DESCRIPTION:
Acyclovir Sodium Injection is a synthetic nucleoside analog, active against herpes viruses. It is a sterile, aqueous solution for intravenous infusion, containing 50 mg acyclovir per mL in Water for Injection, USP. The concentration is equivalent to 54.9 mg of acyclovir sodium per mL in Water for Injection, USP. The sodium content is approximately 5.1 mg/mL. The pH range of the solution is 10.85 to 11.50. Further dilution of Acyclovir Sodium Injection in an appropriate intravenous solution must be performed before infusion (see DOSAGE AND ADMINISTRATION, Administration).

The chemical name of acyclovir sodium is 9-[2-(Hydroxyethoxy)methyl] guanine, and has the following structural formula:

![Chemical Structure](attachment:image.jpg)

Acyclovir sodium is a white, crystalline powder with the molecular formula C8H10N5NaO3 and a molecular weight of 247.19. The maximum solubility in water at 25°C exceeds 100 mg/mL. At physiologic pH, acyclovir sodium exists as the unionized form with a molecular weight of 225 and a maximum solubility in water at 37°C of 2.5 mg/mL. The pKa’s of acyclovir are 2.27 and 9.25.

VIROLOGY:
Mechanism of Antiviral Action
Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2) and varicella-zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities
The quantitative relationship between the in vitro susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC50), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC50 against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC50 for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with an IC50 of 1.35 mcg/mL.

Drug Resistance
Resistance of HSV and VZV to acyclovir can result from quantitative or qualitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from such patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY:
Pharmacokinetics
The pharmacokinetics of acyclovir after intravenous administration have been evaluated in adult patients with normal renal function during Phase 1/2 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. Average steady-state peak and trough concentrations from 1-hour infusions administered every 8 hours are given in Table 1.

Table 1: Acyclovir Peak and Trough Concentrations at Steady-State

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Cmax (mcg/mL)</th>
<th>Cmin (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/kg q 8 h</td>
<td>9.8 range: 5.5 to 13.8</td>
<td>0.7 range: 0.2 to 1</td>
</tr>
<tr>
<td>10 mg/kg q 8 h</td>
<td>22.9 range: 14.1 to 44.1</td>
<td>1.9 range: 0.5 to 2.9</td>
</tr>
</tbody>
</table>

Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%) and drug interactions involving binding site displacement are not anticipated.

Renal excretion of unchanged drug is the major route of acyclovir elimination accounting for 62% to 91% of the dose. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine accounting for up to 14.1% of the dose in patients with normal renal function.

The half-life and total body clearance of acyclovir are dependent on renal function as shown in Table 2.

Table 2: Acyclovir Half-life and Total Body Clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Half-life (h)</th>
<th>Total Body Clearance (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>50-80</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>15-50</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>0 (Auricure)</td>
<td>19.5</td>
<td>29</td>
</tr>
</tbody>
</table>

Special Populations
Adults With Impaired Renal Function
Acyclovir was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 mcg/mL and 0.7 mcg/mL, respectively.

Consult DOSAGE AND ADMINISTRATION section for recommended adjustments in dosing based upon creatinine clearance.

Pediatrics
Acyclovir pharmacokinetics were determined in 16 pediatric patients with normal renal function ranging in age from 3 months to 16 years at doses of approximately 10 mg/kg and 20 mg/kg every 8 hours (Table 3). Concentrations achieved at these regimens are similar to those in adults receiving 5 mg/kg and 10 mg/kg every 8 hours, respectively (Table 1). Acyclovir pharmacokinetics were determined in 71 pediatric patients ranging in age from birth to 3 months at doses of 5 mg/kg, 10 mg/kg, and 15 mg/kg every 8 hours (Table 3).

Table 3: Acyclovir Pharmacokinetics in Pediatric Patients (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Birth to 3 Months of Age (n=12)</th>
<th>3 Months to 12 Years of Age (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (mL/min/kg)</td>
<td>4.46±1.61</td>
<td>8.44±2.92</td>
</tr>
<tr>
<td>VDSS (L/kg)</td>
<td>1.08±0.35</td>
<td>1.01±0.28</td>
</tr>
<tr>
<td>Elimination half-life (hours)</td>
<td>3.80±1.19</td>
<td>2.36±0.97</td>
</tr>
</tbody>
</table>

Geriatrics
Acyclovir plasma concentrations are higher in geriatric patients compared to younger adults, in part due to age-related changes in renal function. Dosage reduction may be required in geriatric patients with underlying renal impairment (see PRECAUTIONS: Geriatric Use).

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

CLINICAL TRIALS: Herpes Simplex Infections in Immunocompromised Patients
A multicenter trial of acyclovir at a dose of 250 mg/m² every 6 hours (750 mg/m²/day) for 7 days was conducted in 98 immunocompromised patients (73 adults and 25 children) with orofacial, esophageal, genital and other localized infections (52 treated with acyclovir and 46 with placebo).
Acyclovir decreased virus excretion, reduced pain, and promoted healing of lesions.

**Initial Episodes of Herpes Genitalis**

In placebo-controlled trials, 56 patients with initial genital herpes were treated with intravenous acyclovir 5 mg/kg every 8 hours or vidarabine (15 mg/kg/day) for 10 days (28 were treated with acyclovir and 34 with vidarabine). Overall mortality at 12 months for patients treated with acyclovir was 32% compared to 12% of patients treated with vidarabine (15 mg/kg/day) for 10 days (28 were treated with acyclovir and 34 with vidarabine). The proportion of patients treated with acyclovir functioning normally or with only mild sequelae (e.g., decreased attention span) was 52% compared to 12% of patients treated with vidarabine.

Patients less than 30 years of age and those who had the least severe neurologic involvement at time of entry into study had the best outcome with treatment with acyclovir. An additional controlled study performed in Europe demonstrated similar efficacy.

**Herpes Simplex Encephalitis**

Sixty-two patients ages 6 months to 79 years with epidemic herpes simplex encephalitis were randomized to receive either acyclovir (10 mg/kg every 8 hours) or vidarabine (15 mg/kg/day) for 10 days (28 were treated with acyclovir and 34 with vidarabine). Overall mortality at 12 months for patients treated with acyclovir was 25% compared to 59% for patients treated with vidarabine. The proportion of patients treated with acyclovir functioning normally or with only mild sequelae (e.g., decreased attention span) was 52% compared to 12% of patients treated with vidarabine.

**Neonatal Herpes Simplex Virus Infection**

Two hundred and two infants with neonatal herpes simplex infections were randomized to receive either acyclovir 10 mg/kg every 8 hours (n=107) or vidarabine 25 mg/kg every 8 hours (n=95) for 10 days. Outcomes are presented in Table 4.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Acyclovir (n=107)</th>
<th>Vidarabine (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEM* (n=80)</td>
<td>0.04</td>
<td>0.31</td>
</tr>
<tr>
<td>CNST (n=71)</td>
<td>5.35</td>
<td>5.96</td>
</tr>
<tr>
<td>DigiS* (n=46)</td>
<td>11.18</td>
<td>14.28</td>
</tr>
</tbody>
</table>

*SEM refers to localized infection with disease limited to skin, eye, and/or mouth.

**Varicella-Zoster Infections in Immunocompromised Patients**

A multicenter trial of acyclovir at a dose of 500 mg/m2 every 8 hours for 7 days was conducted in immunocompromised patients with zoster infections (shingles). Ninety-four (94) patients were evaluated (52 patients were treated with acyclovir and 42 with placebo). Acyclovir was superior to placebo as measured by reductions in cutaneous dissemination and visceral dissemination.

**INDICATIONS AND USAGE: Herpes Simplex Infections in Immunocompromised Patients**

Acyclovir Sodium Injection is indicated for the treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) in immunocompromised patients.

**Initial Episodes of Herpes Genitalis**

**Herpes Simplex Encephalitis**

**Herpes Simplex Infections in Immunocompromised Patients**

**Varicella-Zoster Infections in Immunocompromised Patients**

**CONTRAINDICATIONS:**

Acyclovir Sodium Injection is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

**WARNINGS:**

Acyclovir Sodium Injection is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

**DISS:***

<table>
<thead>
<tr>
<th>Event</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS† (n=71)</td>
<td>5/35 5/36</td>
</tr>
</tbody>
</table>

**PREFERENCES:**

**General**

Precipitation of acyclovir crystals in renal tubules can occur if the solubility of free acyclovir (2.5 mg/mL at 37°C in water) is exceeded or if the drug is administered by bolus injection. Ensuring renal function has been shown to reduce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient’s hydration. Renal impairment, and the rate of drug administration. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and antacids can further renal impairment with acyclovir more likely.

Administration of acyclovir by intravenous infusion must be accompanied by adequate hydration.

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

Approximately 1% of patients receiving intravenous acyclovir developed encephalopathic changes characterized by 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.

**Drug Interactions**

See CLINICAL PHARMACOLOGY: Pharmacokinetics.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 30 mg/kg/day (10 mg/kg every 8 hours, dosing appropriate for treatment of herpes zoster or herpes encephalitis), or 15 mg/kg (5 mg/kg every 8 hours, dosing appropriate for treatment of primary genital herpes or herpes zoster infections in immunocompromised patients). Plasma drug concentrations in animals studies are expressed as multiples of human exposure to acyclovir at the higher (and lower) dosing schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

**Adverse Reactions:**

The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at approximately 5 mg/kg (250 mg/m2) 3 times daily, and approximately 300 patients who received approximately 10 mg/kg (500 mg/m2) 3 times daily.

The most frequent adverse reactions reported during administration of acyclovir were dermatologic and phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine (less than 1.5 times normal levels). These concentrations would potentially expose the patient to a dose of acyclovir up to 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

**Pediatric Use**

See DOSAGE AND ADMINISTRATION.

**Gelati**

Clinical studies of acyclovir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other clinical experience has identified differences in the severity of CNS adverse events among patients who have undergone neurologic involvement such as their control or without CNS involvement.

**Varicella-Zoster Infections in Immunocompromised Patients**

Acyclovir was positive in genetic toxicity assays. The following hematologic abnormalities occurred at a frequency of less than 1%: anemia, neutropenia, thrombocytopenia, leukocytosis, and neutrophilia. In addition, anorexia and hematuria were observed.

**Observed During Clinical Practice:**

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of Acyclovir Sodium Injection in the treatment of herpes simplex infections in immunocompromised patients. These events are reported voluntarily from a population of unknown size, estimates of frequency cannot be provided. These events have been included or for inclusion due to their seriousness, frequency of reporting, potential causal connection to acyclovir, or a combination of these factors.

**General:**

Anaphylaxis, angioedema, fatigue, fever, headache, pain, peripheral edema.

**Dietetic:**

Abdominal pain, diarrhea, gastrointestinal distress, nausea.

**Cardiovascular:**

Hypotension.
Hematologic and Lymphatic: Disseminated intravascular coagulation, hemolysis, leukocytoclastic vasculitis, leukopenia, lymphadenopathy.

Hepatobiliary Tract and Pancreas: Elevated liver function tests, hepatitis, hyperbilirubinemia, jaundice.

Musculoskeletal: Myalgia.

Nervous: Aggressive behavior, agitation, ataxia, coma, confusion, delirium, dizziness, dysarthria, encephalopathy, hallucinations, obtundation, paresthesia, psychosis, seizure, somnolence, tremor. These symptoms may be marked, particularly in older adults (see PRECAUTIONS).

Skin: Alopecia, erythema multiforme, photosensitive rash, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria. Severe local inflammatory reactions, including tissue necrosis, have occurred following infusion of acyclovir into extravascular tissues.

Special Senses: Visual abnormalities.

Urogenital: Renal failure, elevated blood urea nitrogen, elevated creatinine (see WARNINGS).

OVERDOSAGE: Overdoses involving ingestions of up to 20 g have been reported. Adverse events that have been reported in association with overdosage include agitation, coma, seizures, and lethargy. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Overdose has been reported following bolus injections or inappropriate high doses, and in patients whose fluid and electrolyte balance were not properly monitored. This has resulted in elevated BUN and serum creatinine, and subsequent renal failure. 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 - Rapid or bolus intravenous Dosings and Precautions: Intramuscular or subcutaneous injection must be avoided (see WARNINGS and Precautions).

Herpes simplex infections, doses of 10 mg/kg (infused at a constant rate over 1 hour every 8 hours) have been used; the safety and efficacy of these doses are not known.

Varicella-Zoster Infections Zoster in Immunocompromised Patients:

Adults and Adolescents (12 years of age and older):
10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Pediatrics (Under 12 years of age):
20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Obese Patients:
Obese patients should be dosed at the recommended adult dose using ideal body weight.

Table 5: Dosage Adjustments for Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min/1.73 m²)</th>
<th>Percent of Recommended Dose</th>
<th>Dosing Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
<td>8</td>
</tr>
<tr>
<td>25-50</td>
<td>100%</td>
<td>12</td>
</tr>
<tr>
<td>10-25</td>
<td>100%</td>
<td>24</td>
</tr>
<tr>
<td>0-10</td>
<td>50%</td>
<td>24</td>
</tr>
</tbody>
</table>

Hemodialysis
For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 6 hours. This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore, the patient’s dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis
No supplemental dose appears to be necessary after adjustment of the dosing interval.

Administration
The calculated dose should be further diluted in an appropriate intravenous solution at a volume selected for administration during each 1 hour infusion. Infusion concentrations of approximately 7 mg/mL or lower are recommended. In clinical studies, the average 70 kg adult received between 60 and 150 mL of fluid per dose. Higher concentrations (e.g., 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not recommended.

Once diluted for administration, each dose should be used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

How SUPPLIED:
Acyclovir Sodium Injection is available as:

<table>
<thead>
<tr>
<th>Product</th>
<th>NDC No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>302510</td>
<td>63323-325-10</td>
<td>Acyclovir Sodium Injection equivalent to acyclovir, 50 mg/mL in a 10 mL plastic vial, in packages of 10.</td>
</tr>
<tr>
<td>302520</td>
<td>63323-325-20</td>
<td>Acyclovir Sodium Injection equivalent to acyclovir, 50 mg/mL in a 20 mL plastic vial, in packages of 10.</td>
</tr>
</tbody>
</table>

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Discard unused portion.

Vial stoppers do not contain natural rubber latex.