Foscavir 24 mg/ml Solution for Infusion

Summary of Product Characteristics Updated 05-Oct-2017 | Clinigen Healthcare Ltd

1. Name of the medicinal product

Foscavir 24 mg/ml Solution for Infusion

2. Qualitative and quantitative composition

Foscarnet trisodium hexahydrate 24 mg/ml.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion.

Clear and colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Foscavir is indicated for induction and maintenance therapy of cytomegalovirus (CMV) retinitis in patients with AIDS.

Foscavir is also indicated for the treatment of mucocutaneous Herpes Simplex Virus (HSV) infections, clinically unresponsive to aciclovir in immunocompromised patients. The safety and efficacy of Foscavir for the treatment of other HSV infections (e.g. retinitis, encephalitis); congenital or neonatal disease; or HSV in immunocompetent individuals has not been established.

The diagnosis of aciclovir unresponsiveness can be made either clinically by treatment with intravenous aciclovir (5–10 mg/kg t.i.d) for 10 days without response or by *in vitro* testing.

Foscavir is not recommended for treatment of CMV infections other than retinitis or HSV or for use in non-AIDS or non-immunocompromised patients.

4.2 Posology and method of 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. Individually dispensed doses of foscarnet should be aseptically transferred and diluted with equal parts of 0.9% sodium chloride (9 mg/ml) or 5% dextrose (50 mg/ml) by the hospital pharmacy. The diluted solutions should be used as soon as possible after preparation but can be stored for up to 24 hours if kept refrigerated.

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

Adults: Induction therapy for CMV retinitis: Foscavir is administered over 2–3 weeks depending on the clinical response, as intermittent infusions every 8 hours at a dose of 60 mg/kg in patients with normal renal function. Dosage must be individualised for patient's renal function (see dosing chart below). The infusion time should not be shorter than 1 hour.

Maintenance therapy: For maintenance therapy, following induction therapy of CMV retinitis, Foscavir is administered seven days a week as long as therapy is considered appropriate. In patients with normal renal function, it is recommended to initiate therapy at 60 mg/kg. Increase to a dose of 90–120 mg/kg may then be considered in patients tolerating the initial dose level and/or those with progressive retinitis. A number of patients have received 90 mg/kg over a 2 hour period as a starting dose for maintenance therapy. Dosage must be reduced in patients with renal insufficiency (see dosage chart at end of dosage section).

Patients who experience progression of retinitis while receiving maintenance therapy may be re-treated with the induction regimen.

Induction therapy of mucocutaneous HSV infections unresponsive to aciclovir: Foscavir is administered for 2–3 weeks or until healing of lesions, as intermittent infusions at a dose of 40 mg/kg over one hour every 8 hours in patients with normal renal function. Dosage must be individualised for patients renal function (see dosing chart below). The infusion time should not be shorter than 1 hour.

Efficacy of Foscavir maintenance therapy following induction therapy of aciclovir unresponsive HSV infections has not been established.

Caution: Do not administer Foscavir by rapid intravenous injection.

Table 1 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 Dose (mg/kg/day in not less than one hour)
> 1.6	60*
1.6–1.4	55
1.4–1.2	49
1.2–1.0	42
1.0–0.8	35
0.8–0.6	28
0.6–0.4	21
< 0.4	Treatment not recommended

*A number of patients have received 90 mg/kg as a starting dose for maintenance therapy.

Foscavir is not recommended in patients undergoing haemodialysis since dosage guidelines have not been established.

Hydration: Renal toxicity of Foscavir can be reduced by adequate hydration of the patient. It is recommended to establish diuresis by hydration with 0.5–1.0 litre of normal saline at 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.

Elderly: As for adults.

Paediatric population: The safety and efficacy of foscarnet in children have not been established. Please refer to sections 4.4 and 5.3.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Foscavir should be used with caution in patients with reduced renal function. Since renal function impairment may occur at any time during Foscavir 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 section 4.2). The renal function of patients with renal disease or receiving concomitant treatment with other nephrotoxic medicinal products must be closely monitored (see section 4.5).

Due to the sodium content of Foscavir (240 micromoles (5.5 mg) of sodium per ml), its 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.

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.

Foscarnet has been associated with cases of prolongation of QT interval and more rarely with cases of torsade de pointes (see section 4.8). Patients with known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances (hypokalaemia, hypomagnesaemia), bradycardia, as well as patients with underlying cardiac diseases such as congestive heart failure or who are taking medications known to prolong the QT interval should be carefully monitored due to increased risk of ventricular arrhythmia. 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 section 5.3.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Since Foscavir 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 Foscavir can reduce serum levels of ionised 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 during concurrent treatment with Foscavir and i.v. pentamidine. Abnormal renal function has been reported in connection with the use of Foscavir in combination with ritonavir and/or saquinavir.

Due to the potential increased risk of QT prolongation and torsade de pointes, Foscavir should be used with caution with drugs known to prolong QT interval, notably class IA (e.g. quinidine) and III (e.g. amiodarone, sotalol), antiarrhythmic agents or neuroleptic drugs. Close cardiac monitoring should be performed in cases of co-administration.

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

Pharmaceutical interactions (incompatibilities for infusion) are described in section 6.2.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data available regarding the influence of Foscavir on fertility.

No effects on fertility were observed in animal studies (see section 5.3).

Women of childbearing potential / contraception in males and females

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.

Pregnancy

There are no or limited amount of data from the use of foscarnet in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Foscavir is not recommended during pregnancy.

Lactation

There is insufficient information on the excretion of foscarnet in human milk.

Available pharmacodynamic/toxicological data in animals have shown excretion of foscarnet in milk (for details see section 5.3).

A risk to the newborns/infants cannot be excluded.

Foscavir should not be used during breast-feeding. .

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Foscavir therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Foscavir has moderate influence on the ability to drive and use machines. Due to the disease itself and possible undesirable effects of Foscavir (such as dizziness and convulsions, see section 4.8), the ability to drive and use machines can be impaired. 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.

4.8 Undesirable effects

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 sections 4.2 and 4.4).

Table 2 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
Nervous system disorders	Very common	Dizziness, headache, paraesthesia
	Common	Coordination abnormal, convulsion, hypoaesthesia, muscle contractions involuntary, neuropathy peripheral, tremor
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	Glomerulonephritis, nephrotic syndrome
	Not known	Renal pain, renal tubular acidosis, crystal nephropathy, haematuria
Reproductive system and breast disorders	Common	Genital discomfort and ulceration[c]
General disorders and	Very common	Asthenia, chills, fatigue, pyrexia

administration site conditions	Common	Malaise, oedema, chest pain[d], injection site pain, injection site inflammation
	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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.

4.9 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 Foscavir elimination and may be of benefit in relevant cases.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct acting antivirals; phosphonic acid derivatives, ATC code: J05AD01

Foscarnet is an antiviral agent with a broad spectrum inhibiting 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 a reverse transcriptase at concentrations that do not affect cellular DNA polymerases. Foscarnet does not require activation (phosphorylation) by thymidine kinase or other kinases and therefore is active *in vitro* against HSV mutants deficient in thymidine kinase. CMV strains resistant to ganciclovir may be sensitive to foscarnet. Sensitivity test results expressed as concentration of the drug required to inhibit growth of virus by 50% in cell culture (IC_{50}) vary greatly depending on the assay method used and cell type employed. A number of sensitive viruses and their IC_{50} are listed below.

Table 3 Foscarnet inhibition of virus multiplication cell culture

Virus	IC_{50}(µm)
CMV	50–800 *
HSV-1, HSV-2	10–130
VZV	48–90
EBV	<500**
HHV-6	49
Ganciclovir resistant CMV	190
HSV - TK Minus Mutant	67
HSV - DNA Polymerase Mutant	5–443
HIV-1	11–32
Zidovudine resistant HIV-1	10–32

* Mean = 269 micrograms

** 97% of viral antigen synthesis inhibited at 500 micrograms

If no clinical response to foscarnet is observed, viral isolates should be tested for sensitivity to foscarnet since naturally resistant mutants may exist or emerge under selective pressure both *in vitro* and *in vivo*.

The mean foscarnet 50% inhibition value for more than one hundred clinical CMV isolates was approximately 270 micrograms/L, while a reversible inhibition of normal cell growth was observed at about 1000 micrograms/L.

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

5.2 Pharmacokinetic properties

Foscarnet is eliminated by the kidneys mainly through glomerular filtration. The plasma clearance after intravenous administration to man varies between 130–160 ml/min and the renal clearance is about 130 ml/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 L/kg. There is no metabolic conversion of foscarnet and the binding to human plasma proteins is low (<20%). 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.

5.3 Preclinical safety data

The most pronounced effects noted during general toxicity studies performed with foscarnet 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 foscarnet to form chelate with divalent metal ions. The reduction of ionised calcium and magnesium is, most probably the explanation to seizures/convulsions seen during and shortly after the infusion of high doses of foscarnet. 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 foscarnet 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 foscarnet. It has been shown that hydration, to induce diuresis, significantly reduces kidney changes during foscarnet 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 foscarnet, due to the structural similarity to phosphate is incorporated into the hydroxyapatite. Autoradiographic studies showed that foscarnet 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.

Mutagenicity studies showed that foscarnet has a genotoxic potential. The possible explanation for the observed effect in the mutagenicity studies is an inhibition of the DNA polymerase in the cell line used. Foscarnet therapeutically acts by inhibition of the herpes virus specific DNA polymerase. The human cellular polymerase is about 100 times less sensitive to foscarnet. The carcinogenicity studies performed did not disclose any oncogenic potential. The information gained from teratogenicity and fertility studies did not reveal any adverse events upon the reproductive process. However, the results are of limited value since the dose levels used in these studies are below or at most similar (75–150 mg/kg sc) to those used in man for treatment of CMV retinitis.

6. Pharmaceutical particulars

6.1 List of excipients

Water for injection

Hydrochloric acid (E507)

6.2 Incompatibilities

This medicinal product must not be mixed with any other medicinal products except those mentioned in section 4.2.

Foscarnet is not compatible with dextrose 30% solution, amphotericin B, aciclovir sodium, ganciclovir, pentamidine isethionate, trimethoprim-sulfamethoxazole 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.

6.3 Shelf life

Unopened: 3 years.

Once opened:

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Do not store above 30°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.

For storage conditions after first opening and/or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Infusion glass bottles of 250 ml.

6.6 Special precautions for disposal and other handling

Individually dispensed doses of foscarnet can be aseptically transferred to plastic infusion bags by the hospital pharmacy. The physico-chemical stability of foscarnet and dilutions thereof in equal parts with 0.9% sodium chloride (9 mg/ml) or 5% dextrose (50 mg/ml) in PVC bags is 7 days. However, diluted solutions should be refrigerated and storage restricted to 24 hours.

Each bottle of Foscavir should only be used to treat one patient with a single infusion.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 31644/0001

9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

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