Product Information

VISTIDE®

Concentrated solution for injection

NAME OF THE DRUG

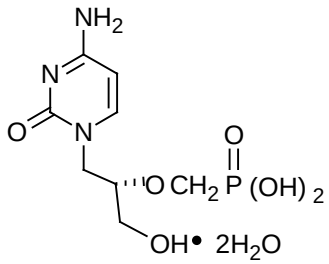
Non-proprietary name: cidofovir

Chemical name: 1-[(S)-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine dihydrate (HPMPC).

CAS Number: CAS 113852-37-2 (cidofovir anhydrous)
CAS 149394-66-1 (cidofovir dihydrate)

DESCRIPTION

VISTIDE® (cidofovir) is an acyclic nucleoside phosphonate analogue. Cidofovir is a white crystalline powder with an aqueous solubility of ≥170 mg/mL at pH 6-8. Its molecular formula is $C_8H_{14}N_3O_6P \bullet 2H_2O$ and has a molecular weight of 315.22 (279.19 for anhydrous). Its structural formula is:



VISTIDE is a sterile, hypertonic aqueous solution for intravenous injection only. The solution is clear and colourless. It is supplied in clear glass vials, each containing 375 mg of the anhydrous cidofovir in 5 mL aqueous solution at a concentration of 75 mg/mL. The formulation is pH adjusted to 7.4 with sodium hydroxide and/or hydrochloric acid and contains no preservatives. In addition to cidofovir, the ingredients are water for injections, sodium hydroxide and hydrochloric acid.

PHARMACOLOGY

Pharmacodynamics

Cidofovir has *in vitro* and *in vivo* activity against human cytomegalovirus (HCMV).

Mechanism of Action

Cidofovir suppresses CMV replication by selective inhibition of viral DNA synthesis. Biochemical data support selective inhibition of HSV-1, HSV-2 and CMV 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. In addition, a cidofovir phosphate-choline adduct is formed. The metabolism of cidofovir is neither dependent on, nor facilitated by, viral infections. Prolonged antiviral effects of cidofovir are related to the half-lives of metabolites; cidofovir diphosphate persists inside cells with a half-life of 17-65 hours. Additionally, the phosphate-choline species has a half-life of 87 hours.

Antiviral Activity

Cidofovir is active *in vitro* against CMV, a member of the herpesviridae family. Antiviral activity is seen at concentrations significantly below those which cause death in cell monolayers. The *in vitro* sensitivity to cidofovir is shown in the following table.

Table 1.

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[1]	0.59 (± 0.07)

[1] Two strains only were tested.

Viral Resistance

Following *in vitro* selection of ganciclovir-resistant human CMV isolates, cross-resistance between ganciclovir and cidofovir was seen with ganciclovir-selected mutations in the CMV 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.

Pharmacokinetics

Cidofovir must be administered with probenecid. The pharmacokinetics of cidofovir, without and with probenecid are described below.

The pharmacokinetics of cidofovir without probenecid were evaluated in 27 HIV-infected patients with or without asymptomatic CMV infection. Dose-independent pharmacokinetics were demonstrated after one hour infusions of 1.0 (n=5), 3.0 (n=10), 5.0 (n=2) and 10.0 (n=8) mg/kg. (See Table 2 for pharmacokinetic parameters). There was no evidence of cidofovir accumulation after 4 weeks of repeated administration of 3 mg/kg/week (n=5) without probenecid. In patients with normal renal function, approximately 80 to 100% of the VISTIDE dose was recovered unchanged in urine within 24 hours (n=27). The renal clearance of cidofovir was greater than creatinine clearance, indicating renal tubular secretion contributes to the elimination of cidofovir. No metabolites of cidofovir have been detected in serum or urine of patients.

The pharmacokinetics of cidofovir administered with probenecid were evaluated in 12 HIV-infected patients with or without asymptomatic CMV infection and 10 patients with relapsing CMV retinitis. Dose-independent pharmacokinetics were observed for cidofovir, administered with probenecid, after one hour infusions of 3.0 (n=12), 5.0 (n=6) and 7.5 (n=4) mg/kg (See Table 2). Approximately 70 to 85% of the VISTIDE dose administered with concomitant probenecid was excreted as unchanged drug within 24 hours. When the cidofovir dose was administered with probenecid, the renal clearance of cidofovir was reduced to a level consistent with creatinine clearance, suggesting that probenecid blocks active renal tubular secretion of cidofovir.

Table 2.

Cidofovir pharmacokinetic parameters following 3.0 and 5.0 mg/kg infusions, without and with probenecid.

Parameters	**VISTIDE administered without probenecid**		**VISTIDE administered with probenecid**	
	3 mg/kg (n=10)	5 mg/kg (n=2)	3 mg/kg (n=12)	5 mg/kg (n=6)
AUC (mcg/hr/mL)	20.0±2.3	28.3	25.7±8.5	40.8±9.0
Cmax (end of infusion) (mcg/mL)	7.3±1.4	11.5	9.8±3.7	19.6±7.2
Vdss (mL/kg)	537±126 (n=12)		410±102 (n=18)	
Clearance (mL/min/1.73m^2)	179±23.1 (n=12)		148±38.8 (n=18)	
Renal Clearance (mL/min/1.73 m^2)	150±26.9 (n=12)		98.6±27.9 (n=11)	

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.

Clinical Trials

Three phase II/III clinical studies of VISTIDE have been conducted in HIV-infected patients with CMV retinitis. Studies directly comparing VISTIDE with ganciclovir or foscarnet have not been conducted. The use of VISTIDE has been investigated only in situations where foscarnet and/or ganciclovir were ineffective or where the retinitis was in an early stage.

Study GS-93-106 was an open-label, multi-centre study, involving 48 previously untreated patients with peripheral CMV retinitis. Patients were randomised to either immediate treatment with VISTIDE (5 mg/kg once a week for 2 weeks, then 5 mg/kg every other week), or to have VISTIDE therapy delayed until disease progression. Concomitant intravenous hydration and oral probenecid were administered with each dose of VISTIDE. Forty-eight patients were enrolled in the study, 23 were randomised to the deferred treatment group and 25 to the immediate treatment group. Sixteen of the 23 patients in the deferred treatment group, crossed over and received VISTIDE treatment following documented progression. The two groups were comparable with regard to baseline characteristics. Retinal progression was recorded by full field bilateral retinal photographs. The median time to progression for the deferred treatment group was 22 days (95% Confidence limits, 10 to 27 days) and for the immediate treatment group was 120 days (95% Confidence limits 40 to 134 days). This difference was statistically significant. However limited numbers of patients remained on treatment over time.

In another open-label study, GS-93-107, 100 patients with relapsing CMV retinitis (failing treatment with ganciclovir and/or foscarnet or demonstrating intolerance to either of these agents), were randomised to receive VISTIDE 5 mg/kg/week for 2 weeks and then either 5 mg/kg (n=49) or 3 mg/kg (n=51) every second week. Patients also received concomitant probenecid and intravenous hydration with each VISTIDE dose. Based on the masked readings of retinal photographs, the median (95% CI) time for retinal progression for the 5 mg/kg group and the 3 mg/kg group was 115 days (70, not reached) and 49 days (35, 52) respectively. The difference was statistically significant. However, limited numbers of patients remained on treatment over time.

Study GS-93-105 was a randomised controlled multi-centre study of VISTIDE for the treatment of previously untreated peripheral CMV retinitis in HIV-positive patients. Patients were randomised to immediate or deferred treatment, with cross-over allowed following clinical ophthalmic documentation of CMV retinitis progression. The induction dose was 5 mg/kg/week for the first two weeks, and then maintenance therapy of either 3 mg/kg (low group) or 5 mg/kg (high group) every second week. The results from an interim review of the first 64 patients have been analysed, with 26 patients assigned to the deferral group, 26 to the low dose group, and 12 patients assigned to the high dose group. The major outcome measure was retinitis progression, with the low dose group having a median (95% CI) time to progression of 64 days compared with 21 days (10, 27) for the deferred group. The high dose group had not reached the median (95% CI) time to progression (25, not reached), compared to the deferred group. The rates of visual loss were similar among the three groups.

INDICATIONS

VISTIDE is indicated in patients 12 years and over, for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).

CONTRAINDICATIONS

VISTIDE is contraindicated in patients with renal impairment [serum creatinine > 0.133 mmol/L (> 1.5 mg/dL) or creatinine clearance ≤ 0.92 mL/s (≤ 55 mL/min) or proteinuria ≥ 100 mg/dL (≥ 2+ proteinuria)]. Concomitant administration of cidofovir and potentially nephrotoxic agents is contraindicated. Patients should discontinue such agents at least 7 days before starting treatment with cidofovir. Examples of agents having potential nephrotoxicity include: amphotericin B, foscarnet, intravenous pentamidine, intravenous aminoglycoside antibiotics, vancomycin and non-steroidal anti-inflammatory agents.

The benefits of VISTIDE must be weighed against the risk of renal damage in patients who have been recently treated with nephrotoxic drugs.

VISTIDE is also contraindicated in patients with hypersensitivity to cidofovir.

VISTIDE is contraindicated in patients with a history of clinically significant hypersensitivity to probenecid or other sulfur-containing medicines**.**

VISTIDE is contraindicated during pregnancy.

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

PRECAUTIONS

VISTIDE should be infused only into veins with adequate blood flow to permit rapid dilution and distribution. Therapy should be accompanied by administration of oral probenecid and adequate intravenous saline prehydration.

VISTIDE should not be used in patients unable to receive probenecid because of hypersensitivity. In patients unable to receive probenecid because of a clinically significant hypersensitivity to the drug, a probenecid desensitisation program is not recommended for use.

Renal Impairment

Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to administration of VISTIDE. Patients previously treated with foscarnet may have an increased risk of nephrotoxicity. Proteinuria, as measured by urinalysis in a clinical laboratory, may be an early indication of nephrotoxicity. Some patients receiving VISTIDE have had evidence of proximal tubular cell injury, which may result in glycosuria, decreases in serum phosphate, uric acid, and bicarbonate, elevations in serum creatinine, and/or acute renal failure, in some cases, resulting in the need for dialysis. Renal function that did not return to baseline after drug discontinuation has been observed in clinical studies of VISTIDE.

Renal impairment is the major toxicity of VISTIDE. To minimise possible nephrotoxicity, intravenous hydration with normal saline and oral administration of probenecid must be given with each VISTIDE injection. Renal function must be monitored (serum creatinine and urine protein) prior to each dose and dose may need to be adjusted for changes in renal function as appropriate.

Uveitis and/or iritis may occur during VISTIDE therapy. Treatment with corticosteroids with or without cycloplegic agents may be considered. In some cases, reduced intraocular pressure has been reported in conjunction with uveitis/iritis.

Decreased intraocular pressure/ocular hypotony may develop during VISTIDE therapy and in some cases has been associated with decreased visual acuity. The risk of decreased intraocular pressure may be increased in patients with pre-existing diabetes mellitus. Intraocular pressure should be monitored during VISTIDE therapy.

Neutropenia has been observed in patients receiving VISTIDE. Neutrophil counts should be monitored while receiving VISTIDE therapy.

Check the following before use

Renal function (serum creatinine and urine protein) must be measured and the results reviewed, within 48 hours prior to each dose of VISTIDE. Interruption, and possibly discontinuation, is required for changes in renal function (see Dosage and Administration).

Neutrophil counts should be monitored regularly.

Animal Toxicity

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 30 mg/kg of probenecid given orally.

Carcinogenicity, Mutagenicity and Impaired Fertility

In animal studies VISTIDE was genotoxic, carcinogenic and teratogenic, and caused hypospermia. VISTIDE should be considered a potential carcinogen in humans. Male patients should be advised that VISTIDE caused reduced testes weight and hypospermia in animals. Such changes may occur in humans and cause infertility. Men should be advised to practise barrier contraceptive methods during and for 3 months after treatment with VISTIDE.

Chronic, two year carcinogenicity studies in rats and mice have not been carried out to evaluate the carcinogenic potential of cidofovir. However, a 26 week toxicology study evaluating once weekly subscapular subcutaneous injections of cidofovir in rats was terminated at 19 weeks because of the induction, in females, of palpable masses, the first which was detected after six doses. The masses were diagnosed as mammary adenocarcinomas which developed at doses as low as 0.6 mg/kg/week, equivalent to 0.04 times the human systemic exposure at the recommended intravenous cidofovir dose based on AUC comparisons.

In a 26-week intravenous toxicology study in which rats received 0.6, 3, or 15 mg/kg cidofovir once weekly, a significant increase in mammary adenocarcinomas in female rats as well as a significant increase in Zymbal's gland carcinomas (no human equivalent) in male and female rats were seen at the high dose but not at the lower two doses. The high dose was equivalent to 1.1 times the human systemic exposure at the recommended dose of cidofovir, based on the comparisons of AUC measurements. In light of the results of these studies,

cidofovir should be considered to be a carcinogen in rats as well as a potential carcinogen in humans.

Cynomolgus monkeys received intravenous cidofovir, alone and in conjunction with concomitant oral probenecid, intravenously once weekly for 52 weeks at doses resulting in exposures of approximately 0.7 times the human systemic exposure at the recommended dose of cidofovir. No tumours were detected. However, the study was not designed as a carcinogenicity study due to the small number of animals at each dose and the short duration of treatment.

Cidofovir induced chromosomal aberrations in human peripheral lymphocytes *in vitro* (without metabolic activation) and an increase in micronucleated polychromatic erythrocytes *in vivo.* Cidofovir was not genotoxic in microbial mutagenicity assays *(Salmonella typhimurium* (Ames) and *Escherichia coli).*

Studies show that cidofovir caused inhibition of spermatogenesis in rats and monkeys. However, no adverse effects on fertility or 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 (equivalent to 1.1 times the recommended human dose based on AUC comparisons). Female rats dosed intravenously once weekly at 1.2 mg/kg/week (equivalent to 0.09 times the recommended human dose based on AUC) or higher, for up to 6 weeks prior to mating and for two 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.

Use in Pregnancy

Category D

Cidofovir was embryotoxic (reduced fetal body weights) in rats and rabbits at subtherapeutic dose levels, following daily intravenous dosing during the period of organogenesis. An increased incidence of fetal external, soft tissue and skeletal anomalies (meningocele, short snout, and short maxillary bones) occurred in rabbits at the high dose (1.0 mg/kg/day) which was maternally toxic but less than the recommended human dose based on AUC.

There are no adequate and well controlled studies in pregnant women. The drug should not be used during pregnancy.

Women of childbearing potential should be advised to use effective contraception during and for 1 month after treatment with cidofovir.

Use in lactation

It is not known whether cidofovir is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers should be instructed to discontinue cidofovir or discontinue nursing if they continue to receive cidofovir. Passage of drug-related compound across the placental barrier was observed in pregnant rats. Excretion of drug-related material into milk of lactating animals was not examined.

Interaction with Other Drugs and Other Forms of Interaction

Probenecid: Probenecid is known to interact with the metabolism or renal tubular secretion of many drugs (e.g., paracetamol, aciclovir, angiotensin-converting enzyme inhibitors, aminosalicylic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, frusemide, nonsteroidal anti-inflammatory agents, theophylline, and zidovudine). Concomitant medications should be carefully assessed.

Patients who are being treated with zidovudine should temporarily discontinue zidovudine administration or decrease their zidovudine dose by 50% on days when cidofovir is administered, because probenecid reduces the clearance of zidovudine.

Nephrotoxic agents: Concomitant administration of VISTIDE and agents with nephrotoxic potential (e.g. intravenous aminoglycosides, amphoteracin B, foscarnet, intravenous pentamidine, vancomycin, and non-steroidal anti-inflammatory agents) is contraindicated.

The benefits of VISTIDE must be weighed against the risk of renal damage in patients who have been treated recently with nephrotoxic drugs.

Interactions of cidofovir, probenecid, and anti-HIV drugs, including anti-HIV protease inhibitors, have not been investigated in clinical trials.

Effects on Ability to Drive and Use Machines

Adverse effects such as asthenia may occur during VISTIDE 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.

ADVERSE REACTIONS

In three pivotal clinical trials with VISTIDE, in patients with AIDS and CMV retinitis, the adverse events which were reported in more than 10% of patients were: proteinuria 41%, serum creatinine increase 18%, neutropenia 17%, alopecia 15%, fever 14%, asthenia 14% and nausea without vomiting 11%. These incidence figures were calculated from all adverse events considered to be possibly or probably related to cidofovir.

The incidence of decreased intraocular pressure (≥ 50% decrease from pretreatment baseline) was 9%.

The adverse events which occurred in at least 10% of the patients and were possibly or probably related to probenecid were: fever 16%, rash 13%, nausea with vomiting 13% and nausea without vomiting 11%.

In clinical trials, VISTIDE was withdrawn due to adverse events in approximately 25% of patients treated with 5 mg/kg every other week as maintenance therapy.

Uveitis or iritis has been reported in 18 of 247 (7%) patients receiving VISTIDE therapy. See Precautions for treatment.

The incidence of adverse reactions reported in more than 5% of patients in the three pivotal clinical studies in patients with CMV retinitis, possibly or probably related to the study drug,

are reported in Table 3. (Includes adverse events from the administration of cidofovir therapy to 30 days after last infusion).

Table 3. Adverse reactions possibly or probably related to VISTIDE reported in at least 5% of all patients treated with VISTIDE and concomitant oral probenecid.

	Total Number of Patients with Adverse Reactions							
Body system[a]	**Study 105**		**Study 106**		**Study 107**		**Total**	
	(N=58)		**(N=41)**		**(N=148)**		**(N=247)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total number of patients with adverse reactions	36	62	36	88	116	78	188	76
Body as a whole[b]	5	9	22	54	45	30	72	29
Asthenia	1	2	16	39	17	11	34	14
Fever	3	5	10	24	21	14	34	14
Headache	0	0	7	17	16	11	23	9
Pain	0	0	5	12	7	5	12	5
Urogenital system	29	50	19	46	69	67	117	47
Creatinine increased [c]	5	9	5	12	35	24	45	18
Proteinuria [c]	28	48	16	39	58	39	102	41
Digestive system	2	3	18	44	39	26	59	24
Nausea with vomiting	1	2	8	20	13	9	22	9
Nausea without vomiting	0	0	8	20	19	13	27	11
Haemic and Lymphatic	9	16	11	27	28	19	40	19
Decreased serum bicarbonate	3	5	2	5	29	20	34	14
Neutropenia [c]	9	16	11	27	22	15	42	17
Special Senses	6	10	9	22	32	22	47	19
Decreased intraocular pressure[d]	5	9	0	0	17	11	22	9
Skin and appendages	2	3	14	34	38	26	54	22
Alopecia	1	2	10	24	26	18	37	15
Rash	0	0	4	10	14	9	10	7

a body system category; No. (%) of patients who reported one or more events in the same body system category, with each patient with multiple reports of the same event counted only once within a category. Frequencies shown for body system are overall frequencies; i.e. they also include events that occurred in <1% of patients.

b description of event; No. (%) of patients who reported the event, with each patient with multiple reports of the same event counted only once for that particular event.

c definitions: increased creatinine (≥ 0.133 mmol/L), proteinuria (≥ 100 mg/dL) and neutropenia (absolute neutrophil count ≤ 500 cells/mm3) decreased serum bicarbonate (less than or equal to 16 mEq/L).

d Intraocular pressure less than or equal to 50% of baseline.

Serious adverse reactions possibly or probably related to VISTIDE reported in clinical trials with an incidence of less than 5% or in post marketing experience:

Body as a whole: allergic reaction, infection, chills, malaise, no drug effect

Cardiovascular system: tachycardia, hypotension

Digestive System: anorexia, diarrhoea, hepatomegaly, abnormal liver function test results

Haemic and lymphatic system: anaemia, thrombocytopenia

Metabolic and nutritional system: oedema, hyperlipidaemia, hypocalcaemia, increased AST, dehydration, weight loss, acidosis, hyperglycaemia

Musculoskeletal system: myalgia

Nervous system: neuropathy, peripheral neuritis, dizziness, confusion, somnolence

Respiratory system: dyspnoea, hyperventilation

Special Senses: uveitis, iritis, retinal detachment

Urogenital system: acute kidney failure, Fanconi-like syndrome, glycosuria, abnormal kidney function, proteinuria, toxic nephropathy, urinary retention, increased serum urea.

DOSAGE AND ADMINISTRATION

Before each administration of VISTIDE, serum creatinine and urine protein levels should be investigated.

The recommended dosage, frequency, or infusion rate must not be exceeded. VISTIDE must be diluted in 100 mL 0.9% (normal) saline prior to administration. To minimise potential nephrotoxicity, oral probenecid and intravenous saline prehydration must be administered with each VISTIDE infusion.

VISTIDE must not be administered by intraocular injection.

Dosage in Adults and in Children 12 years and over

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

Maintenance Treatment. Beginning two weeks after the completion of induction treatment, the recommended maintenance dose of VISTIDE is 5 mg/kg body weight (given as an intravenous infusion at a constant rate over 1 hr) administered once every two weeks.

Dosage reduction guidelines. For patients with changes in renal function during therapy, the dose of cidofovir must be reduced from 5 mg/kg to 3 mg/kg for an increase in serum creatinine of 0.027 to 0.043 mmol/L (0.3 to 0.4 mg/dL) above baseline.

VISTIDE therapy should be discontinued and intravenous hydration is advised if serum creatinine increases by ≥ 0.044 mmol/L (≥ 0.5 mg/dL), or if persistent proteinuria ≥ 2+ develops.

Probenecid. A course of probenecid, administered orally with each VISTIDE dose may reduce the potential for nephrotoxicity. All clinical trials relevant to clinical efficacy evaluation were performed using probenecid concomitantly with cidofovir. Therefore to minimise the potential for nephrotoxicity, a course of probenecid should be administered orally with each VISTIDE dose. Two grams should be administered 3 hours prior to the VISTIDE dose and one gram administered at 2 and again at 8 hours after completion of the 1 hr VISTIDE 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 (see section 4.3, Contraindications).

Hydration. To minimise the potential for nephrotoxicity, patients should receive a total of one litre of 0.9% (normal) saline solution intravenously immediately prior to each infusion of VISTIDE. 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 VISTIDE. The first litre of saline solution should be infused over a 1 hr period immediately before the VISTIDE infusion, and the second litre, if given, infused over a 1-3 hr period beginning simultaneously with the VISTIDE infusion or starting immediately after the infusion of VISTIDE.

Dosage in Elderly

The safety and efficacy of VISTIDE 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 VISTIDE.

Dosage in Children and Neonates

The safety and efficacy of VISTIDE have not been established for the treatment of CMV disease in patients under twelve years of age. Therefore, VISTIDE is not recommended for use in children under twelve years.

Dosage in Renal Insufficiency

Renal insufficiency is a contraindication for the use of VISTIDE (see also Contraindications). Treatment with VISTIDE should not be initiated in patients with serum creatinine > 0.133 mmol/L (> 1.5 mg/dL), creatinine clearance ≤ 0.92 mL/s (≤ 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.

Dosage in Hepatic Insufficiency

The safety and efficacy of VISTIDE have not been established in patients with hepatic disease.

Monitoring Advice

Proteinuria appears to be an early and sensitive indicator of cidofovir-induced nephrotoxicity. Patients receiving VISTIDE must have their serum creatinine and urine protein levels determined on specimens obtained within 24 to 48 hours prior to the administration of each dose of VISTIDE. In patients exhibiting ≥ 2+ proteinuria, intravenous hydration should be performed and the test repeated. If following hydration, a ≥ 2+ proteinuria is still observed, VISTIDE therapy should be discontinued. Continued administration of VISTIDE 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.

During treatment, these parameters should be investigated prior to the administration of each infusion, and the treatment should be stopped in case of abnormality. In case of complete recovery, the reintroduction of cidofovir has not yet been evaluated.

White blood cell counts, including the differential neutrophil count, should also be performed prior to each dose of VISTIDE.

Patients should be monitored for signs and symptoms of uveitis/iritis during VISTIDE therapy.

Patients receiving VISTIDE should be advised to have regular follow-up ophthalmologic examinations.

Incompatibilities

The chemical and physical stability of VISTIDE 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.

No data are available to support the addition of other drugs or supplements to the recommended admixture for intravenous infusion. Compatibility with Ringer's Solution, Lactated Ringer's Solution or bacteriostatic infusion fluids has not been evaluated.

Instructions for Use and Handling

Method of Preparation and Administration

As with all parenteral products, VISTIDE vials should be visually inspected for particulate matter and discolouration prior to administration. Do not re-autoclave prior to use.

With a syringe, transfer under aseptic conditions the appropriate dose of VISTIDE 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. VISTIDE should be administered by health care professionals adequately experienced in the care of AIDS patients.

Handling and Disposal

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

OVERDOSAGE

Two cases of VISTIDE overdose have been reported. In both cases, the overdose occurred during the first induction dose and no additional VISTIDE 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. Both patients were hospitalised and received prophylactic oral probenecid and vigorous hydration for 3 to 7 days. One of these patients experienced a minor transient change in renal function, while the other patient had no change in renal function.

Treatment is symptomatic and supportive, including respiratory and cardiovascular function. Hydration should be considered following overdose as clinically indicated. Monitor electrolytes and fluid status following a significant exposure. Evaluate renal function including urinalysis for proteinuria with all suspected overdoses. Obtain full blood count with differential following a significant overdose or as indicated.

High flux haemodialysis has been shown to reduce the serum concentrations of cidofovir by approximately 75%, although rebound was displayed after dialysis was stopped.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

Nature and Contents of Container

Sterile VISTIDE solution is supplied in single use 5 mL clear glass vials with a 5 mL nominal fill volume. Each pack contains one 5 mL vial together with the package leaflet.

Special Precautions For Storage

Store at a temperature below 25°C.

If not intended for use immediately after preparation, VISTIDE infusion admixtures may be stored temporarily for up to 24 hours in a refrigerator (2-8°C) when reconstitution is performed under aseptic conditions. Storage beyond 24 hours or freezing is not recommended. Refrigerated solutions should be allowed to warm to room temperature prior to use.

VISTIDE is supplied in single-use vials. Partially used vials should be discarded.

SPONSOR

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