ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VISTIDE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cidofovir equivalent to 375 mg/5 mL (75 mg/mL) cidofovir anhydrous. The formulation is adjusted to pH 7.4.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Cidofovir is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction. Until further experience is gained, cidofovir should be used only when other agents are considered unsuitable.

4.2 Posology and Method of Administration

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

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

Dosage in 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 hr) 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 hr) administered once every two weeks.

Cidofovir therapy should be discontinued and intravenous hydration is advised if serum creatinine increases by $\geq$ 44 µmol/L ($\geq$ 0.5 mg/dL), or if persistent proteinuria $\geq$ 2+ develops.

- Probenecid. A course of probenecid, administered orally with each cidofovir 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 cidofovir dose. Two grams should be administered 3 hrs prior to the cidofovir dose and one gram administered at 2 and again at 8 hrs after completion of the 1 hr 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 (see section 4.3, Contraindications).

• Hydration. To minimise the potential for nephrotoxicity, patients should receive a total of one liter 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 liters of 0.9% saline intravenously with each dose of cidofovir. The first liter of saline solution should be infused over a 1 hr period immediately before the cidofovir infusion, and the second liter, if given, infused over a 1-3 hr period beginning simultaneously with the cidofovir infusion or starting immediately after the infusion of cidofovir.

Dosage in Elderly

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 cidofovir.

Dosage in Children and Neonates

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

Dosage in Renal Insufficiency

Renal insufficiency is a contraindication for the use of cidofovir (See also 4.3 Contraindications.) Treatment with cidofovir should not be initiated in patients with serum creatinine > 133 µmol/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 cidofovir 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 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. 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.

During treatment, these parameters should be investigated prior to 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 cidofovir.

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

4.3 Contraindications

Cidofovir is contraindicated in patients with renal impairment [serum creatinine > 133 µmol/l (> 1.5 mg/dL) or creatinine clearance ≤ 0.92 mL/s (≤ 55 mL/min) or proteinuria ≥ 100 mg/dL (≥ 2+ proteinuria)]. The safety of cidofovir has not been evaluated in patients receiving other known potentially nephrotoxic agents such as aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine and vancomycin. Concomitant administration of cidofovir and these agents is contraindicated. Cidofovir is also contraindicated in patients with hypersensitivity to the drug.

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 Special Precautions for Use

Cidofovir is formulated for intravenous infusion only and should not be administered by intraocular injection. Cidofovir 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. In patients unable to receive probenecid because of a clinically significant hypersensitivity to the drug or to other sulpha-containing medications, cidofovir administration should only be considered if the potential benefits of therapy outweigh the potential risks. Such use of cidofovir without concomitant probenecid has not been clinically investigated. A probenecid desensitization program is not recommended for use.

Renal function (serum creatinine and urine protein) must be monitored prior to each dose of cidofovir. Interruption and possibly discontinuation, is required for changes in renal function (see 4.2 Posology).

Renal Impairment

Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to administration of cidofovir. Proteinuria, as measured by urinalysis in a clinical laboratory, may be an early indicator of nephrotoxicity. Patients receiving weekly intravenous cidofovir at a dose of 0.5 or 1.0 mg/kg, without concomitant probenecid, with or without intravenous saline prehydration, did not show evidence of significant drug-related nephrotoxicity (as defined by serum creatinine ≥ 177 µmol/l (≥ 2.0 mg/dL), while patients treated at 3.0, 5.0 or 10.0 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.

Haematology

Reversible neutropenia has been observed in patients receiving cidofovir. This has not been associated with clinical sequelae and does not appear to be dose-dependent. Resolution has occurred in some cases while on continued cidofovir therapy and in others following discontinuation of the drug.

Laboratory Tests

Renal function tests (routine urinalysis and serum creatinine) must be measured, and the results reviewed, prior to administration of each cidofovir dose. Neutrophil counts also should be monitored regularly.

Other

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

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.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

Probenecid is known to interact with the metabolism or renal tubular secretion of many drugs (e.g., paracetamol, acyclovir, angiotensin-converting enzyme inhibitors, aminosalicyclic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, nonsteroidal anti-inflammatory agents, theophylline, and zidovudine).

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.

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

4.6 Use During Pregnancy and Lactation

Cidofovir is embryotoxic in rats and rabbits and at subtherapeutic dose levels. 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.

There are no studies of cidofovir in pregnant women. The drug should not be used during pregnancy.

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

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 the placenta barrier of drug-related compound was observed in pregnant rats. Excretion of drug-related material into milk of lactating animals was not examined.

Refer to section 4.4 (Special Warnings and Special Precautions for Use) for further information.

4.7 Effects on Ability to Drive and Use Machines

Adverse effects 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

In controlled clinical trials with cidofovir in patients with AIDS and CMV retinitis, the most frequently reported adverse events were: proteinuria 51%, fever 43%, asthenia 32%, nausea with vomiting 26%, and rash 19%. These incidence figures were calculated independent of relationship to study drugs (cidofovir or probenecid) or severity. The adverse events reported as serious and which occurred in at least 5% of patients were: proteinuria 13%, neutropenia 10%, fever 9%, death 8%, infection 8%, creatinine increase 8%, dyspnea 7%, pneumonia 7%, asthenia

6%, and nausea with vomiting 5%. All deaths occurring during study were attributed to complications of AIDS and not to cidofovir.

The adverse events which occurred in at least 10% of the patients and were possibly or probably related to cidofovir were: proteinuria 41%, neutropenia 18%, asthenia 15%, creatinine increase 14%, fever 13%, alopecia 12%, and nausea without vomiting 10%.

The serious adverse events which occurred in at least 5% of patients and were possibly or probably related to cidofovir were: proteinuria 11%, neutropenia 9%, and creatinine increase 7%.

The adverse events which occurred in at least 10% of the patients and were possibly or probably related to probenecid were: fever (18%), rash (13%), nausea with vomiting (12%), and nausea without vomiting (10%).

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

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. Both patients were hospitalized 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Antiviral for Systemic Use (ATC Code J05)

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 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. In contrast to ganciclovir, 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 hrs. Additionally, the phosphate-choline species has a half-life of 87 hrs.

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.

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 human CMV 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 studies relevant for efficacy assessment (studies GS-93-106 and GS-93-105, both conducted in patients previously untreated for CMV retinitis) 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 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.

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/hr/kg, 388 (± 125) mL/kg and 2.2 (± 0.5) hr, 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 mg/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 one gram 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, tumors 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 (≥ 2000 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.

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, behavior, 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. The no-observable-effect dosages for embryotoxicity was 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

Hydrochloric Acid

Water for Injection

6.2 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 I.V. administration sets. Other types of I.V. 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.

6.3 Shelf Life

VISTIDE vials are stable for 2 years when stored between 15°C and 30°C.

6.4 Special Precautions For Storage

Store at a temperature between 15° and 30°C.

If not intended for use immediately after preparation, VISTIDE infusion admixtures may be stored temporarily for up to 24 hrs 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.

6.5 Nature and Contents of Container

Sterile cidofovir solution is supplied in single use 5 mL clear glass vials with a 5 mL nominal fill volume. The container/closure components include: Type I clear borosilicate glass vials, Teflon™ faced gray butyl plug stoppers, and aluminum crimp seals with a flip off plastic tab. Each pack contains one 5 mL vial together with the package leaflet.

6.6 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 discoloration prior to administration.

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.

7. MARKETING AUTHORIZATION HOLDER

Gilead Sciences Limited, UK
Springfield House, Hyde Street, Leeds
West Yorkshire LS2
United Kingdom

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF TEXT

ANNEX II

THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for import and batch release in the European Economic Area

Pharmacia & Upjohn N.V./S.A.
Rijksweg 12
2870 Puurs
Belgium

A manufacturing authorisation was issued on 12 March 1996 by Ministerië van Sociale Zaken, Volksgezondheid en Leefmilieu-Ministère des Affaires Sociales, de la Santé Publique et de l'Environnement (Rijksadministratief Centrum, Vesalius Gebouw, Oratoriënberg 20, 1010 Brussel-Bruxelles, Belgium).

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to non renewable restricted medical prescription.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

Vial Label:

Lot: **Exp**:	See Package Insert for dosage and full prescribing information. Store at temperature between 15°–30°C. Contains no preservative. Dispose after use. **Gilead Sciences Limited, UK** © Gilead Sciences Limited, UK	Vistide cidofovir **Equivalent to 75 mg/ml anhydrous cidofovir,** **concentrate for solution for infusion,** **5 mL vial** 375 mg cidofovir per single-use vial **Dilute before use.** **For Intravenous Infusion Only** Keep Out of Reach of Children *Marketing Authorization No.*

Carton Label:

Vistide
cidofovir

Lot:
Exp:

Vistide cidofovir Store at temperature between 15°–30°C. Medicinal product subject to medical prescription Cidofovir is formulated in Water for Injection and pH adjusted with Sodium Hydroxide and Hydrochloric Acid. Contains no preservatives. Dispose after use. **For Intravenous Infusion Only**	Vistide cidofovir **Equivalent to 75 mg/ml anhydrous cidofovir,** **concentrate for solution for infusion,** **5 mL vial** 375 mg cidofovir per single-use vial **Dilute before use.** **For Intravenous Infusion Only**	Vistide cidofovir **Gilead Sciences Limited, UK** Springfield House Hyde Street, Leeds West Yorkshire LS2 United Kingdom	Vistide cidofovir **Equivalent to 75 mg/ml anhydrous cidofovir,** **concentrate for solution for infusion,** **5 mL vial** 375 mg cidofovir per single-use vial **Dilute before use.** **For Intravenous Infusion Only**

See Package Insert for dosage and full prescribing information.	Keep Out of Reach of Children	©Gilead Sciences Limited, UK	Keep Out of Reach of Children *Marketing Authorization No.*

B. PACKAGE LEAFLET

This leaflet contains important information about VISTIDE. If you want to know more information about your illness or your medication, ask your doctor or pharmacist.

The name of your medication is:
VISTIDE, cidofovir, equivalent to 75 mg/mL anhydrous cidofovir, concentrate for solution for intravenous infusion.

What does VISTIDE contain?
VISTIDE is supplied as a sterile solution in clear, glass vials containing 375 mg of the active ingredient, anhydrous cidofovir, in 5 mL formulated in Water for Injection at a concentration of 75 mg/mL. The formulation is pH-adjusted with sodium hydroxide (and hydrochloric acid, if needed) and contains no preservatives.

How does VISTIDE work?
VISTIDE is an antiviral medication which blocks the replication of cytomegalovirus (CMV) by interfering with viral DNA production.

Who is the marketing authorisation holder?
The product marketing authorisation is held by:

Gilead Sciences Limited, UK
Springfield House, Hyde Street, Leeds
West Yorkshire LS2
United Kingdom

The Manufacturer responsible for batch release in the European Economic Area is :
Pharmacia & Upjohn N.V./S.A.
Rijksweg 12
2870 Puurs
Belgium

What is this medicine used for?
VISTIDE is indicated in the treatment of CMV retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS). VISTIDE will not cure your CMV retinitis but may improve your condition by delaying progression of the disease.

VISTIDE is for intravenous (into a vein) infusion and is not for intraocular injection (direct injection into the eye).

What is CMV retinitis?
CMV retinitis is an eye infection caused by a virus named cytomegalovirus (CMV). CMV attacks the retina of the eye and may cause loss of vision, and eventually lead to blindness. Patients with acquired immunodeficiency syndrome (AIDS) are at high risk of developing CMV retinitis or other forms of CMV disease such as colitis. Treatment for CMV retinitis is necessary to reduce the potential for blindness.

Things to consider prior to using VISTIDE

Your doctor will discuss with you the possible benefits and risks of VISTIDE therapy. However, you should note the following:

Reasons for not giving VISTIDE:

- VISTIDE should not be given to you if you have pre-existing kidney disease.

- VISTIDE should not be given to you if you are allergic to this drug, or if you cannot take the medication probenecid because of a serious allergy to probenecid or other sulfa-containing medications (e.g., sulfamethoxazole).

- You should not be given VISTIDE if you are pregnant. If you become pregnant while taking this medication, you must inform your doctor immediately. VISTIDE has been shown to cause damage in unborn animals and should not be used during pregnancy unless the potential benefits justify the risks to the foetus. Women of childbearing potential should use birth control methods during and for 1 month following treatment with VISTIDE.

- You should not be given VISTIDE if you are breast feeding. It is not known whether VISTIDE is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers should discontinue VISTIDE or stop nursing if they continue to receive VISTIDE.

What you should know prior to using VISTIDE:

- Kidney damage is the major side effect of VISTIDE treatment. To minimise the potential for damage to the kidneys, you will receive intravenous fluids (normal saline) and probenecid tablets with each dose of VISTIDE. Your doctor may also instruct you to drink plenty of fluids. Your doctor will monitor your kidney function prior to each dose of VISTIDE. Your treatment with VISTIDE may be discontinued by your doctor if changes in kidney function occur.

  A list of the most common side effects is provided below in section “What are the possible side effects of therapy?”

- Tell your doctor if you have diabetes mellitus. VISTIDE should be used with caution in diabetic patients due to the potential increased risk of developing ocular hypotony (low pressure in the eye).

- VISTIDE may cause transient side effects such as fatigue or weakness. If you drive or operate machinery, discuss this with your doctor to get their recommendation about discontinuing these activities based upon the condition of your disease and your tolerance of the medication.

- VISTIDE caused reduced testes weight and hypospermia (low sperm count) in animals. Although not observed in human studies of VISTIDE, such changes may occur in humans and cause infertility. Men should practice barrier birth control methods during and for 3 months after treatment with VISTIDE.

What to do if you are taking other medications

- Tell your doctor about all medications you currently take. Probenecid may interact with other drugs commonly used in the treatment of AIDS and AIDS-related illnesses, such as zidovudine (AZT). If you are taking zidovudine, you should discuss with your doctor the option to either temporarily discontinue zidovudine or decrease the dose of zidovudine by 50% on days when VISTIDE and probenecid are administered.

- You may continue taking antiretrovirals (anti-HIV medications) and medication to prevent AIDS-related opportunistic infections. However, because the side effects of VISTIDE include kidney damage, it will be necessary to stop taking all other medications that may also cause kidney damage. You should tell your doctor if you are receiving other medications which are known to potentially damage the kidney, such as aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, and vancomycin.

- The potential for interactions between VISTIDE and anti-HIVprotease inhibitors has not been studied.

How is VISTIDE given?

VISTIDE is administered by intravenous infusion and must not be administered by intraocular injection. VISTIDE must be administered by a health care professional.

To minimise the potential for kidney damage, probenecid tablets and intravenous saline solution must be administered with each VISTIDE infusion.

The recommended dosage, frequency of use, or rate of infusion must not be exceeded. VISTIDE must be diluted in 100 milliliters 0.9% (normal) saline prior to administration.

Dosage in Adults

Induction Treatment. The recommended dose of VISTIDE in patients with normal kidney function 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 completion of induction treatment, the recommended maintenance dose of VISTIDE in patients with normal kidney function is 5 mg/kg body weight (given as an intravenous infusion at a constant rate over 1 hr) administered once every two weeks.

Dose Adjustment. If you have decreased kidney function, VISTIDE may not be appropriate therapy for you. Samples of your urine and/or blood will be obtained prior to each infusion of VISTIDE and used for testing kidney function. For patients with evidence of decreased kidney function, your VISTIDE dose may be interrupted or discontinued depending on your individual case.

If you have accidentally taken a dose of VISTIDE greater than prescribed for you, tell your doctor immediately.

Why is the medication probenecid given with VISTIDE?

Probenecid tablets are given to minimise the potential for kidney damage. You must receive a course of probenecid tablets administered orally with each VISTIDE dose. Two grams must be administered 3 hours prior to the VISTIDE dose and one gram administered at 2 hours and again at 8 hours after completion of the 1 hour VISTIDE infusion (for a total of 4 grams). Probenecid is only taken on the same day that VISTIDE is administered.

What are the possible side effects of probenecid?

Potential side effects of probenecid include headache, nausea, vomiting, and allergic reactions. To decrease the potential for nausea and/or vomiting associated with taking probenecid, you

should eat food prior to each dose of probenecid. Other measures, such as antihistamines and/or paracetamol, are available to your doctor to decrease or prevent allergic reactions.

Why is normal saline solution given with VISTIDE?

Normal saline is given to minimise the potential for kidney damage. You should receive a total of one liter of 0.9 % (normal) saline solution intravenously with each infusion of VISTIDE. The saline solution should be infused over a 1 hour period immediately before the VISTIDE infusion. If you can tolerate the additional fluid load, your doctor may administer a second liter of fluid. If administered, the second liter of saline should be initiated either at the start of the VISTIDE infusion or immediately afterwards, and infused over a 1 to 3 hour period. Your doctor may also instruct you to drink plenty of fluids.

Use in children

Vistide has not been studied in children. Therefore, this medication should not be used in children.

Can VISTIDE be mixed with other medications prior to use?

The chemical stability of VISTIDE mixed in saline solution has been demonstrated in glass bottles, in infusion bags composed of either polyvinyl chloride (PVC) composition or ethylene/propylene copolymer, and in PVC based vented I.V. administration sets. Other types of I.V. set tubing and infusion bags have not been studied. No other medications or supplements should be added to the VISTIDE infusion bag.

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

How will VISTIDE be prepared and given?

VISTIDE vials should be inspected visually prior to use. If visible particles or discoloration are observed, the vial should not be used.

The health care professional (e.g., physician/nurse) will transfer the appropriate dose of VISTIDE from the vial to an infusion bag containing 100 mL 0.9% (normal) saline solution. The entire volume of the bag will be infused intravenously into you at a constant rate over a period of 1 hour by use of a standard infusion pump.

If not intended for use immediately after preparation, VISTIDE infusion bags 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 bags should be allowed to warm to room temperature prior to use.

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

VISTIDE should be administered by health care professionals adequately experienced in the care of AIDS patients. 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.

What are the possible side effects of therapy?

The major side effect observed with VISTIDE has been damage to the kidneys. Side effects which occurred in at least 10% of patients and were possibly or probably related to VISTIDE were: protein in the urine, low white blood cell counts, weakness/fatigue, increase in serum creatinine, fever, hair loss, and nausea without vomiting.

Side effects of probenecid which occurred in at least 10% of patients were: fever, rash, nausea with vomiting, and nausea without vomiting.

If you experience any of these or any other undesirable effect not mentioned in this leaflet, inform your doctor or pharmacist immediately. These side effects usually disappear when treatment with VISTIDE is stopped. Your Doctor might instruct you to take other medications (e.g., antihistamines or antiemetics) to decrease the side effects of probenecid.

How should VISTIDE vials be stored?

VISTIDE vials should be stored at a temperature between 15° and 30°C. Store out of the reach of children.

Review the expiration date on the label prior to use. Do not use after this date.