SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Virafosc 24 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 24 mg foscarnet sodium hexahydrate.

Excipient with known effect
This medicinal product contains 1.38 g 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.

The solution is isotonic with a pH of 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Virafosc is indicated as follows in adult patients:

- In haematopoietic stem cell transplant (HSCT) patients; induction and maintenance therapy of cytomegalovirus (CMV) viraemia and CMV disease.
- Induction and maintenance therapy of CMV retinitis in patients with AIDS.
- Induction therapy of CMV infections in the upper and lower gastrointestinal tract in patients with AIDS.
- Induction therapy of aciclovir-unresponsive mucocutaneous Herpes Simplex Virus (HSV) infections in patients with AIDS.

4.2 Posology and method of administration

Posology in adults

Induction therapy:

- *CMV viraemia in HSCT patients*
  Virafosc is administered over at least 2 weeks, as intermittent infusions every 12 hours at a dose of 60 mg/kg body weight in patients with normal renal function. The dosage must be adjusted for patients with renal dysfunction (see Table 1). The infusion time should not be shorter than 1 hour.

- *CMV disease in HSCT patients*

Virafosc is administered over at least 2-3 weeks, depending on clinical response, as intermittent infusions every 8 hours at a dose of 60 mg/kg body weight or every 12 hours at a dose of 90 mg/kg body weight in patients with normal renal function. The dosage must be adjusted for patients with renal dysfunction (see Table 1). The infusion time should not be shorter than two hours for the 90 mg/kg dose twice daily or one hour for the 60 mg/kg dose three times daily.

- *CMV retinitis in AIDS patients*
  Virafosc is administered over 3 weeks depending on the clinical response, as intermittent infusions every 8 hours at a dose of 60 mg/kg body weight or every 12 hours at a dose of 90 mg/kg body weight in patients with normal renal function. The dosage must be adjusted for patients with renal dysfunction (see Table 1). The infusion time should not be shorter than two hours for the 90 mg/kg dose twice daily or one hour for the 60 mg/kg dose three times daily.

- *CMV infections in the upper and lower gastrointestinal tract*
  Virafosc is administered as intermittent infusions every 12 hours at a dose of 90 mg/kg body weight in patients with normal renal function. Most patients will have remission of their symptoms within 2-4 weeks. The dosage must be adjusted for patients with renal dysfunction (see Table 1). The infusion time should not be shorter than two hours.

- *Aciclovir-unresponsive mucocutaneous herpes simplex virus infections*
  Virafosc is administered over 2-3 weeks, or until the lesions have healed, as intermittent infusions every 8 hours at a dose of 40 mg/kg body weight in patients with normal renal function. The dosage must be adjusted for patients with renal dysfunction (see Table 1). The infusion time should not be shorter than one hour.

Regular monitoring of the renal function and any dose adjustment is recommended (see section 4.4). In the event of recurrences, the course may be repeated.

Table 1: Virafosc dosing regimen for induction therapy

Creatinine clearance	CMV viraemia (HSCT)	CMV disease (HSCT) and CMV retinitis (AIDS)	CMV disease (HSCT), CMV retinitis (AIDS) and CMV in GIT	HSV infection
	Regimen for 60 mg/kg		Regimen for 90 mg/kg	Regimen for 40 mg/kg
(ml/kg/min)	(mg/kg)		(mg/kg)	(mg/kg)
>1.4	60 **	60 ***	90 **	40 ***
>1.0 to ≤1.4	45 **	45 ***	70 **	30 ***
>0.8 to ≤1.0	35 **	35 ***	50 **	20 ***
>0.6 to ≤0.8	25 **	40 **	80 *	25 **
>0.5 to ≤0.6	20 **	30 **	60 *	20 **
>0.4 to ≤0.5	15 **	25 **	50 *	15 **
<0.4	Treatment is not recommended	Treatment is not recommended	Treatment is not recommended	Treatment is not recommended
* every 24 hours (= once daily) ** every 12 hours (= twice daily) *** every 8 hours (= three times daily) GIT upper and lower gastrointestinal tract				

Maintenance therapy:

The risks of maintenance therapy should be weighed against the benefits.

- *CMV viraemia in HSCT patients*

For maintenance therapy, following induction therapy of CMV viraemia, Virafosc is administered seven days a week as long as therapy is considered appropriate. In patients with normal renal function, the maintenance dose is 90-120 mg/kg, administered as a once daily infusion over 2 hours. The dosage must be adjusted for patients with renal dysfunction (see Table 2). The infusion time should not be shorter than 2 hours.

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

- *CMV disease in HSCT patients*

For maintenance therapy, following induction therapy of CMV viraemia, Virafosc is administered seven days a week as long as therapy is considered appropriate. In patients with normal renal function, the maintenance dose is 90-120 mg/kg, administered as a once daily infusion over 2 hours. The dosage must be adjusted for patients with renal dysfunction (see Table 2). The infusion time should not be shorter than 2 hours.

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

- *CMV retinitis in AIDS patients*

For maintenance therapy, following induction therapy for CMV retinitis, Virafosc is administered seven days a week as long as therapy is considered appropriate. In patients with normal renal function, the maintenance dose is 90 mg/kg, administered as a once daily infusion over 2 hours. In patients re-treated with the induction regimen due to a relapse, or in patients who experience progression of retinitis, dose escalation up to 120 mg/kg/day may be considered if patients showed good tolerance to the lower dose. The dosage must be adjusted for patients with renal dysfunction (see Table 2). The infusion time should not be shorter than two hours.

Patients who experience progression of retinitis while receiving maintenance therapy may be re-treated with the induction regimen. Treatment with a combination of foscarnet and ganciclovir may be considered in patients with difficult-to-treat recurrent CMV retinitis, taking into consideration the tolerability of the combination therapy. Because of physical incompatibility, foscarnet and ganciclovir must **not** be mixed.

Table 2: Virafosc dosing regimen for maintenance therapy

Creatinine clearance (ml/min/kg)	(mg/kg for 2 hours)	
>1.4	90 *	120 *
>1.0 to ≤1.4	70 *	90 *
>0.8 to ≤1.0	50 *	65 *
>0.6 to ≤0.8	80 #	105 #
>0.5 to ≤0.6	60 #	80 #
>0.4 to ≤0.5	50 #	65 #
<0.4	Treatment is not recommended	Treatment is not recommended
* every 24 hours (= once daily) # every 48 hours		

Re-treatment of aciclovir-unresponsive herpes simplex virus infections

Maintenance therapy with Virafosc against recurrences of treated aciclovir-unresponsive HSV infection has not been sufficiently investigated. If there is a recurrence, then the unresponsiveness of the virus to aciclovir must be reconfirmed, either by insufficient response to an adequate treatment with aciclovir (5-10 mg/kg for 10 days), or by in-vitro tests.

Hydration
Renal toxicity can be reduced by adequate hydration of the patient. It is recommended that 0.5– 1.0 litre of physiological saline is administered by infusion prior to the first Virafosc infusion and that 0.5– 1.0 litre of physiological saline is subsequently added to each intermittent Virafosc infusion.

Hydration is also possible through oral regimens. In this case, 0.5 to 1 litre of saline should be drunk before and after the Virafosc infusion. Hydration should only be administered to suitable patients.

Posology in dialysis patients
Virafosc is not recommended in haemodialysis patients. Dosage guidelines have not been established.

Posology in the elderly
As for adults.

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

Posology in patients with 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.

Method of administration
Virafosc should be administered by the intravenous route, either by a central venous line or directly into a peripheral vein.

When the infusion is given by a **central venous** line, the foscarnet 24 mg/ml solution may be used. Dilution with 5% glucose or physiological saline to a concentration of 12 mg/ml or less is recommended when **peripheral** veins are used.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Caution - Do not administer Virafosc by rapid intravenous injection.

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

Virafosc may only be prescribed by expert specialists.

Virafosc should be used with caution in patients with reduced renal function. Since renal function impairment may occur at any time during Virafosc 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 Virafosc 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.
Virafosc 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 Virafosc's propensity to chelate bivalent metal ions, such as calcium, Virafosc administration may be associated with an acute decrease of ionized serum calcium proportional to the rate of Virafosc infusion, which may not be reflected in total serum calcium levels. The electrolytes, especially calcium and magnesium, should be assessed prior to and during Virafosc 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.

Virafosc is deposited in teeth, bone and cartilage. Animal data show that deposition is greater in young animals. The safety of Virafosc 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 Virafosc 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.

Virafosc 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 Virafosc 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 Virafosc therapy and a change to an appropriate other medicinal product should be considered.

When Virafosc is administered for CMV viraemia, observe carefully for organ-specific infection. If symptoms of infection occur, adjust the administration dosage rapidly in accordance with CMV disease (see section 4.2) and take appropriate measures.

4.5 Interaction with other medicinal products and other forms of interaction

Since Virafosc 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 Virafosc 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 Virafosc and i.v. pentamidine.

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

Due to the potential increased risk of QT interval prolongation and torsade de pointes, Virafosc 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 on the effect of Virafosc on fertility in humans.
In animal studies, no effects on fertility have been reported.

Women of childbearing potential/contraception in males and females
Women of child-bearing age and sexually active men must use effective contraception for up to six months after treatment.

Pregnancy
There are insufficient data on the use of foscarnet in pregnant women. In animal studies reproductive toxicity has been reported (see section 5.3). Virafosc should only be given to pregnant women where absolutely necessary, where there is no safe alternative and where treatment cannot be withdrawn.

Lactation
There is no data on whether foscarnet passes into breast milk. From animal studies it appears that foscarnet is excreted in the mother's milk (see section 5.3). Due to the risk of side effects in nursing infants, breastfeeding must be discontinued before starting treatment.
Women with HIV infection should not breastfeed to prevent the transfer of HIV to the infant.

4.7 Effects on ability to drive and use machines

Virafosc has moderate influence on the ability to drive and use machines. Due to the disease itself and possible undesirable effects of Virafosc (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 severity 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 Virafosc are severely immuno-compromised and suffering from serious viral infections. Patients' physical status, the severity of the underlying disease, other infections and other concurrent therapies contribute to adverse events observed during use of Virafosc.

The undesirable effects reported with Virafosc 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 (frequency 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 3: 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
	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, gastrointestingal 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 Not known	Myalgia Muscular weakness, myopathy, myositis, rhabdomyolysis
Renal and urinary disorders	Very common	Renal impairment
	Common	Renal failure acute, dysuria, polyuria, proteinuria

	Uncommon	Glomerulonephritis, nephrotic syndrome, renal tubular disorder
	Not known	Renal pain, renal tubular acidosis, renal 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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdose has been reported during the use of Virafosc, 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 Virafosc is in accordance with the known adverse event profile of the drug.

Haemodialysis increases Virafosc elimination and may be of benefit in relevant cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Antiviral properties

Foscarnet is an antiviral agent with selective activity in cell cultures against all known human viruses of the herpes group (Herpes simplex type 1 and 2, Varicella zoster, Epstein-Barr and cytomegalovirus (CMV)) and some retroviruses, including human immunodeficiency virus (HIV). Foscarnet also inhibits the viral DNA polymerase of the hepatitis B virus.

Foscarnet exerts its antiviral activity by a direct inhibition of virus-specific DNA polymerase and reverse transcriptase. Foscarnet does not require activation by phosphorylation by thymidine kinase or other kinases and is therefore active *in vitro* against HSV mutants deficient in thymidine kinase.

CMV strains unresponsive to ganciclovir are generally sensitive to foscarnet.

Clinical efficacy and safety

In vitro tests are of limited value in predicting the effectiveness *in vivo*. The foscarnet concentration that inhibits CMV replication in cell cultures depends on the test conditions. The mean IC_{50} for foscarnet in more than 100 CMV isolates was approximately 270 µmol/l. A reversible toxicity to human cells was observed at concentrations of 500–1000 µmol/l foscarnet.

In the event of clinical unresponsiveness to foscarnet, the viral isolate should be tested for sensitivity to foscarnet.

Therapeutic properties

CMV viraemia in HSCT patients

In a pivotal clinical study the efficacy of foscarnet (n=110) for CMV viraemia after allogeneic HSCT was investigated and compared to ganciclovir (n=103). Following induction therapy of 2 weeks, Virafosc was demonstrated to be as effective as ganciclovir in a prospective clinical trial. The proportion of patients who survived without events after transplant (when events were defined as the occurrence of CMV disease or death from any cause) within 180 days after transplant (primary endpoint) was 66% in the foscarnet group and 73% in the ganciclovir group, with no statistically significant difference (p=0.6, log-rank test).

CMV disease in HSCT patients

Published literature demonstrates that when Virafosc is administered for CMV disease (induction treatment 180 mg/kg/day, maintenance treatment 90-120 mg/kg/day) where there were tolerability issues relating to the use of ganciclovir or resistance to ganciclovir therapy, there was an improvement in CMV disease.

CMV retinitis in AIDS patients

Following induction therapy over 2–3 weeks, Virafosc produced stabilisation of retinal lesions in approximately 90% of patients. However, since CMV generally causes latent infections and since foscarnet only exerts a virustatic activity, relapses occur in the majority of patients with persistent immunodeficiency. Institution of a once daily maintenance regimen at doses ranging from 90–120 mg/kg/day, following completion of induction therapy, produces a delay in time to retinitis progression. In patients experiencing progression of retinitis while receiving maintenance therapy or after discontinuation of therapy, reinstitution of induction therapy has shown equal efficacy as the initial course.

CMV infections in the upper and lower gastrointestinal tract in AIDS patients

In patients with proven CMV infection in the upper and lower gastrointestinal tract, induction therapy over 2–4 weeks at a dose of 90 mg/kg twice daily produced improvement in symptoms in 80% of patients and a macroscopic improvement in 72% of patients. On microscopic examination, 61% of patients had an improvement in the degree of inflammation and in 80% of patients the number of CMV inclusion bodies was strongly decreased or no longer demonstrable.

Foscarnet maintenance therapy is occasionally instituted upon completion of induction therapy.

Aciclovir-unresponsive HSV infections in immunocompromised patients
In a prospective randomised study in patients with AIDS, the lesions healed within 11–25 days, patients had complete relief of pain within 9 days and stopped shedding HSV virus within 7 days.

5.2 Pharmacokinetic properties

Distribution
Seven days after completion of foscarnet therapy, a percentage of up to 20% of the cumulative intravenous dose has not been excreted in the urine of humans and can be assumed to have been deposited in bone (tissue). The molecular similarity to phosphate and pyrophosphate and the ability to form metal-ion complexes, including with calcium ions, are probably the reasons why foscarnet exhibits rapid exchange with calcium deposits, including the inorganic bone matrix. Foscarnet binding to the inorganic bone matrix does not have a known effect on bone marrow.

Binding to human plasma proteins is low (< 20%). The volume of distribution of foscarnet at steady state ranges from 0.4–0.6 l/kg.

Foscarnet is distributed to the cerebrospinal fluid. Concentrations ranging from 13–68% of the plasma concentration have been observed in HIV-infected patients.

Metabolism
There is no metabolic conversion.

Elimination
Following intravenous administration in humans, the foscarnet plasma concentration exhibits tri-exponential decay with different half-lives. The mean half-lives of the three phases were 0.45, 3.3 and 18 hours.

Foscarnet is eliminated by the kidneys through glomerular filtration and tubular secretion. The renal clearance is about 150 ml/min.

5.3 Preclinical safety data

Subcutaneous administration of Foscarnet caused skeletal abnormalities in rats and rabbits at a systemic exposure lower than human therapeutic levels.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (E507) (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Virafosc is not compatible with: glucose 30% solution, Ringer acetate, amphotericin B, aciclovir, ganciclovir, pentamidine, trimethoprim/sulfamethoxazole, vancomycin hydrochloride or solutions containing calcium. It is recommended that Virafosc is not infused concomitantly with other medicinal products in the same line.

Virafosc is compatible with: sodium chloride 0.9%, glucose 5% and glucose 10%.

6.3 Shelf life

Unopened: 2 years.

Once opened: Once the sterility seal of a bottle has been broken the solution should be used within 24 hours from a microbiological viewpoint. 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

Store below 25°C. Do not refrigerate or 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 sections 6.3 and 6.6.

6.5 Nature and contents of container

Pack containing 1 glass bottle 250 ml.

6.6 Special precautions for disposal and other handling

Individually prepared doses of foscarnet can be aseptically transferred to plastic infusion bags. The physico-chemical stability of foscarnet and dilutions in equal parts with physiological saline or 5% glucose in PVC bags is 7 days. However, diluted solutions should be refrigerated and storage restricted to 24 hours.

Accidental skin and eye contact with foscarnet may cause local irritation and a 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2022-11-29