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**Cliente** *Customer*
REIG JOFRE

**Colores** *Colors print*
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SALACLOVIR 250 mg
RJ-PAN MALAYAN

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**Medidas** *Format*
140 x 400 mm

**Plegado** *Fold*
35 x 100 mm
***Lomo en 100***

**Material** *Material*
Specialprint 40 g

**Plano** *Layout leaflet*
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>

**Aprobado** *Approved*
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París 1 - 7, Nave 2, Pol. Ind. Cova Solera, 08191 Rubí - Barcelona - España
Tlf. 93 697 04 12 - Fax 93 697 49 56 ● diseño&preimpresión: alfonso@graficas-agarcia.com ● www.graficas-agarcia.com

**PACKAGE INSERT**

# SALACLOVIR 250 mg powder for solution for infusion

## 1. NAME OF THE MEDICINAL PRODUCT

SALACLOVIR 250 mg powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg aciclovir (as aciclovir sodium).
After reconstitution
Each ml of solution for infusion contains 25 mg aciclovir.
Excipient with known effect
Each vial contains 45 mg sodium.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion.
Spongy pastille white or almost white freeze-dried sterile powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SALACLOVIR is indicated in non-immunocompromised patients for the treatment of

- Severe initial genital herpes.
- Varicella zoster virus infection.
- Herpes simplex encephalitis.

SALACLOVIR is indicated in immunocompromised patients for the treatment of

- Herpes simplex infection.
- Varicella zoster infection.
- Prophylaxis of herpes simplex infection.
- Herpes simplex encephalitis.

### 4.2 Posology and method of administration

Posology
A course of treatment with SALACLOVIR usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes simplex encephalitis and neonatal Herpes simplex infection usually lasts 10 days.
The duration of prophylactic administration of SALACLOVIR is determined by the duration of the period at risk.

*Adults*
Obese patients should be dosed at the recommended adult dose using ideal body weight rather than actual body weight.

| ***Indication*** | ***Immune status*** | ***Dose*** |
|---|---|---|
| Herpes simplex infections (except herpes simplex encephalitis) | Normal or immunocompromised | *5 mg/kg body weight every 8 hours* |
| Varicella zoster infections | Normal | *5 mg/kg body weight every 8 hours* |
| Varicella zoster infections | Immunocompromised | *10 mg/kg body weight every 8 hours* |
| Herpes simplex encephalitis | Normal or immunocompromised | *10 mg/kg body weight every 8 hours* |

*Special populations*
*Paediatric population*
The dose of SALACLOVIR in neonates and infants up to 3 months of age is calculated on the basis of body weight. Although its use in neonatal herpes is still experimental, doses of 10 mg/kg have been employed.
The dose of SALACLOVIR for children aged between 3 months and 12 years is calculated on the basis of body surface area.
Children, 3 months of age or older, with herpes simplex (except herpes simplex encephalitis) or varicella zoster infections should be given SALACLOVIR in doses of 250 mg per square metre of body surface area every 8 hours.
In immunocompromised children with varicella zoster infections or children with herpes simplex encephalitis, this medicinal product should be given in doses of 500 mg per square metre of body surface area every 8 hours if renal function is not impaired.
Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

*Elderly patients*
The possibility of renal impairment in the elderly must be considered and the dose should be adjusted accordingly (see "Patients with renal impairment" below). Adequate hydration should be maintained.

*Patients with renal impairment*
Caution is advised when administering aciclovir i.v. for infusion to patients with impaired renal function. Adequate hydration should be maintained.

The following modifications in dose are recommended:

| ***Creatinine clearance*** | ***Dose*** |
|---|---|
| 25-50 ml/min | *The dose recommended above (5 or 10 mg/kg body weight) should be given every 12 hours.* |
| 10-25 ml/min | *The dose recommended above (5 or 10 mg/kg body weight) should be given every 24 hours.* |
| 0 (anuric)-10 ml/min | *In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.* |

Method of administration
SALACLOVIR is intended for intravenous use.
The required dose of SALACLOVIR should be administered by slow intravenous infusion over a one-hour period.
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to valaciclovir.

### 4.4 Special warnings and precautions for use

Patients with renal impairment and elderly patients
Aciclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment (see section 4.2).
Elderly patients are likely to have reduced renal function and therefore the need for dose adjustment must be considered in this group of patients.
Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).
Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment (see section 5.1).
In patients receiving aciclovir at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.
Reconstituted SALACLOVIR has a pH of approximately 11 and should not be administered by mouth.

Excipients
This medicinal product contains 45 mg sodium per vial.

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

No clinically significant interactions have been identified.
Aciclovir is eliminated primarily unchanged in the urine *via* active renal tubular secretion. Any medicines administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However no dose adjustment is necessary because of the wide therapeutic index of aciclovir.
In patients receiving i.v. aciclovir, caution is required during concurrent administration with medicines which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both agents or their metabolites.
Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients have been shown when the medicines are coadministered.
Care is also required (with monitoring for changes in renal function) if administering intravenous aciclovir with medicines which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

### 4.6 Fertility, pregnancy and lactation

Pregnancy
The use of SALACLOVIR should be considered only when the potential benefits outweigh the possibility of unknown risks.
A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The birth defects amongst aciclovir-exposed subjects showed no uniqueness or consistent pattern to suggest a common cause.

Breastfeeding
Following oral administration of 200 mg aciclovir five times a day, aciclovir has been detected in human breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir doses of up to 0.3 mg/kg body weight/day. Caution is therefore advised if SALACLOVIR is to be administered to a nursing woman.

Fertility
There is no information on the effect of aciclovir oral formulations or i.v. for infusion on human female fertility. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology (See 'Preclinical safety data' in section 5.3).

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

SALACLOVIR is generally used in an in-patient hospital population and information on ability to drive and operate machinery is not usually relevant.
There have been no studies to investigate the effect of this medicine on driving performance or the ability to operate machinery.

### 4.8 Undesirable effects

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

The following convention has been used for the classification of undesirable effects in terms of frequency
Common ≥ 1/100 and < 1/10,
Uncommon ≥ 1/1000 and < 1/100,
Very rare < 1/10,000.

| ***MedDRA SOC*** | ***Frequency*** | ***Undesirable effect*** |
|---|---|---|
| Blood and lymphatic system disorders | Uncommon | Decreases in haematological indices (anaemia, thrombocytopenia, leukopenia) |
| Immune system disorders | Very rare | Anaphylaxis |
| Psychiatric and nervous system disorders | Very rare | Headache, dizziness, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma[1] |
| Vascular disorders | Common | Phlebitis |
| Respiratory, thoracic and mediastinal disorders | Very rare | Dyspnoea |

| | | |
|---|---|---|
| Gastrointestinal disorders | Common | Nausea, vomiting |
| | Very rare | Diarrhoea, abdominal pain |
| Hepatobiliary disorders | Common | Reversible increases in liver-related enzymes |
| | Very rare | Reversible increases in bilirubin, jaundice, hepatitis |
| Skin and subcutaneous tissue disorders | Common | Pruritus, urticaria, rashes (including photosensitivity) |
| | Very rare | Angioedema |
| Renal and urinary disorders | Common | Increases in blood urea and creatinine[2] |
| | Very rare | Renal impairment, acute renal failure, renal pain[3] |
| General disorders and administration site conditions | Very rare | Fatigue, fever, local inflammatory reactions[4] |

[1]The above events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see section 4.4).

[2]Rapid increases in blood urea and creatinine levels are believed to be related to the peak plasma levels and the state of hydration of the patient. To avoid this effect the medicine should not be given as an intravenous bolus injection but by slow infusion over a one-hour period.

[3]Adequate hydration should be maintained. Renal impairment usually responds rapidly to rehydration of the patient and/or dose reduction or withdrawal of the medicine. Progression to acute renal failure, however, can occur in exceptional cases.
Renal pain may be associated with renal failure.

[4]Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when aciclovir has been inadvertently infused into extracellular tissues.

### 4.9 Overdose

Symptoms and signs

Overdose of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure.
Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdose.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose of this medicine.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, nucleosides and nucleotides, excl. reverse transcriptase inhibitors, ATC code: J05AB01
Aciclovir is an antiviral agent which is highly active *in vitro* against Herpes simplex virus (HSV) types I and II and Varicella zoster virus (VZV). Toxicity to mammalian host cells is low.
Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the HSV- or VZV-coded thymidine kinase.
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.

### 5.2 Pharmacokinetic properties

In adults, the terminal plasma half-life has been determined as about 2.9 hours.
Most of the medicine is excreted unchanged in the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration contributes to the renal elimination of aciclovir.
9-Carboxymethoxymethylguanine is the only significant metabolite of aciclovir, and accounts for 10-15% of the dose excreted in the urine.

When aciclovir is given one hour after 1 gram of probenecid the terminal half- life and the area under the plasma concentration-time curve is extended by 18% or 40% respectively. In adults, mean steady state peak plasma concentration ($C_{ss}$max) following a one-hour infusion of 2.5mg/kg, 5mg/kg and 10mg/kg were 22.7μMol (5.1μg/ml), 43.6μMol (9.8μg/ml), 92μMol (20.7μg/ml), respectively. The corresponding trough plasma levels ($C_{ss}$min) 7 hours later were 2.2μMol (0.5μg/ml), 3.1μMol (0.7μg/ml) and 10.2μMol (2.3μg/ml), respectively. In children over 1 year of age similar mean $C_{ss}$max and $C_{ss}$min levels were observed when a dose of 250mg/m$^2$ was substituted for 5mg/kg and a dose of 500mg/m$^2$ was substituted for 10mg/kg. In neonates and young infants (0-3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8 hours the $C_{ss}$max was found to be 61.2μMol (13.8μg/ml) and the $C_{ss}$min to be 10.1μMol (2.3μg/ml). The terminal plasma half-life in these patients was 3.8 hours. In the elderly total body clearance falls with increasing age associated with decreases in creatinine clearance although there is little change in the terminal plasma half -life.

In patients with chronic renal failure the mean terminal half- life was found to be 19.5 hours. The mean aciclovir half -life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis. Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels. Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binging site displacement are not anticipated.

### 5.3 Preclinical safety data

Teratogenicity

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

Mutagenicity

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.

Carcinogenicity

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

Fertility

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium hydroxide

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

Prior to reconstitution

As indicated on the outer packaging.
From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
Once reconstituted, the solution must be used within a maximum of 8 hours if stored below 25℃

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after reconstitution of the medicinal product, see section 6.3

### Nature and contents of container

Type II transparent glass vial with chlorobutyl stopper and aluminium and polypropylene flip-off cap.
The vials are packed into carton boxes.
Each carton box contains 1, 5 or 50 vials.
Not all pack sizes may be marketed

### 6.6 Special precautions for disposal and other handling

Prepare immediately prior to use. Discard any unused solution.
For intravenous infusion only.
For single use only.

Reconstitution

Each vial (containing the equivalent of 250 mg aciclovir) should be reconstituted by the addition of 10 ml of either water for injection or sodium chloride intravenous infusion (0.9% w/v). This provides a solution containing 25 mg aciclovir per ml.
From the calculated dose, determine the appropriate number of vials to be used. To reconstitute each vial, add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.
SALACLOVIR contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out either under full aseptic conditions or immediately before use and any unused solution should be discarded.
The reconstituted or diluted solutions should not be refrigerated. Should visible turbidity or crystallisation appear in the solution, before or during the infusion, the mixture should be discarded.

Administration

The required dose of SALACLOVIR should be administered by slow intravenous infusion over a one-hour period. After reconstitution SALACLOVIR may be administered by a controlled-rate infusion pump. Alternately, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.
Add the required volume of reconstituted solution to the chosen infusion solution, as recommended below, and shake well to ensure adequate mixing occurs. For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum it is recommended that dilution is on the basis of 4 ml reconstituted solution (100 mg aciclovir) added to 20 ml of infusion fluid.
For adults, it is recommended that infusion bags containing 100 ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus one 100 ml infusion bag may be used for any dose between 250 mg and 500 mg aciclovir (10 and 20 ml of reconstituted solution), but a second bag must be used for doses between 500 and 1000 mg.
SALACLOVIR when diluted in accordance with the above schedules to give a concentration not greater than 0.5% w/v of aciclovir, is known to be compatible with the following infusion fluids and stable up to 8hr if stored below 25℃:

- Sodium chloride intravenous infusion (0.45% and 0.9% w/v).
- Sodium chloride (0.18% w/v) and Glucose (4% w/v) intravenous infusion.
- Sodium chloride (0.45% w/v) and Glucose (2.5% w/v) intravenous infusion.
- Compound Sodium lactate intravenous infusion (Hartmann's solution).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. PRODUCT OWNER

Laboratorio Reig Jofre, S.A
Gran Capita 10
Sant Joan Despí- Barcelona
Spain

## 8. DATE OF REVISION OF THE TEXT

08/2021



REIG JOFRE