SUMMARY OF PRODUCT CHARACTERISTICS
CIDOFOVIR RAZ 75 mg/ml

1 NAME OF THE MEDICINAL PRODUCT

CIDOFOVIR RAZ 75 mg/ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 75 mg cidofovir anhydrous (84.679 mg of Cidofovir Dihydrate)

Each vial contains 375 mg/5 ml cidofovir anhydrous as the active substance.

Excipients with known effect:

Each vial contains approximately 2.5 mmol (or 57 mg) sodium per vial (5 ml) as a constituent of the excipients.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear colourless solution.

The concentrate for solution is adjusted to pH 7.1-7.7.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cidofovir is indicated for the treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction. It should be used only when other medicinal products are considered unsuitable.

4.2 Posology and method of administration

The therapy should be prescribed by a physician experienced in the management of HIV infection.

Before each administration of cidofovir, serum creatinine and urine protein levels should be investigated. It must be administered with oral probenecid and intravenous saline as described below (see section 4.4 for appropriate recommendations, and under section 6.6 for information on obtaining probenecid).

Posology

Adults:

Induction treatment. The recommended dose of cidofovir is 5 mg/kg body weight (given as an intravenous infusion at a constant rate over 1 hour) administered once weekly for two consecutive weeks.

Maintenance treatment. Beginning two weeks after the completion of induction treatment, the recommended maintenance dose of cidofovir is 5 mg/kg body weight (given as an intravenous infusion at a constant rate over 1 hour) administered once every two weeks. Suspension of maintenance treatment with cidofovir should be considered in accordance with local recommendations for the management of HIV infected patients.

Elderly population:

The safety and efficacy of cidofovir have not been established for the treatment of CMV disease in patients over 60 years of age. Since elderly individuals frequently have reduced glomerular function, particular attention should be paid to assessing renal function before and during administration of the medicinal product.

Renal insufficiency:

Renal insufficiency [creatinine clearance ≤ 55 ml/min or ≥ 2+ proteinuria (≥100 mg/dl)] is a contraindication for the use of cidofovir (see sections 4.3 and 4.4).

Hepatic insufficiency:

The safety and efficacy of cidofovir have not been established in patients with hepatic disease and therefore it should be used with caution in this patient population.

Paediatric population:

The safety and efficacy of cidofovir in children below 18 years of age have not been established. No data are available. It is not recommended for use in children below 18 years of age.

Method of administration

Precautions to be taken before handling or administering the medicinal product:

Adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration and disposal of cidofovir. The preparation of cidofovir reconstituted solution should be done in a laminar flow biological safety cabinet. Personnel preparing the reconstituted solution should wear surgical gloves, safety glasses and a closed front surgical-type gown with knit cuffs. If cidofovir contacts the skin, wash membranes and flush thoroughly with water (see section 6.6).

CIDOFOVIR RAZ 75mg/ml is for intravenous infusion only. The recommended dose, frequency, or infusion rate must not be exceeded. It must be diluted in 100 millilitres 0.9% (normal) saline prior to administration. The entire volume should be infused intravenously into the patient at a constant rate over a period of 1 hour by use of a standard infusion pump. To minimise potential nephrotoxicity, oral probenecid and intravenous saline prehydration must be administered with each CIDOFOVIR RAZ 75 mg/ml (see section 4.4).

4.3 Contraindications

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

Cidofovir administration is contraindicated in patients unable to receive probenecid or other sulfa containing medication (see section 4.4 Prevention of nephrotoxicity).

Cidofovir is contraindicated in patients with renal insufficiency (see section 4.2).

Concomitant administration of cidofovir and other potentially nephrotoxic agents is contraindicated (see section 4.4).

Direct intraocular injection of cidofovir is contraindicated; direct injection may be associated with significant decreases in intraocular pressure and impairment of vision.

4.4 Special warnings and precautions for use

CIDOFOVIR RAZ 75 mg/ml is formulated for intravenous infusion only and must not be administered by other methods including intraocular injection or topically. It should be infused only into veins with adequate blood flow to permit rapid dilution and distribution.

The safety and efficacy of cidofovir has not been demonstrated in diseases other than CMV retinitis in adults with AIDS.

Renal insufficiency/Haemodialysis

Treatment with cidofovir must not be initiated in patients with creatinine clearance ≤55 ml/min, or ≥ 2+ proteinuria (≥ 100 mg/dl), as the optimum induction and maintenance doses for patients with moderate to severe renal impairment are not known. The efficacy and safety of cidofovir in such conditions has not been established.

High flux haemodialysis has been shown to reduce the serum levels of cidofovir by approximately 75%. The fraction of the dose extracted during haemodialysis is 51.9 ± 11.0%.

Nephrotoxicity

Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to administration of cidofovir (see section 4.8). The safety of cidofovir has not been evaluated in patients receiving other known potentially nephrotoxic agents (e.g. tenofovir, aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, adefovir and vancomycin).

Cidofovir should not be administered concurrently with medicinal products containing tenofovir disoproxil fumarate due to the risk of Fanconi syndrome (see section 4.5).

It is recommended to discontinue potentially nephrotoxic agents at least 7 days before starting cidofovir.

Patients treated at 3.0 mg/kg, 5.0 mg/kg or 10 mg/kg without concomitant probenecid developed evidence of proximal tubular cell injury, including glycosuria, and decreases in serum phosphate, uric acid and bicarbonate, and elevations in serum creatinine. The signs of nephrotoxicity were partially reversible in some patients. Concomitant use of probenecid is essential for reducing the pronounced nephrotoxicity of cidofovir to an extent that results in an acceptable benefit/risk balance of cidofovir therapy.

Prevention of nephrotoxicity

Therapy must be accompanied by administration of oral probenecid and adequate intravenous saline prehydration (see section 6.6 for information on obtaining probenecid) with each cidofovir dose. All clinical trials relevant to clinical efficacy evaluation were performed using probenecid concomitantly with cidofovir. Two grams of probenecid should be administered 3 hours prior to the cidofovir dose and one gram administered at 2 and again at 8 hours after completion of the 1 hour cidofovir infusion (for a total of 4 grams). In order to reduce the potential for nausea and/or vomiting associated with administration of probenecid, patients should be encouraged to eat food prior to each dose of probenecid. The use of an anti-emetic may be necessary.

In patients who develop allergic or hypersensitivity symptoms to probenecid (e.g., rash, fever, chills and anaphylaxis), prophylactic or therapeutic use of an appropriate antihistamine and/or paracetamol should be considered.

Cidofovir administration is contraindicated in patients unable to receive probenecid because of a clinically significant hypersensitivity to the active substance or medicinal product or to other sulfa containing medicines. Use of cidofovir without concomitant probenecid has not been clinically investigated. A probenecid desensitisation program is not recommended for use.

In addition to probenecid, patients must receive a total of one litre of 0.9% (normal) saline solution intravenously immediately prior to each infusion of cidofovir. Patients who can tolerate the additional fluid load may receive up to a total of 2 litres of 0.9% saline intravenously with each dose of cidofovir. The first litre of saline solution should be infused over a 1 hour period immediately before the cidofovir infusion, and the second litre, if given, infused over a 1-3 hour period beginning simultaneously with the cidofovir infusion or starting immediately after the infusion of cidofovir.

Cidofovir therapy should be discontinued and intravenous hydration is advised if serum creatinine increases by ≥ 44 µmol/l (≥ 0.5 mg/dl), or if persistent proteinuria ≥ 2+ develops. In patients exhibiting ≥ 2+ proteinuria, intravenous hydration should be performed and the test repeated. If following hydration, a ≥ 2+ proteinuria is still observed, cidofovir therapy should be discontinued. Continued administration of cidofovir to patients with persistent ≥ 2+ proteinuria following intravenous hydration may result in further evidence of proximal tubular injury, including glycosuria, decreases in serum phosphate, uric acid and bicarbonate, and elevations in serum creatinine.

Interruption, and possibly discontinuation, is required for changes in renal function. For those patients who fully recover from cidofovir associated renal toxicity, the benefits-risk balance of reintroducing cidofovir has not yet been evaluated.

Patient monitoring

Proteinuria appears to be an early and sensitive indicator of cidofovir-induced nephrotoxicity. Patients receiving cidofovir must have their serum creatinine and urine protein levels determined on specimens obtained within 24 hours prior to the administration of each dose of cidofovir. Differential white blood cell counts should also be performed prior to each dose of cidofovir (see section 4.8).

Ocular events

Patients receiving cidofovir should be advised to have regular follow-up ophthalmologic examinations for possible occurrence of uveitis/iritis and ocular hypotony. In case of uveitis/iritis cidofovir should be discontinued if there is no response to treatment with a topical corticosteroid or the condition worsens, or if iritis/uveitis reoccurs after successful treatment.

Other

Cidofovir should be considered a potential carcinogen in humans (see section 5.3).

Caution should be applied when considering cidofovir treatment of patients with diabetes mellitus due to the potential increased risk of developing ocular hypotony.

Male patients should be advised that cidofovir caused reduced testes weight and hypospermia in animals. Although not observed in clinical studies of cidofovir, such changes may occur in humans and cause infertility. Men should be advised to practice barrier contraceptive methods during and for 3 months after treatment with cidofovir (see sections 4.6 and 5.3).

Appropriate precautions should continue to be employed to prevent transmission of HIV.

Excipients

This medicinal product contains approximately 2.5 mmol (or 57 mg) sodium per vial which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

There is a risk that concomitant treatment of cidofovir with products containing tenofovir disoproxil fumarate may give rise to a pharmacodynamic interaction and increase the risk of Fanconi syndrome (see section 4.4).

Probenecid increases the AUC of zidovudine. Patients receiving both medicinal products should be closely monitored for zidovudine induced haematological toxicity.

For other nucleoside reverse transcriptase inhibitors (NRTI) administered concomitantly with probenecid, reference should be made to their respective prescribing information for any appropriate recommendations.

Interactions of cidofovir/probenecid and anti-HIV medicinal products or medicinal products used to treat common chronic viral infections in this population, such as HCV- and HBV-related hepatitis, have not been investigated in clinical trials.

Probenecid is known to increase the exposure of many substances (e.g., paracetamol, acyclovir, angiotensin-converting enzyme inhibitors, aminosalicyclic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, nonsteroidal anti-inflammatory agents, theophylline, and zidovudine).

Therefore, when co-prescribing cidofovir/probenecid with other drugs, it is important for prescribers to consult the current probenecid SmPC (or an appropriate medicinal product reference source) and the respective prescribing information of the other co- administered products for full information regarding drug interactions and other features of that product.

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential/Contraception in males and females:

Due to genotoxic potential of cidofovir (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with cidofovir and for six months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while recieving cidofovir and for three months following completion of treatment.

Pregnancy:

There are no data from the use of cidofovir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Cidofovir is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding:

It is unknown whether cidofovir/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with cidofovir.

Fertility:

There are no studies of cidofovir on the fertility of men or women. Male patients should be advised that cidofovir caused reduced testes weight and hypospermia in animals. Although not observed in clinical studies of cidofovir, such changes may occur in humans and cause infertility.

4.7 Effects on ability to drive and use machines

Cidofovir has negligible influence on the ability to drive and use machines. Adverse reactions such as asthenia may occur during cidofovir therapy. 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 his recommendation in the individual case.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trials or post- marketing surveillance by system organ class (SOC) and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: 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) or not known (cannot be estimated from the available data). Adverse reactions identified from post-marketing experience are included in italics.

Adverse reactions possibly or probably related to cidofovir based on clinical trial experience and post-marketing surveillance

System Organ Class	Adverse reactions
Blood and lymphatic system disorders	
Very common	Neutropenia
Nervous system disorders	
Very common	Headache
Eye disorders	
Common	Iritis, uveitis, hypotony of the eye (see section 4.4)
Ear and labyrinth disorders	
Not known	*Hearing impaired*
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnea
Gastrointestinal disorders	
Very common	Nausea, vomiting
Common	Diarrhoea
Not known	*Pancreatitis*
Skin and subcutaneous tissue disorders	
Very common	Alopecia, rash
Renal and urinary disorders	
Very common	Proteinuria, blood creatinine increased (see section 4.4)
Common	*Renal failure*
Uncommon	*Fanconi syndrome acquired*
General disorders and administration site conditions	
Very common	Asthenia, fever
Common	Chills

Reports of renal failure (plus events possibly caused by renal failure, e.g. blood creatinine increased, proteinuria, glycosuria) received during post-marketing surveillance include some which were fatal. Cases of acute renal failure have been reported after only one or two doses of cidofovir.

The finding of any glycosuria, proteinuria/aminoaciduria, hypouricemia, hypophosphatemia and/or hypokalemia, should prompt for the consideration of cidofovir-related Fanconi syndrome.

The following table lists adverse reactions possibly or probably related to probenecid based on clinical trial experience:

System Organ Class	Adverse reactions
Nervous system disorders	
Common	Headache
Gastrointestinal disorders	
Very common	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Very common	Rash
General disorders and administration site conditions	
Very common	Fever
Common	Asthenia, chills

In addition probenecid may also cause other adverse reactions including anorexia, gingival pain, flushing, alopecia, dizziness, anaemia, and pollakiuria. Hypersensitivity reactions, with dermatitis, pruritus, urticaria and, rarely, anaphylaxis, and Stevens- Johnson syndrome have occurred. There have been reports of leukopenia, hepatic necrosis, nephrotic syndrome, and aplastic anaemia. Haemolytic anaemia has also occurred, and may be associated with G6PD deficiency. Therefore, when co- prescribing probenecid with cidofovir, it is important for prescribers to consult the current probenecid SmPC (or an appropriate drug reference source) for full information on the safety profile and other features of that product.

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

Two cases of cidofovir overdose have been reported. In both cases, the overdose occurred during the first induction dose and no additional cidofovir therapy was administered. One patient received a single dose of 16.4 mg/kg and the other patient received a single dose of 17.3 mg/kg.

Symptoms

One of these patients experienced a minor transient change in renal function, while the other patient had no change in renal function (see section 4.4).

Management

Both patients were hospitalised and received prophylactic oral probenecid and vigorous hydration for 3 to 7 days.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB12

General

Cidofovir is a cytidine analogue with in vitro and in vivo activity against human cytomegalovirus (HCMV). HCMV strains resistant to ganciclovir may still be susceptible to cidofovir.

Mechanism of action

Cidofovir suppresses HCMV replication by selective inhibition of viral DNA synthesis. Biochemical data support selective inhibition of HSV-1, HSV-2 and HCMV DNA polymerases by cidofovir diphosphate, the active intracellular metabolite of cidofovir.

Cidofovir diphosphate inhibits these viral polymerases at concentrations that are 8- to 600-fold lower than those needed to inhibit human cellular DNA polymerases alpha, beta, and gamma. Incorporation of cidofovir into viral DNA results in reductions in the rate of viral DNA synthesis.

Cidofovir enters cells by fluid-phase endocytosis and is phosphorylated to cidofovir monophosphate and subsequently to cidofovir diphosphate. Prolonged antiviral effects of cidofovir are related to the half-lives of its metabolites; cidofovir diphosphate persists inside cells with a half-life of 17-65 hours and a cidofovir phosphate-choline adduct has a half-life of 87 hours.

Antiviral activity

Cidofovir is active *in vitro* against HCMV, a member of the herpesviridae family. Antiviral activity is seen at concentrations significantly below those which cause cell death.

The *in vitro* sensitivity to cidofovir is shown in the following table:

Cidofovir inhibition of virus multiplication in cell culture	
Virus	IC_{50} (μM)
wild-type CMV isolates	0.7 (± 0.6)
ganciclovir-resistant CMV isolates	7.5 (± 4.3)
foscarnet-resistant CMV isolates	0.59 (± 0.07)

In vivo activity against HCMV was confirmed with controlled clinical studies of cidofovir for the treatment of CMV retinitis in patients with AIDS, which demonstrated statistically significant delays in time to CMV retinitis progression for patients on cidofovir when compared to control patients. The median times to retinitis progression in the two efficacy studies (GS-93-106 and GS-93-105), were 120 days and not reached for the treatment arms vs. 22 days and 21 days for the untreated (deferred treatment) arms, respectively.

In study GS-93-107 conducted in patients who had relapsed after treatment with other agents, the median time to retinitis progression was 115 days.

Viral resistance

Following *in vitro* selection of ganciclovir-resistant HCMV isolates, cross-resistance between ganciclovir and cidofovir was seen with ganciclovir-selected mutations in the HCMV DNA polymerase gene but not with mutations in the UL97 gene. No cross-resistance between foscarnet and cidofovir was seen with foscarnet-selected mutants. Cidofovir-selected mutants had a mutation in the DNA polymerase gene and were cross-resistant to ganciclovir, but susceptible to foscarnet.

5.2 Pharmacokinetic properties

The major route of elimination of cidofovir was by renal excretion of unchanged drug by a combination of glomerular filtration and tubular secretion. In patients with normal renal function, 80 to 100% of the intravenous dose was recovered in the urine over 24 hours as unchanged cidofovir. No metabolites of cidofovir have been detected in serum or urine of patients.

At the end of a one-hour infusion of cidofovir 5 mg/kg administered with concomitant oral probenecid, the mean (± SD) serum concentration of cidofovir was 19.6 (± 7.18) μg/ml. The mean values of total serum clearance, volume of distribution at steady-state and terminal elimination half-life were 138 (± 36) ml/h/kg, 388 (± 125) ml/kg and 2.2 (± 0.5) h, respectively. Dose-independent kinetics were demonstrated with single doses of cidofovir given over the dose range 3 to 7.5 mg/kg.

In vitro protein binding

In vitro protein binding of cidofovir to plasma or serum protein was 10% or less over the cidofovir concentration range 0.25 to 25 μg/ml.

5.3 Preclinical safety data

Preclinical animal studies demonstrated that nephrotoxicity was the major dose- limiting toxicity of cidofovir. Evidence for a nephroprotective effect for probenecid was shown in a 52-week study conducted in cynomolgus monkeys administered cidofovir 2.5 mg/kg once weekly intravenously with 1 g of probenecid given orally.

Carcinogenesis

In a 26-week intravenous toxicity study, a significant increase in incidence of mammary adenocarcinomas was seen in female rats and of Zymbal's gland carcinomas in male and female rats at subtherapeutic plasma levels of cidofovir. In a separate study, once weekly subcutaneous injections of cidofovir for 19 consecutive weeks resulted in mammary adenocarcinomas in female rats at doses as low as 0.6 mg/kg/week. In both studies, tumours were observed within 3 months of dosing. No tumours were observed in cynomolgus monkeys administered cidofovir intravenously once weekly for 52 weeks at doses up to 2.5 mg/kg/week.

Mutagenicity and reproductive toxicology

Studies have shown that cidofovir is clastogenic in vitro at 100 μg/ml and is embryotoxic in rats and rabbits.

No mutagenic response was elicited by cidofovir at dose levels up to 5 mg/plate, in the presence and absence of metabolic activation by rat liver S-9 fraction, in microbial assays involving *Salmonella typhimurium* for base pair substitutions or frameshift mutations (Ames) and *Escherichia coli* for reverse mutations.

An increase in formation of micronucleated polychromatic erythrocytes was observed *in vivo* in mice receiving a high, toxic intraperitoneal dose of cidofovir (≥ 2,000 mg/kg).

Cidofovir induced chromosomal aberrations in human peripheral blood lymphocytes in vitro without metabolic activation (S-9 fraction). At the 4 cidofovir levels (12.5 to 100 μg/ml) tested, the percentage of damaged metaphases and number of aberrations per cell increased in a concentration-dependent manner.

Male patients should be advised that cidofovir caused reduced testes weight and hypospermia in animals. No adverse effects on fertility or general reproduction were seen following once weekly intravenous injections of cidofovir in male rats for 13 consecutive weeks at doses up to 15 mg/kg/week. Female rats dosed intravenously once weekly at 1.2 mg/kg/week or higher for up to 6 weeks prior to mating and for 2 weeks post mating had decreased litter sizes and live births per litter and increased early resorptions per litter. Peri- and post-natal development studies in which female rats received subcutaneous injections of cidofovir once daily at doses up to 1.0 mg/kg/day from day 7 of gestation through day 21 postpartum (approximately 5 weeks) resulted in no adverse effects on viability, growth, behaviour, sexual maturation or reproductive capacity in the offspring. Daily intravenous administration of cidofovir during the period of organogenesis led to reduced fetal body weights when administered to pregnant rats at 1.5 mg/kg/day and to pregnant rabbits at 1.0 mg/kg/day. A significantly increased foetal incidence of external, soft tissue and skeletal anomalies occurred in rabbits at 1.0 mg/kg/day, which was also maternally toxic.
The no-observable-effect doses for embryotoxicity were 0.5 mg/kg/day in rats and 0.25 mg/kg/day in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH – adjustment)
Hydrochloric acid (for pH – adjustment)
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials. From a microbiological point of view, the product must be used immediately.

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2- 8°C when dilution is performed under controlled and validated aseptic conditions. Storage beyond 24 hours or freezing is not recommended. Refrigerated solutions should be allowed to warm to room temperature prior to use.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml clear glass vials with a 5 ml nominal fill volume.
The container/closure components include: Type I clear glass vials, dark grey bromobutyl rubber stoppers, and aluminium seals with a flip off plastic tab. Each pack contains one 5 ml vial.

CIDOFOVIR RAZ 75 mg/ml is supplied in single-use vials. Partially used vials should be discarded.

6.6 Special precautions for disposal

Method of preparation and administration

CIDOFOVIR RAZ 75 mg/ml vials should be visually inspected for particulate matter and discolouration prior to administration.

With a syringe, transfer under aseptic conditions the appropriate dose of cidofovir from the vial to an infusion bag containing 100 ml 0.9% (normal) saline solution, and mix thoroughly.
The entire volume should be infused intravenously into the patient at a constant rate over a period of 1 hour by use of a standard infusion pump. It should be administered by health care professionals adequately experienced in the care of AIDS patients.

The chemical and physical stability of CIDOFOVIR RAZ 75 mg/ml admixed with saline has been demonstrated in glass bottles, in infusion bags composed of either polyvinyl chloride (PVC) or ethylene/propylene copolymer, and in PVC based vented IV administration sets. Other types of IV set tubing and infusion bags have not been studied.

Compatibility with Ringer's Solution, Lactated Ringer's Solution or bacteriostatic infusion fluids has not been evaluated.

Handling and disposal

Adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration and disposal of cidofovir. The preparation of cidofovir reconstituted solution should be done in a laminar flow biological safety cabinet. Personnel preparing the reconstituted solution should wear surgical gloves, safety glasses and a closed front surgical-type gown with knit cuffs.
If cidofovir contacts the skin, wash membranes and flush thoroughly with water. Excess cidofovir and all other materials used in the admixture preparation and administration should be placed in a leak-proof, puncture-proof container for disposal. Any unused product or waste material should be disposed of in accordance with local requirements.

Obtaining probenecid

Probenecid is not supplied with cidofovir and should be obtained via the Marketing Authorisation Holder of probenecid. However, in case of difficulty in obtaining probenecid the local representative of the Marketing Authorisation Holder of CIDOFOVIR RAZ 75 mg/ml should be contacted for information (see also sections 4.2 and 4.4).

7 MARKETING AUTHORISATION HOLDER

RAZ PHARMACEUTICS LTD.,
6 Hamatechet st., Kadima, Israel.

8 MANUFACTURER

MAIVA PHARMA PVT LTD.,
Tamil Nadu, India.

9 REGISTRATION NUMBER

167-09-35697-00

Revised in May 2022 according to MOHs guidelines.

RAZS0174-01