# Larifan Injection

## Official Product Information

Complete prescribing information for Larifans 2.5 mg/2 ml solution for injections, including therapeutic indications, dosage, administration, and safety data.

# Product Overview and Clinical Information

### Name of the Medicinal Product

Larifans 2.5 mg/2 ml solution for injections

### Qualitative and Quantitative Composition

**Active substance:** One injection vial contains 2.5 mg of double-stranded ribonucleic acid (Acidum ribonucleinicum duplicatum).

**Excipient:** 0.9% (isotonic) sodium chloride solution for injection.

### Pharmaceutical Form

Colourless solution for injection.

# Clinical Information

## 4.1 Therapeutic Indications

- Recurrent herpesvirus infection of various locations.
- Secondary immunodeficiency of any etiology, including those induced by tumour therapy.

## 4.2 Dosage and Method of Administration

Larifan, after thawing and warming to room temperature, is administered subcutaneously.

### For recurrent herpesvirus infection:

2.5 mg once daily, four times with a 3-day interval.

### For immunodeficiency treatment:

Course of 2.5 mg once daily, four times at weekly intervals, courses repeated after a 1- or 2-month break.

**Important:** Data for paediatric use are limited; therefore, use in children is not recommended.

Clinical experience indicates no dose adjustment is required for elderly patients.

Clinical trial data do not suggest adverse effects on liver function, so dose adjustment for liver impairment is not necessary.

Clinical trial data do not indicate adverse effects on renal function.

Patients with a history of autoimmune diseases may use Larifan at physician discretion.

## 4.3 Contraindications

- Hypersensitivity to the active substance.
- Severe renal disease.
- Pregnancy and lactation.

## 4.4 Special Warnings and Precautions

Caution in patients with a history of allergic reactions and autoimmune diseases.

## 4.5 Drug Interactions and Other Forms of Interaction

It is not recommended to use Larifan concurrently with interferon or other cytokine medicines, as combined use may enhance the risk of adverse effects.

Concurrent use with corticosteroids is not recommended, as they may diminish Larifan's effectiveness.

## 4.6 Pregnancy and Lactation

No studies have been conducted in pregnant women or breastfeeding mothers, and it is unknown if the drug is excreted in breast milk, therefore its use is not recommended during pregnancy or lactation.

If, in the opinion of the physician, Larifan use is strictly necessary, breastfeeding should be discontinued during treatment.

Animal experiments on Larifan excretion in milk do not reflect data in women, as the enzyme ribonuclease III, which specifically cleaves double-stranded RNA, is present only in primates and not in lower mammals.

## 4.7 Effects on Ability to Drive and Use Machines

No effects on the ability to drive or operate machinery have been observed.

Patients who experience adverse reactions—fever, headache, hypotension—should exercise caution.

## 4.8 Undesirable Effects

Frequently observed: transient, short-term increase in body temperature; less frequently, fever and headache; very rarely, arterial hypotension, skin itching.

**Frequency classification:** very common (≥1/10), common (≥1/100 to <1/10), less common (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), unknown (cannot be estimated from available data).

Table 1. Adverse Effects Observed in Clinical Studies with Larifans 2.5 mg Solution for Injection:

| System Organ Class | Frequency | Adverse Event |
|---|---|---|
| Immune system reactions | Common | Transient increase in body temperature |
| | Less common | Fever |
| Nervous system disorders | Less common | Headache |
| Vascular disorders | Very rare | Hypotension |
| Skin and subcutaneous | Very rare | Skin itching |

## 4.9 Overdose

No cases of overdose have been reported.

High doses may lead to more pronounced adverse effects as above. Administration of antipyretic agents, antihistamines, and vasotonic agents is justified if hypotension occurs.

# Pharmacological Properties and Product Information

## 5. Pharmacological Properties

### 5.1 Pharmacodynamic Properties

**Pharmacotherapeutic group:** Immunostimulant. **ATC code:** L03AX.

Larifan is a naturally-derived double-stranded ribonucleic acid (dsRNA) isolated from Escherichia coli cells infected with bacteriophage.

Larifan exhibits pleiotropic biological activities such as interferon induction, antiviral, immunomodulatory, antitumour, and antimutagenic effects.

#### Interferon-inducing activity

Proven in both humans and animals. Induced interferon titres and dynamics depend on the route of administration: in human serum, interferon is detected 10 hours after rectal suppository, 6–10 hours after subcutaneous or intramuscular injection, and as early as 2 hours after aerosol administration.

#### Antiviral effects

Like interferon, Larifan can be considered a universal antiviral agent disrupting virus replication at common stages for all viruses. Antiviral effects observed both in vitro and in vivo (herpes, influenza, tick-borne encephalitis, encephalomyocarditis, Semliki, Sindbis, Venezuelan encephalitis, Aujeszky's, rabies, and other viruses).

#### Additional effects

Inhibitory effect on experimental chlamydial infection in mice was observed. Antitumour effects demonstrated in various experimental tumour models. Immunomodulatory activity recorded with both local and parenteral administration. Antimutagenic action registered in special systems.

Human conjunctival washings show significant increase in alpha interferon titres 4 hours after Larifan ointment application.

Preclinical studies show that Larifan is not carcinogenic, mutagenic, locally irritating, or allergenic.

### 5.2 Pharmacokinetic Properties

In the organism, ribonucleic acids are subject to the action of ribonucleases (RNases). Widely distributed RNases easily break down single-stranded RNA and, to some extent, dsRNA. Only RNase III specifically cleaves dsRNA, and it is characteristic of primates only.

In humans, RNase III degrades dsRNA to oligonucleotides within minutes, indistinguishable from normal metabolites; free dsRNA in human serum rapidly loses interferon-inducing activity, and its breakdown products are biologically inert.

Temperature rise after Larifan reflects individual response and can vary; the response is related to pyrogenic cytokine production, mainly interferon.

### 5.3 Preclinical Safety Data

Standard preclinical studies on pharmacological safety, repeated-dose toxicity, and carcinogenicity do not indicate any special risks for humans. Mutagenicity studies show no mutagenic properties.

**Reproductive toxicity:** high doses caused reduced embryo numbers and preimplantation mortality in rats; doses used greatly exceeded human therapeutic range.

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## 6. Pharmaceutical Information

### 6.1 List of Excipients

- Sodium chloride
- Water for injections

### 6.2 Incompatibilities

The product should not be mixed in a single syringe with other medicines or solutions.

### 6.3 Shelf Life

Frozen solution: 3 years

### 6.4 Special Precautions for Storage

Store Larifan solution in a freezer (temperature not above –18 to –20 °C; no minimum temperature specified).

### 6.5 Packaging Type and Content

Colourless glass vial (glass type BK 1-2), with rubber stopper, aluminium cap, and removable white polypropylene cover. Each vial contains 2 ml solution. Carton box contains one vial.

### 6.6 Instructions for Preparation and Disposal

Thaw Larifan shortly before use and warm to room temperature. Once thawed, may be kept refrigerated for up to 72 hours; any unused solution after this time is the user's responsibility. Any unused medicine or waste material should be disposed of in accordance with local requirements.

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## 7. Marketing Authorisation Holder

SIA "Larifāns"
Kurbada street 2b
Riga, LV-1009
Latvia

#### Marketing Authorisation Number

04-0230

#### Date of Registration

29.04.2004

# Larifans 2,5 mg/2ml solution for injection - Introduction

1

## Therapeutic Category & Active Substance

The drug “Larifan 2.5 mg / 2 ml solution for injection” belongs to the therapeutic category - antiviral and immunomodulating agents. The active substance is a double-stranded ribonucleic acid (dsRNA) of biological origin, obtained biotechnologically from E. coli bacteria infected with a bacteriophage. This specific form of RNA is formed during bacteriophage multiplication as a transient replicative intermediate. The commercial name of the active substance is Larifan.

2

## Mechanism of Action: Interferon Induction

dsRNA-Larifan induces the formation of interferon in the body. The effect of the drug is determined by the induced interferon, as well as the activity of the dsRNA molecule itself. The fact that the action occurs through interferon causes a wide range of antiviral effects of the drug. In the experimental systems, all viruses that were still being studied were sensitive.

# Antiviral Spectrum

## Broad Spectrum

The antiviral spectrum of dsRNA-Larifan is very broad (tick-borne encephalitis, encephalomyocarditis, horse encephalomyelitis, Sindbis, Semiliki, rabies and other viruses).

## Clinical Experience

Clinical experience so far has shown pronounced antiviral activity mainly with herpes and papillomas, as well as infections caused by respiratory viruses, including influenza.

# Oncology Applications

### Experimental Tumor Models

Data obtained in experimental tumor models showed inhibition of the growth of primary tumors under the influence of dsRNA-Larifan and, especially, on the metastasis of malignant tumors.

### Clinical Observations

In the oncology clinic, a therapeutic effect was observed with basal cell carcinomas, good results were obtained with metastatic pleurisy and peritonitis.

### Immunotherapy Potential

Larifan is especially promising for immunotherapy for malignant neoplasms, since at the same time it is an antitumor agent and an immunomodulator.

# Immunological Effects

### Primary Immunogenesis

dsRNA-Larifan activates primary immunogenesis, which is inhibited during oncopathology.

### T-cell & NK-cell Activation

dsRNA-Larifan directly activates T cells, NK cells, gives an immunoadjuvant effect.

### Gene Expression

There are indications to the expression of certain genes what are important in the implementation of antitumor immunity.

# LARIFAN's Impact On Immunologically Significant Parameters

## Key Immunological Effects

Larifan significantly modulates various immunologically significant parameters, as detailed below:

## Induced Factors

1

### Chemokines

- Macrophage inflammatory protein 1β
- I-309
- TARC

2

### Proinflammatory Cytokines

- IL-6
- Tumor necrosis factor -α
- Granulocyte macrophage colony-stimulating factor

3

### Anti-inflammatory

- IL-10

4

### Cellular Immunity Mediators

- IL-23
- Interferon-γ

## Suppressed Factors

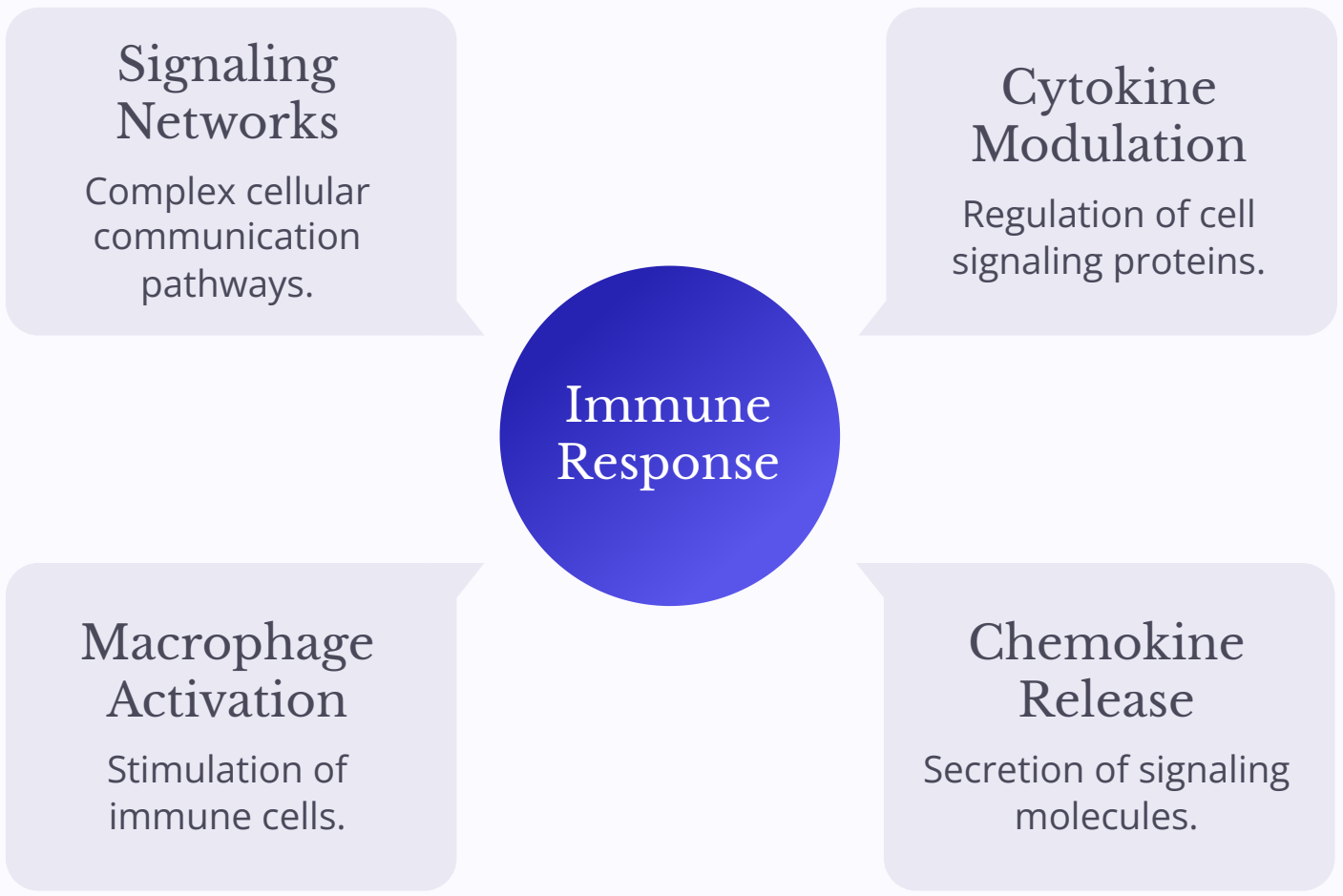
IL-16

Chemokine stromal cell-derived factor 1 a+b

Interferon gamma-induced protein 10

## Pleiotropic Effect on Immune Response

The observed network of molecules responding to the presence of Larifan reveals the profound pleiotropic effect this product exerts on the immune response.




*Ex vivo cytokine production in peripheral blood mononuclear cells after their stimulation with dsRNA of natural origin (2014) Veinalde R., Petrovska R., Brūvere R., Feldmane G., Pjanova D.

# Larifans 2,5 mg/2ml solution for injection*

| | |
|---|---|
| **Medicinal product name** | **Larifans 2.5 mg/2 ml solution for injection** |
| **Pharmaceutical form** | **Solution for injection** |
| **Strength** | **2.5 mg/2 ml** |
| **Legal status** | **Rx Prescription (Pr.)** |
| **ATC code** | **L03AX – *Immunostimulants*** |
| **Marketing authorization No.** | **04-0230** |

*Medicinal Product Register Of Latvia – State Medicines Agency of Republic Of Latvia (2025) **Latvijas Zāļu reģistrs**

# Effectiveness of LARIFAN In The Experimental Form Severe Acute Respiratory Syndrome

## Study Overview

Studies have been carried out to study the effectiveness of the high-molecular inducer of interferon Larifan® in relation to the experimental form of severe acute respiratory syndrome in Syrian hamsters.

## Treatment Schemes

### Preventive Scheme

Larifan® is effective when applied as a prophylactic measure before exposure to the virus.

### Emergency Prevention Scheme

Larifan® is also effective for immediate intervention following potential exposure.

## Therapeutic Effectiveness

The following coefficients of therapeutic action highlight Larifan's effectiveness across key parameters:


### Virological & Hematological Parameters

(ð<0,01)


### Biochemical Parameters

(ð<0,01)

*Studying the Effectiveness of Lariphan® in the Experimental Form Severe Acute Respiratory Syndrome (2019) S. YA. LOGINOVA, V. N. SHCHUKINA, *S. V. BORISEVICH, R. A. HAMITOV, V. A. MAKSIMOV

# Larifan's Antiviral Activity Against SARS-CoV-2

Presence of Larifan reduces the replication of SARS CoV-2 both in vitro, in Calu3 cells and HSAEC, and in vivo in the SARS-CoV-2 infection model of golden Syrian hamsters.

## Antiviral Activity Overview

Larifan's potent antiviral activity significantly reduces the viral RNA copy number of SARS-CoV-2 across various experimental settings. This indicates its potential in combating viral replication in both cellular and organismal contexts.

## Research Results

### In Vitro Effects

Larifan demonstrates a reduction in SARS-CoV-2 replication in cell cultures, specifically in:

- Calu3 cells
- Human Small Airway Epithelial Cells (HSAEC)

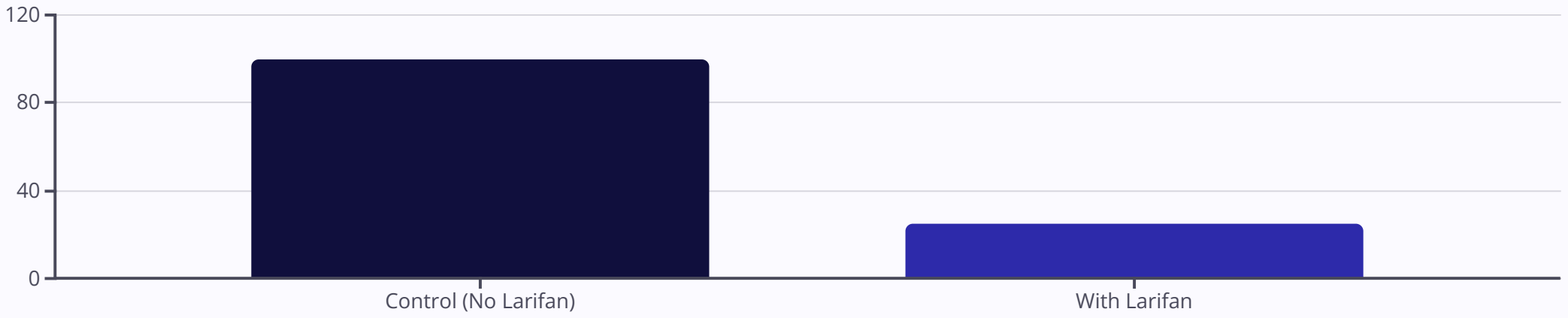
### In Vivo Effects

In animal models, Larifan effectively reduces the viral RNA copy number within the:

- SARS-CoV-2 infection model of golden Syrian hamsters

## Viral RNA Copy Number Reduction

The chart below illustrates the significant drop in SARS-CoV-2 viral RNA copy numbers observed in experimental conditions with the presence of Larifan, highlighting its efficacy in inhibiting viral replication.




*Bacteriophage-Derived Double-Stranded RNA Exerts Anti-SARS-CoV-2 Activity In Vitro and in Golden Syrian Hamsters In Vivo (2022) Kristine Vaivode, Irina Verhovcova, Dace Skrastina, Ramona Petrovska, Madara Kreismane, Daira Lapse, Zane Kalnina, Kristine Salmina, Diana Rubene and Dace Pjanova.

DOUBLE-STRANDED-dsRNA-LARIFAN-IN-MEDICAL-PRACTICE (1).pdf

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