

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Vistide 75 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 75 mg cidofovir anhydrous. Each vial contains 375 mg/5 ml cidofovir anhydrous as the active substance.

Excipients:

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.

Clear solution.

The formulation is adjusted to pH 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vistide is indicated for the treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction. Vistide should be used only when other agents 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 Vistide, serum creatinine and urine protein levels should be investigated. Vistide 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 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.

Renal insufficiency:

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

Hepatic insufficiency:

The safety and efficacy of Vistide 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 Vistide in children below 18 years of age have not been established. No data are available. Vistide 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 Vistide. The preparation of Vistide 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 Vistide contacts the skin, wash membranes and flush thoroughly with water. (See section 6.6.)

Vistide is for intravenous infusion only. The recommended dose, frequency, or infusion rate must not be exceeded. Vistide 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 Vistide infusion (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

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

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

Direct intraocular injection of Vistide 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

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

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

Renal insufficiency/Haemodialysis

Treatment with Vistide must not be initiated in patients with creatinine clearance ≤ 55 ml/min, or $\geq 2+$ 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 $51.9 \pm 11.0\%$.

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).

Vistide 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 $\geq 44 \mu\text{mol/l}$ ($\geq 0.5 \text{ mg/dl}$), or if persistent proteinuria $\geq 2+$ develops. In patients exhibiting $\geq 2+$ proteinuria, intravenous hydration should be performed and the test repeated. If following hydration, a $\geq 2+$ proteinuria is still observed, cidofovir therapy should be discontinued. Continued administration of cidofovir to patients with persistent $\geq 2+$ 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 Vistide 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 drugs should be closely monitored for zidovudine induced haematological toxicity.

For other NRTI drugs administered concomitantly with probenecid, reference should be made to their respective prescribing information for any appropriate recommendations.

Interactions of cidofovir/probenecid and anti-HIV drugs or drugs 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, aminosalicylic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, nonsteroidal anti-inflammatory agents, theophylline, and zidovudine).

Therefore, when co-prescribing cidofovir/probenecid with other agents, it is important for prescribers to consult the current probenecid SmPC (or an appropriate drug 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:

Women of childbearing potential have to use effective contraception during and after treatment with cidofovir. Men should be advised to practice barrier contraceptive methods during and for 3 months after treatment with cidofovir (see section 4.4).

Pregnancy:

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

Vistide 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) 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	<i>Hearing impaired</i>
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnea
Gastrointestinal disorders	
Very common	Nausea, vomiting
Common	Diarrhoea
Not known	<i>Pancreatitis</i>
Skin and subcutaneous tissue disorders	
Very common	Alopecia, rash
Renal and urinary disorders	
Very common	Proteinuria, blood creatinine increased (see section 4.4)
Common	<i>Renal failure</i>
Uncommon	<i>Fanconi syndrome acquired</i>
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 G6DP 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.

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 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 (see section 4.4).

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 (\pm SD) serum concentration of cidofovir was 19.6 (\pm 7.18) μ g/ml. The mean values of total serum clearance, volume of distribution at steady-state and terminal elimination half-life were 138 (\pm 36) ml/h/kg, 388 (\pm 125) ml/kg and 2.2 (\pm 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 μ g/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 μ g/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 (\geq 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 μ g/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
Hydrochloric acid
Water for injections

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

3 years.

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 30°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 borosilicate glass vials, Teflon faced grey butyl plug stoppers, and aluminium crimp seals with a flip off plastic tab. Each pack contains one 5 ml vial.

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

6.6 Special precautions for disposal and other handling

Method of preparation and administration

Vistide vials should be visually inspected for particulate matter and discolouration 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.

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.

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 Vistide. The preparation of Vistide 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 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. Any unused product or waste material should be disposed of in accordance with local requirements.

Obtaining probenecid

Probenecid is not supplied with Vistide 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 Vistide should be contacted for information (see also sections 4.2 and 4.4).

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/037/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 23 April 1997
Date of last renewal : 23 April 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

Medicinal product no longer authorised

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill Co. Cork
Ireland

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

Medicinal product no longer authorised

Medicinal product no longer authorised

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Vistide 75 mg/ml concentrate for solution for infusion
Cidofovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 75 mg cidofovir anhydrous. Each vial contains 375 mg/5 ml cidofovir anhydrous.

3. LIST OF EXCIPIENTS

Sodium hydroxide
Hydrochloric acid
Water for injections

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial
375 mg/5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Dilute before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/037/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vistide 75 mg/ml concentrate for solution for infusion
Cidofovir
For intravenous use only.

2. METHOD OF ADMINISTRATION

Dilute before use.
Should not be administered by intraocular injection.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

375 mg/5 ml

6. OTHER

EU/1/97/037/001

Medicinal product no longer authorised

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vistide 75 mg/ml concentrate for solution for infusion Cidofovir

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Vistide is and what it is used for
2. Before you use Vistide
3. How to use Vistide
4. Possible side effects
5. How to store Vistide
6. Further information

1. What Vistide is and what it is used for

Vistide is used to treat an eye infection called CMV retinitis in patients with AIDS (Acquired Immunodeficiency Syndrome). Vistide will not cure CMV retinitis but may improve your condition by delaying progression of the disease.

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

Vistide must be administered by a healthcare professional (doctor or nurse) in a hospital setting.

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 AIDS are at high risk of developing CMV retinitis or other forms of CMV disease such as colitis (an inflammatory bowel disease). Treatment for CMV retinitis is necessary to reduce the potential for blindness.

Vistide is an antiviral medicine which blocks the replication of CMV by interfering with viral DNA production.

2. Before you use Vistide

Do not use Vistide

- **If you are allergic (*hypersensitive*) to cidofovir or any of the other ingredients of Vistide.**
- **If you have ever had kidney disease.**
- **If you cannot take the medicine probenecid** because of a serious allergy to probenecid or other sulfa-containing medicines (e.g. sulfamethoxazole).

If any of these apply to you, talk to your doctor. **You are not to be given Vistide.**

Take special care with Vistide

- **Kidney damage is the major side effect of Vistide treatment.** To reduce the risk of kidney damage, you will receive **intravenous fluids (normal saline)** before each dose of Vistide and **probenecid tablets** before and after each dose of Vistide (see section 3 below for more information). Your doctor may also instruct you to drink plenty of fluids. Your doctor will monitor your kidney function before each dose of Vistide. Your treatment with Vistide may be stopped by your doctor if changes in kidney function occur.
- **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 low pressure in the eye (*ocular hypotony*).
- **During treatment with Vistide you should receive regular follow-up eye examinations** for possible eye irritation, inflammation or swelling. **If you get pain, redness or itching of the eye or changes in your vision, tell your doctor promptly.**
- Vistide caused reduced testes weight and low sperm count (*hypospermia*) 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.**
- Vistide is not used for the treatment of HIV infection. Vistide will not stop you passing HIV infection onto other people so **you should continue to take precautions to avoid infecting others.**

Use in children

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

Using other medicines

- **Tell your doctor or pharmacist if you are taking or have recently taken any other medicines**, including medicines obtained without a prescription, as these may interact with Vistide or probenecid.

It is very important to tell your doctor if you are receiving other medicines that may damage your kidneys.

These include:

- tenofovir containing medicines, used to treat HIV-1 infection and/or chronic hepatitis B infection
- aminoglycosides, pentamidine or vancomycin (for bacterial infections)
- amphotericin B (for fungal infection)
- foscarnet (for viral infection)
- adefovir (for HBV infection)

These medicines must be stopped **at least 7 days** before taking Vistide.

- Probenecid may interact with other medicines 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 whether to temporarily stop taking zidovudine or decrease the dose of zidovudine by 50% on days when Vistide and probenecid are given.
- The potential for interactions between Vistide and anti-HIV protease inhibitors has not been studied.

Using Vistide with food and drink

Food should be taken before you are given Vistide. Your doctor may instruct you to drink plenty of fluids before receiving Vistide.

Pregnancy and breast-feeding

- **You should not be given Vistide if you are pregnant.** If you become pregnant while receiving 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. **If you could get pregnant, you must use an effective method of contraception** to stop you getting pregnant during treatment with Vistide and for 1 month afterwards.
- **You should not be given Vistide if you are breast-feeding.** It is not known whether Vistide is passed on to the baby in human milk. Because many medicines are passed through to human milk, nursing mothers should stop Vistide or stop breast-feeding if they continue to receive Vistide.
- **In general, women with HIV should not breast-feed** in order to avoid passing HIV to their infant through the milk.

Driving and using machines

Vistide may cause short-term side effects such as fatigue or weakness. **If you drive or operate machinery, discuss this with your doctor** to get their advice about stopping these activities based upon your disease and your tolerance of the medicine.

Important information about some of the ingredients of Vistide

This medicine contains 2.5 mmol (or 57 mg) sodium per vial which should be taken into consideration if you are on a controlled sodium diet.

3. How to use Vistide

Vistide is given by intravenous infusion (a drip into a vein). It must **not** be administered by other methods including intraocular injection (direct injection into the eye) or topically (on the skin). Vistide must be given by a doctor or nurse with appropriate experience in treating people with AIDS.

The doctor or 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 into your vein at a constant rate over a period of 1 hour using a standard infusion pump. The recommended dose, frequency of use, or rate of infusion must not be exceeded. At the end of this leaflet, there is further information for healthcare professionals on how to administer Vistide.

To lower the risk of kidney damage, probenecid tablets and intravenous fluids (saline solution) must be given on the day of each Vistide infusion. (See sub-sections “How to take probenecid with Vistide” and “How IV fluids are given before Vistide” below.)

Dose in adults

The dose you will need is calculated based on your body weight.

Starting (induction) treatment

The recommended dose of Vistide in patients with normal kidney function is 5 mg per kg of body weight given **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 per kg of body weight given **once every two weeks**.

Dose adjustment

If you have kidney problems, Vistide may not be appropriate treatment for you. Samples of your urine and/or blood will be taken before 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 stopped depending on your individual case.

If you have accidentally been given more Vistide than prescribed for you, **tell your doctor immediately**.

How to take probenecid with Vistide

Probenecid tablets are given to lower the risk of kidney damage. You must take 3 doses of probenecid tablets orally on the same day as Vistide as shown in the following table:

Time	Dose
3 hours before start of Vistide infusion	2 g probenecid
2 hours after end of Vistide infusion	1 g probenecid
8 hours after end of Vistide infusion	1 g probenecid
Total	4 g probenecid

Probenecid is only taken on the same day that Vistide is given.

How IV fluids are given before Vistide

Normal saline is given to lower the risk of kidney damage. You should receive a total of one litre of 0.9% (normal) saline solution intravenously (as a drip into a vein) before each Vistide dose. 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 litre of fluid. If administered, the second litre of saline should be given either at the start of the Vistide infusion or immediately afterwards, and infused over a 1 to 3 hour period. Your doctor may also tell you to drink plenty of fluids.

If you have any further questions on the use of this product, **ask your doctor or pharmacist**.

4. Possible side effects

Like all medicines, Vistide can cause side effects, although not everybody gets them.

These side effects usually disappear when treatment with Vistide is stopped. **If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist immediately.**

The most common side effect observed with Vistide is damage to the kidneys.

Very common side effects

(These can affect more than 1 user in 10)

- low white blood cell counts, headache, nausea, vomiting, protein in the urine, increase in blood creatinine (a measure of kidney function), hair loss, rash, weakness/fatigue and fever.

Common side effects

(These can affect 1 to 10 users in 100)

- inflammation of the eye, reduced pressure in the eyes, difficult or laboured breathing, shortness of breath, diarrhoea and chills.

Any pain, redness or itching of the eye or changes in your vision should be promptly reported to your doctor so that your treatment can be reviewed.

Additional reactions reported from post-marketing experience include kidney failure, damage to kidney tubule cells, inflammation of the pancreas and hearing impairment.

Possible side effects of taking probenecid

Very common side effects possibly related to probenecid

(These can affect more than 1 user in 10)

- nausea, vomiting, rash and fever.

Common side effects possibly related to probenecid

(These can affect 1 to 10 users in 100)

- headache, weakness/fatigue, chills and allergic reactions.

To reduce the risk of nausea and/or vomiting associated with taking probenecid, **you should eat food before each dose**. Your doctor might instruct you to take other medicines such as anti-emetics (anti sickness medicines), antihistamines and/or paracetamol to decrease the side effects of probenecid.

Probenecid may also cause other side effects including loss of appetite, sore gums, flushing, hair loss, dizziness, reduced red blood cell count and increased frequency of passing water (urinating). Allergic reactions, with skin inflammation, itching, hives and, rarely, severe allergic reactions, and serious skin reaction have occurred. There have been reports of reduced white blood counts, liver toxicity, kidney toxicity and destruction of red blood cells. Reductions in blood cell and platelet counts have also occurred.

Therefore before giving you probenecid your doctor should consult the current prescribing information regarding the safety of probenecid. **You should also read the probenecid package leaflet.**

5. How to store Vistide

Keep out of the reach and sight of children.

Do not use Vistide after the expiry date which is stated on the label.

Do not store above 30°C. Do not refrigerate or freeze.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Vistide contains

The active substance of Vistide 75 mg/ml is cidofovir. Each ml contains 75 mg cidofovir anhydrous. Each vial contains 375 mg/5 ml cidofovir anhydrous.

The other ingredients are

- Sodium hydroxide
- Hydrochloric acid
- Water for injections

What Vistide looks like and contents of the pack

Vistide is supplied as a sterile concentrate for solution for infusion in clear, glass vials containing 375 mg of the active ingredient, anhydrous cidofovir, formulated in 5 ml water for injections at a concentration of 75 mg/ml. The formulation is pH-adjusted with sodium hydroxide (and hydrochloric acid if needed) and contains no preservatives.

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Manufacturer

Gilead Sciences Limited
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

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

Adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration and disposal of Vistide. The preparation of Vistide diluted solution should be done in a laminar flow biological safety cabinet. Personnel preparing the solution 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.

The appropriate dose of Vistide should be transferred from the vial to an infusion bag containing 100 ml 0.9% (normal) saline solution. The entire volume of the bag should be infused into the patient's vein at a constant rate over a period of 1 hour using a standard infusion pump. The recommended dose, frequency of use, or rate of infusion must not be exceeded.

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 IV administration sets. Other types of IV set tubing and infusion bags have not been studied.

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

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 infusion 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.

Medicinal product no longer authorised