

**PRESCRIBING INFORMATION**

**Pr ACYCLOVIR SODIUM INJECTION**

**500 mg / 20 mL (25 mg / mL)  
acyclovir (as acyclovir sodium)**

Antiviral Agent

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Date of Revision:  
August 9, 2017

Control Number: 207141

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### ACTIONS AND CLINICAL PHARMACOLOGY

Acyclovir, a synthetic acyclic purine nucleoside analog, is a substrate with a high degree of specificity for herpes simplex and varicella-zoster-specified thymidine kinase. Acyclovir is a poor substrate for host cell-specified thymidine kinase. Herpes simplex and varicella-zoster-specified thymidine kinase transform acyclovir to acyclovir monophosphate which is then transformed by number of cellular enzymes to acyclovir diphosphate and acyclovir triphosphate. Acyclovir triphosphate is both an inhibitor of, and a substrate for, herpes virus-specified DNA polymerase. Although the cellular  $\alpha$ -DNA polymerase in infected cells may also be inhibited by acyclovir triphosphate, this occurs only at concentrations of acyclovir triphosphate which are higher than those which inhibit the herpes virus-specified DNA polymerase. Acyclovir is selectively converted to its active form in herpes virus-infected cells and is thus preferentially taken up by these cells. Acyclovir has demonstrated a very much lower toxic potential *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular  $\alpha$ -DNA polymerase has a lower sensitivity to the action of the active form of the drug. A combination of the thymidine kinase specificity, inhibition of DNA polymerase and premature termination of DNA synthesis results in inhibition of herpes virus replication. No effect on latent non-replicating virus has been demonstrated. Inhibition of the virus reduces the period of viral shedding, limits the degree of spread and level of pathology, and thereby facilitates healing. During suppression, there is no evidence that acyclovir prevents neural migration of the virus. It aborts episodes of recurrent herpes due to inhibition of viral replication following reactivation.

## **PHARMACOKINETICS**

The pharmacokinetics of acyclovir has been evaluated in 95 patients (9 studies). Results were obtained in adult patients with normal renal function during Phase I/II studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Pharmacokinetics was also determined in pediatric patients with normal renal function ranging in age from 1 to 17 years at doses of 250 mg/m<sup>2</sup> or 500 mg/m<sup>2</sup> every 8 hours. In these studies, dose-independent pharmacokinetics is observed in the range of 0.5 to 15 mg/kg. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing.

Renal excretion of unchanged drug by glomerular filtration and tubular secretion is the major route of acyclovir elimination, accounting for 62 to 91% of the dose administered. The half-life and total body clearance of acyclovir in pediatric patients over 1 year of age is similar to those in adults with normal renal function.

## **INDICATIONS AND CLINICAL USE**

Acyclovir Sodium Injection is indicated for the treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) infections and varicella-zoster (shingles) infections in immunocompromised adults and children. It is also indicated for severe initial episodes of herpes simplex infections in patients who may not be immunocompromised. Use in other herpes group infections is the subject of ongoing study.

The indications are based on the results of a number of double-blind, placebo-controlled studies which examined changes in virus excretion, total healing of lesions and relief of pain. Because of the wide biological variations inherent in herpes simplex infections, the following summary is presented merely to illustrate the spectrum of responses observed to date. As in the treatment of any infectious disease, the best response may be expected when the therapy is begun at the earliest possible moment.

### **Herpes Simplex Infections in Immunocompromised Patients**

A multicentre trial of acyclovir at a dose of 250 mg/m<sup>2</sup> every 8 hours infused over 1 hour (750 mg/m<sup>2</sup>/day) for 7 days was conducted in 98 immunocompromised patients with oro-facial,

oesophageal, genital and other localized infections (52 treated with acyclovir and 46 with placebo). Acyclovir significantly decreased virus excretion, reduced pain and promoted scabbing and rapid healing of lesions.

### **Initial Episodes of Herpes Genitalis**

A controlled trial was conducted in 28 patients with initial severe episodes of herpes genitalis with an acyclovir dosage of 5 mg/kg, infused over 1 hour, every 8 hours for 5 days (12 patients with acyclovir and 16 with placebo). Significant treatment effects were seen in elimination of virus from lesions and in reduction of healing times.

In a similar study, 15 patients with initial episodes of genital herpes were treated with acyclovir 5 mg/kg, infused over 1 hour, every 8 hours for 5 days and 15 patients with placebo. Acyclovir decreased the duration of viral excretion, new lesion formation, duration of vesicles and promoted more rapid healing of all lesions.

### **Varicella-Zoster Infections in Immunocompromised Patients**

A multicentre trial of acyclovir at a dose of 500 mg/m<sup>2</sup> every 8 hours for 7 days was conducted in immunocompromised patients with zoster infections (shingles). Ninety-four patients were evaluated (52 patients were treated with acyclovir and 42 with placebo). Acyclovir halted progression of infection as determined by significant reductions in cutaneous dissemination, visceral dissemination or the proportion of patients deemed treatment failures.

A comparative trial of acyclovir and vidarabine was conducted in 22 severely immunocompromised patients with zoster infections. Acyclovir was shown to be superior to vidarabine as demonstrated by significant differences in the time of new lesion formation, the time to pain reduction, the time to lesion crusting, the time to complete healing, the incidence of fever and the duration of positive viral cultures. In addition, cutaneous dissemination occurred in none of the 10 acyclovir recipients compared to 5 of the 10 vidarabine recipients who presented with localized dermatomal disease.

## **Healing Process**

Because complete re-epithelialization of herpes-disrupted integument necessitates recruitment of several complex repair mechanisms, the physician should be aware that the disappearance of visible lesions is somewhat variable and will occur later than the cessation of virus excretion.

## **Diagnosis**

Whereas cutaneous lesions associated with herpes simplex and varicella-zoster infections are often pathognomonic, Tzanck smears prepared from lesion exudate or scrapings may assist in diagnosis. Positive cultures for herpes simplex virus offer the only absolute means for confirmation of the diagnosis. Appropriate examinations should be performed to rule out other sexually transmitted diseases. The Tzanck smear does not distinguish varicella-zoster from herpes simplex infections.

## **CONTRAINDICATIONS**

Acyclovir Sodium Injection is contraindicated for patients who have hypersensitivity to the drug.

## **WARNINGS**

Acyclovir Sodium Injection is for slow intravenous infusion only. Intravenous infusions must be given over a period of at least one hour to reduce the risk of renal tubular damage (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses associated with infections which may not respond to continued acyclovir therapy. This, however, remains to be clearly established and should be considered as a factor when undertaking therapy. The effect of the use of acyclovir on the natural history of herpes simplex or varicella-zoster infection is unknown.

## **PRECAUTIONS**

Precipitation of acyclovir crystals in renal tubules can occur if maximum solubility (2.5 mg/mL at 37°C in water) is exceeded. This phenomenon is reflected by a rise in serum creatinine and blood urea nitrogen and a decrease in creatinine clearance. With sufficient renal tubular compromise, urine output decreases.

Acute increases in serum creatinine and decreased creatinine clearance have been observed in humans receiving Acyclovir Sodium Injection who were poorly hydrated; or receiving concomitant nephrotoxic drugs (e.g. amphotericin B and aminoglycoside antibiotics); or had pre-existing renal compromise or damage; or had the dose administered by rapid intravenous injection (less than 10 minutes). Observed alterations in renal function have been transient, in some instances resolving spontaneously without change in acyclovir dosing regimen. In other instances, renal function improved following increased hydration, dosage adjustment or discontinuation of acyclovir therapy.

Administration of acyclovir by intravenous infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first 2 hours following infusion, particular attention should be given to establishing sufficient urine flow during that period in order to prevent precipitation in renal tubules. Recommended urine output is  $\geq 500$  mL per gram of drug infused.

When dosage adjustments are required, they should be based on estimated creatinine clearance (see **DOSAGE AND ADMINISTRATION**).

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma. Acyclovir should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving concomitant intrathecal methotrexate or interferon.

### **Nursing Mothers**

Acyclovir is excreted in human milk. Caution should therefore be exercised when acyclovir is administered to a nursing mother.

### **Use in Pregnancy**

Teratology studies carried out to date in animals have been negative in general. However, in a non-standard test in rats, there were fetal abnormalities such as head and tail anomalies and maternal toxicity. Since such studies are not always predictive of human response, acyclovir should not be used during pregnancy unless the physician feels the potential benefit justifies the risk of possible harm to the fetus. The potential for high concentrations of acyclovir to cause chromosome breaks *in vitro* should be taken into consideration in making this decision.

No data exist at this time, that demonstrate that the use of acyclovir will prevent transmission of herpes simplex infection to other persons.

Consideration should be given to an alternative treatment regimen if after 5 days of treatment there is no expected clinical improvement in the signs and symptoms of the infection.

Strains of herpes simplex virus which are less susceptible to acyclovir have been isolated from herpes lesions and have also emerged during intravenous treatment with acyclovir.

### **Drug Interactions**

Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

### **ADVERSE REACTIONS**

The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at ~5 mg/kg (250 mg/m<sup>2</sup>) and approximately 200 patients who received ~10 mg/kg (500 mg/m<sup>2</sup>).

The most frequent adverse reactions reported during acyclovir administration were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% of patients [the higher incidence occurred usually following rapid (less than 10 minutes) intravenous infusion]. Nausea and/or vomiting occurred in

approximately 7% of the patients (the majority occurring in non-hospitalized patients who received 10 mg/kg). Itching, rash or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1 to 2% of patients.

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma (see **PRECAUTIONS**).

Adverse reactions which occurred at a frequency of less than 1% and which were probably or possibly related to intravenous acyclovir administration were: anemia, anuria, haematuria, hypotension, edema, anorexia, lightheadedness, thirst, headache, diaphoresis, fever, neutropenia, thrombocytopenia, abnormal urinalysis (characterized by an increase in formed elements in urine sediment) and pain on urination.

Other reactions have been reported with a frequency of less than 1% in patients receiving acyclovir, but a causal relationship between acyclovir and the reaction could not be determined. These include pulmonary edema with cardiac tamponade, abdominal pain, chest pain, thrombocytosis, leukocytosis, neutrophilia, ischemia of digits, hypokalemia, purpura fulminans, pressure on urination, hemoglobinemia and rigors.

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Overdose has been reported following administration of bolus injections, or inappropriately high doses, and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations in BUN, serum creatinine and subsequent renal failure. Lethargy, convulsions and coma have been reported rarely. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see **PRECAUTIONS**).

A six-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria,



the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

## **DOSAGE AND ADMINISTRATION**

**CAUTION:** ACYCLOVIR SODIUM INJECTION IS FOR SLOW INTRAVENOUS INFUSION ONLY, OVER A PERIOD OF AT LEAST ONE HOUR.

### **Herpes Simplex Infections**

#### Mucosal and Cutaneous Herpes Simplex (HSV-1 and HSV-2) in Immunocompromised Patients

**Adults:** 5 mg/kg infused at a constant rate over at least 1 hour, every 8 hours for 7 days in adult patients with normal renal function.

**Children:** In children under 12 years of age, equivalent plasma concentrations are attained by infusing 250 mg/m<sup>2</sup> at a constant rate over at least 1 hour, every 8 hours for 7 days.

#### Severe Initial Clinical Episodes of Herpes Genitalis in Immunocompetent Patients

The same dose given above - administered for 5 days.

### **Varicella-Zoster Infections**

#### Zoster in Immunocompromised Patients

**Adults:** 10 mg/kg infused at a constant rate over at least 1 hour, every 8 hours for 7 days in adult patients with normal renal function.

**Children:** In children under 12 years of age, equivalent plasma concentrations are attained by infusion 500 mg/m<sup>2</sup> at a constant rate over at least 1 hour, every 8 hours for 7 days.

Obese patients should be dosed at 10 mg/kg (Ideal Body Weight).

A maximum dose equivalent to 500 mg/m<sup>2</sup> every 8 hours should not be exceeded for any patient.

### **Patients with Acute or Chronic Renal Impairment**

Use the recommended doses and method of administration and adjust the dosing interval as indicated in the following table:

<u>Creatinine Clearance</u> (mL/min/1.73 m <sup>2</sup> )	<u>Percent of</u> <u>Recommended Dose</u>	<u>Dosing Interval</u> (hours)
>50	100	8
25-50	100	12
10-25*	100	24
0-10*	50	24-48

\* Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during dialysis is approximately 5 hours, which results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Recommended doses should be administered every 24 to 48 hours and after hemodialysis

## PHARMACEUTICAL INFORMATION

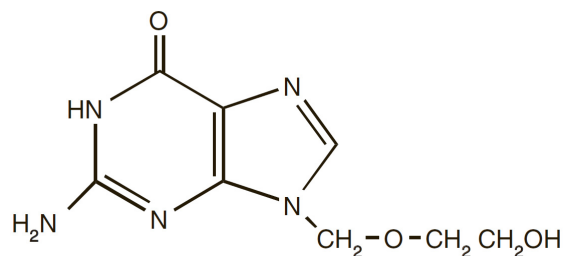
### Drug Substance

**Common Name:** Acyclovir

**Chemical Name:** 9-[(2-Hydroxyethoxy)methyl]guanine \*

\* Acyclovir sodium is prepared *in situ* with the aid of sodium hydroxide.

### Chemical Structure:



**Molecular Formula:** C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>

**Molecular Weight:** 225.21

**Description:** A white to almost white crystalline powder. Sparingly to slightly soluble in water; practically insoluble in alcohol and most organic solvents; soluble in dilute aqueous solutions of alkali hydroxides and mineral acid. Melting point of 256.5 to 257°C.

### Composition

500 mg of per vial. Each mL contains 25 mg / mL acyclovir (as the sodium salt) in water for injection. Hydrochloric acid or sodium hydroxide may be used to adjust pH to 10.7 to 11.7.

### Stability and Storage Recommendations

Acyclovir Sodium Injection should be stored between 15 and 25°C, protected from light and freezing.

### **Diluted Solutions for Intravenous Infusion**

The calculated dose of the solution should be removed and added to an appropriate intravenous solution listed below at a volume selected for administration during each 1-hour infusion. Infusion concentrations exceeding 10 mg/mL are not recommended.

Since the vials do not contain any preservatives, any unused portion of the solution should be discarded.

The diluted solution should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration.

#### Solutions for Intravenous Infusion

5% Dextrose Injection

5% Dextrose and 0.9% Sodium Chloride Injection

5% Dextrose and 0.2% Sodium Chloride Injection

Ringer's Injection

Normal Saline Injection

Lactated Ringer's Injection

### **Stability and Storage of Solution**

Once diluted, the admixtures are to be administered within 24 hours of the initial preparation. The admixtures are not to be refrigerated.

Unused portions of the diluted solution should be discarded.

### **Incompatibility**

Acyclovir should not be added to biologic or colloidal fluids (e.g. blood products, protein hydrolysates, amino acids or fat emulsions).

## **AVAILABILITY OF DOSAGE FORMS**

Acyclovir Sodium Injection is available in:

- 20 mL vial containing acyclovir sodium equivalent to 500 mg acyclovir as a 25 mg / mL solution.

**The format is a single-use vial.**

Last revised August 9, 2017