SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 30 July 2005. For scientific information on procedures after this date please refer to module 8B

1. Introduction

Cidofovir is a monophosphate analogue of deoxycitidine with *in vitro* and *in vivo* activity against human cytomegalovirus (CMV). Cidofovir, unlike other nucleoside analogues such as acyclovir and ganciclovir, is phosphorylated in order to bypass the initial viral dependent phosphorylation.
After *in vivo* conversion into the diphosphate and triphosphate analogues, cidofovir acts as a specific inhibitor of viral DNA polymerases in a broad spectrum of herpes virus including CMV.

CMV retinitis is the most common ocular complication in HIV infection, usually occurring late in the disease in up to a fifth of patients. Untreated, the condition is rapidly progressive causing blindness within weeks or months. Since anticytomegalovirus drugs, including Vistide, are only virustatic, treatment aims to halt disease progression rather than achieve a cure. Lifelong treatment is therefore required. Currently licensed drugs for the treatment of this disease are ganciclovir and foscarnet.

Viral resistance or drug toxicity may require a change in the antiviral agent used in the treatment of CMV retinitis. Vistide has been evaluated for the treatment of CMV retinitis in AIDS patients.

2. Chemical, pharmaceutical and biological aspects

Cidofovir is an optically active substance with a single chiral centre and used as a single (S)-enantiomer.

Vistide is supplied as a sterile, clear solution in a 5 ml sterile borosilicate type I flint glass vial which contains 375 mg of cidofovir in 5 ml of water at a concentration of 75 mg/ml. Formulation and preparation methods were identical for all 75 mg/ml batches used in clinical trials.

Vistide is intended for intravenous infusion following dilution into an intravenous infusion bag containing saline.

The final formulation for Vistide was selected based on the clinical dosing requirements and the physicochemical properties of cidofovir. Due to the infrequent dosing schedule, Vistide is formulated as a non-preserved, single use product. The medicinal product strength was based on estimated clinical dosing requirements. One vial of Vistide can be used for patients with a bodyweight of up to 76 kg at the 5 mg/kg dose.

Development pharmaceutics

The different parts of the dossier substantiate the development of a concentrate for solution for infusion of acceptable chemical and pharmaceutical quality.

Preformulation studies were carried out in order to identify the solubility and stability characteristics of cidofovir. The stability of cidofovir in water is highest at pH between 8.5 and 10.5 but delamination of glass vials occurs at this high pH. A pH of 7.4 was selected as a compromise between maximum chemical stability, aqueous solubility, buffering capacity of cidofovir and container compatibility. Therefore apart from sodium hydroxide or hydrochloric acid necessary to adjust pH to 7.4, no other excipients are present in the formulation to be marketed.

The good chemical stability of cidofovir allows the product to be terminally sterilised and supports an extended shelf-life. A validated moist heat based terminal sterilisation method was adopted.

A program of drug substance stress testing under conditions of extremes of heat, light, acid/base and oxidative conditions has been performed. Deamination to the corresponding uracil analog-HPMPU appears to be the only route of degradation. HPMPU is formed up to 6% levels cumulatively during the terminal sterilisation and during shelf-life. A proposed 1% overage is incorporated into the product to compensate for part of this loss. Toxicological relevance of the expected HPMPU level of exposure in routine clinical use has been considered not significant based on dosing considerations and the results from specific pre-clinical studies conducted to assess HPMPU toxicity.

Method of preparation

The manufacturing process is well controlled and in-process testing is adequate to ensure consistent quality in the product.

The two following minor points of clarification have been addressed. The maximal holding time prior to filtration had initially been considered too long and has been reduced to 72 hours. Overkilling conditions during the terminal steam sterilisation are used to provide a sterility assurance level (SAL) of 10^{-6}. The impact on HPMPU formation is minor, from 0.4% to 0.6%.

Levels of residual solvents are below those of toxicological relevance based on historical batch data. However since the applicant is intending to test 10 more productions batches these data should be provided on an ongoing basis for further reassurance.

Control of starting materials

Cidofovir is manufactured as a single isomer by controlling the chiral purity of the synthetic starting materials. The enantiomeric purities of all batches of drug substance produced to date are above 97% (S)-enantiomer. Extensive studies on cidofovir solutions over a wide range conditions have demonstrated that racemisation does not occur. Furthermore, no decreases in enantiomeric purity were seen in drug product stability studies for 27 months.

Batch analysis covering the period 1990 to 1995 for use in clinical, preclinical and formulation/stability studies have been provided. The impurities are all related to cidofovir and have all been present in lots of drugs substances used in toxicology and clinical studies. None of the impurities are metabolites. Levels of impurities present in the drug substance manufactured at full scale are low, total related substances appear to be less than 2.6 % and enantiomeric purity is greater than 99.4 %. Limits of impurities and degradants in drug substance have been narrowed to levels which comply with both stability data and ICH guidelines, except for HPMPU.

Control of finished product

The finished product consists of an aqueous solution (75 mg/ml) adjusted to a target pH value of 7.4. A rationale for the routine tests selected and specifications is presented. The excipients used in the manufacture of Vistide are water for injection, sodium hydroxide, hydrochloric acid and nitrogen which are of the appropriate compendial quality.

For immediate packaging material, studies have been performed for the selection of the appropriate vials resistant to the high pH of Vistide. Satisfactory specifications for the container and closure components have been provided. The packaging materials have been subjected to rigorous integrity testing and have been found to be satisfactory.

Particular emphasis has been placed on the sourcing of glass vials. Particulates found in early stability studies were identified as glass, resulting from delamination of the vials. This has been considered critical. However an acceptable quality level for the presence of glass particles detected by visual inspection has been provided, on the basis of a protocol for stress testing all new lots of glass vials prior to use in the manufacture of Vistide. Each batch of vials used is required to be qualified using satisfactory methodology. So far only two lots have been tested and further results have to be submitted on an ongoing basis.

Limits of impurities and degradants in drug product have been narrowed to levels which comply with both stability data and ICH guidelines, except for HPMPU.

Stability tests on starting materials

The drug substance is stable and there is no evident degradation to the uracil analog of other degradants. In the long term, the accelerated and the light stability tests show that neither degradation nor significant changes in the chemical and physical characteristics have been observed in cidofovir when stored under the recommended storage conditions and placed into tightly closed high density polyethylene containers.

Stability of the finished product

The stability tests on the finished product on Vistide were performed on 3 registration batches manufactured by Ben Venue Laboratories which is the intended site for commercial manufacturing. The finished product has been stored under a variety of storage conditions which includes 30°C for up to 27 months and 40°C for 6 months. Freeze thaw cycling studies (at 5°C/40°C and -20°C/30°C) have been performed with untoward effect.

The most relevant results from the stability evaluation are the variations in potency and HPMPU assays. A slight increase of total impurity levels is observed upon preparation of the sterile aqueous injectable, ranging from 0.9 % to 2.1 % in the batches prepared to date. This is mainly due to HPMPU whose levels further increase to 5.1 % after 27 months stability testing at 30°C. The HPMPU has been observed upon extended storage as well. Based on analyses of either the loss of cidofovir potency or the formation of HPMPU, a shelf-life of 36 months at controlled room temperature (15°C-30°C) is justified.

Compatibility studies indicated that cidofovir is stable for 24 hours in intravenous admixtures and containers (0.9% sodium chloride, 5 % dextrose). Clarification has been provided with regard to the manufacturer supplying the bag and tubing used in the compatibility studies of the infusions solutions with often used intravenous administration tubing. In addition a precautionary statement under section 6.2 of the SPC has been included.

Aside from a few minor remarks, two major concerns in the chemical and pharmaceutical part of the documentation were raised. The first one was the formation of the HPMPU upon sterilisation and storage. An overage of 1.0 % was proposed to compensate for losses of cidofovir during the terminal sterilisation cycle and storage. This was considered as acceptable since the concern regarding the toxicity risk from this degradant has been properly addressed. The second one regarded the compatibility of glass vials with the high pH necessary for cidofovir stability. This has been resolved by careful selection of supplies of glass vials and by stress testing of all new lots of glass vials prior to the manufacture of Vistide.

3. Toxico-pharmacological aspects

Pharmacodynamics

Cidofovir is an acyclic phosphonate analogue of deoxycitidine monophosphate. In cells it is converted to the active form, cidofovir diphosphate, by cellular enzymes. Unlike regular nucleosides, cidofovir contains a phosphate-carbon bond which is not susceptible to degradation by hydralases like the phosphate-oxygen-carbon linkage. Cidofovir is not dependent on viral infection for its phosphorylation and can therefore prime cells to an antiviral state prior to infection.

Intracellular metabolism of cidofovir progresses via the monophosphate, diphosphate and choline phosphate compounds. Data from cell cultures indicate extended half-lives of 17 and >48 hours for cidofovir diphosphate and cidofovir-choline phosphate respectively. These compounds were suggested to act as a possible intracellular cidofovir reservoir.

Animal studies suggested that uptake of cidofovir into cells was slow using an endocytosis mechanism.

Cidofovir diphosphate is the intracellularly active molecule that inhibits DNA polymerase. The incorporation of a single molecule of cidofovir causes DNA synthesis to slow down. Selectivity is achieved because cidofovir diphosphate has a higher affinity for viral DNA polymerase than for mammalian polymerases.

Cidofovir has shown activity in a broad spectrum of herpes viruses including CMV. In several animal models of viral infections, i*n vivo* efficacy was shown following infrequent dosing post-inoculation and following prophylactic doses administered several days pre-inoculation. However studies of inhibition of human CMV replication are limited. Some data have been obtained in *in vivo* experiments and in animal models using human and non human viruses.

Cidofovir inhibited human CMV DNA synthesis in cell culture in a concentration-dependent manner within the concentration range of 0.04 to 4 µg/ml. At 4 µg/ml viral DNA synthesis was completely

inhibited. Cidofovir affected cell proliferation only at a concentration that was 100- to 500 fold higher than effective antiviral concentrations. Since these data are very concise they can only be used to support the treatment of human CMV infections.

Combination of cidofovir with ganciclovir, foscarnet or acyclovir produced synergistic inhibition of human CMV replication.

Very limited data are presented on the selection of cidofovir resistant human CMV strains either *in vitro* or *in vivo*. *In vitro* cross resistance to cidofovir occurred with ganciclovir selected mutations in DNA polymerase gene but not with mutations in the gene involved in the phosphorylation of ganciclovir (UL97 gene). No cross resistance between foscarnet and cidofovir was seen with foscarnet-selected mutants. *In vitro* resistance induction experiments demonstrated the selection of a human CMV harboring a mutation in the polymerase gene. This virus was 20-fold less susceptible to cidofovir than the wild type isolate and expressed 8-fold reduced susceptibility to ganciclovir, but unchanged sensitivity to foscarnet.

Cidofovir did not interact with several antiviral agents commonly used to treat AIDS patients. Combination of zidovudine inhibited bone marrow cell growth in a dose dependent manner.

In clinical isolates, ganciclovir resistant human CMV remained sensitive to inhibition by cidofovir. Cidofovir selected mutants were cross resistant to ganciclovir but remained susceptible to foscarnet.

The reporting of the secondary pharmacology studies was generally inadequate to allow assessment. In the one adequately reported study a single dose of cidofovir 5 mg/kg administered intravenously to the rat had no effect on blood pressure and heart rate. Therefore reassurance concerning this aspect of the safety of cidofovir must be gained from the clinical data.

Pharmacokinetics

In vitro protein binding of cidofovir in plasma and serum in rat and human was very low, <0.5% and <10% respectively. Volume of distribution of cidofovir in various species was generally above 0.5l/kg suggesting distribution in total body water. After administration of radiolabelled cidofovir to rabbits a wide distribution of drug-related compound was observed. The highest levels were seen in kidney tissue. Passage of the blood brain barrier was observed but levels were much lower than those observed in kidney tissue. In rabbits the ocular levels reached in were lower than those in plasma. Passage of radiolabelled cidofovir across the placenta barrier was observed in pregnant rats. Excretion into milk was not examined in lactating animals.

After a single intravenous cidofovir dose the terminal half-lives ranged from 1-9 hours in animals. Using radiolabelled material, a longer terminal half-life of 33 hours was observed in monkeys attributed to the long intracellular half-life of the phosphorylated metabolites of cidofovir.

In all species cidofovir is predominantly eliminated unchanged via the kidney. Phosphorylated metabolites were not observed in plasma or urine and limited data on rats suggest that metabolism is negligible. The renal clearance of cidofovir was stated to exceed the corresponding published glomerular filtration rates indicating an active tubular secretion of cidofovir.

Toxicokinetic data indicated that cidofovir exposure increased proportionally with increasing dose. In the repeated dose studies, the exposure increased over time and at the higher doses which likely occurred as a result of the renal toxicity.

Coadministration of probenecid may reduce nephrotoxicity by reducing the accumulation of cidofovir in kidney tissue by blocking the anion transport system responsible for active tubular secretion. Results of two monkey and two rabbit studies were not conclusive as to whether or not probenecid influences cidofovir disposition.

<u>Dose extrapolation</u>

Interspecies scaling of cidofovir exposure was calculated on the basis of the area under the plasma concentration curve (AUC) for the various species. To obtain similar exposure of animals as that of humans, 1.5 (monkey), 2 (rabbit) or 5 (rat) times higher doses were estimated to be required.

Toxicology

The single dose toxicity after intravenous administration was evaluated in rodents, rabbits and in cynomolgus monkeys. The maximum non-lethal intravenous dose was >800 mg/kg in rodents, >100 mg/kg in rabbits and 40 mg/kg in monkeys (corresponding to a human dose of about 27 mg/kg). Nephrotoxicity was the primary systemic toxicity in all species, occurring at 50 mg/kg in rabbits (corresponding to a human dose of 9 mg/kg) and 150 mg/kg in monkeys.

The main repeat dose toxicity studies with intravenous administration of cidofovir were conducted in rats (up to 26 weeks) and cynomolgus monkeys (up to 13 weeks). In both species, nephrotoxicity was the dose limiting toxicity. Coadministration of probenecid resulted sometimes in amelioration of nephrotoxicity. No conclusion can be drawn whether the probenicid regimens used in toxicology studies were optimally protective. Consequently, relevance of the probenicid treatment regimens used in the toxicology studies for the human patient situation is unknown.

Decreased red and white blood cell parameters, bone marrow (erythroid and/or myeloid) depletion, hypospermia, testicular degeneration, lymphoid depletion of thymus and lymph nodes were also observed. In addition, rats showed uterine glandular epithelial hyperplasia and monkeys hepatocellular hypertrophy. Comparisons of AUC values showed that all toxicological findings occurred at subtherapeutic exposure levels.

There was one 52 week study where monkeys received weekly bolus injections of cidofovir with or without coadministration of probenecid. This study indicated that probenecid resulted in some less nephrotoxicity but was without effect on testicular toxicity. However, due to lack of data it is not possible to evaluate the relevance of probenecid treatment for the human situation.

The toxicity of the uracil analogue degradation product was studied in a single study and a repeat dose study in rats. The minimum lethal single intravenous dose was >100 mg/kg. There were no changes in rats administered intravenous HPMPU once a week for 4 consecutive weeks at doses up to 120 mg/kg/week.

In acute and subchronic safety studies, HPMPU has been shown to be safe and well tolerated at doses greater than 200 times the potential human exposure.

Although the enantiomeric purity of the drug substance has been established, the applicant has undertaken toxicology studies of the (S/R)-isomer mix or the (R)-isomer in both rats and monkeys. No deaths were observed. In one monkey study there were signs of toxicity in a single animal: increased body weight and creatinine clearance. Since the enantiomeric purity of cidofovir is carefully controlled at the drug substance level and no racemisation has been observed under any storage condition, no clinical or safety issues regarding the (R)-enantiomeric are expected.

The reproductive toxicity of cidofovir was evaluated in rats (segment I-III) and rabbits (segment II). The doses used were low. In the rat and rabbit reproductive toxicity studies, cidofovir was embryo-toxic and embryo-lethal at maternotoxic dose levels.

In the segment III study the rationale for the subcutaneous route of administration and the dose levels employed were not stated. There were no adverse treatment related effects, but the value of this study is uncertain.

Local injection site lesions recorded in a rat 13 week intravenous repeat dose study were considered to be related to the administration technique and concentration of the compound. They did not occur in a subsequent 26 weeks study.

Genotoxicity studies showed that cidofovir was not mutagenic in the Ames test. However, it showed a dose dependent clastogenic effect in human peripheral lymphocytes and it was clastogenic at high toxic/lethal doses in the *in vivo* mouse micronucleus assay.

Carcinogenicity studies were not conducted. In the repeat dose toxicity studies there were also findings of tumours. Mammary adenocarcinomas were observed in female rats after 26 weeks intravenous administration (50% of the rats) and 19 weeks subcutaneous administration (a dose related increase in mammary adenocarcinomas in female rats was noticed with subcutaneous administered cidofovir at doses up to 15 mg/kg/week). Both studies reported carcinomas in the Zymbal's gland of the external auditory ear canal, with the highest incidence after intravenous administration (13% of

males and 7% of females from the high dose 15 mg/kg/week equivalent in humans based on AUC to 2.8 mg/kg/week). It was suggested, that a genotoxic mechanism may be behind the observed tumours since cidofovir was found to be clastogenic both *in vitro* and *in vivo*. No neoplastic or pre-neoplastic lesions were observed in monkeys exposed to cidofovir for 52 weeks.

The findings of tumours in rats are a cause of concern since they appeared after short periods of exposure. Furthermore, safety margins can not be established since, based on AUC values, tumours were observed at systemic exposure in rats lower than that observed in clinical use. These tumors are unlikely to have any clinical relevance because the duration of treatment in the patient population is relatively short. Therefore use of cidofovir should be acceptable in AIDS patients with short life expectation.

The applicant has provided a brief discussion of the possible risk to the environment. Based on the low yearly volume predicted for use and the fact that the product will undergo considerable dilution in the sewerage system upon disposal, it is unlikely that the clinical use of cidofovir will result in any untoward environmental concerns.

4. Clinical aspects

Clinical pharmacology

Studies GS-92-101, GS-92-102 and **GS-92-103** were phase I/II studies conducted on HIV infected patients with (GS-92-101 and GS-92-103) or without (GS-92-102) asymptomatic CMV infection. Patients received doses ranging from 0.5 to 10 mg/kg/week via different routes of administration and following various dosage schedules. Dose dependent nephrotoxicity was the major limiting toxicity and the main dose defining criterion both for induction and maintenance treatments. The applied dose regimens were based on the non toxic effect levels of the drug without considering antiviral activity. In order to prevent toxicity, probenecid and intravenous hydration was administered. However, no explanations of the chosen administration regimens were provided. Due to lack of antiviral activity data, the efficacy of cidofovir can not be evaluated in these studies.

With respect to safety, nephrotoxicity was the main dose limiting toxicity. There were also signs of bone marrow toxicity as well as probenecid related allergic reactions.

Pharmacokinetic studies

The human pharmacokinetics of single and repeated doses of cidofovir have been investigated in 48 patients in studies GS-92-101, GS-92-102, GS-92-103 and in one clinical study, GS-93-107. Pharmacokinetics of cidofovir at the 5 mg/kg intravenous dose with concomitant oral probenecid and previous saline hydration has only been studied in 6 patients (3 from study 103 and 3 from study 107). The mean oral bioavailability of cidofovir at a 10 mg/kg dose was less than 3%.

All intravenous infusion administrations were given as a 1 hour infusion after dilution in 100 ml of 0.9% saline. The mean serum levels after a single intravenous infusion of 3 mg/kg without intravenous hydration and without probenecid or 5 mg/kg was 7±2 µg/ml or 20±7µg/ml, respectively. In both cases, terminal half life was 2±1 hour, systemic clearance was 150 ml/hr/kg and the steady state volume of distribution was 0.5±0.2 l/kg. Intravenous single doses of 1-10 mg/kg cidofovir demonstrated dose independent kinetics. The presented pharmacokinetic data are not enough to demonstrate a consistent effect of probenecid and/or hydration on the volume of distribution of cidofovir.

Binding of cidofovir to plasma proteins was evaluated in preclinical studies over the concentration range of 0.25 µgr/ml to 25 µg/ml using ^{14}C labeled cidofovir in pooled rat plasma or serum and was found to be negligible (< 0.5%) over the entire concentration range.

The major route of elimination is by renal excretion of unchanged drug via glomerular filtration and tubular secretion. In patients with normal renal function, over 90% of the intravenous dose was recovered unchanged in the urine over 24 hours.

Kinetics in patients with renal or hepatic impairment have not been investigated. No data are available concerning the pharmacokinetics of cidofovir in elderly and children. A meaningful comparative analysis of the efficacy and safety profiles of intravenous cidofovir between genders could not be conducted due to the small number of females who have been treated with the drug.

Interactions with probenecid are complex and not fully understood. Studies included multiple combinations of hydration and dosing with probenecid. Protocol GS-92-101 reported that administration of probenecid as a 4 g course, together with prehydration with a litre of normal saline had no significant effect on the kinetics of 3 mg/kg cidofovir. In protocol GS-92-103 a 2 g course of probenecid in conjunction with prehydration did not affect kinetics of 5 mg/kg cidofovir, while a 4 g course with the same hydration resulted in an approximate doubling of the end of infusion cidofovir concentration (from 12 to 26 µg/ml), doubling of the AUC, and reduction of the clearance and volume of distribution values to roughly half those seen with hydration alone.

Kinetics of zidovudine alone and in conjunction with several dose levels of cidofovir were evaluated in a small numbers of patients in protocol GS-92-102. Results showed considerable variability and no consistent effect on the kinetics of either drug was demonstrated.

Clinical experience

Efficacy

As the demonstration of a prolonged intracellular effect on the inhibition of CMV replication by cidofovir or any of its known metabolites was not done, efficacy analysis relied solely on the demonstration of a positive effect of the drug on the clinical progression of retinitis.

The diagnosis of CMV retinitis was made by indirect opthalmoscopy and supported by culture of CMV from urine, blood throat, or other sites. A negative CMV culture did not rule out CMV retinitis.

Efficacy analysis was based mainly on study GS-93-106 with some additional information from study GS-93-107. Both trials presented data on time to progression of retinal lesions as the primary endpoint.

Study GS-93-105 was a multicenter, randomised controlled phase II/III trial designed to evaluate the efficacy and safety of intravenous cidofovir in the treatment of previously untreated peripheral CMV retinitis. Sixty four patients were randomised to one of three groups: deferred treatment (no treatment until CMV retinitis progression); or immediate treatment with cidofovir injection 5 mg/kg once weekly for 2 weeks (induction) followed by intravenous maintenance at 3 mg/kg once every other week; or immediate treatment with cidofovir injection 5 mg/kg once weekly for 2 weeks (induction) followed by intravenous maintenance at 5 mg/kg once every other week.

Time to progression of CMV retinitis was assessed at regular time-points by direct opthalmoscopy (retinal photographs). Patients were to be treated until clinical evidence of progression, extraocular CMV disease , treatment limiting toxicity or death.

The median time to progression of retinitis was 64 days for the 3 mg/kg maintenance group compared to 21 days in the deferred treatment group (log-rank p=0.052). The median time to progression was not reached for the 5 mg/kg maintenance group (log-rank p=0.004 for the comparison with deferred treatment). The median time of taking cidofovir was 8 months.

Rates of increase of retinal area affected by CMV over time were significantly smaller in both cidofovir treated groups when compared to the deferred patients, with the 5 mg/kg dose showing better results than the 3 mg/kg dose (0.34%/month and 0.8%/month increases of retinal area affected by CMV, respectively).

The effect of both treatment regimens on CMV viraemia or viruria was not statistically significant and was not considered relevant for efficacy analysis.

Study GS-93-106 was a multicenter, randomised and controlled study of the safety and efficacy of intravenous cidofovir for the treatment of peripheral CMV retinitis in AIDS patients previously untreated for retinitis.

Eligibility criteria included diagnosis of HIV infection according to CDC (Center of Disease Control) criteria, previously untreated CMV retinitis, age between 13 to 60, preserved renal, hepatic and hematological functions. Exclusion criteria included evidence of retinitis considered as non peripheral, previous or ongoing therapy with ganciclovir, foscarnet, CMV hyperimmune immunoglobulin, acyclovir or any other anti CMV investigational drugs (although previous prophylaxis with either agent could be considered), clinically significant cardiac disease or concomitant treatment with

potentially nephrotoxic agents.

Forty-eight patients were randomised to receive either deferred (n=23, no treatment until CMV retinitis progression) or immediate treatment with cidofovir at the dose of 5 mg/kg once weekly for 2 weeks (induction) followed by 5 mg/kg every 2 weeks (n=25 maintenance). All patients received prehydration with 1 l saline and a 4 g course of oral probenecid (2g 3 hours prior to infusion, and 1g 2 and 8 hours after). Sixteen of the 23 patients in the deferred group crossed over and received cidofovir treatment following CMV progression. Forty six patients (96%) were male. The mean age was 38 years. The median CD4 cell counts were 6/mm^3 and 9/mm^3 for immediate and deferred groups respectively, revealing advanced immunosuppression. A third of patients received AZT during the study. The protocol required dose reduction to 3 mg/kg if proteinuria occurred, and this was done in 5 immediate treatment patients and 7 crossover patients.

The primary efficacy endpoint was median time to progression of retinitis or death. Retinitis was assessed using retinal photographs evaluated by staff blinded to treatment allocation.

Median time to retinitis progression in the treatment group (n=25) was 120 days (95% CI 40-134 days). In the deferred treatment group (n=23) the median time was 22 days (95% CI 10-27 days $p<0.001$;log rank test). CMV retinitis progression occurred in 10 of 25 immediate treatment patients and in 18 of the deferred patients. At the time of data cut-off, only one patient was still receiving cidofovir and was still at risk of CMV retinitis progression.

Nineteen of 25 patients (76%) in the immediate treatment group showed decreased or absent lesions, compared to 4 out of 21 (19%) in the deferred group.

Additional evidence of a cidofovir treatment effect was obtained by comparing retinal photographs documenting time to first progression for deferred patients to time to second progression (first on cidofovir treatment) for patients receiving crossover cidofovir. The median time to first CMV retinitis progression for evaluable deferred patients was 21 days (95% CI 13 to 23 days) before the start of the crossover. In contrast the probability of progression in the crossover period never rose above 20 % as only 3 patients had documented CMV retinitis progression while on therapy. The difference in time to progression was statistically significant.

Thirty-one out of 48 patients were taken out of the study before an endpoint was reached. Twelve of these were withdrawn due to adverse experiences related to one of the study drugs of which 10 presented with signs of nephrotoxicity.

Mortality rates were similar between the immediate group (n=12) and the deferred group (n=17). The median survival time based on the Kaplan Meier analysis were 410 and 319 days.

Secondary endpoints were planned to consider changes in visual acuity and CMV shedding in blood and urine/semen cultures. Virology assessments were conducted on a small minority of patients at 3 out of 8 centres, using different methodologies. Excretion of CMV in the urine has not been demonstrated to be predictive of CMV disease in humans. Likewise viraemia does not necessarily precede nor is associated with the development of CMV disease in humans. Consequently the value of these measures to monitor the virologic effect of therapy is questionable and does not contribute to any significant evidence of efficacy.

Study GS-93-107 was an open label, randomised multicenter study designed to compare the efficacy and safety of two maintenance treatment regimens of cidofovir (5 mg/kg versus 3 mg/kg every other week) in AIDS patients with CMV retinitis progression despite treatment with ganciclovir and/or foscarnet, or with intolerance to these drugs.

This study randomised up to 150 patients. Of these patients, only the first 100 were assessed by retinal photographs and included in the primary efficacy analysis. The patients, predominantly male, had a mean age of 40 years. Median CD4 cell counts were of 5-7/mm^3. 12% of the patients received zidovudine during the study.

All patients received the standard induction dose of 5 mg/kg/week for 2 weeks. All cidofovir infusions were given after prehydration with 1l saline and with probenecid (4 g course). All patients received a second litre of saline infusion over 1-3 hours either during or after cidofovir infusion.

Median time to retinitis progression was 115 days for the 5 mg/kg/week (95% CI 70 days-upper limit

not reached) and 49 days for 3 mg/kg/week groups (95% CI 35-52 days). The difference in time to progression was statistically significant (p=0.0017; log rank test). Decreased or absent lesions were reported in 33 of 44 (75%) patients in the high dose group and 19 of 42 (45%) in the lower dose group. These differences were statistically significant. There was no evidence for an effect on visual acuity outcome.

Safety

Nephrotoxicity was the major toxic effect observed in patients receiving cidofovir. Evidence of renal dysfunction was manifested by proteinuria (≥ 2+, ≥ 100 mg/dl) in 36% of the patients and plasma creatinine increase in 16%. The renal injury may be irreversible in as much as half of the affected patients. Proteinuria (≥3+) and creatinine increase (≥2.0 mg/dl, ≥ 177 µmol/ml) considered as serious adverse experiences were present in 14% and 8% of the patients, respectively.

The nephrotoxic potential of cidofovir is a matter of concern. Nephrotoxicity was the cause for treatment discontinuation in 10% of the patients included in the pilot studies, 24% of patients included in pivotal study 106 (n=40) and 15% of the patients in study 107 (N=98).

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 recommended cidofovir dose-reduction from 5 mg/kg to 3 mg/kg, once some sign of renal dysfunction developed, in study 107 did not seem to decrease in a significant way the nephrotoxic effects of the drug. Care must be taken in order to ensure that the clinical use of cidofovir will not increase the already important morbidity of this group of patients. In particular, it is important to monitor renal function (including proteinuria) carefully both pre- and on-treatment in order to avoid treatment of patients with pre-existing renal dysfunction and to suspend treatment as soon as biological signs of nephrotoxicity develop.

To minimise the potential for nephrotoxicity, patients should receive a course of probenecid, administered orally with each cidofovir dose. 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. Suspected reactions to probenecid (fever, rash, headache, and/or nausea) were reported in at least half the treated patients, although these were mostly transient and required discontinuation in only 3-7% of patients.
Concomitant administration of cidofovir and other potentially nephrotoxic agents is contraindicated. The safety of cidofovir has not been evaluated in patients receiving other known potentially nephrotoxic agents. It is recommended to discontinue potentially nephrotoxic agents at least 7 days before starting cidofovir.

Haematological toxicity was also evident in most of the studies. Both the red and white cell lines seem to have been affected, although neutropenia was more frequently observed. Both early and pivotal trials indicated that cidofovir might cause neutropenia which was reversible.

Ocular hypotony was observed in four patients (3 from study 107 and one from study 103). Its potential consequences on eye function were unclear. The condition seems to be reversible at cessation of treatment. Following these reports ocular pressure measurements were added to the protocol.

In the first periodic safety update (PSUR, 23 April 1997 to 22 October 1997) the CPMP attention was drawn to 28 cases of iritis/uveitis among cidofovir treated patients. As reported by the Marketing Authorisation Holder, acute iritis developed in 11/43 patients occurring at a mean of 4.9 days after infusion of cidofovir. Hypotony of the ocular globe, defined as a 50% reduction in intraocular pressure, occurred in 4 patients with iritis and in no patients without iritis. Five of six eyes with hypotony had clinically significant ophtalmological problems associated with it (choroidal detachment, retinal detachment, macular fold or a significant reduction of visual acuity). This information has been included in the relevant parts of the product information.

Following the 3rd and 4th periodic safety updates with the occurrence of hearing disturbances, pancreatitis and ocular hypotony and including updated information on nephrotoxicity (fatalities reported in patients with cidofovir-related renal failure), the relevant parts of the product information (section 4.8 of the SPC and PL) were updated.

Mortality rates were similar in both immediate and deferred treatment groups in protocol 106 and in both dosage groups of protocol 107. All patients were considered to have died from medical complications of AIDS, except for one suicide. Analysis of deaths in study 105, 106, 107 indicates that mortality following initiation of intravenous cidofovir has not been drug related and survival appears comparable to patients receiving standard therapies for CMV retinitis.

Non-AIDS-related malignancies were not reported during or after cidofovir treatment. However, the follow-up period for most patients is relatively short. Recent advances in prophylaxis for AIDS related infections, general improvement in care and the development of new anti HIV drugs may help in prolonging the life expectancy for these patients, therefore increasing the risk for occurrence of cidofovir related malignancies.

Overall up to about a third of patients discontinued cidofovir because of adverse effects. Nephrotoxicity is the major side effect observed in patients treated with Vistide. Evidence of renal dysfunction is manifested by proteinuria and plasma creatinine increase. In order to minimise the potential for damage to the kidneys, intravenous fluids and probenecid tablets are administered with each dose of Vistide. Neutropenia, nausea without vomiting, alopecia, asthenia and fever expected frequencies are also very common. Other adverse events expected to occur commonly are: iritis/uveitis, decreased intraocular pressure, dyspnoea, pneumonia and nausea with vomiting. Ocular hypotony, hearing disturbances and pancreatitis were reported through the post-marketing spontaneous reporting system.Very common undesirable effects in controlled clinical trials possibly or probably related to probenecid include: gastrointestinal disorders (nausea with and without vomiting), skin disorders (rash), general disorders (fever).

Undesirable effects reported through the postmarketing spontaneous reporting system include: eye disorders (uncommon: uveitis/iritis; rare: ocular hypotony), ear disorders (very rare: hearing disturbances); gastrointestinal disorders (rare: pancreatitis); Renal and urinary disorders (uncommon: renal failure).

5. Overall conclusions and benefit/risk assessment

Vistide is an intravenous formulation of cidofovir, a cytidine nucleotide analogue inhibitor of human CMV replication intended for induction and maintenance treatment of CMV retinitis in AIDS patients.

Major potential benefits for cidofovir include its efficacy, demonstrated in clinical studies, in slowing the progression of CMV retinitis in AIDS patients and a more favourable regimen of drug administration over the other two currently available drugs (ganciclovir and foscarnet) both in terms of the need for intravenous catheter placement and reduction in hospitalisation.

Efficacy of cidofovir with concomitant probenecid in delaying the progression of CMV retinitis in AIDS patients was demonstrated based on two controlled studies GS-93-105 and GS-93-106.

Additionally, data from study GS-93-107 supports the efficacy of the maintenance treatment regimen of 5 mg/kg.

Major risk factors associated with cidofovir treatment include significant nephrotoxicity and potential carcinogenicity. On the basis of preclinical and clinical studies, a safety margin for the use of cidofovir in patients could not be calculated. With regard to treatment dosage regimens, the induction and maintenance dosages were calculated mainly on the basis of the toxicity profile of the drug.

Although the potential for nephrotoxicity of cidofovir, even with concomitant probenecid, is a major point of concern, avoidance of treatment in patients with pre-existing renal dysfunction, careful monitoring of renal function and discontinuation of therapy once signs of renal dysfunction are observed may permit an overall incidence of serious nephrotoxicity similar to that reported for alternative products.

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.