizes body temperature, the subjective symptoms disappear. Regression process continues and subjective complaints disappear after second and third injection, the process is completely eliminated after the fourth injection. Relapse duration, on average 2-3 times shorter. In half of patients relapse does not appear in the next 6 months	Side effects are manifested in some patients in the form of temporary fever, often after the first injection. In three patients the temperature rose to 39 ° C, in 9 was subfebrile. Sometimes t ^o reaction occurs after second injection, but no later. No other side effects were observed. Clinical and biochemical analyzes showed no deviations from the norm	Larifan by subcutaneous injection provides a pronounced therapeutic effect in patients with recurrent herpes infection; The drug was well tolerated. In some patients there was a transient increase in body temperature; Larifan by its therapeutic activity is superior to other comparable antiviral drugs
<i>Severe recurrent herpes infection</i>							
Reports on clinical trials at the Department of Dermatology of the Kiev Institute of Postgraduate Medical, 1989	Severe recurrent herpes infection with itching, pain, burning sensation, fatigue, and weakness.	Injection form, 10 mg administered s/c, at an interval of three days.	17 patients with relapses 1 - 2 times a month. Duration of the disease before treatment till 8 years	Regimen: 4 doses with the three-day Examinations: Evaluation of dynamics of objective and subjective symptoms after each subsequent injection	Further development of the process stops after the first injection. Convalescence continues after second and third injection, the process is completely eliminated after the fourth injection.	In three of the patients after the second injection was observed transient increase in body temperature (up to 38 ° C), which gone without the use of medication. No other side effects were observed. Haematological parameters without changes	Subcutaneous injection of Larifan cause pronounced therapeutic effect in cases of recurrent herpesvirus infection and prevents the occurrence of a new relapse. The drug is not toxic and does not cause side effects

Viral infections of the neural system

<p>G.Feldmane, A.Volrate, E.Krike, G.Enina, G.Laganovska, I.Logina, A.Zilevica. Clinical utility of an interferon inducer Larifan. European Society for Clinical Virology Progress in Clinical Virology, Bologna, Itali, 1997, 203.</p>	<p>Viral infections of the neural system: tick-borne encephalitis and varicella zoster viruses caused neurological symptoms - fever, meningeal syndromes, ganglionits</p>	<p>Injection form, 5 - 10 mg , given s/c, once a day, 3 – 4 days at an interval of three days.</p>	<p>24 patients. Age range 15 to 63 years. 18 patients with tick-borne encephalitis, (1st and 2nd stage), 6– varicella zoster, CMV</p>	<p>Regimen: s/c inj. 3-4 times at an interval off three days. Evaluation of objective and subjective symptoms</p>	<p>In tick-borne encephalitis and serous meningitis patients - significant acceleration (2x) of liquor sanation, fast normalization of body temperature, rapid disappearance of meningeal syndrome. In varicella zoster patients - stops the formation of eruption, reduces period of eruption and pain, greatly accelerates the time of treatment. Marked increase in the level of interferon is observed in the blood serum.</p>	<p>In three cases a transient increase in body temperature is observed. No other side effects were observed.</p>	<p>Larifan is an important drug in the treatment of neuroinfection of viral etiology (if the treatment is carried out during the period of viraemia)</p>
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Herpes simplex ceratoconjunctivitis

<p>G.Feldmane, A.Volrate, E.Krike, G.Enina, G.Laganovska, I.Logina, A.Zilevica. Clinical utility of an interferon inducer Larifan. European Society for Clinical Virology Progress in Clinical Virology, Bologna, Itali, 1997, 203.</p>	<p>Herpes simplex ceratoconjunctivitis</p>	<p>Injection form, 0.1%, 0.2 ml, once subconjunctival.</p>	<p>12 patients (10 men ,2 women), age range 19 – 47 years. Three months before starting Larifan therapy, patients did not receive any other antiviral therapy.</p>	<p>Patients received 0.2 ml of 0.1% subconjunctival Larifan injection one time per day. The 10 control group patients used 3% acyclovir ointment 5 times a day . Estimation – epithelization of the cornea.</p>	<p>Very fast epithelialization of the cornea, during 1-2 days. In the control group average 5 days</p>	<p>Transient turgid and irritation of the conjunctiva</p>	<p>In this study larifan was very effective in treating ceratoconjunctivitis caused by herpes simplex, because of rapid epithelization of the damaged cornea, which is important to avoid late complications.</p>
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Metastatic exudative pleuritis

<p>R. Brūvere, G. Feldmane, A. Dūks, J. Zariņa. A study of the immunomodulating action of a double-stranded RNA drug Larifan. Proc Latv. Acad. Sci. 1991, Nr. 11, p. 120-124. G. Feldmane, R. Brūvere, Ā. Volrāte, J. Zariņa. The effect of Larifan on the exudative processes in patients with metastatic pleuritis. - First International Meeting on Advances in the Knowledge of Cancer Management. June 28 to July 1, 1997. Abstracts. Viena, Austria, 1997, p. 74.</p>	<p>Metastatic exudative pleuritis after primary bronchogenic carcinoma, primary carcinoma of the breast, ovarian carcinoma, mesothelioma, hypernephroma.</p>	<p>Intrapleural administration of Larifan at a dose of 5 or 10 mg during each aspiration of exudate while the aspiration is required.</p>	<p>30 patients, (age range 32 – 80 years) with exudative pleuritis after primary bronchogenic carcinoma, primary carcinoma of the breast, ovarian carcinoma, mesothelioma, hypernephroma</p>	<p>Patients received Larifan during each aspiration of exudate. During Larifan therapy patients did not receive other anticancer drugs. Control - patients who, after aspiration of exudate did not receive anything</p>	<p>In all patients after the introduction of Larifan sharply decreased excretion of fluid in the pleural cavity after the first injection. After 3-5 introductions exudation decreased markedly facilitating a status of the patient, as well as increasing the life expectancy of these terminal patients. In sediment of exudate increased activity of tumorocidal lymphocytes is observed and over a time, malignant cells are not detected.</p>	<p>Injections of Larifan are well tolerated, no adverse effects were observed, except transient increase in body temperature in 3 cases.</p>	<p>Intrapleural introduction of Larifan in patients with metastatic exudative pleuritis substantially facilitates a status of the patient, improves quality of life and increases its duration. The observed effect is based on immune cell activation</p>
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Trial of the tolerability and harmlessness

<p>G.Ya.Feldmane, B.K.Kipena, et al. Clinical safety and tolerability of larifan in cancer patients. Collection of articles "Study of interferon inductor - double-stranded RNA in various biological systems" Riga 1989 141 – 147, 1987 - 1989</p>	<p>Trial of the tolerability and harmlessness of Larifan injection during repetitive and prolonged use of the drug 1987 – 1989</p>	<p>Subcutaneous injections at a doses 10.0, 5.0, 2.5 mg</p>	<p>75 patients, patients (24 men ,51 women), Age range 15 to 75 years. Dg – ca gl. mammae,, Ca rectu, melanoma, Sa.</p>	<p>S/c injections at doses of 10 mg, 5 mg, at least 2.5 mg. In the course 4 injections at monthly intervals. Courses of treatment continued from a few to 10 months. Side effects, and results of clinical and biochemical tests were evaluated</p>	<p>The transient increase in body temperature up to 37.2 - 38 0C (rarely up to 39 ° C) in 4%, fever – 1.9 %, headache – 1 %, hypotension - 1%. Clinical and biochemical tests were within the physiological range and does not change during prolonged use of Larifan. Observations of the stabilization process of cancer, as well as the direct antitumoral impact were collected at the same time.</p>	<p>Side effects - the transient increase in body temperature, fever, headache, hypotension. They does not cumulate with repeated administration of the drug</p>	<p>The study results indicate good tolerability and safety of Larifan injection not only at short-term (using larifan as antiviral drug), but also at long-term use of the drug. Serious and severe side effects were observed.</p>
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Different pathologies

<p>Clinical study results of Larifan reviewed by profesor Muceniec A. R.Malickaite. Immunomodulation of the secondary immunodeficiencies. Dissertation for the Medical Science Doctor's degree. Heart Surgery Clinic of Vilnius University. G. Feldmane, Ā. Volrāte, I. Logina, G. Lagonovska, J. Bikova, T. Mileiko. Antiviral activity of Lariphana - a double-stranded RNA: clinical studies. Xth International Congress of Virology, Jerusalem, Israel, 11-16 august, 1996, p. 196, Abstr. PW 32-28. Zilevica A., Ancupane I., Erenpreiss J., Miltins A., Feldmane G., Efficacy of a new antiviral drug Lariphana in the treatment of urogenital infections Abstract Book of XI th International Congress of Virology 9 - 13 August 1999. Sydney Australia p. 310. S. Garjane, G. Feldmane, I.Cema "Larifan and its application in Dentistry." Poster presentation 1. Nordic- Baltic Oral Medicine Conference. "2007.16.-18.08.Abstacts, Malmo, Sweden I.Cema, S. Garjane, G.Feldmane, I.Saveja, A. Vidzis: "Drugs developed in Latvia: Application in Oral Medicine." Stomatologija-Baltic Dental and Maxillo-facial Journal., 2007/suppl 1(4), p 56</p>	<p>Larifan injection and other forms at different pathologies. 1987 - 1999 years</p>	<p>Injection form, 2.5 - 5 - 10 mg with different dosage regimens</p>	<p>Patients with oncopathology (155), patients with STD and virus infections, with prostatitis, mastitis, oophoritis, purulent inflammation of the skin, a.o.. (188 patients)</p>	<p>Repeated use, dosage regimen depends on the each pathology</p>	<p>The treatment of patients with different pathologies simultaneously creates their resistance against viral infections, including influenza. There are changes in the immunological status of tumor patients – mild immunoactivation , particularly of T-system, prevention of secondary immunodeficiency induced by traditional cancer therapies. The treatment of STD patients and patients with bacterial infections stabilize effect of antibacterial therapy due to activation of phagocytosis, Conclusively proven tolerability and harmlessness of larifan</p>		<p>Detected pronounced therapeutic effect of Larifan injections in viral infections. In oncologic patients prevents secondary immunodeficiency caused by conventional methods of anticancer therapy. In some patients transient increase in body temperature is observed, apparently associated with the induction of pyrogenic cytokines that is typical for dsRNA structures. Over a 10-year period (1989-1999.) in various clinics there were not found dose dependency (even a 4-fold increase in dose) or in respect of a therapeutic effect, or in respect of safety and tolerability.</p>
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SUMMARY DATA ON THE CLINICAL EFFICACY OF LARIFAN OINTMENT 0.05%

OVERVIEW TABLE OF CLINICAL STUDIES

The name of the medical institution	Time of the study	Diagnosis	The number of patients
Clinic for skin diseases of 1st Moscow Medical Institute	1988	Recurrent herpes	52
Laboratory for the study of reparative processes in the skin of the 1st Moscow Medical Institute	1989	Recurrent herpes	52
Specialized outpatients hospital of dermatovenereology of the Republic of Lithuania	1992	Herpes,	30
		Warts, Genital warts,	15
		Lichen ruber planus	5
Department of dermatology Riga Medical Institute		Verruca vulgares	61
		Herpes simplex labialis,	21
		Herpes simplex progenitalis,	58
		Herpes zoster	9
Department of dermatology Riga Medical Institute, Specialized outpatients hospital of dermatovenereology of Riga City	1985 - 1988	Genital warts,	11
		Balanoposthitis,	12
		Lichen ruber planus	15
Riga City Specialized outpatients hospital of Dermatovenereology	1988 - 1991	Herpes	88
		Warts	33
Republican Specialized outpatients hospital of dermatovenereology of the Republic of Latvia	1986 - 1991	Herpes,	53
		Warts, genital warts	30
Latvian Medical Academy, Department of eye diseases	1999	Dendroid herpetic ceratitis	30

SUMMARY OF CLINICAL DATA

References	Indications studied	Dosage range, posology and dosage form	Patient characteristics	Study design	Main results	Side effects	Conclusions
<i>Severe recurrent herpes infection</i>							
Reports on clinical trials of the 1st Moscow Medical Institute, 1988	Recurrent herpes infection, with often relapses, with changes in the general health condition - fever, increased body temperature, weakness, fatigue, headache, ganglio radiculoneuritis	Larifan ointment 0.05% . Ointment was applied to the lesions 3 - 4 times per day.	52 patients (36 men and 16 women). Age range 18 to 67 years. The relapse rate - from 1 to 3 times per month. The duration of the disease prior to initiating therapy from 6 months to 20 years. Localization of the process: herpes proenitalis, herpes glutealis, herpes labialis et facialis, disseminated herpes. In 13 patients changes in the general health condition - fever, increased body temperature, weakness, fatigue, in 6 patients, - ganglio radiculoneuritis	administration schedule - ointment was applied to the lesions 3 - 4 times per day. The criteria for evaluating the effectiveness of therapy - subjective sensations, regression and extinction of vesicular rash, the duration of the next relapse, severity of symptoms. The ointment administered to complete disappearance of lesions	Application during the precursors of relapse eliminate pain, itching and burning at the site of injury, relieves inflammation and stops the formation of eruption in 8 – 12 hours. Applications on the first 1 to 2 days t relieves pain, itching and burning at the site of injury in 8 to 12 hours. It reduces fatigue, weakness. vesicles regress 2 times faster (27 patients) and 4 - 5 days earlier (13 patients) normal timing. Used on the third day of the relapse it does not influence conventional terms of recovery.	Adverse effects with Larifan ointment was not observed. The drug was well tolerated	Larifan ointment 0.05% has a therapeutic effect in patients with recurrent herpes when used in the early days of the disease. Adverse effects with ointment are not noted
<i>Recurrent herpes infection</i>							
Reports on clinical trials in a laboratory for the study of reparative processes in the skin of the 1st Moscow Medical Institute, 1989	Recurrent herpes infection	Larifan ointment 0.05%	52 patients with severe herpes infections, with continuous relapsing . 20 men, 25 women, 7 children. Age range 8 to 65 years. Localization of the process: herpes zoster (17), herpes simplex (19), herpes labialis (11), herpes nasalis (5).	Larifan ointment was applied to the lesions 3 - 4 times a day.	The therapeutic effect depends on the time of initiation of treatment. Ointment application at the very beginning of the process stops the further development, rash, erosion do not appear. Used at the culmination of an outbreak, ointment does not suspend the process - it takes place, but in a more "erased" form. In 20% of patients (11/52) for one year of observation found recurrence of disease but in a mild form	No side effects have been observed	Larifan treatment not cause a shift in terms of clinical and biochemical analyzes. Clinicians evaluate the results obtained very positive.

Viral dermatoses

<p>Review from Specialized outpatients hospital of dermatovenereology of the Republic of Lithuania, 1992</p>	<p>Viral dermatoses</p>	<p>Larifan ointment 0.05%</p>	<p>50 patients. The patients' age from 19 to 78 years. Diagnosis: Herpes labialis (13), herpes progenitalis (8), herpes zoster (9), Verrucae vulgaris et planae (12), Condyloma acuminata (3), Lichen ruber planus (5)</p>	<p>The ointment was used to damage 3 - 4 times per day until the defect has disappeared.</p>	<p>Patients with disorders caused by the herpes virus: 1) in the first day after the beginning of treatment disappeared subjective disorders 2) 5 - 7 days to reduce the term of rash (with Herpes zoster), 3) during the observation period no recurrences were observed. A 100% therapeutic effect was observed in the treatment of damage caused by the papilloma virus - warts and condylomas. When treating patients with Lichen ruber planus both subjective objective disorder decreased since the 3rd day. Complete recovery was observed after: Herpes simplex (12days), herpes zoster (18 –22 days), Verrucae vulgaris et planae (3 – 4 weeks), Condyloma acuminata (4-5 weeks), Lichen ruber planus (3-6 weeks)</p>	<p>No side effects have been observed</p>	<p>The use of Larifan ointment 0.05% gives pronounced therapeutic effect in the treatment of patients with viral dermatoses</p>
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Condylomae, Balanopostitis, Lichen ruber planus

<p>Reviews of clinicians from Department of dermatology Riga Medical Institute and Specialized dermatovenereology outpatients hospital of Riga City, 1985 - 1988</p>	<p>Condylomae, Balanopostitis, Lichen ruber planus</p>	<p>Larifan ointment 0.05%</p>	<p>38 patients with Condylomae(11), Balanopostitis (12), Lichen ruber planus (15). All patients before applying Larifan ointment long and unsuccessfully treated with other conventional methods. In 5 patients with Condyloma acuminata ointment treatment combined with electrocoagulation.</p>	<p>Patients received ointment on average 1-2 times per day</p>	<p>Medical professionals therapy with larifan ointment are appreciated as successful</p>	<p>No side effects have been observed</p>	<p>Larifan ointment application was effective for the treatment of patients with Lichen ruber planus, Condyloma acuminata and Balanopostitis vulgaris, before unsuccessfully treated by conventional methods The treatment rejected relapse within 2 years.</p>
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Viral dermatoses

<p>Department of dermatology, Riga Medical Institute</p> <p>Dz.Branta, G..Feldmane. The results of the application of double-stranded RNA in viral skin diseases. In collection of articles "The study of interferon inductor - double-stranded RNA in various biological systems " Riga 1989, 138 – 140. RU</p>	<p>Viral dermatoses</p>	<p>Larifan ointment 0.05%</p>	<p>149 patients with verrucae vulgares (61), herpes labialis (21), Herpes progenitalis (58), Herpes zoster (9) Age range 12 – 52 years</p>	<p>Ointment is used 1-3 times a day in the form of an occlusive compress, at the herpes labialis treatment begins in pre-eruptive period and continues in remission, at the herpes progenitalis - 3 to 4 weeks.</p>	<p>Warts disappear in 3 week – 1.5 month. With herpes zoster - removes pain and shortens the rash period of 5 -7 days. After repeated courses of treatment relapses no longer appears</p>	<p>The drug was well tolerated. Blood and urine analysis without deviations. In 40% of patients a small, transient lymphocytosis was observed</p>	<p>Larifan ointment used by occlusive method gives a marked effect on viral dermatoses</p>
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Viral dermatoses

<p>Reviews of clinicians of Riga City Specialized outpatients hospital of Dermatovenereology 1988 – 1991.</p> <p>Г.Я.Фелдмане, М.Р.Акерс, Р.Ж.Брувере, А.Э.Дук А.Х.Буйкис, Б.К.Кипена, Влияние индуктора интерферона на пролиферативные процессы у людей В сборнике «Неспецифические стимуляторы в иммунотерапии опухолей». Рига 1985, 205-209 G. Feldmane, Ā. Volrāte, I. Logina, G. Lagonovska, J. Bikova, T. Mileiko. Antiviral activity of Lariphān - a double-stranded RNA: clinical studies. Xth International Congress of Virology, Jerusalem, Israel, 11-16 august, 1996, p. 196, Abstr. PW 32-28.</p>	<p>Viral dermatoses</p>	<p>Larifan ointment 0.05%</p>	<p>121 patient, age range 15 – 71year, (men72, women 49). Relapse rate 2-10 times per year. Dg: Herpes labialis (31), Herpes progenitalis (57), Verrucae, Condyroma (33).</p>	<p>Ointment was applied twice a day, 1-3 weeks or more, patients started on treatment in the second day of illness, part on 3 - 4 days.</p>	<p>Subjective disorders disappear in the 2 - 3 day, eruption ceases at 1 - 3 day, regression comes on day 5 -6, recovery on 7 - 14 days. Reduce the number of relapses. Complete recovery of warts (vulgar, genital) in 30 of 33</p>	<p>No side effects have been observed</p>	<p>The high therapeutic efficacy of Larifan ointment is observed in the treatment of viral dermatosis. Therapeutic activity of Larifan is considerably higher as of other antiviral ointments.</p>
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Herpes simplex labialis, facialis et progenitalis, Verrucae vulgares, Condyloma acuminatum

<p>Republican Specialized outpatients hospital of dermatovenereology of the Republic of Latvia, 1986 – 1991</p> <p>Г.Я.Фелдмане, М.Р.Акерс, Р.Ж.Брувере, А.Э.Дук А.Х.Буйкис, Б.К.Кипена, Влияние индуктора интерферона на пролиферативные процессы у людей В сборнике «Неспецифические стимуляторы в иммунотерапии опухолей». Рига 1985, 205-209</p> <p>G. Feldmane, Ā. Volrāte, I. Logina, G. Lagonovska, J. Bikova, T. Mileiko. Antiviral activity of Lariphphan - a double-stranded RNA: clinical studies. Xth International Congress of Virology, Jerusalem, Israel, 11-16 august, 1996, p. 196, Abstr. PW 32-28.</p>	<p>Herpes simplex labialis, facialis et progenitalis, Verrucae vulgares, Condyloma acuminatum</p>	<p>Larifan ointment 0.05%</p>	<p>83 patients Age range 18 - 63 years (men 53, women 30). Dg. herpes simplex (53), Verrucae vulgares (17), Condyloma acc. (13).</p>	<p>Applications performed twice daily by occlusive method for 1-3 weeks or longer, depending on the diagnosis. Treatment started 2 - 3 days after the rash appears, but in pretreated - in the prodrome. In recurrent herpes treatment was continued for another 2 weeks.</p>	<p>Herpes infection - subjective disorder is reduced in 2 - 3 days. The duration of the eruption is reduced in all patients. The recurrence rate sharply reduced, the existing go on in the "erased" form. In 15 patients (out of 53) relapses not appeared in 3 years. Papilloma virus infection – the complete disappearance of warts in 15 patients from 17. Genital warts - fully cured patients in the initial stages (5), in advanced cases (8) combining with physical therapy</p>	<p>No side effects have been observed</p>	<p>Larifan ointment 0.05% is effective in treatment of viral dermatoses</p>
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Dendroid herpetic ceratitis

<p>Г.А.Лагановска, И.В.Валькова, Г.Я.Фелдмане. К вопросу о лечении герпетического кератита. Офтальмологический Журнал, Одесса, 1999, 26 102 – 105.</p>	<p>Dendroid herpetic ceratitis</p>	<p>Larifan ointment 0.05%</p>	<p>75 patients divided in 5 groups</p>	<p>Randomized trial. Antiviral ointments (acyclovir or larifan were applied three times a day. Treatment were performed with or without removal of damaged corneal epithelium.</p>	<p>Antiviral ointments with preceding removal of epithelium has a good th effect</p>	<p>No side effects have been observed</p>	<p>Larifan ointment has a good antiherpetic effect in dendroid ceratitis.</p>
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DATA ON THE CLINICAL EFFICACY OF LARIFAN SUPPOSITORIES 4.0 mg

References	Pathological process	Dosage range, posology and dosage form	Patient characteristics	Study design	Main results	Side effects	Conclusions
<i>Recurrent herpes infection</i>							
Guna Feldmane, Evita Niedrite "Anti-Herpetic Therapeutic: A New Approach to Treatment of Herpes Infection" BIT Life Sciences 1st Annual World Summit of Antivirals, July 20-22, 2008, Kunming, China	Recurrent herpes infection.	Suppositories form, 4 mg, the course – 25 doses during 26 weeks	30 patients (12 men and 18 women). Age range 18 to 50 years. The recurrence rate of 6 to 24 times per year. The duration of disease before treatment from 12 months to 18 years. Distribution of patients according to the localization of process: Herpes labialis 14 patients, Herpes progenitalis -9, Herpes facialis -6, Herpes zoster -1	Application scheme - 5 courses between them 4 week intervals. In each course 5 suppositories, one for 1st, 2nd, 6 th, 10 th and 14 th day. The clinical efficacy and tolerance of the method was investigated. Regular control of the clinical, biochemical and immunological analyzes was performed. The criterion for evaluating efficacy was the change in the clinical course of the disease and the number of relapses in the period of observation. The observation period - 1 year.	Half of the patients achieved a complete therapeutic effect, ie, disease-free period for a year or more. In neither case was not complete lack of efficacy. Recurrences that occur during and after treatment, are mild. The mean number of relapses per group after the treatment is reduced by 10 times. Clinical and biochemical parameters tested during and after treatment remained within normal limits. An increased level of interferon in blood serum was observed	Treatment is well tolerated, undesirable side effects have not been found.	Results demonstrate the high therapeutic efficacy of the suppositories "Larifan Supo 4,0 mg" applied by this regimen. In the clinical efficacy treatment with the use of Larifan Supo 4,0 mg is superior to other currently applied methods of antiherpetic therapy

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