DESCRIPTION:
Acyclovir Sodium Injection is a synthetic nucleoside analog, active against herpesviruses. 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:

\[
\text{\text{H}_2\text{N}} \quad \text{\text{O}} \quad \text{\text{N}} \quad \text{\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}} \quad \text{\text{Na}^+}
\]

Acyclovir sodium is a white, crystalline powder with the molecular formula C_{12}H_{11}N_3O_5NaO_4 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 a mean IC50 of 1.35 mcg/mL.

Drug Resistance
Resistance of HSV and VZV to acyclovir can result from qualitative or quantitative 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. Proportionality between dose and plasma levels is seen after single doses and steady-state after multiple dosing. Average steady-state peak and trough concentrations from 1-hour infusions administered every 8 hours are shown in Table 1.

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Cmax (mg/mL)</th>
<th>Cmin (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/kg q 8 h (n=7)</td>
<td>9.8 to 13.6</td>
<td>0.7 to 1</td>
</tr>
<tr>
<td>10 mg/kg q 8 h (n=7)</td>
<td>22.9 to 44.1</td>
<td>1.9 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 82% to 91% of the dose. The only major urinary metabolite detected is 9-carboxymethyl-oxymethylguanine 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.

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 12 patients ranging in age from birth to 3 months at doses of 4 mg/kg, 10 mg/kg, and 15 mg/kg every 8 hours (Table 3).

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
Co-administration 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/m^2 every 8 hours (750 mg/m^2/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

PRECAUTIONS, Dosing and Administration...
Acyclovir and 46 with placebo). Acyclovir decreased virus excretion, reduced pain, and promoted healing of lesions.

**Early Episodes of Herpes Genitalis**
In placebo-controlled trials, 58 patients with initial genital herpes were treated with intravenous acyclovir (25 mg/kg every 8 hours) and 50 with placebo. (27 treated with acyclovir and 31 treated with placebo) every 8 hours for 5 days. Acyclovir decreased virus excretion of viral excretion, new lesion formation, and duration of vesicles, and promoted healing of lesions.

**Herpes Simplex Encephalitis**
Sixty-two patients ages 6 months to 79 years with brain biopsy-proven herpetic simplex encephalitis were randomly assigned 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., demyelination, ataxia, cognitive impairment) 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 study performed in Europe demonstrated similar findings.

**Neonatal Herpes Simplex Virus Infection**
Two hundred and two infants with neonatal herpes simplex infections were evaluated. Patients received either acyclovir (10 mg/kg every 8 hours) or vidarabine (15 mg/kg/day) for 10 days. Outcomes are presented in Table 4.

**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). Acrivir was superior to placebo as measured by reductions in cutaneous dissemination and visceral dissemination at 7 days.

**INDICATIONS AND Usage: Herpes Simplex Infections in Immunocompromised Patients**
Acyclovir was superior to placebo as measured by reductions in cutaneous dissemination and visceral dissemination at 7 days.

**Table 4: Mortality at 1 Year**

<table>
<thead>
<tr>
<th>HSV Disease Classification</th>
<th>Treatment Group</th>
<th>Acyclovir (n=107)</th>
<th>Vidarabine (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir*</td>
<td>SEM=0.85</td>
<td>0.34</td>
<td>0.31</td>
</tr>
<tr>
<td>CNS‡</td>
<td>SEM=0.71</td>
<td>5/35</td>
<td>5/36</td>
</tr>
<tr>
<td>DIS§</td>
<td>SEM=0.46</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.
‡CNS refers to central nervous system with comparable neurologic and CSF findings.
§DIS refers to visceral organ involvement such as hepatic or pancreatic involvement with or without CNS involvement.

**Rates of neurologic sequelae at 1 year were comparable between the treatment groups.**

**Varicella-Zoster Infections in Immuno- compromised Patients**
Acyclovir was superior to placebo as measured by reductions in cutaneous dissemination and visceral dissemination at 7 days.

**Initial Episodes of Herpes Genitalis**
Acyclovir Sodium Injection is indicated for the treatment of severe initial clinical episodes of herpes genitalis in immunocompetent patients.

**Herpes Simplex Encephalitis**
Acyclovir Sodium Injection is indicated for the treatment of herpes simplex encephalitis.

**Herpes Simplex Virus Infection**
Acyclovir Sodium Injection is indicated for the treatment of neonatal herpes infections.

**Varicella-Zoster Infections in Immuno- compromised Patients**
Acyclovir Sodium Injection is indicated for the treatment of varicella-zoster (shingles) infections in immunocompromised patients.

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

**Warnings**
Acyclovir Sodium Injection is intended for intravenous infusion only, and should not be administered intramuscularly, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 hour to reduce the risk of renal tubular damage (vii).

**Adverse Reactions**
Renal failure, in some cases resulting in death, has been observed in acyclovir therapy (see ADVERSE REACTIONS, Observed During Clinical Practice and OVERDOSE). Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir therapy.

**Precautions**

**General**
Precipitation of acyclovir crystals in renal tubules can occur if the maximum 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 tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can develop as a result of acyclovir administration and depends on the state of the patient’s hydration, other treatments, and the rate of drug administration. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make renal failure more likely.

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

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 encephalopathy/psychiatric reactions characterized by either lethargy, obtundation, tremors, or hallucinations, agitation, seizures, or coma. Acyclovir should be used with caution in those patients who have underlying neurologic abnormalities (e.g., 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/day (5 mg/kg every 8 hours, dosing appropriate for treatment of primary genital herpetic or herpes simplex infections in immunocompromised patients). Plasma drug concentrations in animal studies are expressed as the ratio of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered intraperitoneally. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations in both the newt and zebrafish were lower than concentrations in humans.

Acyclovir was tested in 16 in vitro and in vivo genetic toxicity assays. Acyclovir was positive in 5 of the assays.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, PO) or in rats (25 mg/kg/day, SC). In the mouse study, plasma levels were the same as human levels, while in the rat study, plasma levels were 5 times human levels. At higher doses (50 mg/kg/day, SC) in rats and rabbits (1 to 2 and 1 to 3 times human levels, respectively), acyclovir decreased fertility efficacy, but not litter size, was decreased. In a rat peri- and postnatal study at 50 mg/kg/day, SC, there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

Testicular atrophy and spermatogenesis were observed in rats and dogs at higher dose levels.

**Pharmacokinetics**
Acyclovir Sodium Injection is intended for administration by intravenous infusion. Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in nonhospitalized patients who received acyclovir at approximately 5 mg/kg (250 mg/m²) 3 times daily, and approximately 0.3% of patients who received 10 mg/kg (500 mg/m²) 3 times daily.

The most frequent adverse reactions reported during administration of acyclovir were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum transaminases or alkaline phosphatase in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients.

The following hematologic abnormalities occurred at a frequency of less than 1%: anemia, neutropenia, thrombocytopenia, thrombocytopenia, leukocytopenia, and neutropenia. In addition, anemia, anorexia and neutropenia 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 clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen 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.

**Dietary**
Abdominal pain, diarrhea, gastrointestinal distress, nausea.
HERPES SIMPLEX INFECTIONS

Dosage

10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 mg/kg or 20 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):
20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 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.

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT section for recommended doses, and adjust the dosing interval as indicated in Table 5.

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>12</td>
</tr>
<tr>
<td>25 to 50</td>
<td>100%</td>
<td>24</td>
</tr>
<tr>
<td>10 to 20</td>
<td>50%</td>
<td>24</td>
</tr>
<tr>
<td>0 to 10</td>
<td>50%</td>
<td>24</td>
</tr>
</tbody>
</table>

OVERDOSE:

Overdoses involving ingestions of up to 20 g have been reported. Adverse events that have been reported in association with overdose 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 inappropriately 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 INJECTION MUST BE AVOIDED (see WARNINGS and PRECAUTIONS).
- INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED (see WARNINGS).
- Therapy should be initiated as early as possible following onset of signs and symptoms of herpes infections.
- A maximum dose equivalent to 20 mg/kg every 8 hours should not be exceeded for any patient.

Dosage HERPES SIMPLEX INFECTIONS

MUCOSAL AND CUTANEOUS HERPES SIMPLEX (HSV-1 and HSV-2) INFECTIONS IN IMMUNOCOMPROMISED PATIENTS:

Adults and Adolescents (12 years of age and older):
5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

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

SEVERE INITIAL CLINICAL EPISODES OF HERPES GENITALIS:

Adults and Adolescents (12 years of age and older):
5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 5 days.

HERPES SIMPLEX ENCEPHALITIS:

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 (3 months to 12 years of age):
20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Neonatal Herpes Simplex Virus Infections

(Birth to 3 months):
10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 mg/kg or 20 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.

Hemodialysis

For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 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 No.</th>
<th>NDC No.</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>302510</td>
<td>63233-325-10</td>
<td>500 mg per 10 mL (50 mg per mL) Acyclovir Sodium Injection equivalent to acyclovir, in a 10 mL plastic vial, in packages of 10.</td>
</tr>
<tr>
<td>302520</td>
<td>63233-325-20</td>
<td>1,000 mg per 20 mL (50 mg per mL) Acyclovir Sodium Injection equivalent to acyclovir, 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.

This container closure is not made with natural rubber latex.

Fresenius Kabi USA, LLC
Lake Zurich, IL 60047

45769H
Revised: March 2014