Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Foscarnet sodium hexahydrate Tillomed 24 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 24 mg foscarnet sodium hexahydrate.
Each 250 ml bottle contains 6000 mg foscarnet sodium hexahydrate

Each bottle of 250 ml contains 1375 mg (60 mmol) sodium as a constituent of the active substance.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear and colourless solution, practically free from particles
pH: Between 7.2 and 7.6
Osmolality: Between 240 mOsmol/ kg and 300 mOsmol/ kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Foscarnet Tillomed should only be used in patients with acquired immunodeficiency syndrome (AIDS).
- Life threatening or eye-threatening disease caused by cytomegalovirus (CMV). Treatment with Foscarnet Tillomed should only be given if cytomegalovirus has been detected.
- For acute, mucocutaneous infections caused by aciclovir-resistant herpes viruses (HSV). Foscarnet Tillomed therapy should be given if there are no medically acceptable therapeutic alternatives. Due to the risk profile of the active ingredient, a strict indication is required.
If there is a relapse, the aciclovir resistance must be reviewed.
The generally accepted guidelines for the appropriate use of medicines to treat cytomegalovirus or herpes simplex infections in HIV-infected patients must be followed.

4.2 Posology and method of administration

For intravenous application.

Posology

CMV infection:
Adults:
Induction therapy
In CMV infection therapy, foscarnet sodium hexahydrate can be administered as 60 mg/kg body weight, 3 times a day (Foscarnet Tillomed 2.5 ml/kg body weight, thrice a day) at an interval of 8 hours or twice a day of foscarnet sodium hexahydrate at 90 mg/kg bw (Foscarnet Tillomed 3.75 ml/kg bw twice a day) at an interval of 12 hours.

The infusion duration for foscarnet sodium hexahydrate 60 mg/kg body weight must not be less than 1 hour and for foscarnet sodium hexahydrate 90 mg/kg body weight, not less than 2 hours (see "method of administration").

Maintenance therapy:
To prevent recurrence of a CMV infection, an infusion of foscarnet sodium hexahydrate at 90-120 mg/kg body weight (Foscarnet Tillomed 3.75 - 5 ml/kg body weight) is administered once a day for 2 hours.

Therapy should be initiated with 90 mg foscarnet sodium hexahydrate/kg and may be titrated up to 120 mg foscarnet sodium hexahydrate/kg if the retinitis is progressive and Foscarnet Tillomed is well tolerated.

Patients who experience progression of retinitis while receiving maintenance therapy may be re-treated with the induction regimen. After patient stabilization, maintenance therapy with foscarnet sodium hexahydrate can be initiated.

Special population

Paediatric population

The safety and efficacy of foscarnet sodium hexahydrate in children and adolescents under 18 years of age has not been established. For more information, see sections 4.4 and 5.3.

Elderly patients

As foscarnet sodium hexahydrate is excreted by the kidneys, it should be noted that renal function may be impaired in elderly patients despite normal serum creatinine levels. Renal function is assessed using the calculation of creatinine clearance. For the use of foscarnet sodium hexahydrate in the elderly, the same dose adjustments are valid as described under "Dosage in patients with renal impairment" in Tables 1 and 2.

Patients with renal impairment

In case of impaired renal function, the dosage should be adjusted to the creatinine clearance (see table. 1 + 2). Renal function should be monitored at baseline and regularly during therapy and the dosage should be calculated accordingly (see section 4.4).

The creatinine clearance can be calculated from the serum creatinine concentration as follows:

Males: Cl_{creat} [ml/min/kg] = 140 - age[years]
72 x Serum creatinine concentration (mg/dl)

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

Table. 1 Dosing scheme in renal impairment for initial therapy in CMV infection.

	Foscarnet sodium hexahydrate dosage *			
Creatinine Clearance (ml/min/kg bw)	90 mg/kg bw (Infusion duration: min. 2 hours)	In intervals of	60 mg/kg bw (Infusion duration: min.1 hour)	In 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	No therapy recommendation			

Table. 2 Dosing regimen in renal impairment for maintenance therapy of CMV infection

	Foscarnet sodium hexahydrate dosage *			
Creatinine Clearance (ml/min/kg bw)	90 mg/kg bw (Infusion duration: min. 2 hours)	In intervals of:	120 mg/kg bw (Infusion duration: min. 2 hours)	In 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	No therapy recommendation			

* Note: Data are based on studies of pharmacokinetics after single dose of foscarnet sodium hexahydrate in patients with varying degrees of impaired renal function.

Foscarnet Tillomed is not recommended for patients on dialysis as no dosing guidelines have been developed.

Patients with hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Duration of treatment

Duration of induction therapy of CMV infection is determined by the clinical response and is generally about 2 to 3 weeks.

To prevent relapses a subsequent transition to maintenance therapy is made. This therapy is of longer duration, 6 months is the minimum, but possibly even of life-long duration.
The decision on whether a maintenance therapy should be stopped should be based on generally accepted current therapy guidelines.

***Herpes* infection:**
Posology
Adults:
Aciclovir-resistant herpes infection is treated 3 times daily with foscarnet sodium hexahydrate 40 mg/kg body weight (= 3 times 1.7 ml <Foscarnet Tillomed>/kg bw), 3 times a day at an interval of 8 hours.
The duration of the infusion must not be less than 1 hour (see "Method of administration")

Special population
Paediatricpopulation
The safety and efficacy of foscarnet sodium hexahydrate in children and adolescents under 18 years of age has not been established. For more information, see sections 4.4 and 5.3.

Elderly
Because foscarnet sodium hexahydrate is excreted renally, it should be noted that renal function may be impaired in elderly patients despite normal serum creatinine levels. Renal function is determined using the calculation of creatinine clearance. The same dose titrations apply to the use of foscarnet sodium in the elderly as described in "Patients with renal impairment" in Table 3

Patients with renal impairment
If renal function is impaired, the dosage of creatinine clearance must be adjusted (see Table 3; for the calculation of creatinine clearance, see formula in the section for CMV infection). Renal function should be monitored at baseline and regularly during therapy and the dose calculated accordingly.

Table 3: Dosage scheme for renal impairment in the therapy of herpes infection

	Foscarnet-Sodium -Hexahydrate Dosage *	
Creatinine- Clearance (ml/min/kg bw)	40 mg/kg bw (Infusion duration: min. 1 hour)	In 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	No therapy recommendations	

* Note: Data are based on studies of pharmacokinetics after single dose of foscarnet sodium hexahydrate in patients with varying degrees of impaired renal function.
Foscarnet sodium hexahydrate is not recommended for patients on dialysis, as no guidelines for dosing have been developed.
Patients with hepatic impairment
No dose titration is required in patients with hepatic impairment

Duration of treatment
Therapy of aciclovir resistant herpes infection should be carried out until there is a total remission of lesions (complete re-epithelialization). This usually requires a therapy period of 2 to 3 weeks. If there is no effect after a therapy period of 1-week, further therapy must be critically examined from the point of view of benefit/risk.
Relapse prevention after aciclovir-resistant herpes infection with foscarnet sodium hexahydrate has not been adequately investigated. If a relapse occurs, a review of the resistance is necessary.

Method of administration
Foscarnet Tillomed should **not** be administered as a short-term intravenous injection.
When infused via central veins, dilution of the infusion solution is not necessary. When infused into a peripheral vein, the infusion solution must be diluted before use See section 6.6 for dilution instructions).
For further information on the preparation and storage of the ready-to-use solution, see sections 6.2 and 6.4.

Hydration

The renal toxicity of foscarnet sodium hexahydrate can be reduced by adequate fluid intake. Before the first administration of Foscarnet Tillomed , adequate diuresis should be created by infusing 0.5 - 1.0 litre of 0.9% sodium chloride solution. Subsequently, 0.5 - 1.0 litre of 0.9% sodium chloride solution should be given with each infusion. In patients with good compliance, appropriate fluid intake can also be given orally. A clinically manifest fluid deficiency should be compensated for before starting therapy with Foscarnet Tillomed.

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

Foscarnet Tillomed should be used with caution in patients with reduced renal function. Since renal function impairment may occur at any time during Foscarnet Tillomed 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 medical Foscarnet Tillomed s must be closely monitored (see section 4.5).

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

Foscarnet sodium hexahydrate 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 (hypokalemia, 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.

Foscarnet sodium hexahydrate is deposited in teeth, bone and cartilage. Animal data show that deposition is greater in younger animals. The safety of foscarnet sodium hexahydrate and its effects 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 foscarnet sodium hexahydrate 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.

Foscarnet use should be avoided when a saline load cannot be tolerated (e.g. in cardiomyopathy)

Foscarnet sodium hexahydrate 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 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 Foscarnet Tillomed 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 sodium hexahydrate. In this case, termination of Foscarnet Tillomed therapy and a change to an appropriate other medicinal Foscarnet Tillomed should be considered.

This medicinal Foscarnet Tillomed contains 1375 mg of sodium per 250 ml bottle, equivalent to 69% of the WHO recommended maximum daily intake of 2g sodium for an adult.

The maximum daily dose of this Foscarnet Tillomed during maintenance treatment (i.e. 120mg/kg/day) and without dilution for a patient of 70 kg body weight is equivalent to 96% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this Foscarnet Tillomed during maintenance treatment (i.e. 120mg/kg/day) and diluted with sodium chloride 9 mg/ml (0.9%) solution to concentration 12 mg/ml for a patient of 70 kg body weight is equivalent to 158% of the WHO recommended maximum daily intake for sodium.

Foscarnet Tillomed is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

Since foscarnet sodium hexahydrate 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 sodium hexahydrate can reduce serum levels of ionized calcium, extreme caution is advised when used concurrently with other active substances 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 foscarnet sodium hexahydrate and i.v. pentamidine. Abnormal renal function has been reported in connection with the use of foscarnet sodium hexahydrate in combination with ritonavir and/or saquinavir.

Due to the potential increased risk of QT prolongation and torsade de pointes, Foscarnet Tillomed should be avoided with drugs known to prolong QT interval, notably class IA (e.g. quinidine) and III (e.g. amiodarone, sotalol), antiarrhythmic agents or neuroleptic active substances. 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 foscarnet sodium hexahydrate on fertility.
No effects on fertility were observed in animal studies (see section 5.3).

Women of child-bearing potential/contraception in men and women
Women of childbearing potential and sexually active men have to use effective contraception during and up to 6 months after therapy.

Pregnancy
There are no or limited amount of data from the use of foscarnet sodium hexahydrate in pregnant women.
Animal studies are insufficient with respect to reFoscarnet Tillomed ive toxicity (see section 5.3).
Foscarnet Tillomed is not recommended during pregnancy.

Lactation
There is insufficient information on the excretion of foscarnet sodium hexahydrate in human milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of foscarnet sodium hexahydrate in milk (for details see section 5.3).

A risk to the newborns/infants cannot be excluded.

Foscarnet Tillomed should not be used during breast-feeding.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from foscarnet therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman must be taken into account.

4.7 Effects on ability to drive and use machines

Foscarnet sodium hexahydrate has minor influence on the ability to drive and use machines. Due to the disease itself and possible undesirable effects of foscarnet (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 Foscarnet Tillomed are severely immuno-compromised and suffering from serious viral infections. Patient's physical status, the severity of the underlying disease, other infections and concurrent therapies contribute to adverse events observed during use of Foscarnet Tillomed.

The undesirable effects reported with foscarnet sodium hexahydrate 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 4: Frequency of adverse events.

MedDRA system organ class	Frequency	Adverse event
Blood and lymphatic system disorders	Very common	Granulocytopenia, anemia
	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	Hypernatremia
Psychiatric disorders	Common	Aggression, anxiety, agitation, confusional state, depression, nervousness
Nervous system disorders	Very common	Dizziness, headache, paraesthesia
	Common	coordination abnormal, convulsion, hypoesthesia, 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	Diarrhea, nausea, vomiting
	Common	Abdominal pain, constipation, dyspepsia, pancreatitis, gastrointestinal haemorrhage
	Not known	Oesophageal ulcer
Hepatobiliary disorders	Common	hepatic function abnormal
Skin and subcutaneous tissue 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	Muscle weakness, myopathy, myositis, rhabdomyolysis
Renal and urinary disorders	Common	renal impairment, renal failure acute, dysuria, polyuria, proteinuria
	Uncommon	Renal tubular disease, glomerulonephritis, nephrotic syndrome
	Not known	Renal pain, renal tubular acidosis, renal tubular

		necrosis, acute renal tubular necrosis, crystal nephropathy, hematuria
ReFoscarnet Tillomed ive 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, hemoglobin decreased
	Common	Creatinine renal clearance decreased, electrocardiogram abnormal, gammaglutamyl transferase 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 sodium hexahydrate 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 sodium hexahydrate is excreted in high concentrations in the urine and may be associated with significant irritation and ulceration in the genital area, especially after prolonged therapy
[d]Transient chest pain has been reported as part of infusion reactions to foscarnet sodium hexahydrate.

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Overdose has been reported during the use of foscarnet sodium hexahydrate, the highest being some 20 times the recommended dose. Some of the cases were relative overdoses, in that the dose of active substances 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 symptoms reported in association with an overdose of foscarnet sodium hexahydrate is in accordance with the known adverse event profile of the active substance (see section 4.8).

Hemodialysis increases foscarnet sodium hexahydrate 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 hexahydrate 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 sodium hexahydrate also inhibits the viral DNA polymerase from hepatitis B virus.

Foscarnet sodium hexahydrate has a virostatic effect against cytomegaloviruses and herpes viruses, i.e. it suppresses the growth of the viruses, but cannot eliminate cytomegalovirus or herpes viruses. The results obtained using clinical isolates in vitro for a 50% reversible inhibition of cytomegalovirus replication (IC_{50}) was 270 µmol/l on average. Against HSV-1 and HSV-2,

the IC_{50} values were ranged from 10 µmol/l to 130 µmol/l. The IC_{50} for inhibition of normal human cell growth is 1000 µmol/l foscarnet sodium hexahydrate.

5.2 Pharmacokinetic properties

Absorption
The plasma levels measured in a clinical study with a continuous intravenous infusion of 16 g / 24 h (0.13 - 0.19 mg/kg bw/min) of foscarnet sodium hexahydrate are 75-265 µmol foscarnet / l (=foscarnet sodium hexahydrate 22.5 - 79.5 mg/l). With a continuous infusion, steady-state conditions are reached after about 2 days.

Distribution
The concentration-time profile in plasma using a multi-compartment model is used to describe the situation after a single i.v. administration of foscarnet sodium hexahydrate in humans. The volume of distribution is 0.4 - 0.6 l/kg body weight and the concentration reached in the cerebrospinal fluid is 10 - 70% of the plasma concentration. The plasma protein binding is below 20%.

Biotransformation
Foscarnet sodium hexahydrate is not metabolized.

Elimination
Foscarnet sodium hexahydrate is excreted exclusively renally through glomerular filtration and tubular secretion. Renal clearance is of the order of 150 ml/min. The plasma half-life in normal renal function is 2 to 4 hours.

The terminal half-life is 1 to 8 days, which is probably due to the slow release of foscarnet sodium hexahydrate from the bones.

Table 5 shows the pharmacokinetic parameters that were determined for the initial therapy of CMV infections in AIDS patients for the twice daily and three times daily administration of Foscarnet sodium hexahydrate.

Tab. 5

Parameter	3 times daily dose of 60 mg/kg body weight every 8 hours *	Twice daily dose of 90 mg/kg body weight every 12 hours *
C_{max} in distribution equilibrium (µM)	589 ± 192 (24)	623 ± 132 (19)
C_{min} in distribution equilibrium (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)
Total bodily 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 ± standard deviation (number of patients examined) for each parameter
** 50 mg/kg body weight every 8 hours for 28 days, samples were taken 3 hours after the end of the one-hour infusion
*** 90 mg/kg body weight every 12 hours for 28 days, samples were taken 1 hour after the end of the two-hour infusion.

5.3 Preclinical safety data

Chronic toxicity
Chronic toxicity studies have shown the kidneys and bones to be the target organs for toxic effects.

Tubular atrophies were observed in dogs and rats, after high i.v. doses (15 and 180 mg / kg body weight) of foscarnet sodium hexahydrate. The mechanism of action for renal damage is currently unknown.

Osteologic changes have been described as increased osteoclastic activity and bone resorption. Approximately 20% of the drug administered is absorbed into the bones and cartilage and the deposition is higher in young animals and growing animals. This effect has only been observed in dogs. One explanation for these changes could be that foscarnet sodium hexahydrate is included in the hydroxyapatite due to its structural similarity to phosphate.

Autoradiographic studies showed that foscarnet sodium hexahydrate has a clear affinity for bone tissue. Regeneration studies have shown that the bone changes are reversible. Foscarnet sodium hexahydrate has been shown to affect the development of tooth enamel in mice and rats. The effects of this deposit on skeletal development have not been studied.

Other uncommon findings were a reduced hemoglobin concentration and disruption of the incisor amelogenesis in the rat (6-month study).

Carcinogenicity
The carcinogenic potential of foscarnet sodium hexahydrate was investigated in mice and rats after oral administration (250 and 500 mg/kg body weight, respectively). There were no indications of carcinogenic effects in either the mouse or the rat.

Due to the DNA polymerase inhibitory properties of foscarnet sodium hexahydrate and the related genotoxicity at high concentrations, a carcinogenic potential of long-term high-dose foscarnet sodium hexahydrate infusion therapy cannot be excluded.

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

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

In the micronucleus test at a dose of 175 mg/kg foscarnet sodium hexahydrate/kg body weight i.v. no signs of a statistically significant increase in the number of polychromatic erythrocytes with micronuclei were found, but was found at the maximum tolerable dose of 350 mg foscarnet sodium hexahydrate/kg body weight i.v.

The results of these studies indicate a genotoxic potential of this substance at high doses.

ReFoscarnet Tillomed ive Toxicology
Teratogenicity studies in rats and rabbits showed an increase in the incidence of skeletal abnormalities after administration of foscarnet sodium hexahydrate. A fertility study in rats and a peri- and postnatal study in rats showed no side effects that could be attributed to foscarnet sodium hexahydrate. In these studies, foscarnet sodium hexahydrate s.c. administered in dose ranges up to 75 or 150 mg/kg body weight.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, dilute (for pH adjustment)
Water for injections

6.2 Incompatibilities

Foscarnet Tillomed is not compatible with glucose solution ≥ 30 %, Ringer's acetate, amphotericin B, aciclovir sodium, ganciclovir, pentamidine isethionate, trimethoprim-sulfamethoxazole, and vancomycin hydrochloride. Neither is Foscarnet Tillomed compatible with electrolyte solutions that contain divalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+}.It is recommended that other drugs should not be infused concomitantly in the same line.

Foscarnet Tillomed should not be co-administered with other medicinal Foscarnet Tillomed s through the same infusion cannula.

The medicinal Foscarnet Tillomed must not be mixed with other medicinal Foscarnet Tillomed s except those listed in section 6.6.

6.3 Shelf life

Unopened:
2 years
After opening:

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the Foscarnet Tillomed should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After dilution:
Chemical and physical in-use stability has been demonstrated for 36 hours at 2-8 and 20-25 , when solution is diluted from 24 mg/ml to 12 mg/ml of foscarnet sodium hexahydrate in PVC bags.
From a microbiological point of view, the Foscarnet Tillomed 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 , unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not refrigerate or freeze.

Foscarnet Tillomed should not be kept below 8°C precipitation can occur at lower temperatures. Precipitation remains even if the infusion solution is frozen and thawed again.
Foscarnet Tillomed can be made ready for use again if it has been accidentally stored at refrigerator temperatures or if the infusion solution has been exposed to temperatures below freezing. The bottle should then be shaken vigorously several times and kept at room temperature for 4 hours until all precipitation has completely dissolved.
For storage conditions after dilution of the medicinal Foscarnet Tillomed, see section 6.3.

6.5 Nature and contents of container

250 ml solution for infusion in glass bottle and bromobutyl rubber stopper with aluminium seal and plastic flip off seal.
Pack sizes: 1 bottle and 10 bottles
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

When infused into peripheral veins, the solution should be diluted from 24 mg/ml of foscarnet sodium hexahydrate to 12 mg/ml of foscarnet sodium hexahydrate before use with 50 mg/ml (5%) glucose solution or 9 mg/ml (0.9%) sodium chloride solution.

Individually dispensed doses of Foscarnet Tillomed should be aseptically transferred to plastic infusion bags (PVC bags) by the hospital pharmacy and diluted with equal parts of 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution.

Accidental contact of foscarnet sodium hexahydrate with the skin and eyes can cause local irritation and burning. The affected area should be rinsed off with plenty of water.

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

7 MARKETING AUTHORISATION HOLDER

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