# FOSCAVIR® Infusion 24 mg/ml

Solution for infusion

## Composition

Solution for intravenous infusion.

1 ml contains 24 mg (80 µmol) foscarnet trisodium hexahydrate*, hydrochloride acid (E507) q.s. and water for injection q.s. The solution is sterile, clear and isotonic with a pH of 7.4.

*foscarnet sodium (rINN) or trisodium phosphonoformate hexahydrate or phosphonoformic acid trisodium salt hexahydrate.

## Description

### Antiviral and pharmacological properties

Foscarnet is an antiviral agent with a broad antiviral spectrum which inhibits all known human viruses of the herpes group, herpes simplex virus type 1 and 2, human herpes virus 6, varicella zoster virus, Epstein-Barr virus and cytomegalovirus (CMV) and some retroviruses, including human immunodeficiency virus (HIV) at concentrations not affecting normal cell growth. Foscarnet also inhibits the viral DNA polymerase from hepatitis B virus. Foscarnet exerts its antiviral activity by a direct inhibition of viral specific DNA polymerase and reverse transcriptase.

The mean Foscavir 50% inhibition value ($IC_{50}$) for more than one hundred clinical CMV isolates is approximately 270 µmol/l, while a reversible inhibition of normal cell growth was observed at about 1000 µmol/l.

In several animal species foscarnet is rapidly cleared from the blood and other soft tissues after intravenous administration.

The most pronounced effects noted during general toxicity studies performed with Foscavir are perturbation of some serum electrolytes, and kidney and bone changes.

An observed reduction of serum electrolytes such as calcium and magnesium can be explained by the property of Foscavir to form chelate with divalent metal ions. The reduction of ionized calcium and magnesium is, most probably, the explanation to seizures/convulsions seen during and shortly after the infusion of high doses of Foscavir. This reduction may also have a bearing on heart function (e.g. ECG) although the toxicological studies performed did not disclose any such effects. The rate of infusion of Foscavir is critical to disturbances in the homeostasis of some serum divalent cations.

The mechanism behind the kidney changes, e.g. tubular atrophy, mainly confined to juxtamedullary nephrons, is less clear. The changes were noted in all species investigated. It is known that other complex binders of divalent cations (EDTA and biphosphonates) can cause changes of the kidney similar to those of Foscavir. It has been shown that hydration, to induce diuresis, significantly reduces kidney changes during Foscavir treatment.

The bone changes were characterised as increased osteoclast activity and bone resorption. Roughly 20% of the administered drug is taken up into bone and cartilage and deposition is greater in young and growing animals. This effect has only been seen in the dog. The reason to these changes may be that Foscavir, due to the structural similarity to phosphate, is incorporated into the hydroxyapatite. Autoradiographic studies showed that Foscavir has a pronounced affinity to bone tissue. Recovery studies revealed that the bone changes were reversible. Foscarnet sodium has been demonstrated to adversely affect development of tooth enamel in mice and rats. The effects of this deposition on skeletal development have not been studied.

The plasma clearance of foscarnet after intravenous administration to man varies between 130-160 ml/min and the renal clearance is about 130ml/min.

The half-life is in the order of 2-4 hours in patients with normal renal function.

The mean volume of distribution of foscarnet at steady state varies between 0.4-0.6 litre/kg. Foscarnet is mainly eliminated by the kidney through glomerular filtration and tubular secretion.

Foscarnet is distributed to the cerebrospinal fluid and concentrations in the order of 70% of the concurrent plasma concentrations have been observed in HIV infected patients.

There is no metabolic conversion of foscarnet, and the binding to human plasma proteins is less than 20%.

## Therapeutic properties

Following induction therapy, either administered as a continuous infusion or as intermittent infusions every eight hours, foscarnet has produced a stabilization of retinal lesions in approximately 90% of cases treated. However, since CMV usually causes latent infections and since foscarnet exerts a virustatic activity, relapses are likely in the majority of patients with persistent immunodeficiency once treatment is discontinued. Institution of a once daily maintenance therapy, following completion of induction therapy has produced a delay in time to retinitis progression. In patients experiencing progression of retinitis while receiving maintenance therapy or off therapy, reinstitution of induction therapy has shown equal efficacy as the initial course.

There is no evidence of an increased myelotoxicity when foscarnet is used in combination with zidovudine (AZT).

## Indication

Cytomegalovirus (CMV) retinitis in patients with the acquired immunodeficiency syndrome (AIDS).

## Contraindication

Hypersensitivity to foscarnet.

## Precautions and Warnings

Foscarnet should be used with caution in patients with reduced renal function. Since renal function impairment may occur at any time during foscarnet administration, serum creatinine should be monitored every second day during induction therapy and once weekly during maintenance therapy and appropriate dose adjustments should be performed according to renal function. Adequate hydration should be maintained in all patients (See Dosage and Administration). The renal function of patients with renal disease or receiving concomitant treatment with other nephrotoxic medicinal products must be closely monitored (see Interactions).

This medicinal product contains 1.38 g of sodium per 250 ml bottle, equivalent to equivalent to 69% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
The maximum recommended daily dose of this product is 12 g of Foscavir per day (180 mg/kg/day in average 70 kg patient), which is equivalent to 138% of the WHO recommended maximum daily dietary intake for sodium.
Foscavir is considered high in sodium. This should be particularly taken into account for those on a low sodium diet. Its use should be avoided when a saline load cannot be tolerated (e.g. in cardiomyopathy).

Due to foscarnet's propensity to chelate bivalent metal ions, such as calcium, foscarnet administration may be associated with an acute decrease of ionized serum calcium proportional to the rate of Foscavir infusion, which may not be reflected in total serum calcium levels. The electrolytes, especially calcium and magnesium, should be assessed prior to and during Foscavir therapy and deficiencies corrected.

Foscarnet has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and Torsade de pointes in patients taking foscarnet. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, as well as patients with underlying cardiac diseases such as congestive heart failure should be carefully monitored due to increased risk of ventricular

arrhythmia. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic risk.

Patients should be advised to promptly report any cardiac symptoms.

Foscavir is deposited in teeth, bone and cartilage. Animal data show that deposition is greater in young animals. The safety of Foscavir and its effect on skeletal development have not been investigated in children. Please refer to Description section.

Seizures, related to alterations in plasma minerals and electrolytes, have been associated with Foscavir treatment. Cases of status epilepticus have been reported. Therefore, patients must be carefully monitored for such changes and their potential sequelae. Mineral and electrolyte supplementation may be required.

Foscavir is excreted in high concentrations in the urine and may be associated with significant genital irritation and/or ulceration. To prevent irritation and ulceration, close attention to personal hygiene is recommended and cleaning of the genital area after each micturition is recommended.

Should patients experience extremity paraesthesia or nausea, it is recommended to reduce the speed of infusion.

When diuretics are indicated, thiazides are recommended.

Development of resistance: If the administration of Foscavir does not lead to a therapeutic response or leads to a worsened condition after an initial response, this may result from a reduced sensitivity of viruses towards foscarnet. In this case, termination of Foscavir therapy and a change to an appropriate other medicinal product should be considered.

## Fertility, pregnancy and lactation

There are no data available regarding the influence of Foscavir on fertility. No effects on fertility were observed in animal studies.

Women capable of childbearing should use effective contraception methods during Foscavir therapy. Men treated with Foscavir should not father a child during or up to 6 months after therapy.

Since there is no clinical experience or investigational data available, foscarnet should not be given to pregnant women or during lactation.

## Effects on the ability to drive and operate machinery

Adverse effects such as dizziness and convulsions may occur during Foscavir therapy. The

physician is advised to discuss this issue with the patient, and based upon the condition of the disease and the tolerance of medication, give a recommendation in the individual case.

## Adverse events

The majority of patients who receive Foscavir are severely immuno-compromised and suffering from serious viral infections. Patients' physical status, the severity of the underlying disease, other infections and concurrent therapies contribute to adverse events observed during use of Foscavir.

The undesirable effects reported with Foscavir during clinical trials and post-marketing surveillance are shown in the table below. They are listed by System-Organ Class (SOC) and in order of frequency, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Please note that in these clinical trials, hydration and attention to electrolyte balance was not consistently given; the frequency of some adverse events will be lower when current recommendations are followed (see Dosage and Administration, and Precautions and Warnings sections).

**Table: Frequency of adverse events**

| SOC | Frequency | Event |
|---|---|---|
| Blood and lymphatic system disorders | Very common | Granulocytopenia, anaemia |
| | Common | Leukopenia, thrombocytopenia, neutropenia |
| | Uncommon | Pancytopenia |
| Immune system disorders | Common | Sepsis |
| | Not known | Hypersensitivity (including anaphylactic reactions), anaphylactoid reactions |
| Endocrine disorders | Not known | Diabetes insipidus |
| Metabolism and nutrition disorders | Very common | Decreased appetite, hypokalaemia, hypomagnesaemia, hypocalcaemia |
| | Common | Hyperphosphataemia, hyponatraemia, hypophosphataemia, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, hypercalcaemia, dehydration |
| | Uncommon | Acidosis |
| | Not known | Hypernatraemia |
| Psychiatric disorders | Common | Aggression, agitation, anxiety, confusional state, depression, nervousness |
| | Not known | Mental status changes |
| Nervous system disorders | Very common | Dizziness, headache, paraesthesia |
| | Common | Coordination abnormal, convulsion, hypoaesthesia, muscle contractions involuntary, neuropathy peripheral, tremor |
| | Not known | Encephalopathy, status epilepticus |

| SOC | Frequency | Event |
|---|---|---|
| Cardiac disorders | Common | Palpitations, tachycardia |
| | Not known | Electrocardiogram QT prolonged, ventricular arrhythmia, Torsade de pointes |
| Vascular disorders | Common | Hypertension, hypotension, thrombophlebitis[a] |
| Gastrointestinal disorders | Very common | Diarrhoea, nausea, vomiting |
| | Common | Abdominal pain, constipation, dyspepsia, pancreatitis, gastrointestinal haemorrhage |
| | Not known | Oesophageal ulceration |
| Hepatobiliary disorders | Common | Hepatic function abnormal |
| Skin and subcutaneous disorders | Very common | Rash |
| | Common | Pruritus |
| | Uncommon | Urticaria, angioedema |
| | Not known | Erythema multiforme, toxic epidermal necrolysis, Stevens Johnson syndrome[b] |
| Musculoskeletal and connective tissue disorders | Common | Myalgia |
| | Not known | Muscular weakness, myopathy, myositis, rhabdomyolysis |
| Renal and urinary disorders | Common | Renal impairment, renal failure acute, dysuria, polyuria, proteinuria |
| | Uncommon | Renal tubular disorder, glomerulonephritis, nephrotic syndrome |
| | Not known | Renal pain, renal tubular acidosis, renal tubular necrosis, acute tubular necrosis, crystal nephropathy, Fanconi syndrome acquired, haematuria |
| Reproductive system and breast disorders | Common | Genital discomfort and ulceration[c] |
| General disorders and administration site conditions | Very common | Asthenia, chills, fatigue, pyrexia |
| | Common | Malaise, oedema, chest pain[d], injection site pain, injection site inflammation |
| | Uncommon | Localised oedema |
| | Not known | Extravasation |
| Investigations | Very common | Blood creatinine increased, haemoglobin decreased |
| | Common | Creatinine renal clearance decreased, electrocardiogram abnormal, gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased |
| | Uncommon | Amylase increased, blood creatine phosphokinase increased |

[a]Thrombophlebitis in peripheral veins following infusion of undiluted foscarnet solution has been observed.

[b] Cases of vesiculobullous eruptions including erythema multiforme, toxic epidermal necrolysis, and Stevens Johnson syndrome have been reported. In most cases, patients were taking other medications that have been associated with toxic epidermal necrolysis or Stevens Johnson syndrome.

[c] Foscarnet is excreted in high concentrations in the urine and may be associated with significant irritation and ulceration in the genital area, particularly after prolonged therapy.

[d] Transient chest pain has been reported as part of infusion reactions to foscarnet.

## Dosage and administration

### Method of Administration

Foscarnet should be administered by the intravenous route only, either by a central venous line or in a peripheral vein.

When peripheral veins are used, the solution of foscarnet 24 mg/ml must be diluted with dextrose 5% or normal saline to a concentration of 12 mg/ml immediately prior to administration.

The solution of foscarnet 24 mg/ml may be given without dilution via a central vein.

## Adults

*Induction therapy*

Foscarnet can be administered either as a continuous infusion over 24 hours or as intermittent infusions every 8 hours at a dose of 60 mg/kg in patients with normal renal function. (see dosing chart below).

When foscarnet is administered as a continuous infusion the treatment is started with an intravenous infusion of 20mg/kg body weight over a period of 30 minutes followed by a continuous intravenous infusion at a dose determined by renal function as assessed by estimated creatinine clearance.
When administered as intermittent infusions every 8 hours, the dose of foscarnet should be adjusted to the renal function as assessed by estimated creatinine clearance. The infusion time should not be shorter than 1 hour.

*Maintenance therapy*

For maintenance therapy foscarnet is administered seven days a week as a once daily infusion over 2 hours at a dose determined by renal function as assessed by the estimated creatinine clearance, as long as therapy is considered appropriate. In patients with normal renal function the dose range is 90 - 120 mg/kg.

The dose recommendations are approximate and final dosing should be based on the clinical situation.

**Caution – Do not administer foscarnet by rapid intravenous injection.**

## Foscarnet Dosing Chart

*Induction Therapy*

| Creatinine clearance (ml/kg/min) | Intermittent infusion Dose: mg/kg every 8 hours over 1 hour | Continuous infusion Dose: mg/kg/24hours |
|---|---|---|
| >1.6 | 60 | 200 |
| 1.6-1.4 | 55 | 175 |
| 1.4 – 1.2 | 49 | 133 |
| 1.2 – 1.0 | 42 | 110 |
| 1.0 – 0.8 | 35 | 85 |
| 0.8 – 0.6 | 28 | 40 |
| 0.6 – 0.4 | 21 | 20 |
| <0.4 | Treatment not recommended | |

*Maintenance therapy*

| Creatinine clearance (ml/kg/min) | One infusion Dose: mg/kg/day over 2 hours |
|---|---|
| > 1.4 | 90 - 120 |
| 1.4 – 1.2 | 78 - 104 |
| 1.2 – 1.0 | 75 - 100 |
| 1.0 – 0.8 | 71 - 94 |
| 0.8 – 0.6 | 63 - 84 |
| 0.6 – 0.4 | 57 - 76 |
| < 0.4 | Treatment not recommended |

Foscarnet is not recommended for use in patients undergoing haemodialysis as dosage guidelines have not been established.

Hydration

Renal toxicity can be reduced by adequate hydration of the patient. It is recommended to add 2.5 litres over 24 hours when foscarnet is given as continuous infusion and to add 0.5 - 1.0 litre of normal saline to each infusion when on intermittent therapy. In compliant patients, oral hydration with similar hydration regimens has been used. Clinically dehydrated patients should have their condition corrected before initiating Foscavir therapy.

Duration of Treatment

An initial induction treatment period of 2-3 weeks is recommended, depending on the clinical response followed by maintenance therapy for as long as considered appropriate.

**Elderly:** As for adults.

**Paediatric population:** The safety and efficacy of foscarnet in children have not been established. Please refer to Description, and Precautions and Warnings sections.

**Renal or hepatic insufficiency:** The dose must be reduced in patients with renal insufficiency according to the creatinine clearance level as described in the table above. Dose adjustment is not required in patients with hepatic insufficiency.

## Interactions

Since foscarnet can impair renal function, additive toxicity may occur when used in combination with other nephrotoxic drugs such as aminoglycosides, amphotericin B, ciclosporin A, aciclovir, methotrexate and tacrolimus. Moreover, since foscarnet can reduce serum levels of ionized calcium, extreme caution is advised when used concurrently with other drugs known to influence serum calcium levels, like i.v. pentamidine. Renal impairment and symptomatic hypocalcaemia (Trousseau's and Chvostek's signs) have been observed in 4 patients during concurrent treatment with foscarnet and i.v. pentamidine.

Abnormal renal function has been reported in connection with the use of Foscavir in combination with ritonavir and/or saquinavir.

There is no pharmacokinetic interaction with zidovudine (AZT), ganciclovir, didanosine (ddI), zalcitabine (ddC) or probenecid.

Pharmaceutical interactions (incompatibilities for infusion) are described in the Pharmaceutical Incompatibilities section.

## Overdose

Overdose has been reported during the use of Foscavir, the highest being some 20 times the recommended dose. Some of the cases were relative overdoses, in that the dose of drug used had not been promptly adjusted for a patient experiencing reduced renal function.

There are cases where it has been reported that no clinical sequelae were consequent on the overdose.

The pattern of adverse events reported in association with an overdose of Foscavir is in accordance with the known adverse event profile of the drug.

Haemodialysis increases foscarnet elimination and may be of benefit in relevant cases.

## Pharmaceutical Incompatibilities

Foscarnet is not compatible with dextrose 30% solution, amphotericin B, acyclovir sodium, ganciclovir, pentamidine isethionate, trimethoprim-sulphamethoxazole and vancomycin hydrochloride. Neither is foscarnet compatible with solutions containing calcium. It is recommended that other drugs should not be infused concomitantly in the same line.

## Shelf-life

24 months.

## Special storage conditions

Do not store above 25°C. Do not refrigerate.

If refrigerated or exposed to temperatures below freezing point precipitation may occur. By keeping the bottle at room temperature with repeated shaking, the precipitate can be brought into solution again.

Foscarnet contains no preservatives and once the sterility seal of a bottle has been broken the solution should be discarded within 24 hours.

For doses prepared by the hospital pharmacy, foscarnet could be transferred to plastic infusion bags to be used within 24 hours.

Accidental skin and eye contact with the Foscavir solution may cause local irritation and burning sensation. If accidental contact occurs the exposed area should be rinsed with water.

## Package quantity

Infusion bottle 250 ml.

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