

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Sitavig 50 mg, muco-adhesive buccal tablets.

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of aciclovir.

Excipient with known effect: lactose (traces of lactose derived from milk protein concentrate).

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

Sitavig 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*

Sitavig 50 mg muco-adhesive buccal tablet should be applied only once to the upper gum region (canine fossa).

Sitavig should be applied within one hour after the onset of prodromal symptoms or signs (see section 5.1). Sitavig can be applied concomitantly to food and drinks intakes.

##### *Paediatric population*

Sitavig is only indicated in adults. No data are available in children

##### Method of administration

##### *Precaution to be taken before handling or administering the medicinal product*

Sitavig should be applied within one hour of the occurrence of any prodromal symptoms or signs. 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 incisor tooth (canine fossa) 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. Sitavig 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, Sitavig stays in position and gradually dissolves during the day.

Food and drink can be taken normally when Sitavig 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 Sitavig 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 Sitavig 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 Sitavig 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 Sitavig may occur. If Sitavig is accidentally swallowed it is recommended to drink a glass of water.

There is no experience of the use of Sitavig in immunocompromised patients. Sitavig should not be used in immunocompromised patients, as an increased risk of resistance to aciclovir cannot be excluded.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed with Sitavig. Aciclovir is primarily eliminated unchanged in the urine via active tubular secretion. Although plasma concentrations of aciclovir following administration of Sitavig 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 Sitavig application, interactions are unlikely to be of clinical relevance.

### **4.6 Fertility, pregnancy and lactation**

#### Fertility

There is no experience on the effect of Sitavig 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.

#### Pregnancy

A large amount of data on pregnant women indicates no malformative or feoto/neonatal toxicity of aciclovir. Consequently, Sitavig can be used during pregnancy if clinically needed.

#### Breast-feeding

Limited human data show that aciclovir passes into breast milk following systemic administration. Given the anticipated low absorption of Sitavig, Sitavig use may be considered during breast-feeding.

#### 4.7 Effects on ability to drive and use machines

Sitavig does not affect the ability to drive or use machines.

#### 4.8 Undesirable effects

The safety profile of Sitavig is based on 1 clinical trial of 775 patients of whom 378 received Sitavig. Adverse reactions by system organ and frequency are listed below (very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The most commonly reported adverse reactions (ADRs) are general disorders and administration site conditions.

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

\* Also Common in the placebo group; \*\* Common in the placebo group

Local suspected related adverse reactions are uncommon ( $< 1\%$ ) and include application site pain, application site irritation, aphthous stomatitis and gingival pain. Discontinuation of Sitavig 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 Sitavig 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 Sitavig 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  $\geq 5$  episodes) and with prodromal symptoms in at least 50% of the recurrent episodes were included in a phase 3 randomised (Sitavig 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 Sitavig 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 Sitavig group vs 5.95 days in the placebo group in ITT ( $p=0.002$ ) and 7.0 days vs 7.6 days in mITT ( $n= 521$ ,  $p=0.015$ ). Sitavig significantly increased ( $p=0.042$ ) the percentage of patients who did not develop primary vesicular lesions (herpes episodes aborted at prodromal symptoms and/or at the papular stage) in the Sitavig group (ITT, 34.9%) vs placebo (28.1%). In addition, Sitavig significantly reduced the overall duration of the herpes episode to 5.57 days in the Sitavig group versus 6.38 days in the control group ( $p=0.003$ ). The duration of symptoms (e.g. pain, tingling,) ( $p=0.0098$ ) and symptom intensity ( $p=0.008$ ) were reduced as compared to the control group. Finally, the percentage of patients with non-primary ( $n=101$ ) vesicular lesions was significantly reduced in the Sitavig group (ITT: 10.4% vs 15.7%;  $p=0.037$ ).

In the pivotal study, 85% of patients applied Sitavig within 1 hour of the onset of prodromal symptoms. There are no data to support the efficacy of Sitavig 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 Sitavig group versus the control group.

Patient satisfaction was significantly higher in the Sitavig group (81.8%) vs the placebo group (72.4%,  $p=0.002$ ).

Paediatric populationThe European Medicines Agency has deferred the obligation to submit the results of studies with Sitavig 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  $0.350 \pm 0.100 \mu\text{g/mL}$  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 Sitavig 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 Sitavig 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**

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir is unlikely to pose a genetic risk to man.

Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

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 2x1 tablets.

### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

## **7. MARKETING AUTHORISATION HOLDER**

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**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**

2017-12-06