Summary of product characteristics
(Extract)

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)
Picornaviridae family, Enterovirus genus, 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 is an oncolytic virus that belongs to the group of medicines known as immunomodulators. 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
Post excision of a tumour (when the wound has healed).

Rigvir course I: for three consecutive days 2 ml are administered intramuscularly (i.m.) with respect to regional localization of the tumour to activate the regional lymph nodes.

Rigvir course II and III: for three consecutive days 2 ml are administered every 3-4 weeks.

Subsequent Rigvir courses: on the first year 2 ml once a month; on the first half of the second year every 6 weeks, beginning with the second half of the second year – every two months. Comply with the immunostimulation sequence of the regional lymph nodes.

If the lymph nodes are extirpated, use 4 intensive courses
Rigvir course I: for three consecutive days 2 ml are administered in the contralateral site of lymphadenectomia (for example, if right axillary lymphadenectomy has been done, then Rigvir i.m. is administered in the left *musculus gluteus).*

Rigvir courses II, III and IV: for three consecutive days 2 ml are administered every 3-4 weeks, involving other remote groups of regional lymph nodes.
Subsequent Rigvir courses: on the first year 2 ml once a month; on the first half of the second year every 6 weeks, beginning with the second half of the second year – every two months. Comply with the immunostimulation sequence of the regional lymph nodes.

For local treatment of cutaneous and subcutaneous melanoma metastases
If the patient has not received Rigvir, immunotherapy is started by administering Rigvir for 3 consecutive days intramuscularly in the lymph node region that is distant of metastatic lesions. After 7-14 days Rigvir (at a dose of 0.5-1.0 ml depending on the size of the metastases) is injected peritumorally near one or two metastatic foci by selecting the most recent metastasis. After one week, an intratumoural injection is given (at a dose of 0.5 to 1.0 ml, depending on the size of metastases). This local immunotherapy (alternating peri- and intra-tumoural) is repeated every week. If regression of metastases is observed, local immunotherapy is continued with 2-3 weeks' intervals. Concomitantly with the local immunotherapy, general immunotherapy is administered as well, according to the regional principle.

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). Infections, stress situations and other negative factors, including cancer aggressiveness, lead to a failure of the immune system in the form of hyperactivation of certain phases that can progress into total immunosuppression or non-reactivity (see. Table).

Changes	**Compensation phase**		**Immunodiscorrelation**		**Immunodiscorrelation in some organs**			
	Primary activation	normalization	moderate suppression	hyper-activation	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	post excision of the primary lesion	post excision of the primary	**none –** symptomatic and detoxifycation	post excision of the primary lesion	post lymph-adenectomia	most effectively post surgery	most effectively post surgery

	lesion		lesion	therapy				

Most characteristic immune status indicators for compensation phase are immune cell counts in peripheral blood, which are normal. Immunodiscorrelation 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 immunodiscorrelation - 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, Rigvir is essentially 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 Rigvir 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	Un-common	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)

Side effects are temporary and do not require special treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the State Agency of Medicines, Jersikas iela 15, Riga, LV-1003 Tel.: + 37167078400; Fax: +37167078428.
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

Mechanism of action

Rigvir is a naturally occurring viral immunomodulator that due to its structurally functional organization is able to act with a variety of immunomodulatory, oncotropic activity on the immune system and on the tumour cells.

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 promoting specific immunity against itself, it activates the cells of immune system. It is vital that on the surface of non-lysed malignant cells Rigvir promotes the appearance of tumour associated differentiation antigen (expression) and inhibits the expression of MAGE group antigens that are 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 to 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 Rigvir virotherapy, it is possible to achieve gradual and complete regression of tumour lymph node micrometastases and subcutaneous metastases. Rigvir stimulates humoral immunity - B cell activation, production of antibodies and interferon induction as well as cellular T system of immunity activation processes - increasing the cytotoxic $CD8^+$ cells, helper - $CD4^+$ cells, the activated $CD38^+$ cell counts in peripheral blood and apoptosis receptor $CD95^+$ expression on lymphocytes. This indicates of the activation of the cytotoxic immune response. Activation of non-specific immune cells also occurs: natural killer cells (NK) and monocytes/macrophages. The function of the lymph nodes is activated and infiltration of lymphocytes increases in the tumour lesion, which indicates of the local immune activation processes influenced by Rigvir. Rigvir takes part in realization of immunological adaptogenic mechanisms (immune cell differentiation, recirculation). Melanoma susceptibility for Rigvir is obtained by adapting ECHO-7 viruses in melanoma tissues.

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 induced (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 (rat sarcoma KRS-321, tumours induced in mice with methylcholanthrene, Moloney sarcoma virus-induced tumour in mice, human sarcoma graft in hamsters).

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 $2 \times 10^{8)}$, which 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 traces: 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, Atlasa iela 7C, Riga, LV-1026, Latvia
E-mail: rigvir@rigvir.com

8. MARKETING AUTHORISATION NUMBER

Depends on country of registration

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: April 29, 2004