**Package Insert**

**Actavir 250**

**Actavir 500**

## 1. Product Name

Actavir 250

Actavir 500

## 2. Name and Strength of Active Ingredient(s)

Each vial contains:-

Aciclovir Sodium eq. to aciclovir 250 mg

Aciclovir Sodium eq. to aciclovir 500 mg

## 3. Product Description

White sterile powder for injection

## 4. Pharmacodynamics and Pharmacokinetics

Pharmacodynamics

Aciclovir is a synthetic purine nucleoside analogue with in vitro inhibitory activity against HSV-1, HSV-2, and varicella-zoster virus (VZV). In cell culture, aciclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV.

The inhibitory activity of aciclovir in highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts aciclovir into aciclovir monophosphate, a nucleoside analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, aciclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: Competitive inhibition of viral DNA polymerase, incorporation into and termination of the growing viral DNA chain, and inactivation of the viral DNA polymerase. The greater antiviral activity of aciclovir against HSV compared with VZV is due to its more efficient phosphorylation by the viral TK.

Pharmacokinetics

Absorption/ Distribution –

| **Aciclovir Injection Peak and Trough Concentrations at Steady-State** | | |
|---|---|---|
| Dosage regimen | $Css_{max}$ | $Css_{trough}$ |
| 5 mg/kg every 8 hours (n = 8) | 9.8 mcg/mL | 0.7 mcg/mL |
| | Range: 5.5 to 13.8 | Range: 0.2 to 1 |
| 10 mg/kg every 8 hours (n = 7) | 22.9 mcg/mL | 1.9 mcg/mL |
| | Range: 14.1 to 44.1 | Range: 0.5 to 2.9 |

Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%).

Metabolism/ Excretion – Renal excretion of unchanged drug is the major route of aciclovir 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 healthy renal function.

| **Aciclovir Injection Half-Life and Total Body Clearance** | | | |
|---|---|---|---|
| Creatinine clearance (mL/min per 1.73 $m^2$) | Half – life (h) | Total body clearance | |
| | | (mL/min per 1.73 $m^2$) | (mL/min/kg) |
| > 80 | 2.5 | 327 | 5.1 |
| 50 to 80 | 3 | 248 | 3.9 |
| 15 to 50 | 3.5 | 190 | 3.4 |
| 0 (anuric) | 19.5 | 29 | 0.5 |

Special populations –

Renal function impairment: Aciclovir 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.

Elderly: Aciclovir plasma concentrations are higher in elderly patients compared with younger adults, in part due to age-related changes in renal function. Dosage reduction may be required in elderly patients with underlying renal impairment.

**5. Indication**

- Systemic herpes simplex virus infections: Treatment of systemic herpes simplex virus infections.
- Herpes simplex virus, mucocutaneous infection in immunocompromised patients: Treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) in immunocompromised patients.
- Herpes simplex encephalitis: Treatment of herpes simplex encephalitis.
- Herpes simplex virus, genital infection (severe): Treatment of severe initial clinical episodes of genital herpes in immunocompetent patients.
- Herpes simplex virus, neonatal: Treatment of neonatal herpes infections.
- Varicella-Zoster infections: Treatment of varicella (chickenpox) and herpes zoster (Shingles, Zoster)

**6. Recommended Dose**

Adult: For obese patients, administer the recommended adult dose using ideal body weight.

- Systemic herpes simplex virus infections – Usual dosage: 5 mg/kg IV every 8 hours for 7-14 days
- Herpes simplex virus, mucocutaneous – Usual dosage: 5 mg/kg IV every 8 hours for 7 days

  HIV-infected patients – 5 mg/kg/dose IV every 8 hours, followed by oral aciclovir after lesions begin to heal; continue oral therapy until lesions are completely healed.
- Herpes simplex encephalitis – 10 mg/kg IV every 8 hours for 10 days
- Herpes simplex virus, genital (severe initial episodes) – Usual dosage: 5 mg/kg IV every 8 hours for 5 to 7 days
- Varicella-Zoster infections in immunocompromised patients – Usual dosage: 10 mg/kg IV every 8 hours for 7 days

Pediatric:

- Systemic herpes simplex virus infections –

Younger than 12 years: 10 mg/kg IV every 8 hours for 7-14 days

- Herpes simplex virus, mucocutaneous –

12 years and older: See Adult

Younger than 12 years: 10 mg/kg IV every 8 hours for 7 days

- Herpes simplex encephalitis –

12 years and older: 10 mg/kg IV every 8 hours for 10 days

- Herpes simplex virus, genital (severe initial episodes) –

12 years and older: See Adult

- Herpes simplex virus, neonatal –

Birth to 3 months of age: In neonatal herpes simplex infection, doses of 20 mg/kg IV every 8 hours have been used; the safety and efficacy of these doses are not known.

- Varicella-Zoster in immunocompromised patients –

12 years and older: See Adult

Younger than 12 years: Because of increased risk of nephrotoxicity associated with 20 mg/kg/dose, a 10 mg/kg/dose every 8 hours for 7 to 10 days or until no new lesions for 48 hours is recommended by several references.

Renal function impairment:

| **Aciclovir Injection Dosage Adjustments in Renal Impairment** | | |
|---|---|---|
| Creatinine clearance (mL/min/1.73 $m^2$) | Percent of recommended dose | Dosing interval (hours) |
| > 50 | 100% | 8 |
| 25 to 50 | 100% | 12 |
| 10 to 25 | 100% | 24 |
| 0 to 10 | 50% | 24 |

Hemodialysis – The patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

*Adults receiving continuous renal replacement therapy:* One reference suggests a dosage of 5 to 10 mg/kg IV every 24 hours.

The following alternative recommendations assume ultrafiltration and dialysis flow rates of 1 to 2 L/h. A higher dosage is recommended when treating viral meningoencephalitis and varicella-zoster virus infections.

- Continuous venovenous hemofiltration – 5 to 10 mg/kg IV every 24 hours
- Continuous venovenous hemodialysis or continuous venovenous hemodiafiltration – 5 to 10 mg/kg IV every 12 to 24 hours

*Adults receiving intermittent hemodialysis:* 2.5 to 5 mg/kg IV every 24 hours administered after the dialysis session. This recommendation assumes the patient is receiving standard intermittent hemodialysis 3 times per week and completes the full dialysis sessions. Patients receiving extended daily dialysis may require increased doses. A higher dosage is recommended when treating viral meningoencephalitis and varicella-zoster virus infections.

**7. Mode of Administration**

Administration: Administer by constant infusion over 1 hour. Rapid or bolus IV injection must be avoided. Intramuscular (IM) or subcutaneous injection must also be avoided.

Preparation for administration

Reconstitution- The contents of the vial should be dissolved in sterile water for injection as follows:

| **Aciclovir Injection Reconstitution** | |
|---|---|
| Contents of vial | Amount of diluent |
| 250 mg | 10 mL |
| 500 mg | 20 mL |

Solution for infusion in each case of Actavir 250 or Actavir 500 are prepared to give a concentration of aciclovir of 25 mg/mL. Shake the vial well to ensure complete dissolution before measuring and transferring each individual dose.

Dilution –This must then be further diluted to a final concentration not greater than about 5 mg/mL (0.5%) and given over 1 hour. Higher concentrations (eg, 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Once diluted for administration, use each dose within 24 hours.

Admixture compatibilities

When reconstituting the contents of the vial, do not use bacteriostatic water for injection containing benzyl alcohol or parabens. Standard, commercially available electrolyte and glucose solutions are suitable for IV administration, including 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, Ringer's lactate solution; biologic or colloidal fluids (eg, blood products, protein solutions) are not recommended.

Storage/ Stability

The reconstituted solution should be used within 12 hours. Refrigeration of reconstituted solution may result in the formation of a precipitate that will redissolve at room temperature and diluted solution should be used within 24 hours of preparation.

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

**8. Contraindication**

Hypersensitivity to aciclovir, valaciclovir

**9. Warnings/ precautions**

- Administration: Aciclovir for injection is intended for IV infusion only; do not administer topically, IM, orally, subcutaneously, or in the eye. IV infusions must be given over a period of at least 1 hour to reduce the risk of renal tubular damage.
- Thrombotic thrombocytopenic purpura / hemolytic uremic syndrome: Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome, which has resulted in death, has occurred in immunocompromised patients receiving acyclovir therapy.
- Renal effects: Precipitation of aciclovir crystals in renal tubules can occur if the maximum solubility of free aciclovir (2.5 mg/mL at 37 $^{o}$C [98.6$^{o}$F] in water) is exceeded or if the drug is administered by bolus injection. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of aciclovir 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, preexisting renal disease, and dehydration make further renal impairment with aciclovir more likely.

When dosage adjustments are required, they should be based on estimated creatinine clearance.

- Hydration: Administration of aciclovir by IV infusion must be accompanied by adequate hydration.
- Encephalopathic changes: Approximately 1% of patients receiving IV aciclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma. Use aciclovir with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities, or significant hypoxia.
- Extravasation: Extravasation may occur during administration of aciclovir. If signs or symptoms of extravasation occur, stop the infusion immediately. If possible, withdraw 3 to 5 mL of blood to remove some of the drug. Hyaluronidase is an effective antidote for hyperosmolar drug infiltrations; administer promptly within the first few minutes to 1 hour after extravasation. Higher doses (150 units) have primarily been used in adults while lower doses (15 units) have been used in children.
- Renal function impairment: The dose of acyclovir must be adjusted in patients with impaired renal function in order to avoid accumulation of acyclovir in the body.

In patients receiving acyclovir at higher doses, (eg, for herpes encephalitis), take specific care regarding renal function, particularly when patients are dehydrated or have any renal impairment.

Renal failure, in some cases resulting in death, has been observed with aciclovir therapy.

**10. Drug interaction**

Metabolism/ Transport effects: None known.

| **Drug Interactions** | |
|---|---|
| Interacting Drugs or Drug Classes | Summary Description |
| Antifungal Agents | Amphotericin B has been shown to potentiate the antiviral effect of aciclovir against pseudorabies virus in vitro. Ketoconazole and aciclovir have shown dose dependent, synergistic, antiviral activity against herpes simplex virus types 1 and 2 in in vitro. |
| Foscarnet | Foscarnet may enhance the nephrotoxic effect of aciclovir-Valaciclovir. Avoid combination. |
| Methotrexate | IV aciclovir should be used with caution in patients receiving intrathecal methotrexate. |
| Mycophenolate | Aciclovir-Valaciclovir may increase the serum concentration of Mycophenolate. Mycophenolate may increase the serum concentration of Aciclovir-Valaciclovir. Monitor therapy. |

| | |
|---|---|
| Probenecid | Concomitant administration of probenecid and aciclovir has reportedly increased the mean plasma half-life and area under the plasma concentration-time curve (AUC) and decreased urinary excretion and renal clearance of aciclovir. |
| Talimogene Laherparepvec | Antiherpetic Antivirals may diminish the therapeutic effect of Talimogene Laherparepvec. Monitor therapy. |
| Tenofovir Products | Aciclovir-Valaciclovir may increase the serum concentration of Tenofovir Products. Tenofovir Products may increase the serum concentration of Aciclovir-Valaciclovir. Monitor therapy. |
| Varicella Virus Vaccine | Aciclovir-Valaciclovir may diminish the therapeutic effect of Varicella Virus Vaccine. Management: When possible, avoid use of aciclovir or valaciclovir within the 24 hours prior to administration of the varicella vaccine, and avoid use of these antiviral agents for 14 days after vaccination. Avoid combination. |
| Zidovudine | Aciclovir-Valaciclovir may enhance the CNS depressant effect of Zidovudine. Monitor therapy. |
| Zoster Vaccine | Aciclovir-Valaciclovir may diminish the therapeutic effect of Zoster Vaccine. Management: When possible, discontinue antiviral agents with anti-zoster activity (i.e., aciclovir, valaciclovir, famciclovir) for at least 24 hours prior to and 14 days after receiving a live attenuated zoster vaccine. Avoid combination. |

**11. Pregnancy and Lactation**

Pregnancy: Category B. Teratogenic effects were not observed in animal reproduction studies. Aciclovir has been shown to cross the human placenta. Results from pregnancy registry, established in 1984 and closed in 1999, did not find an increase in the number or birth defects with exposure to acyclovir when compared with those expected in the general population. However, because of the small size of the registry and lack of long-term data, the manufacturer recommends using during pregnancy with caution and only when clearly needed. Aciclovir is recommended for the treatment of genital herpes in pregnant women.

Lactation: Aciclovir is excreted in breast milk. The manufacturer recommends that caution be exercised when administering aciclovir to breast-feeding women. Aciclovir may be used for the treatment of genital herpes in breast-feeding women. Breast-feeding mothers with herpetic lesions near or on the breast should avoid breast-feeding.

**12. Undesirable effects/ Adverse Reactions**

The most frequent adverse reactions reported during administration of aciclovir were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or blood urea nitrogen in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] IV infusion). Nausea 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% to 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, thrombocytosis, leukocytosis, and neutrophilia. In addition, anorexia and hematuria were observed.

Postmarketing:

- Cardiovascular – Hypotension
- CNS - 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.
- Dermatologic – 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 aciclovir into extravascular tissues.
- GI – Abdominal pain, diarrhea, GI distress, nausea
- GU – Renal failure, elevated blood urea nitrogen, elevated creatinine
- Hematologic/ Lymphatic – Disseminated intravascular coagulation, hemolysis, leukocytoclastic vasculitis, Vasculitis, leukopenia, lymphadenopathy
- Hepatic – Elevated liver function tests, hepatitis, hyperbilirubinemia, jaundice
- Musculoskeletal – Myalgia
- Special Senses – Visual abnormalities
- Miscellaneous – anaphylaxis, angioedema, fatigue, fever, headache, pain, peripheral edema

**13. Over dosage and treatment**

Overdosage of IV aciclovir has been reported following administration of rapid IV injection or inappropriately high doses and in patients with fluid and electrolyte imbalance, resulting in elevations in BUN and serum creatinine concentration and subsequent renal failure. At renal concentrations exceeding 2.5 mg/mL, aciclovir crystal may precipitate in the renal tubules, possibly causing renal dysfunction and eventual renal failure and anuria. A toxic dose has not been established for these agents. Aciclovir: Adult: Overdose ingestions up to 20 g have been reported, associated with the development of lethargy, agitation, seizures, and coma. Pediatric: A 2-year-old received 800 mg aciclovir IV and developed transient neurotoxicity but recovered. Two neonates, who received 65

mg/kg and 100 mg/kg aciclovir IV had no evidence of toxicity. Transient nephrotoxicity developed in a neonate who received aciclovir 100 mg/kg IV three times daily for 4 days, and another who received 750 mg/kg IV.

Support: management of mild to moderate toxicity: Patients generally do well with supportive care. Nausea and vomiting should be treated with antiemetics. Rashes should be treated with supportive care, discontinuation of the offending agent, and consideration of antihistamines and corticosteroids. With massive overdose, hydrate patients and monitor renal function. Management of severe toxicity: Supportive care remains the mainstay of care in severe toxicity. Seizures should be treated with benzodiazepines as first line therapy, followed by barbiturates or propofol, if seizures persist. Hydrate patients and monitor urine output and renal function. Airway protection should be employed as need for patients with coma.

Decontamination: Hospital: Activated charcoal should be considered in patients with recent, large overdose if they are awake, alert, and willing to drink the charcoal. Gastric lavage has no role, as toxicity is not life threatening.

Antidote: None

Monitoring of patient: Monitor renal function and urine output in patients receiving IV aciclovir with suspected toxicity or after massive oral overdose.

Enhanced elimination procedure: Aciclovir and famciclovir have low protein binding and volumes of distribution, and can be removed by hemodialysis. Hemodialysis has been used to reduce serum aciclovir concentrations in patients with toxicity, but is rarely indicated as patients do well with supportive care.

Patient disposition: Asymptomatic patients with inadvertent ingestion of these products may be observed at home. Patients with deliberate overdose and symptomatic patients should be sent to a healthcare facility for evaluation and treatment. Patients should be observed for 6 hours, primarily monitoring signs of co-ingestant toxicity or development of significant CNS depression. Follow-up renal function tests should be obtained in patients with massive overdose. Admit patients with severe toxicity characterized by CNS effects or renal injury.

**14. Storage condition**

Store below 30 $^{o}$C

**15. Dosage forms and packing available**

Clear glass vial (Type I) with grey chlorobutyl rubber stoppers, sealed with aluminium/polypropylene flip-off caps contains aciclovir sodium eq. to aciclovir 250 mg or aciclovir sodium eq. to aciclovir 500 mg, packed or unpacked in a box of 1, 5, 10, 20, 25, 50 and 100 vials.

**16. Name and address of manufacturing/ marketing authorization holder**

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nongson, Chiangyuen, Mahasarakham 44160, Thailand

**17. Date of revision of package insert**

12 June, 2023