Virux®

Acyclovir USP

COMPOSITION

Virux® 250 IV Injection: Each vial contains sterile Lyophilized Acyclovir Sodium USP equivalent to 250 mg Acyclovir.
Virux® 500 IV Injection: Each vial contains sterile Lyophilized Acyclovir Sodium USP equivalent to 500 mg Acyclovir.

PHARMACOLOGY

Acyclovir exerts its antiviral effects on *Herpes simplex* virus and *Varicella zoster* virus by interfering with DNA synthesis and inhibiting viral replication. In cells infected with Herpes virus, the antiviral activity of Acyclovir appears to depend principally on the intracellular conversion of the drug to Acyclovir Triphosphate. Acyclovir is converted to Acyclovir Monophosphate principally via virus coded thymidine kinase, the monophosphate is phosphorylated to diphosphate via cellular guanylate kinase and then via other cellular enzymes to the Triphosphate, which is the pharmacologically active form of the drug.

PHARMACOKINETICS

In adults the plasma half-life of Acyclovir after administration of Intravenous Infusion is about 2.9 hours. It is widely distributed to the body tissues and fluids including the brain, saliva, lungs, liver, muscle, spleen, uterus, vaginal mucosa and secretions, CSF, and herpetic vesicular fluid. Approximately 60% of the drug is excreted unchanged by the kidney by glomerular filtration and tubular excretion. Mean steady state peak plasma concentrations (C^{SS}max) following a one hour infusion of 5 mg/kg or 10 mg/kg were 9.8 ± 2.6 and 20.7 ± 10.2 µg/ml respectively. In children over 1 year of age similar mean peak (C^{SS}max) levels were observed when a dose of 5 mg/kg was given. In children aged 0-3 months the terminal plasma half-life is approximately 4 hours. In patients with chronic renal failure the mean terminal half-life was found to be 19.5 ± 5.9 hours. The mean Acyclovir half-life during haemodialysis was 5.7 hours. Plasma Acyclovir levels dropped approximately 60% during dialysis. Plasma protein binding is low (9 to 33%).

INDICATION

Virux® IV Injection is indicated in:

1. Acute clinical manifestations of *Herpes simplex* virus in immunocompromised patients
2. Severe primary or non-primary genital herpes in immune competent patients
3. *Varicella zoster* virus infection in immunocompromised patients
4. Herpes zoster (shingles) in immune competent patients who show very severe acute local or systemic manifestations of the disease
5. *Herpes simplex* encephalitis

DOSAGE AND ADMINISTRATION

Indication	Immune status	Dosage
Herpes simplex infection	Normal or immunocompromised	5 mg/kg every 8 hours
Very severe Herpes zoster infection (shingles)	Normal	5 mg/kg every 8 hours
Varicella zoster infection	Immunocompromised	10 mg/kg every 8 hours
Herpes simplex encephalitis	Normal or immunocompromised	10 mg/kg every 8 hours

Each dose should be administered by slow intravenous infusion over a one-hour period.
In patients with renal impairment, Acyclovir should be administered with caution since the drug is excreted through the kidneys. The following modifications in dosage are suggested:

Creatinine Clearance	Recommended dose
25-50 ml/min	5 or 10 mg/kg every 12 hours
10-25 ml/min	5 or 10 mg/kg every 24 hours
0 - 10 ml/min	2.5 or 5 mg/kg every 24 hours and after dialysis

CONTRAINDICATION

Acyclovir IV Injection is contraindicated in patients known to be hypersensitive to Acyclovir or Valacyclovir.

PRECAUTION

Acyclovir IV injection is intended for intravenous infusion only and should not be used through any other route. Reconstituted Acyclovir IV Infusion has a pH of approximately 11.0 and should not be administered by mouth.
Acyclovir IV injection as infusion must be given over a period of at least one hour in order to avoid renal tubular damage. It should not be administered as a bolus injection. Acyclovir IV infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first few hours following infusion, particular attention should be given to establish sufficient urine flow during that period. Concomitant use of other nephrotoxic drugs, pre-existing renal disease and dehydration increase the risk of further renal impairment by Acyclovir.
As Acyclovir has been associated with reversible encephalopathic changes, it should be used with caution in patients with neurological abnormalities, significant hypoxia or serious renal, hepatic or electrolyte abnormalities.

PREGNANCY AND LACTATION

Pregnancy category B.
There have been no adequate and well controlled studies concerning the safety of Acyclovir in pregnant women. It should not be used during pregnancy unless the benefits to the patient clearly outweigh the potential risks to the fetus.
Acyclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

MUTAGENICITY

The results of mutagenicity tests in vitro and in vivo suggest that Acyclovir is unlikely to pose a genetic threat to man at therapeutic dose levels.

CARCINOGENECITY

Lifetime oral dosing studies in mice and rats gave no evidence for tumourogenicity.

EFFECTS ON FERTILITY

There is no experience of the effect of Acyclovir on human fertility.

PEDIATRIC USE

The dose of **Virux®** IV injection in children aged 1-12 years should be calculated on the basis of body surface area. Children in this age group with *Herpes simplex* infections (except *Herpes simplex* encephalitis) or *Varicella zoster* infections should be given **Virux®** IV Infusion in doses of 250 mg per square metre of body surface area (equivalent to 5 mg/kg in adults). Immunocompromised children in this age group with *Varicella zoster* virus infection or with *Herpes simplex* encephalitis should be given **Virux®** IV Infusion in doses of 500 mg per square metre of body surface area (equivalent to 10 mg/kg in adults). Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

GERIATRIC USE

No data are available on this age group. However, as creatinine clearance is often low in the elderly, special attention should be given to dosage reduction.

DURATION OF TREATMENT

It is recommended that Acyclovir IV Injection for Intravenous Infusion should be administered for five to seven days in the treatment of most infections and for at least ten days in the treatment of *Herpes simplex* encephalitis.

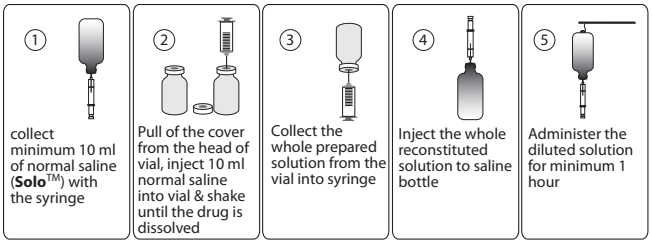
RECONSTITUTION

Each 250 mg vial of Acyclovir IV Injection should be reconstituted by the addition of 10 ml of either Water for Injection BP or Sodium Chloride Intravenous Infusion BP (0.9% w/v). This provides a solution containing 25 mg Acyclovir per ml.
Each 500 mg vial of Acyclovir IV Injection should be reconstituted by the addition of 10 ml of either Water for Injection BP or Sodium Chloride Intravenous Infusion BP (0.9% w/v). This provides a solution containing 50 mg Acyclovir per ml.

ADMINISTRATION

Virux® IV Injection after reconstitution may be injected directly into a vein over one hour by a controlled-rate infusion pump or be further diluted for administration by infusion.

For intravenous infusion each vial of **Virux®** IV Injection should be reconstituted and then, wholly or in part according to the dosage required, added to and mixed with at least 50 mL-100 ml infusion solution. A maximum of 250 mg & 500 mg of Acyclovir may be added to 50 ml & 100 ml infusion solution respectively. After addition of **Virux®** IV Injection to an infusion solution the mixture should be shaken to ensure thorough mixing. **Virux®** IV Injection when diluted in accordance with the above schedule will give an Acyclovir concentration not greater than 0.5% w/v.



Virux® IV Injection is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (below 25°C) when diluted to a concentration not greater than 0.5% w/v Acyclovir.

- Sodium Chloride Intravenous Infusion BP (0.45% and 0.9% w/v)
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion BP
- Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution)

Virux® IV Injection for Intravenous Infusion contains no preservative. Reconstitution and dilution should therefore be carried out immediately before use and any unused solution should be discarded. The solution should not be refrigerated.

ADVERSE REACTIONS

Some infrequent adverse reactions are lethargy, obtundation, tremors, confusion, hallucinations, agitation, somnolence, psychosis, convulsions and coma, phlebitis, nausea, vomiting, reversible increases in liver-related enzymes, pruritus, urticaria, rashes, increases in blood urea and creatinine. Local inflammatory reactions may occur if Acyclovir IV Infusion is inadvertently infused into extracellular tissues.

DRUG INTERACTION

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 correspondingly reduced.
In patients over 60 years of age concurrent use of diuretics increases plasma levels of Acyclovir very significantly.

OVER DOSAGE

Overdosage of intravenous Acyclovir 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 over dosage. Adequate hydration is essential to reduce the possibility of crystal formation in the urine. Haemodialysis significantly enhances the removal of Acyclovir from the blood and may, therefore, be considered an option in the management of overdose of Acyclovir.

STORAGE

Store at 15°C to 25°C. Protected from light and moisture. Keep the medicine out of the reach of children.

HOW SUPPLIED

Virux® 250 IV Injection: Each combipack contains one vial of Acyclovir 250 mg accompanied with 50 ml 0.9% Sodium Chloride solution (**Solo™**), one infusion set, one alcohol pad, one first aid band & one 10 ml sterile disposable syringe.
Virux® 500 IV Injection: Each combipack contains one vial of Acyclovir 500 mg accompanied with 100 ml 0.9% Sodium Chloride solution (**Solo™**), one infusion set, one alcohol pad, one first aid band & one 10 ml sterile disposable syringe.

Manufactured by
SQUARE PHARMACEUTICALS LTD.
Pabna, Bangladesh

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