FOSCAVIR® Product Information

(Foscarnet sodium solution for infusion)

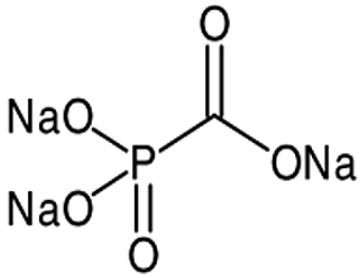
NAME OF THE MEDICINE

Foscarnet sodium hexahydrate

DESCRIPTION

Foscarnet sodium is trisodium phosphonoformate hexahydrate or phosphonoformic acid trisodium salt hexahydrate, MW 300.0.

Structural Formula:



.6H2O

CAS Number: 34156-56-4

A clear, sterile, isotonic solution of foscarnet sodium in Water for Injections, adjusted to pH 7.4 with hydrochloric acid. No preservatives or buffers are contained in FOSCAVIR.

PHARMACOLOGY

Foscarnet is an antiviral agent with a broad antiviral spectrum which inhibits all known human viruses of the herpes group (Herpes simplex 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 polymerases from hepatitis B virus. Foscarnet exerts its antiviral activity by a direct inhibition of viral specific DNA polymerase and reverse transcriptase. Foscarnet does not require activation by thymidine kinase or other kinases and therefore is active *in vitro* against herpes simplex virus (HSV) mutants deficient in thymidine kinase (TK).

In vitro systems are of limited value in predicting *in vivo* effectiveness. The mean foscarnet 50% inhibition value (ID50) for more than one hundred clinical CMV isolates is approximately 270 micromol/L, while a reversible inhibition of normal cell growth is observed at about 1000 micromol/L.

In several animal species foscarnet is rapidly cleared from blood and other soft tissues after intravenous administration. However, dose proportional concentrations have been observed in bone and cartilage in all animal species studied.

Investigations in dogs have shown that foscarnet has no effect on calcium homoeostasis.

Foscarnet was shown to have clastogenic activity in the mouse micronucleus test and in an *in vitro* cytogenetics assay using Chinese hamster cells.

No oncogenic potential has been demonstrated in carcinogenicity studies to date.

Mutagenicity studies showed that foscarnet has a genotoxic potential. The genotoxic effect demonstrated in these studies is possibly due to inhibition of the DNA polymerase in the cell line used. Foscarnet acts therapeutically by inhibition of the herpes virus specific DNA polymerase. The human cellular polymerase α is about 100 times less sensitive to foscarnet.

Pharmacokinetics

Following IV administration in man, foscarnet plasma concentrations follow a multi exponential decay pattern with several half-lives. The initial decline has a half-life of approximately 2-4 hours if renal function is normal. An apparent terminal half-life of approximately 1 to 8 days has been recorded, probably reflecting the slow release of foscarnet from bone.

The plasma clearance of foscarnet after intravenous administration to man varies between 130-160 mL/min. The mean volume of distribution of foscarnet at steady state varies between 0.4-0.6 L/kg.

Foscarnet is distributed to the cerebrospinal fluid and concentrations ranging from 10 to 70% of the concurrent plasma concentrations have been observed in HIV infected patients.

Foscarnet is mainly eliminated by the renal route, by glomerular filtration and tubular secretion. Renal clearance is approximately 130 mL/min.

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

In man, up to 20% of the cumulative intravenous dose has not been excreted in the urine 7 days after cessation of infusion, and can be assumed to have been deposited in bone and cartilage. Deposition is greater in young and growing animals. This effect has only been seen in dogs.

The bone changes were characterised as increased osteoclast activity and bone resorption. The reason for these changes may be that FOSCAVIR, due to its structural similarity to phosphate, is incorporated into the hydroxyapatite. Audioradiographic and other studies have shown FOSCAVIR to have a pronounced affinity for bone tissue. Recovery studies revealed that 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.

Following induction therapy, either administered as a continuous infusion or as intermittent infusions every eight hours, foscarnet has produced stabilisation of retinal lesions in approximately 90% of cases treated.

However, since CMV usually causes latent infections and since foscarnet, like other anti-CMV agents, exerts a virustatic effect, relapses are likely to be seen after therapy in the majority of patients with persistent immunodeficiency once treatment is discontinued.

Institution of 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, re-institution of induction therapy has shown equal efficacy as the initial course.

Special Populations - Adults with Impaired Renal Function:

The pharmacokinetic properties of foscarnet have been determined in a small group of adult subjects with normal and impaired renal function, as summarised in Table 1 below:

Table 1 Pharmacokinetic parameters (mean ± S.D.) after a single 60 mg/kg dose of FOSCAVIR in 4 groups* of adults with varying degrees of renal function

Parameter	Group 1 (N=6)	Group 2 (N=6)	Group 3 (N=6)	Group 4 (N=6)
Creatinine clearance (mL/min)	108±16	68±8	34±9	20±4
Foscarnet clearance (mL/min/kg)	2.13±0.71	1.33±0.43	0.46±0.14	0.43±0.26
Foscarnet half life (hr)	1.93±0.12	3.35±0.87	13.0±4.05	25.3±18.7

*Group 1 patients had normal renal function defined as creatinine clearance (CrCl) of > 80 mL/min; Group 2 CrCl was 50 – 80 mL/min; Group 3 CrCl was 25 - 49 mL/min and Group 4 CrCl was 10 – 24 mL/min.

Total systemic clearance (CL) of foscarnet decreased and half-life increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of foscarnet in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

INDICATIONS

FOSCAVIR is indicated for:

- Treatment of cytomegalovirus (CMV) retinitis in patients with the acquired immunodeficiency syndrome (AIDS).
- Treatment of acyclovir resistant herpes simplex virus (HSV) infections (defined by clinical trial or *in vitro* resistance) in immunocompromised patients with human immunodeficiency virus (HIV) infection.

NOTE: The indication for treatment of acyclovir resistant HSV infections in immunocompromised patients with HIV infections is based primarily on the results of one open label comparative study. This was of patients with HIV infections and herpetic lesions unresponsive to acyclovir administered intravenously for 10 days or more and i*n vitro* documented resistance to acyclovir. Eight patients were randomised to foscarnet (40 mg/kg IV given eight hourly) and 6 were randomised to vidarabine 15 mg/kg IV daily. The results showed a significant difference in favour of the foscarnet treatment group for clinical and virological endpoints, especially in time to complete healing of lesions and time to complete loss of pain. In 177 other patients treated with foscarnet in non-comparative studies, results were sufficiently similar to support the efficacy of foscarnet in this indication.

CONTRAINDICATIONS

Hypersensitivity to foscarnet.

Foscarnet should not be used in patients on treatment with iv pentamidine since both drugs affect the serum calcium level and are potentially nephrotoxic.

Long term treatment with foscarnet is contraindicated in patients with a reasonable prognosis (eg. bone marrow transplant patients) because the animal toxicological data are limited and insufficient to ensure safety in man over an extended period.

PRECAUTIONS

Renal Impairment

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. Appropriate dose adjustments should be made if renal function is affected. (See DOSAGE AND ADMINISTRATION).

To minimize the potential of renal function impairment, adequate hydration should be maintained in all patients. The renal function of patients with renal disease or receiving concomitant treatment with other nephrotoxic medicinal products must be closely monitored (see INTERACTIONS WITH OTHER MEDICINES).

Dosage guidelines have not been established for the use of foscarnet in patients undergoing renal dialysis.

Mineral and Electrolyte Abnormalities

Due to FOSCAVIR's propensity to chelate bivalent metal ions, such as calcium, FOSCAVIR administration may be associated with an acute decrease of ionised 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.

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

Genital irritation and ulceration

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.

Sodium content

Foscarnet is a trisodium salt. Each mL of FOSCAVIR (24 mg/mL foscarnet sodium) contains 240 micromoles (5.5 mg) of sodium. Foscarnet use should be avoided when a saline load cannot be tolerated (e.g. in cardiomyopathy). **This should also be taken into consideration by patients on a controlled sodium diet.**

Diuretics

When diuretics are indicated, thiazides are recommended over loop diuretics because the latter inhibit renal tubular secretion, and may impair elimination of FOSCAVIR, potentially leading to toxicity.

Seizures

Seizures, related to plasma minerals and electrolytes, have been associated with FOSCAVIR treatment. Therefore, patients must be carefully monitored for such changes and their potential sequelae. Mineral and electrolyte supplementation may be required (see PRECAUTIONS – Mineral and electrolyte abnormalities).

Resistance

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.

Geriatric Use

No studies of the efficacy or safety of FOSCAVIR solely in persons 65 years of age or older have been conducted. However, FOSCAVIR has been used in patients aged 65 years and older. The pattern of adverse events seen in these patients is consistent across all age groups. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored (see DOSAGE AND ADMINISTRATION).

Use in pregnancy – Category B3

FOSCAVIR did not adversely affect fertility and general reproductive performance in rats. The results of peri- and post- natal studies in rats were also negative. However, these studies used exposure levels that are inadequate to define the potential for impairment of fertility at human drug exposure levels.

Daily subcutaneous doses up to 75 mg/kg post-partum administered to female rats prior to and during mating, during gestation, and 21 days post-partum caused a slight increase (< 5%) in the number of skeletal abnormalities compared with the control group. Daily subcutaneous doses up to 75 mg/kg administered to rabbits and 150 mg/kg administered to rats during gestation caused an increase in the frequency of skeletal abnormalities/variations. These studies are inadequate to define the potential teratogenicity at levels to which women will be exposed.

On the basis of estimated drug exposure (as measured by AUC), the 150 mg/kg dose in rats and 75 mg/kg dose in rabbits were approximately one-eighth (rat) and one-third (rabbit) the estimated maximal daily human exposure.

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, FOSCAVIR should not be given to pregnant women.

Use in lactation

Animal studies indicate foscarnet passes into the milk of lactating rats at concentrations approximately 3 times higher than those in maternal plasma. No information is available on levels of foscarnet which may appear in human breast milk. Since there is no clinical experience or investigational data available, FOSCAVIR should not be given during lactation.

Paediatric use

The safety of FOSCAVIR and its effect on skeletal development have not been investigated in children. There are insufficient data available either *in vivo* or *in vitro* to establish any possible effect in growing bone. Please refer PHARMACOKINETICS.

Carcinogenicity

No oncogenic potential has been demonstrated in carcinogenicity studies in mice at oral doses up to 250 mg/kg/day for 18 months, or in rats at oral doses up to 500 mg/kg/day for 24 months.

Mutagenicity

Mutagenicity studies showed that foscarnet has a genotoxic potential. Foscarnet was shown to have clastogenic activity in the mouse micronucleus test and in an *in vitro* cytogenetics assay using Chinese hamster cells. The genotoxic effect demonstrated in these studies is possibly due to inhibition of DNA polymerase.

INTERACTIONS WITH OTHER MEDICINES

1. There is no pharmacokinetic interaction when foscarnet is used in combination with zidovudine (AZT), ganciclovir, didanosine (ddI), zalcitabine (ddC) or probenecid.

2. Since FOSCAVIR can impair renal function, additive renal toxicity may occur when used in combination with other nephrotoxic drugs such as aminoglycosides, amphotericin B, ciclosporin A, aciclovir, methotrexate and tacrolimus.

3. Since FOSCAVIR can reduce serum levels of ionized calcium, extreme caution is advised when used concurrently with other drugs known to reduce serum calcium levels, like IV pentamidine . Renal impairment and

symptomatic hypocalcaemia (Trousseau's and Chvostek's signs) have been observed during concurrent treatment with foscarnet and IV pentamidine.

4. Due to their mechanism of action, loop diuretics should not be used during FOSCAVIR therapy.

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

6. Pharmaceutical interactions (incompatibilities for infusion) are described in COMPATABILITY.

ADVERSE EFFECTS

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

Clinical trials experience

The adverse events and frequencies shown in Table 2 below are based on the foscarnet primary clinical trial database. This includes adverse experiences reported at any time during induction, maintenance or follow-up treatment in 5 clinical trials involving 188 patients with CMV retinitis. Adverse events are presented by frequency and system organ class. 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).

Table 2 Frequency of adverse events from the primary clinical trial database

Frequency	System Organ Class	Event
Very common (≥10%)	Blood and lymphatic system disorders	Granulocytopenia
	Metabolism and nutrition disorders	Anorexia, hypomagnesaemia, hypokalaemia
	Nervous system disorders	Headache, paraesthesia, dizziness
	Gastrointestinal disorders	Nausea, vomiting, diarrhoea
	Skin and subcutaneous disorders	Rash
	General disorders and administration site conditions	Asthenia, chills, fatigue, pyrexia
	Investigations	Blood creatinine increased, haemoglobin decreased, hypocalcaemia
Common (≥1% and <10%)	Blood and lymphatic system disorders	Thrombocytopenia, leukopenia
	Immune system disorders	Sepsis
	Metabolism and nutrition disorders	Hyperphosphataemia, hypophosphataemia, hyponatraemia, blood alkaline phosphatase increased, blood lactate dehydrogenase increased
	Nervous System disorders	Coordination abnormal, convulsion,

Frequency	System Organ Class	Event
		hypoaesthesia, muscle contractions involuntary, neuropathy, tremor
	Psychiatric disorders	Aggression, agitation, anxiety, confusional state, depression, nervousness
	Cardiac disorders	Palpitations
	Vascular disorders	Hypertension, hypotension, thrombophlebitis
	Gastrointestinal disorders	Abdominal pain, constipation, dyspepsia
	Hepato-biliary disorders	Hepatic function abnormal, Gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased
	Reproductive system and breast disorders	Genital irritation and ulceration
	Renal and urinary disorders	Renal impairment, renal failure acute, dysuria, polyuria
	General disorders and administration site conditions	Malaise, oedema
	Investigations	Creatinine renal clearance decreased, electrocardiogram abnormal[a]
Uncommon (≥0.1% and <1%)	Metabolism and nutrition disorders	Acidosis[b]

[a] This frequency is based on 2 reports of electrocardiogram abnormal from 188 patients in the primary clinical trial database; the post-marketing reporting rate is 'Very rare'.

[b] This frequency is based on 1 report of acidosis from 188 patients in the primary clinical trial database; the post-marketing reporting rate is 'Rare'.

Post marketing and other experience

Reporting rates for events detected in studies other than those in the primary clinical trial database and/or from spontaneous post-marketing reports are shown in Table 3.

Table 3 Reporting rates for events detected in other clinical studies or from spontaneous post-marketing reports

Reporting rate	System Organ Class	Event
Very common (≥10%)	Blood and lymphatic system disorders	Anaemia
Common (≥1% and <10%)	Renal and urinary disorders	Renal pain[a]
Uncommon (≥0.1% and < 1%)	Renal and urinary disorders	Renal tubular disorder
Rare (≥0.01% and < 0.1%)	Blood and lymphatic system disorders	Neutropenia
	Endocrine disorders	Diabetes insipidus

	Gastrointestinal disorders	Pancreatitis
	Skin and subcutaneous disorders	Pruritis
	Musculoskeletal disorders	Myalgia
	Investigations	Blood amylase increased
Very rare (<0.01%)	Cardiac disorders	Electrocardiogram QT prolonged[b], ventricular arrhythmia
	Musculoskeletal disorders	Myositis, myopathy, rhabdomyolysis, muscular weakness
	Investigations	Blood creatine phosphokinase increased
Not known (cannot be estimated from the available data)	Renal and urinary disorders	renal tubular acidosis, renal tubular necrosis, acute tubular necrosis, crystal nephropathy
	Gastrointestinal disorders	Oesophaegeal ulceration
	Psychiatric disorders	Mental status changes
	Nervous system disorders	Encephalopathy

[a] This reporting rate is based on 7 reports of renal pain from 2 prospective clinical trials involving 107 patients (trials 90FP48 and 91 FP49). There were no reports in the primary clinical trial database; the post-marketing reporting rate is 'Very rare'.

[b] This reporting rate is based on 3 spontaneous reports of QT prolongation from 80000 patients.

Effects on ability to drive and use machinery

Foscarnet has no sedating effects and generally there is no reason to believe that the ability to drive or use machinery is impaired following the administration of foscarnet. However adverse effects such as dizziness and convulsions may occur during therapy and the physician is advised to discuss this issue with the patient.

DOSAGE AND ADMINISTRATION

Contact with the skin and eyes may cause local irritation and a burning sensation. If accidental contact occurs, the exposed area should be rinsed immediately with cold water.

Method of administration

FOSCAVIR must be given by the intravenous route only, either via a central venous line or directly into peripheral veins.

When **peripheral veins** are used, FOSCAVIR 24 mg/mL must be diluted with glucose (dextrose) 5% or normal saline to a concentration of 12 mg/mL immediately prior to administration. (See PRECAUTIONS regarding total daily sodium intake.)

FOSCAVIR 24 mg/mL solution may be given without dilution via a **central vein**. Infusion time should not be less than one hour.

Adults

CMV Retinitis

Induction therapy

Foscarnet can be administered over 2-3 weeks, depending on clinical response, as intermittent infusions every 8 hours at a dose of 60 mg/kg in patients with normal renal function (see dosing chart below).

The dose of foscarnet should be adjusted to the renal function as assessed by estimated creatinine clearance.

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 estimated creatinine clearance. In patients with normal renal function the dose range is 90-120 mg/kg/day. It is recommended to initiate therapy at 90 mg/kg and increase up to 120 mg/kg in patients in whom retinitis is progressing and who show good tolerance to the lower dose.

The dosage used can be calculated from the following dosage charts or from experience obtained with the patient during the induction phase by correlating their renal function with plasma levels.

These dosage recommendations are approximate and actual dosing should always be based on the clinical situation.

HSV infections

Induction therapy

Foscarnet should be administered at a dose of 40 mg/kg, by slow intravenous infusion (over one hour), every 8 hours, in patients with normal renal function (see dosing chart below). Infusions should be maintained for 2-3 weeks or until the lesions have healed.

Maintenance therapy

The efficacy of FOSCAVIR maintenance therapy in the treatment of acyclovir resistant HSV infections has not been established.

CAUTION - Do not administer foscarnet by rapid intravenous infusion.

FOSCAVIR DOSING CHART

Induction Therapy

Creatinine Clearance mL/kg/min	CMV Every 8 hours (mg/kg)	HSV Every 8 hours (mg/kg)
> 1.6	60	40
1.6 - 1.4	55	37
1.4 - 1.2	49	33
1.2 - 1.0	42	28
1.0 - 0.8	35	24
0.8 - 0.6	28	19
0.6 - 0.4	21	14
< 0.4	treatment not recommended	

CMV Maintenance Therapy

Creatinine Clearance mL/kg/min	One Infusion 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. Prior to the first foscarnet infusion it is recommended that diuresis be established by hydration with 0.5-1.0 litre normal saline. Subsequently add 0.5-1.0 litre normal saline to each infusion. 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 PRECAUTIONS and PHARMACOKINETICS.

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.

Compatibility

FOSCAVIR is not compatible with glucose 30% solution, amphotericin B, acyclovir sodium, ganciclovir, pentamidine isethionate, trimethoprim/sulphamethoxazole, vancomycin hydrochloride, or with solutions containing calciumIt is recommended that other drugs should not be infused concomitantly in the same line.

OVERDOSAGE

In case of overdose, immediately contact the Poisons Information Centre (in Australia call 13 11 26) for advice.

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 the 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 occurred following the overdose.

The pattern of adverse events reported in association with 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.

PRESENTATION AND STORAGE CONDITIONS

Intravenous infusion solution containing foscarnet sodium hexahydrate, 24 mg/mL in 250 mL glass bottles.

Store below 30°C. Do not refrigerate.

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

For doses prepared by a hospital pharmacy, foscarnet may be transferred to plastic infusion bags for use within 24 hours.

NAME AND ADDRESS OF SPONSOR

Clinect Pty Ltd

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Melbourne Victoria

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC PRODUCTS (ARTG)

29 September 1992

DATE OF MOST RECENT AMENDMENT

6 July 2015

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 This leaflet is RECYCLABLE.