Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Foscavir 24mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Foscarnet trisodium hexahydrate 24mg/ml
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intravenous Infusion (I.V)

Clear and colourless solution

WARNING
Renal impairment is the major toxicity of Foscavir 24mg/ml. Frequent monitoring of serum creatinine, with dose adjustment for changes in renal function, and adequate hydration with administration of Foscavir 24mg/ml is imperative (see administration section: Hydration).
Seizures, related to alterations in plasma minerals and electrolytes, have been associated with Foscavir 24mg/ml treatment. Therefore, patients must be carefully monitored for such changes and their potential sequelae. Mineral and electrolyte supplementation may be required. Foscavir 24mg/ml is indicated for use only in immunocompromised patients with CMV retinitis (see Indications section).

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).

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 24mg/ml must be diluted. Individually dispensed doses of foscarnet should be aseptically transferred and diluted with equal parts of 0.9% sodium chloride (9mg/ml) or 5% dextrose (50mg/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 24mg/ml may be given without dilution via a central vein.

Adults: Induction therapy for CMV retinitis: Foscavir 24mg/ml is administered over 2-3 weeks depending on the clinical response, as intermittent infusions every 8 hours at a dose of 60mg/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 24mg/ml 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.

Caution: Do not administer Foscavir 24mg/ml by rapid intravenous injection.

Table 1 - Foscavir 24mg/ml Dosing Chart

Induction Therapy

Creatinine Clearance (ml/kg/min)	**CMV Every 8 Hours (mg/kg)**
>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

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 24mg/ml is not recommended in patients undergoing haemodialysis since dosage guidelines have not been established.

Hydration: Renal toxicity of Foscavir 24mg/ml 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 24mg/ml 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 Special Warnings and Special Precautions for Use and 5.3 Preclinical safety data.)

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 24mg/ml should be used with caution in patients with reduced renal function. Since renal function impairment may occur at any time during Foscavir 24mg/ml 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 4.2 Posology and Method of Administration). 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 Interaction with other medicinal products and other forms of interaction).

This medicinal product contains 1.38 g of sodium per 250 ml bottle, equivalent to equivalent to 69% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The maximum recommended daily dose of this product is 12 g of Foscavir 24mg/ml per day (180 mg/kg/day in average 70 kg male), which is equivalent to 138% of the WHO recommended maximum daily dietary intake for sodium.

Foscavir 24mg/ml 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 24mg/ml propensity to chelate bivalent metal ions, such as calcium, Foscavir 24mg/ml administration may be associated with an acute decrease of ionised serum calcium proportional to the rate of Foscavir 24mg/ml 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 24mg/ml 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 Undesirable effects). 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 24mg/ml is deposited in teeth, bone and cartilage. Animal data show that deposition is greater in young animals. The safety of Foscavir 24mg/ml and its effect on skeletal development have not been investigated in children. (Please refer to Section 5.3 Preclinical safety data)

Seizures, related to alterations in plasma minerals and electrolytes, have been associated with Foscavir 24mg/ml 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 24mg/ml 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 24mg/ml 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 24mg/ml 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 24mg/ml 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 24mg/ml 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 24mg/ml and *i.v.* pentamidine. Abnormal renal function has been reported in connection with the use of Foscavir 24mg/ml 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 Incompatibilities.

4.6 Fertility, Pregnancy and Lactation Fertility

There are no data available regarding the influence of Foscavir 24mg/ml on fertility.

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

Women of childbearing potential / contraception in males and females

Women capable of childbearing should use effective contraception methods during Foscavir 24mg/ml therapy.

Men treated with Foscavir 24mg/ml 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 Preclinical safety data).

Foscavir 24mg/ml 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 Preclinical safety data).

A risk to the newborns/infants cannot be excluded.

Foscavir 24mg/ml should not be used during breast-feeding.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Foscavir 24mg/ml 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 24mg/ml has moderate influence on the ability to drive and use machines. Due to the disease itself and possible undesirable effects of Foscavir 24 mg/ml (such as dizziness and convulsions , see section 4.8 Undesirable Effects), 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 24mg/ml 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 24mg/ml.

The undesirable effects reported with Foscavir 24mg/ml 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 Posology and method of administration and 4.4 Special warnings and precautions for use).

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	Unknown	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
Hepato-biliary 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 disorders and connective tissue disorders	Common	Myalgia
	Unknown	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 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Overdose has been reported during the use of Foscavir 24mg/ml, 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 24mg/ml is in accordance with the known adverse event profile of the drug.

Haemodialysis increases Foscavir 24mg/ml 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 HTV-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 Pre-clinical 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 (75-150mg/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 product except those mentioned in section 4.2 Posology and method of administration.

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

The expiry date of the product is indicated on the packaging materials

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 2-8°C.

Each bottle of Foscavir 24mg/ml should only be used to treat one patient with a single infusion.

Any unused medical product or waste material should be disposed os in accordance with local requirements.

6.4 Special Precautions for Storage

Do not store above 25°C. Do not refrigerate. Do not freeze. 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 Shelf-Life.

6.5 Nature and Content of Container

Infusion glass bottles of 250ml

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 (9mg/ml) or 5% dextrose (50mg/ml) in PVC bags is 7 days. However, diluted solutions should be refrigerated and storage restricted to 24 hours.

Each bottle of Foscavir 24mg/ml 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.

7. MANUFACTURER

Fresenius Kabi Austria GmbH

Hafner Strasse 36 A-8055 GRAZ, Austria

8. LICENSE HOLDER

Megapharm Ltd

P.O.B 519, Hod Ha'sharon 4510501, Israel

MARKETING AUTHORISATION NUMBER

068-16-28118

Revised on January 2021 according to MoH guidelines