Summary of product characteristics

(Unofficial translation, Abbreviated version)

1. NAME OF THE MEDICINAL PRODUCT

RIGVIR solution for injection
RIGVIR ECHO –7 virus strain

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 2 ml solution for injection contains virus Rigvir
titre $\geq 10^6$ $TCID_{50}$/ml ($10^6 – 10^8$ $TCID_{50}$/ml).

Active substance – Rigvir (ECHO-7 virus strain)
Gender Picornaviridae, genus Enterovirus, ECHO group, type 7

Excipient with known effect: 2 ml solution for injection contains 0.3 mmol (7 mg) sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Post thawing the solution is clear, colourless or with a slightly pink hue.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rigvir as immunomodulator with viral nature with anti-tumour effect is used in the treatment of melanoma, local treatment of skin and subcutaneous metastases of melanoma, for prevention of relapse and metastasis after radical surgery.

4.2. Posology and method of administration

For prevention of relapse and metastasis of melanoma after radical surgery
If the lymph nodes are extirpated, use 4 intensive courses
For local treatment of cutaneous and subcutaneous melanoma metastases

In order to assess the application of Rigvir for normalization and activation of the immune system, it is essential to determine the patient's immune status and course of disease process following the classic evaluation parameters, before Rigvir therapy is initiated. It requires regular control of blood count and immunological parameters. Immunity changes during the disease. In the early stage an immunoactivation process is ongoing in which all phases of the immune system are involved. Leukopoesis, especially lymphopoesis, is stimulated. A very significant primary immunogenesis takes place in lymphoid tissues and lymph nodes. As the process of the

disease progresses, a phase begins when all indicators in the blood count are manifested as of normalization. This phase can be even very long-termed (6-12 months). Due to infections, stress situations and other negative factors, including as a result of cancer aggressiveness, leads to a failure of the immune system in the form of hyperactivation of certain phases that can progress into total immunosuppression or nonreactivity (see. Table).

Changes	Compensation phase		Immunodyscorrelation		Immunodyscorrelation in some organs			
	Primary activation	normalization	moderate suppression	Hype-ractivation	reactive lymph nodes	lymph node metastasis	liver	lungs
↑	CD8=CD38		HLA-DR **Mo**	**Mo=Ly** CD4 CD8 < CD38 HLA-DR	**Ly** CD4 CD8 CD38 CD19 CD16 HLA-DR	**Mo**	**HLA-DR**	
N	**Ly, Mo** CD4	**Ly, Mo** CD8=CD38 HLA-DR			CD8=CD38	**Ly** CD8=CD38 HLA-DR		**Ly, Mo** HLA-DR CD19, CD16
↓			**Ly** CD8=CD38 CD4		**Mo**	CD4, CD19 CD16	**Ly , Mo** CD4 CD8<CD38 CD19 CD16	CD4 CD8>CD38
Indications for therapy with Rigvir:	post excision of the primary lesion	post excision of the primary lesion	post excision of the primary lesion	**none –** symptomatic and desintoxication therapy	post excision of the primary lesion	post lymphadenectiomia	most effectively post operational therapy	most effectively post operational therapy

Most characteristic immune status indicators for compensation phase are immune cell counts in peripheral blood, which are normal. Immunodyscorrelation is associated with some increase in the number of cells and the simultaneous decrease in the number of other cells. Positive effect of Rigvir is obtainable during the compensation phase when the primary immune system is activated or normalized and during the immunodyscorrelation - when at moderate suppression.

Paediatric population
The safety and efficacy of Rigvir in children aged up to 18 has not yet been established. No clinical studies have been performed. Rigvir is not administered to paediatric population.

Elderly patients
For elderly patients no dose adjustment is required.

Patients with renal and hepatic impairment
For patients with renal and hepatic impairment no dose adjustment is required.

4.3. Contraindications

• Do not use Rigvir during radiotherapy and chemotherapy.
• Do not use in patients with acute infectious diseases.

4.4. Special warnings and precautions for use
Post injection of Rigvir it is desirable to limit the long-term physical activity to not suppress the body's reaction to immunoactivating activity of Rigvir.

If the product has come in contact with the skin or an object, then the product is inactivated by treating the affected area with 70 % alcohol or disinfectant.

Rigvir contains less than 1 mmol sodium (23 mg) per dose, essentially Rigvir is sodium-free.

4.5. Interaction with other medicinal products and other forms of interaction
The optimal time for Rigvir use is at least 5 days before radiation and/or chemotherapy – so the immune system could create antibodies to the injected virus.

The optimal time for Rigvir use post radiotherapy and/or chemotherapy treatment is 3-4 weeks, so upon administration of Rigvir the acute radiation and/or chemotherapy-induced immunosuppression would be reduced.

It is not recommended to use Rigvr in combination with other drugs, to not suppress the body's reaction to immunoactivating activity of Rigvir.

During use of Rigvir there are no restrictions on food and beverage use, unless your doctor has prescribed a special diet.
During treatment with Rigvir, alcohol should be avoided because upon consumption of alcohol - Rigvir therapy is ineffective.

4.6. Pregnancy and breast-feeding
Data on using Rigvir in pregnancy are not available, therefore it should not be used during pregnancy unless decided by the doctor that it is absolutely necessary.

It is unknown whether Rigvir is excreted in human milk. During treatment with Rigvir the patient should not breastfeed.

4.7. Effects on ability to drive and use machines
Rigvir does not affect the ability to drive and use machines.

4.8. Undesirable effects

Frequencies of undesirable effects are defined as follows: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1 000 to <1/100), rarely (≥ 1/10 000 to <1/1 000), very rare (<1/10 000).

Body System	Very common	Common	Uncommon	Rarely	Very rare
General disorders and administration site conditions		Temp. to 37.5 ° C, short-term (1-3 days)			Pain in the area of the tumour, fatigue
Nervous system disorders					Sleepiness
Gastrointestinal disorders					Dyspepsia (diarrhoea)

Undesireble effects are short-term and don't require a special therapy.

Reporting of possible undesirable effects

It is important to report possible undesirable effects after the registration of the medicine. Thus, the benefit/risk balance of the product is continuously monitored. Healthcare professionals are asked to report any possible adverse reactions to the State Agency of Medicines, Jersikas 15, Riga, LV 1003. Phone: +371 67078400; Fax: +371 67078428.
Website: www.zva.gov.lv

4.9. Overdose

There are no reported cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: immunomodulator, ATC-code: L03AX

Mode of action

Rigvir is a viral immunomodulator of natural origin, which, due to its structurally functional organization, can act on both the immune system and the tumor cell with a multidimensional immunomodulatory and oncotropic activity.

The direct anti-tumour activity of Rigvir is due to the oncotropism and oncolysis. Cytolytic activity is selective - in regard only to malignant cells (oncolysis) completely without damaging the normal tissue cells and by encouraging specific immunity against itself, it activates the cells of immune system. It is vital that on the surface of non-lysed malignant cells Rigvir encourages the appearance of tumour associated differentiation antigen (expression) and inhibits the expression of MAGE group antigens that associated with progressive growth of melanoma. Such

abnormal malignant cell surface structures are made target structures to the cytotoxic immune mechanisms.

Immunomodulatory activity of Rigvir is related with the activation of immune cells in the lymph nodes and lymphoid tissues. Rigvir stimulates primary and secondary immunogenesis and repeals the block of local immunity generated by the tumour, by stimulating a specific immune response against self. Activating the immune response against the expressed tumour associated antigens, immunological rejection process of tumour that is apoptotic by nature takes place. As a result of successfully managed repeated use of the preparation virotherapy with Rigvir, it is possible to achieve progressive and complete regression of tumour lymph node micrometastases and subcutaneous metastases.

5.2. Pharmacokinetic properties

Rigvir selectively acts on tumour cells and specifically on immune cells. Small amounts of tumour cells are lysed for a short time as further viral reproduction and related lysis of tumour cell is blocked by the interferon induced by the virus. Henceforward Rigvir stimulates normal primary and secondary immunogenesis and repeals the block of local immunity generated by the tumour.

Rigvir increases the expression of tissue differentiation antigens associated with tumour cells, making the tumour cells in target cells of immune response, which itself has induce (incl., heterogenization).

Rigvir interacts on immune cells, activating them: blast transformation of lymphocytes occurs, activation of dendritic cells, increases in $CD4^+$, $CD8^+$, $CD38^+$ cell counts and expression of apoptosis receptors on $CD95^+$ lymphocytes. This indicates of the activation of the cytotoxic immune response.

It is conclusively proven that Rigvir does not reproduce in other organs and tissues; it is not released into the environment. The examination of the patient material (blood, urine, faeces) with virological methods for infectious virus, anti-virus antibody titre increase in the first week after administration is found in the blood. Maximum titre, which persists for a month, antibodies reach on 10-20th day after administration. In the rest of the material (urine, faeces) detection of the infectious virus fails. It is not found in the material of patient service staff.

5.3. Preclinical safety data

Action of Rigvir has been tested both in cell culture and experimental systems of animal models.

Tissue in cell cultures causes Rigvir cytolysis (oncolytic operation) of sensitive tumour cells (human malignant skin melanoma, sarcoma).

In experimental tumour systems in various animal models anti-tumour activity of Rigvir has been shown.

Preclinical data suggest that in studies with experimental animals - mice, single administered dose of the virus 0.3 ml (titre of 2×10^7 and 2×10^8), which is 50-100 times exceeds the maximum dose rate (20-40 ml) for humans showed no toxicity, LD_{50} was not detectable. Animal studies did not show mutagenicity/carcinogenicity.

Rigvir does not contain antibiotics, preservatives, stimulants, and other potentially toxic substances. Rigvir hinders formation of relapses, stimulates regression processes and prolongs survival of animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sodium chloride, water for injection. MEM medium characters: contains minerals, amino acids, vitamins.

6.2. Incompatibilities
None detected.

6.3. Shelf life
30 months.

6.4. Special storage conditions
Store in a freezer (-20 ± 2°C). To be transported frozen.

6.5. Nature and contents of container
6 ml glass vial with a rubber stopper, aluminium cap (Flip-Tear-Up System). The outer packaging - cardboard box.

6.6. Special precautions for disposal and other handling
Thaw at room temperature. Each vial contains one dose. To be used immediately. Destroy vials according to medical waste disposal requirements.

7. MARKETING AUTHORISATION HOLDER
SIA Latima, reg. Nr. LV40003056769, 9-9 Teātra street, Rīga, LV-1050, Latvia.

8. MARKETING AUTHORISATION NUMBER
04-0229