SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Virono 50 mg muco-adhesive buccal tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of aciclovir.
Excipient with known effect: traces of lactose derived from milk protein concentrate, sodium laurilsulfate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Muco-adhesive buccal tablet.
White to slightly yellow tablets of 8 mm with a rounded side and a flat side debossed with “AL21”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Invented name> is indicated for the treatment of recurrent herpes labialis in immunocompetent adults with frequent herpes episodes (See Section 5.1).

4.2 Posology and method of administration

Posology
Single dose. Gingival use.

Adults
<Invented name> 50 mg muco-adhesive buccal tablet should be applied only once per episode to the upper gum region.
<Invented name> should be applied as soon as the first prodromal symptoms or signs of herpes labialis occur (see section 5.1).

Paediatric population
<Invented name> is only indicated in adults. The safety and efficacy of <Invented name> in children have not been established. No data are available.

Method of administration

Precaution to be taken before handling or administering the medicinal product
<Invented name> should be applied as soon as the first prodromal symptoms or signs of herpes labialis occur. The tablet should be applied with a dry finger immediately after taking it out of the blister. The tablet should be placed to the upper gum just above the second incisor tooth and held in place with a slight pressure over the upper lip for 30 seconds to ensure adhesion. For comfort the rounded side should be placed to the upper gum, but either side of the tablet can be applied. <Invented name> may be used if it sticks inside of the lip instead of the gum. Patients suffering from mouth dryness should drink a glass of water prior to applying the tablet in order to moisten the oral mucous membranes and thus encourage adhesion of the tablet.

Once applied, <Invented name> stays in position and gradually dissolves during the day.

Food and drink can be taken normally when <Invented name> is in place. The tablet should not be sucked, chewed or swallowed.
All situations that could interfere with adhesion of the tablet should be avoided:

- Touching or pressing the tablet already placed.
- Chewing gum.
- Brushing teeth during the treatment day.

If <Invented name> does not adhere or falls off within the first 6 hours, the same tablet should be repositioned immediately. If the tablet cannot be repositioned, a new tablet should be applied.
If <Invented name> is swallowed within the first 6 hours, the patient should drink a glass of water and a new tablet should be applied. The tablet should be replaced only once.

If <Invented name> falls off or is swallowed accidentally after 6 hours, no replacement of the tablet should be done.

4.3 Contraindications
Hypersensitivity to aciclovir or to any of the excipients listed in section 6.1.
Allergy to milk or milk derivatives.

4.4 Special warnings and precautions for use
Accidental ingestion of <Invented name> may occur. If <Invented name> is accidentally swallowed it is recommended to drink a glass of water.
There is no experience of the use of <Invented name> in immunocompromised patients. <Invented name> should not be used in immunocompromised patients, as an increased risk of resistance to aciclovir cannot be excluded.

Efficacy of <Invented name> when applied once vesicular lesions have formed has not been shown. Therefore, <Invented name>should only be used as soon as the prodromal symptoms or signs occur.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicine contains milk protein which may cause allergic reactions in people with severe hypersensitivity or allergy to milk protein.

This medicine contains 5.2 mg of sodium laurilsulfate per tablet.
Sodium laurilsulfate can cause local reactions (such as a tingling or burning sensation) or increase reactions caused by other products when they are applied to the same area.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with <Invented name>. Aciclovir is primarily eliminated unchanged in the urine via active tubular secretion. Although plasma concentrations of aciclovir following administration of <Invented name> are low, any medicinal products administered concomitantly that compete with this mechanism may increase aciclovir plasma concentrations. However due to the low dose and the low systemic exposure of aciclovir obtained after <Invented name> application, interactions are unlikely to be of clinical relevance.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

There are no or limited data from the use of <invented name> in pregnant women. Post-marketing records of local or systemic use of acyclovir formulations during pregnancy have not revealed an increase in the number of malformations, compared to the general population. Additionally, the observed malformations showed no unique characteristics or consistent patterns suggestive of a common cause. However, there are currently no epidemiological data available to rule out a risk.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity in doses compared to the therapeutic human dose (see section 5.3).

The use of <Invented name> in pregnant women should only be considered when the potential benefits outweigh possible unknown risks.

Breast-feeding

Based on limited human data aciclovir used orally is excreted to breast milk in very small amounts (relative infant dose about 1%). As C_{max} and AUC in plasma after use of muco-adhesive tablet is about 8-10-fold lower compared to oral administration, use of <Invented name> during breastfeeding is not expected to affect the breastfed infant. Moreover the availability from gastrointestinal tract in the infant is also low.

Although the dose received by a nursing infant following maternal use of <Invented name> would be negligible, <Invented name> use during lactation should only be considered when the potential benefits outweigh possible unknown risks.

Fertility

There is no experience on the effect of <Invented name> muco-adhesive buccal tablet on human female fertility. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

4.7 Effects on ability to drive and use machines

<Invented name> has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The safety profile of <Invented name> is based on 1 clinical trial of 775 patients of whom 378 received <Invented name>. Adverse reactions by system organ and frequency are listed below (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data).
The most commonly reported adverse reactions (ADRs) are general disorders and administration site conditions.

Adverse Reaction by System Organ Class	Frequency
Patients with any related adverse reaction during the study	
Nervous System Disorders	
Headache	Common
Dizziness	Uncommon
General Disorders and Administration Site Conditions	
Application Site Pain	Common
Application Site Irritation	Uncommon
Gastrointestinal Disorders	
Nausea	Uncommon
Aphthous Stomatitis	Uncommon
Gingival Pain	Uncommon
Skin and subcutaneous tissue disorders	
Erythema	Uncommon

Local suspected related adverse reactions are uncommon (<1%) and include application site pain, application site irritation, aphthous stomatitis and gingival pain. Discontinuation of <Invented name> due to adverse reaction did not occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Aciclovir absorption and systemic exposure following application of <Invented name> are minimal. Therefore, the risk of overdose is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct Acting Antivirals, nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05AB01.

Mechanism of action

Aciclovir is an antiviral agent which is highly active in vitro against Herpes Simplex Virus (HSV) types 1 and 2. The inhibitory activity of aciclovir for HSV1 and HSV2 is highly selective.
After entry into herpes infected cells, aciclovir is phosphorylated into the active aciclovir triphosphate compound. The first step in this process is dependent on the presence of the HSV-coded Thymidine kinase. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity of mammalian host cells is low. Aciclovir triphosphate acts as an inhibitor of, and substrate for the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes. The decrease in sensitivity to aciclovir is very rare in immunocompetent patient.

Clinical efficacy and safety

775 adult patients (378 in <Invented name>group versus 397 in placebo group) randomized and treated (771 ITT population) with at least 4 herpes episodes in the previous year (of whom 68.4% had ≥ 5 episodes) and with prodromal symptoms in at least 50% of the recurrent episodes were included in a phase 3 randomised (<Invented name> 50 mg vs placebo), double-blind trial and had to apply their treatment as soon as the first prodromal symptoms or signs occurred. Results showed that the administration of a single dose of <Invented name> 50 mg muco-adhesive buccal tablet significantly reduced the time to healing of the primary vesicular lesion: median duration was 5.03 days in the <Invented name> group vs 5.95 days in the placebo group in ITT (p=0.002) and 7.0 days vs 7.6 days in mITT (n= 521, p=0.015).

The secondary endpoints are presented in the table below:

	Aciclovir 50 mg (N=376)	Placebo (N=395)	P value
Aborted lesions: n (%)	130 (34.9%)	109 (28.1%)	0.0419
Duration of episode (days): median (95% CI)	5.57 (5.03; 6.01)	6.38 (5.93; 6.97)	0.0033
Non primary lesions: n (%)	39 (10.4%)	62 (15.7%)	0.037
Duration of symptoms (days): median (95% CI)	3.57 (3.04; 4.01)	4.16 (3.75; 4.89)	0.0098
Symptom intensity (day 5): median (range)	5.0 (0; 100)	9.0 (0; 100)	0.0078

In the pivotal study, 85% of patients applied <Invented name> within 1 hour of the onset of prodromal symptoms. There are no data to support the efficacy of <Invented name> when applied once vesicular lesions have formed.
In the study, the duration of tablet adhesion was greater than 6 hours in 88.5% of patients.

The safety was not different in the <Invented name> group versus the control group.

Patient satisfaction was significantly higher in the <Invented name> group (81.8%) vs the placebo group (72.4%, p=0.002).

Paediatric population: The European Medicines Agency has waived the obligation to submit the results of studies with <Invented name> in one or more subsets of the paediatric population in the treatment of herpes simplex labialis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The bioavailability of aciclovir administered orally is variable ranging from 15 to 30%. After administration of aciclovir 200 mg tablets, mean peak plasma concentrations (C_{max}) is 0.350 ± 0.100 µg/mL and T_{max} is observed between 1 and 3 hours. Plasma protein binding is in a range of 9 to 33%. Most aciclovir is eliminated unchanged in urine.

After application of <Invented name> 50 mg muco-adhesive buccal tablet as a single-dose in healthy volunteers (n=12), the mean plasma C_{max} of aciclovir was about 28 ng/mL. The C_{max} and AUC in plasma were about 10-fold and 8-fold lower, respectively, following application of <Invented name> 50 mg buccal tablet compared to oral administration of a 200 mg aciclovir tablet. The C_{max} and T_{max} obtained in saliva were 440 000 ng/mL and 7 hours, respectively.

Concentrations of aciclovir in saliva obtained in 56 patients from the phase 3 study are consistent with those obtained in healthy volunteers.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.
Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

Systemic administration of aciclovir in internationally accepted standards tests did not produce embryotoxic or teratogenic effects in rabbits, rats and mice. In a non-standard test in rats, foetal abnormalities were observed only after such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Local tolerance studies (on the jugal mucosa of hamster) did not show any toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone
Hypromellose
Milk protein concentrate with traces of lactose
Colloidal silica anhydrous
Sodium laurilsulfate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Alu/Alu unit dose blisters in cartons of 1x1 or 2x1 tablets.
Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: *To be completed nationally.*
Date of latest renewal: *To be completed nationally.*

10. DATE OF REVISION OF THE TEXT

2025-09-11