PRODUCT INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Foscavir

24 mg/ml, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for infusion contains:
24 mg (= 80 µmol/ml) foscarnet sodium hexahydrate, corresponding to 15.4 mg foscarnet sodium

Excipient with known effect
This medicinal product contains 1.38 gram of sodium per 250 ml bottle.

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 may only be administered to patients with acquired immune deficiency (AIDS).

- Illness from cytomegalovirus (CMV) that is life-threatening or jeopardizes the patient's eyesight. Treatment with Foscavir is indicated only with the proven presence of cytomegalovirus.
- With acute, mucocutaneous infections caused by aciclovir-resistant herpes viruses (HSV). Treatment with Foscavir is indicated only if no medically more tenable therapeutic alternatives are available. A strict indication is required due to the risk profile of the active substance. In the event of a recurrence, the aciclovir-resistance should be re-examined.

The generally recognised guidelines for an appropriate use of medicinal products to treat the cytomegalovirus or herpes simplex infection respectively in HIV infected patients must be observed.

4.2 Posology and method of administration

For intravenous application.

CMV infection

Posology

Adults

Initial therapy
A CMV infection can be treated with 60 mg foscarnet sodium hexahydrate per kg body weight 3 times a

day (= 3 x 2.5 ml Foscavir/kg BW) at intervals of 8 hours, or twice a day with 90 mg foscarnet sodium hexahydrate per kg body weight (= 2 x 3.75 ml Foscavir/kg BW) at 12 hour intervals.

Infusion of 60 mg foscarnet sodium hexahydrate per kg body weight must not take less than 1 hour, infusion of 90 mg foscarnet sodium hexahydrate per kg body weight should take no less than 2 hours (see "Method of administration").

Maintenance therapy
To prevent a recurrence of a CMV infection, an infusion of 90‑120 mg foscarnet sodium hexahydrate per kg body weight (= 3.75 - 5 ml Foscavir/kg BW) shall be administered daily over a period of 2 hours.

This therapy should start with 90 mg foscarnet sodium hexahydrate per kg body weight and may be escalated up to 120 mg foscarnet sodium hexahydrate per kg body weight in cases where the retinitis is progressive and Foscavir is well-tolerated.

Patients whose illness worsens under maintenance therapy may be treated with the dose for initial therapy. Once stabilized, maintenance therapy with foscarnet sodium may be instituted.

Paediatric population
The safety and efficacy of foscarnet sodium in children and adolescents under 18 years of age is not proven. For more information, please see sections 4.4 and 5.3.

Elderly patients
As Foscavir is excreted through the kidneys, it should be considered that the renal function in elderly patients can be impaired despite a normal serum creatinine value. The renal function is determined by calculating the creatinine clearance. For the administration of Foscavir in elderly patients, the same dose adjustments apply as are described under "Patients with renal impairment" in Tables 1 and 2.

Patients with renal impairment
In patients with renal impairment, the dose must be adjusted according to the creatinine clearance (see Tables 1 + 2). The renal function should be checked at the beginning of therapy and regularly during therapy and the dose should be adjusted accordingly (see section 4.4).

The creatinine clearance is calculated from the serum creatinine concentration as follows:

Males: Cl_{creat} [ml/min/kg BW] = $\frac{\text{140 - age [years]}}{\text{72 x serum creatinine concentration [mg/dl]}}$

Females: Cl_{creat} [ml/min/kg BW] = 0.85 x Cl_{creat} males

Table 1 Dosing schedule for initial therapy for CMV infection in patients with impaired renal function

	Foscarnet sodium hexahydrate dosage*			
Creatinine clearance [ml/min/kg BW]	90 mg/kg BW (duration of infusion: at least 2 hours)	At intervals of:	60 mg/kg BW (duration of infusion: at least 1 hour)	At intervals of:
> 1.4	90	12 hours	60	8 hours
1.4 ≥ - > 1	70	12 hours	45	8 hours
1 ≥ - > 0.8	50	12 hours	35	8 hours
0.8 ≥ - > 0.6	80	24 hours	40	12 hours
0.6 ≥ - > 0.5	60	24 hours	30	12 hours

0.5 ≥ - ≥ 0.4	50	24 hours	25	12 hours
< 0.4	Treatment not recommended			

Table 2 Dosing schedule for maintenance therapy for CMV infection in patients with impaired renal function

	Foscarnet sodium hexahydrate dosage*			
Creatinine clearance [ml/min/kg BW]	90 mg/kg BW (duration of infusion: at least 2 hours)	At intervals of:	120 mg/kg BW (duration of infusion: at least 2 hours)	At intervals of:
> 1.4	90	24 hours	120	24 hours
1.4 ≥ - > 1	70	24 hours	90	24 hours
1 ≥ - > 0.8	50	24 hours	65	24 hours
0.8 ≥ - > 0.6	80	48 hours	105	48 hours
0.6 ≥ - > 0.5	60	48 hours	80	48 hours
0.5 ≥ - ≥ 0.4	50	48 hours	65	48 hours
< 0.4	Treatment not recommended			

* Note: These figures are based on studies relating to the pharmacokinetics after a single dose of Foscavir administered to patients with varying degrees of renal impairment.

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

Patients with hepatic insufficiency
Dose adjustment is not required in patients with hepatic insufficiency.

Duration of therapy

The duration of initial treatment in case of CMV infection depends on the clinical response and takes 2 to 3 weeks in general.

To avoid a relapse, this should be followed by maintenance therapy over a longer term, i.e. at least 6 months, possibly continued lifelong. The decision to discontinue a maintenance therapy should be based on the generally recognised current therapy guidelines.

Herpes infection

Posology

Adults
Acyclovir-resistant herpes infection is treated with 40 mg foscarnet sodium hexahydrate per kg body weight 3 times a day (= 3 x 1.7 ml Foscavir/kg BW) at intervals of 8 hours.
The infusion must not take less than 1 hour (see "Method of administration").

Paediatric population
The safety and efficacy of foscarnet sodium in children and adolescents under 18 years of age is not proven. For more information, please see sections 4.4 and 5.3.

Elderly patients
As Foscavir is excreted through the kidneys, it should be considered that the renal function in elderly patients can be impaired despite a normal serum creatinine value. The renal function is determined by calculating the creatinine clearance. For the administration of Foscavir in elderly patients, the same dose adjustments apply as are described under "Patients with renal impairment" in table 3.

Patients with renal impairment
In cases of renal impairment, the dose must be adjusted according to the creatinine clearance (see Table 3; for calculating the creatinine clearance, see formula in the paragraph concerning CMV infection). The renal function should be checked at the beginning of therapy and regularly during therapy and the dose should be adjusted accordingly (see section 4.4).

Table 3 Dosing schedule for the treatment of Herpes infection in patients with impaired renal function

	Foscarnet sodium hexahydrate dosage*	
Creatinine clearance [ml/min/kg BW]	40 mg/kg BW (duration of infusion: at least 1 hour)	At intervals of:
> 1.4	40	8 hours
1.4 ≥ - > 1	30	8 hours
1 ≥ - > 0.8	20	8 hours
0.8 ≥ - > 0.6	25	12 hours
0.6 ≥ - > 0.5	20	12 hours
0.5 ≥ - ≥ 0.4	15	12 hours
< 0.4	Treatment not recommended	

* Note: These figures are based on studies relating to the pharmacokinetics after a single dose of Foscavir administered to patients with varying degrees of renal impairment.

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

Patients with hepatic insufficiency
Dose adjustment is not required in patients with hepatic insufficiency.

Duration of therapy

Therapy of aciclovir-resistant herpes infection must be carried out until the lesions have healed completely (complete re-epithelisation). This generally requires treatment for 2 – 3 weeks. If there is no noticeable effect after 1 week of treatment, the benefits and risks of continuing the therapy must be carefully re-considered.

The use of Foscavir as a prophylaxis against recurrence after an aciclovir-resistant herpes infection has not yet been sufficiently investigated. In the event of a recurrence, the resistance should be re-examined.

Method of administration

Foscavir must **not** be used for rapid intravenous injection.

In the case of an infusion through central veins, the solution for infusion does not need to be diluted. In the case of an infusion through a peripheral vein, the solution for infusion must be diluted prior to administration (see section 6.6).

For further information concerning the preparation and storage of the ready-for-use solution see sections 6.2 and 6.4.

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 prior to the first Foscavir infusion and subsequently add 0.5 - 1.0 litre of 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.

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).

This medicinal product contains 1.38 g of sodium per 250 ml bottle, 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 for an 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 Foscavir's propensity to chelate bivalent metal ions, such as calcium, Foscavir 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 cases of prolongation of QT interval and more rarely with cases of torsade de pointes (see section 4.8). Patients who are known to have 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 arrhythmias. 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 paresthesia 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 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 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 4. 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 4 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
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, 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
	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 Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz,Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: http://www.bfarm.de.

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 sodium is an antiviral substance that has a direct allosteric inhibitory effect on viral enzymes such as DNA polymerase and reverse transcriptase. In cell cultures, foscarnet sodium in vitro was proven to act against all human viruses of the herpes group such as herpes simplex type 1 and type 2, human herpes virus 6, varicella zoster virus, Epstein-Barr virus and cytomegalovirus (CMV) as well as hepatitis B virus and some retroviruses, incl. HIV.

Foscarnet sodium has a virostatic effect against cytomegaloviruses and herpes viruses, i.e. it suppresses the growth of viruses, however, it cannot eliminate cytomegalia or herpes viruses. The mean concentration (IC_{50}) required for a 50% reversible inhibition of the multiplication of cytomegaloviruses when using clinical isolates in vitro was 270 μ mol/l. For HSV 1 and HSV 2, the IC_{50}-values ranged between 10 μ mol/l and 130 μ mol/l.

The IC_{50} for inhibition of normal growth of human cells is 1000 μ mol/l foscarnet.

5.2 Pharmacokinetic properties

Absorption
The plasma levels measured in a clinical study during a continuous intravenous infusion of 16 g foscarnet-sodium-hexahydrate/24h (0.13 – 0.19 mg/kg BW/min) amounted to 75 – 265 µmol Foscarnet/l (=22.5 – 79.5 mg foscarnet-sodium-hexahydrate/l). In the case of a continuous infusion, steady-state conditions are reached after approximately 2 days.

Distribution
After a single i.v. administration of foscarnet sodium in humans, the concentration-time curve in the plasma can be described as a multicompartmental model. The distribution volume is 0.4 – 0.6 l/kg body weight and the concentration reached in the cerebrospinal fluid ranges from 10 – 70 % of the plasma concentration. Plasma protein binding is below 20 %.

Biotransformation

Foscarnet-sodium is not metabolized.

Elimination

Foscarnet-sodium is excreted exclusively through the kidneys by glomerular filtration and tubular secretion. The renal clearance ranges around 150 ml/min. In the case of normal renal function, the plasma half-life is 2 to 4 hours. The terminal half-life is 1 to 8 days, which is most probably due to the slow release of foscarnet sodium from the bones.

Table 5 shows the pharmacokinetic parameters determined for the 2 x and 3 x daily administration of foscarnet sodium in initial therapy of CMV infections in AIDS patients.

Table 5

Parameter	3 x daily administration of 60 mg/kg BW every 8 hours *	2 x daily administration of 90 mg/kg BW every 12 hours *
C_{max} at steady state (µM)	589 ± 192 (24)	623 ± 132 (19)
C_{min} at steady state (µM)	114 ± 91 (14)	63 ± 57 (17)
Distribution volume (l/kg)	0.41 ± 0.13 (12)	0.52 ± 0.20 (18)
Plasma half-life (h)	4.0 ± 2.0 (24)	3.3 ± 1.4 (18)
Systemic clearance (l/h)	6.2 ± 2.1 (24)	7.1 ± 2.7 (18)
Renal clearance (l/h)	5.6 ± 1.9 (5)	6.4 ± 2.5 (13)
CSF/plasma ratio	0.69 ± 0.19 (9)**	0.66 ± 0.11 (5)***

* Mean value ± standard deviation (number of patients tested) for each parameter
** 50 mg/kg BW every 8 hours over 28 days, samples were taken 3 hours after terminating the 1 hour infusion
*** 90 mg/kg BW every 12 hours over 28 days, samples were taken 1 hour after terminating the 2 hour infusion

5.3 Preclinical safety data

Chronic toxicity

In studies on chronic toxicity, the kidney and bones proved to be the target organs of toxic effects.

In the case of dogs and rats, tubular atrophies were noted after high intravenous administrations of foscarnet sodium hexahydrate (15 or 180 mg/kg BW respectively). The action mechanism behind kidney damage is as yet unknown.

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 dogs. 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.

Other occasional findings were reduced hemoglobin concentrations and impaired amelogenesis of the incisors in rats (6-month study).

Carcinogenicity

The carcinogenic potential of foscarnet sodium was investigated in mice and rats after oral administration (250 or 500 mg/kg BW resp.).Neither with the mice nor with the rats was there any indication of a carcinogenic effect. However, carcinogenic potential as a result of long-term treatment with infusions of high doses of foscarnet sodium hexahydrate cannot be ruled out due to the inhibitory effect of foscarnet sodium on DNA polymerase and the associated genotoxicity.

Mutagenicity
The following mutagenicity tests were carried out with foscarnet sodium:
Ames test, mouse lymphoma test, SCE test and chromosome aberration test on CHO cells, cell transformation test and micronucleus test on mice.

Foscarnet sodium showed no indication of genotoxic effects in the Ames test, the mouse lymphoma test and the determination of SCE in CHO cells. At high foscarnet concentrations (3.3 mmol/l without and 10 mmol/l with metabolic activation), the chromosome aberration frequency in CHO cells was above normal. Foscarnet sodium was also active in the cell transformation test.

In the micronucleus test, there were no signs of a statistically significant increase in the number of polychromatic erythrocytes with micronuclei at i.v. doses of 175 mg/kg foscarnet sodium hexahydrate/kg BW; however, there were at the maximum tolerable i.v. dose of 350 mg foscarnet sodium hexahydrate/kg BW.

The results of these tests indicate that this substance has a genotoxic potential at high doses.

Reproduction toxicology
In teratogenicity studies on rats and rabbits, the administration of foscarnet sodium showed an increase in the incidence of skeletal anomalies. A fertility study on rats and a peri- and postnatal study on rats did not show side effects to have been caused by foscarnet sodium. In those studies, foscarnet sodium hexahydrate was administered subcutaneously at doses of up to 75 and 150 mg/kg BW.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid 7% (E507) for pH-adjustment
Water for injection

6.2 Incompatibilities

Foscavir must not be diluted with a glucose solution ≥ 30%. Ringer’ s acetate, amphotericin B or electrolyte solutions containing bivalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+} etc. must not be used for dilution or for the concomitant infusion of Foscavir. Aciclovir, ganciclovir, pentamidine, trimethoprim-sulfamethoxazol and vancomycin must not be added to the solution for infusion.

Foscavir should not be administered concomitantly with other medicinal products through the same infusion cannula.

The medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

When properly stored, the shelf life of Foscavir is two years.

Shelf life after opening:

24 hours

Any unused, diluted solution for infusion remaining after application must be disposed of.

6.4 Special precautions for storage

Do not store above 30° C. Do not refrigerate.

Foscavir must not be stored below 8° C, as precipitation may form at lower temperatures. Precipitation will also occur if the solution for infusion is frozen and then thawed again.

If the solution is mistakenly stored at refrigerator temperatures or if the solution for infusion is exposed to temperatures below freezing, Foscavir can be restored for use. Shake the bottle thoroughly and keep at room temperature for 4 hours until all the precipitation has completely disappeared.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 bottles of 250 ml solution for infusion each [N 1] and 10 bottles of 250 ml solution for infusion each [N 3].

6.6 Special precautions for disposal and other handling

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

In case of an infusion in peripheral veins, the solution of 24 mg foscarnet sodium hexahydrate has to be diluted to 12 mg foscarnet sodium hexahydrate/ml or less immediately prior administration using 5% glucose solution or 0.9% sodium chloride solution.

Accidental contact of foscarnet sodium with the skin or eyes may cause local irritation and burning. In the event of accidental contact, the affected area should be rinsed amply with water.

7. MARKETING AUTHORISATION HOLDER

Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
1118BJ Schiphol
The Netherlands

8. MARKETING AUTHORISATION NUMBER

31435.00.00

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13.02.1995
Date of latest renewal: 21.12.2011

10. DATE OF REVISION OF THE TEXT

28.05.2021

11. RESTRICTIONS FOR MARKETING

Available on prescription only