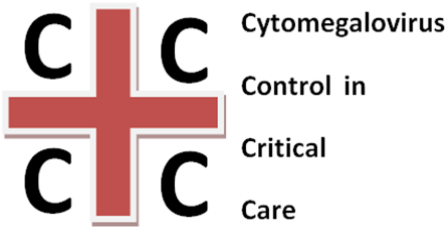

PROJECT TITLE

Anti-viral Prophylaxis for Prevention of Cytomegalovirus (CMV) Reactivation in Immunocompetent Patients in Critical Care

STUDY ACRONYM

Cytomegalovirus Control in Critical Care - CCCC

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Substantial Amendment Sept 18th 2013

On Sept 18th 2013 the Data Monitoring Committee recommended termination of recruitment to the Val/acyclovir arm of the study because of a statistically significantly higher mortality in this group which could not be explained by severity of illness or age. The opinion of the DMC is that the main imbalance resides in the control arm which has a much lower than expected mortality. However, given the relatively small scale of this pilot proof-of-concept study, continuing recruitment to the acyclovir arm is most unlikely to correct this imbalance.

The trial will therefore continue with one active treatment arm – val/ganciclovir.

The analytical plan will compare active treatment (both arms) with control, and each treatment arm with control, for the primary outcome (suppression of CMV reactivation) as previously envisaged. However, the power of the study for the Val/acyclovir arm alone is substantially reduced.

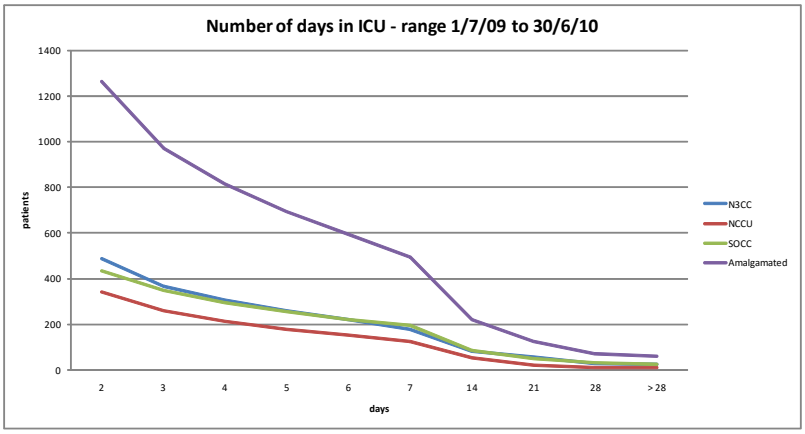
The patient information sheets have been modified accordingly to reflect the single active treatment arm.

As the analysis will retain the option to compare the two antiviral regimens we have inserted this substantial amendment notification here rather than alter the whole protocol.

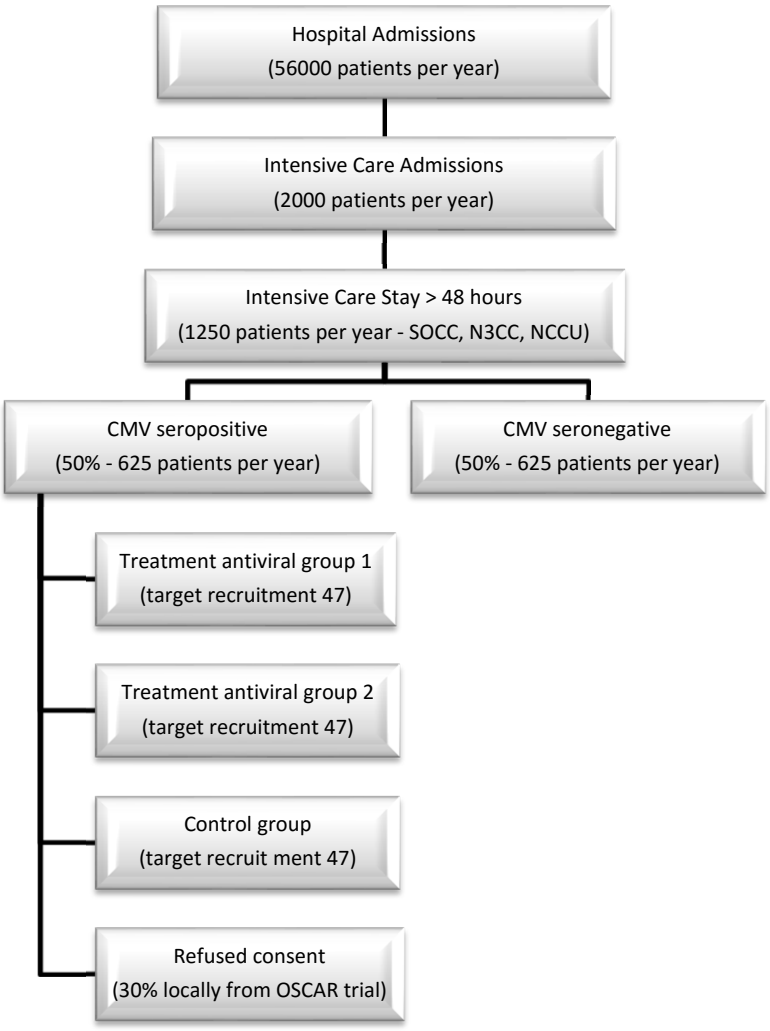
1 SUMMARY OF TRIAL DESIGN

Title	Anti-viral prophylaxis for prevention of cytomegalovirus (CMV) reactivation in immunocompetent patients in critical care
Acronym	CCCC – Cytomegalovirus Control in Critical Care
Design	Single centre, open label , randomised controlled trial
Aim	To evaluate suppression of CMV reactivation using antiviral medication in critically ill patients, compared to usual care
Primary Endpoint	Time to reactivation of CMV PCR
Secondary Endpoints	• CMV outcome measures – Time to reactivation of CMV in urine, throat swab or NDBL at 28 days, Blood secondary outcomes – time to >1000 and 10000 copies per ml, area under curve, peak and initial viral load • IL6, TNF alpha levels (change over time), other herpesviruses • 28 day mortality • Organ Failure free days • Time to ICU discharge • Time to hospital discharge • Safety - Number of SAEs, time to neutropenia (<1.0 $x10^{-9}$/L), time to thrombocytopenia (plt <50 $x10^{-9}$/L), use of GCSF/termination of study drug, plt transfusions, time to renal insufficiency (Cr Cl <30ml/min)
Target accrual	141 patients
Inclusion Criteria	• Total hospital stay at recruitment < 7 days • CMV seropositive • Intensive care stay > 24 hours • Mechanically ventilated, anticipated to continue > 48hrs
Exclusion Criteria	• Age <18 years • Pregnancy or breastfeeding • Known or suspected history of acquired or congenital immunodeficiency • In receipt of immunosuppressive therapy within 30 days, (steroids special case) • In receipt of chemotherapeutic agents within 6 months • Severe neutropenia at screening (<1.0 $x10^{-9}$/L) • Use of systemic antiviral medication within last 7 days (oseltamivir acceptable) • Allergy to study drugs
Anticipated duration of recruitment	one year
Duration of patient follow up	Until hospital discharge or death

2 QEHB ICU Duration of Patient Stay



3 SCHEMA - QEHB PATIENT NUMBERS AVAILABLE FOR RECRUITMENT



4 INTRODUCTION

4.1 CMV latent infection is widespread

Cytomegalovirus is a common herpes virus, and a significant human pathogen. Infection rates vary from country to country, but increase steadily throughout life, with rates around 60% by middle age, increasing to around 90% in the elderly in one North American survey.[1, 2] A British survey of 20,000 pregnant women demonstrated an overall 54% prevalence, with over-representation in Asian and African/Caribbean ethnic groups.[3] Infection is usually mild, and often unnoticed in immunocompetent hosts. After infection, the virus in common with other herpes viruses establishes lifelong latency. Ongoing cell-mediated immunity acts to prevent overt disease unless immunosuppression causes reactivation. Estimates of CMV prevalence in critical care patients can be made from observational studies, and made up 46% of patients in one North American study of 221 patients tested.[4]

4.2 CMV Reactivation

Reactivation of CMV is most frequently seen in patients immunocompromised by HIV infection, solid-organ transplantation, or bone marrow transplantation, as well as those receiving high dose steroids, or other immunosuppressive drugs for autoimmune diseases. CMV disease is a multisystem pathological process, which can affect every organ system, resulting in pyrexia, pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis, and neuropathy. Reactivation of disease may worsen outcome through direct effects of CMV disease, or through an immune modulatory process allowing opportunistic pathogens to proliferate.

4.3 CMV Reactivation in Critical Care

There is an increasing body of evidence linking CMV reactivation with adverse outcomes in patients without known immunosuppressive processes in the critical care setting. A number of observational studies have demonstrated that a third of CMV seropositive critically ill patients will reactivate latent CMV infection.[4-10] A clear association has been established between CMV reactivation and duration of hospital stay and death, with around a doubling in mortality statistics for these patients (see Appendix Three). Numerous mechanisms have been proposed to explain this worsened outcome. CMV end organ disease is not always demonstrated despite reactivation, so although it is likely to contribute to the excess mortality, other mechanisms may be responsible for the worse outcome.

4.4 The Proposed Research is Widely Supported by Experts in the Intensive Care Community

At least four research groups have independently called for interventional studies of antiviral agents to determine whether the suppression of CMV reactivation in critically ill patients would improve their outcome.[4, 9, 11, 12] Numerous editorials in respected intensive care journals have discussed

CMV reactivation, and identified the urgent need to establish the benefit of viral suppression. [13-15] However, no interventional studies have been registered on the clinical trials register to date.

4.5 Evidence for Use of Antivirals to Suppress CMV

There is a large amount of data on the use of antivirals following immunosuppression regimes after solid organ transplantation and stem cell transplantation for haematological malignancy.[16-20] Comparisons have been made between prophylaxis regimens and pre-emptive therapy where treatment is initiated following detection of CMV viraemia before symptomatic CMV disease develops.[18, 20, 21] Both strategies have demonstrable benefit in these groups of patients, each with advantages and disadvantages. Prophylaxis has demonstrated higher levels of side effects than pre-emptive therapy, but effective CMV suppression.[18] Pre-emptive therapy has lower incidence of side effects, perhaps because of the shorter duration of exposure but this approach can lead to treatment delay because of time lag caused by sampling intervals, and sample analysis. Furthermore, CMV end organ disease has been demonstrated in the absence of detectable viral PCR.[22, 23] The prophylaxis strategy is more effective in patient groups at high risk of reactivation, and is therefore seen as particularly suitable to critical care patients preselected as high risk. The onset of treatment for viral reactivation is likely to be time critical in these patients, making a potential time lag of one week between reactivation and its identification unacceptable. Furthermore, it is not clear whether the potential benefit in critical care patients is from prevention of immune modulation caused by CMV reactivation, rather than prevention of clinical CMV disease. CMV end organ disease is not always demonstrated despite reactivation, so although likely to contribute to the excess mortality, other mechanisms may be responsible for the worse outcome. One hypothesis is that the stimuli for CMV reactivation include the proinflammatory cytokines TNF and Interferon; a mechanism for harm might be the persistence of the inflammatory state and associated organ dysfunction. [24]

4.6 Antivirals Effective Against CMV

A number of antiviral agents are available with activity against CMV. There is no human, and limited animal[25, 26] data demonstrating their utility as prophylaxis, or as treatment to critical care patients. In the absence of this information, data from immunosuppressed patients must be used to judge antiviral efficacy.

- Ganciclovir has very good activity against CMV, and is often used as the treatment of choice for CMV infection.[17, 18, 27] It has a significant incidence of side effects (Appendix 1), including renal and haematological toxicity, which has not prevented its use an agent for prophylaxis. It has however, poor oral bioavailability, and so is most effective intravenously.
- Valganciclovir, a prodrug of ganciclovir, has oral bioavailability similar to that on intravenous ganciclovir, [28] making it the current favoured drug for long term prophylaxis in immunosuppressed patients. There is increasing evidence for low doses of valganciclovir for effective prophylaxis, minimising the risk of harmful side effects. [29-34]
- Aciclovir, a drug with relatively few side effects, has been used for prophylaxis for some years, with efficacy against CMV when used intravenously at high dosage.[18] It has

demonstrated poor efficacy against CMV in low or moderate dosage. It has poor oral bioavailability and cannot therefore be recommended for us as an oral preparation.

- Valaciclovir has a similar side effect profile to acyclovir, but has good oral bioavailability, and has proven efficacy when used in high dosage as prophylaxis for renal transplant recipients,[35, 36] and following bone marrow transplant,[27] with few side effects despite the high dose required to suppress CMV. [35] Side effects and incidence rates are listed in appendix 2.
- Other agents with good activity against CMV include Focarnet, and Cidofovir. Unfortunately these drugs have a very poor side effect profile making them unsuitable for prophylaxis in this group of patients.

4.7 Acceptable Tolerability and Side Effects

The administration of these drugs as prophylaxis against CMV infection in high risk groups has been well established. These drugs however are associated with significant side effects. The drugs with most potent activity against CMV are also associated with highest incidence of side effects. Most significantly, their administration can lead to haematological side effects including pancytonenia, and renal impairment. The reasons that we believe these drugs will be well tolerated in the Intensive care setting are:

- Patients currently taking prophylaxis for immunosuppression associated with transplant will take these drugs for up to six months, whereas we expect the duration of risk on the intensive care to last for a much shorter period, of on average two weeks.
- We expect to be able to provide effective CMV suppression in this group of patients using drugs with the least side effects, or in low dosage.
- Side effects requiring therapy or discontinuation of antiviral medication will be identifiable in the intensive care unit in a shorter timeframe than in an outpatient setting, where these drugs are often used.

4.8 Choice of Antiviral and Dosing for CMV Prophylaxis in Critical Care

None of these drugs is ideal for use in critical care patients. A compromise has to be made between clinical efficacy, ease of administration, and side effect profile. The ability to determine whether side effects are drug related, or caused by the underlying disease process will be extremely difficult in this group of patients. For this reason, the study group has elected to use two treatment strategies known to minimise the potential for adverse events, and to compare the relative efficacy of each treatment strategy in the critical care population.

- High dose Valaciclovir, effective against CMV, with a favourable side effect profile. It is anticipated that a proportion of patients will not absorb drugs enterally, as critical illness can cause gastroparesis. In this situation, acyclovir, the parent compound of valaciclovir, which can be administered intravenously, will be administered in high dosage, until enteral absorption is established.
- Low dose Valganciclovir, effective against CMV, with an acceptable side effect profile at this reduced dose. Again, for those unable to absorb enterally, the parent compound ganciclovir will be used, also in low dosage, until enteral absorption is established.

5 TRIAL DESIGN

5.1 Research Question

Does antiviral prophylaxis prevent viral reactivation of latent CMV in immunocompetent critically ill patients?

5.2 Trial Summary

This is a prospective, randomised, open-label single centre study. Patients admitted to the Queen Elizabeth Hospital Birmingham Critical Care Unit (ICU), and identified by study criteria to be at high risk of CMV reactivation will be assessed for inclusion into the study. Blood will be analysed for CMV antibodies to establish past infection, and those patients positive for CMV past infection will be eligible for recruitment into the interventional arm of the study. Recruited patients will be randomised to receive high dose aciclovir/valaciclovir, or low dose ganciclovir/valganciclovir for the duration of their ICU stay, for a minimum of 14 days, and a maximum of 28 days, or to enter the control group. CMV negative patients will not be eligible for inclusion into the interventional arm of the study, although mortality and length of stay information will be collected.

5.3 CMV negative Patients

Patients testing negative for CMV will receive no intervention. No patient identifiers will be retained. Outcome data is currently collected nationally on intensive care patients by the ICNARC national case mix programme, and this will be used to correlate CMV status with outcome.

5.4 Interventional Arm of Study

5.4.1 Research Objective

To determine the impact of preventing CMV reactivation in critically-ill patients.

5.4.2 Trial Objectives

- Identify patients on the critical care unit with CMV antibodies.
- To identify whether treatment of high risk patients with past CMV infection with prophylactic antiviral medication will lead to suppression of CMV viral load in comparison to untreated controls.
- To identify which antiviral drug regimen, using protocols to avoid side effects, provides most effective CMV suppression.
- To use study design and initial data collected from this pilot as a template for the initiation of large national multicentre study to identify any reduction in mortality or hospital length of stay from suppression of CMV in this group of patients in comparison to untreated controls.

5.4.3 Outcome Measures for Efficacy

5.4.3.1 Primary Outcome

- Time to reactivation of blood CMV PCR (defined as above the lower limit of sample assay (28 days).

In the event of patient discharge from hospital or death, the results will be censored at the most proximate blood CMV PCR sample point.

5.4.3.2 Secondary Outcomes

- CMV PCR secondary outcome measures in blood urine, throat swab or NDBL over 28 day period of data collection
    - Time to reactivation of CMV PCR defined as above the lower limit of sample assay (blood values used for primary outcome)
    - time to >1000 and >10000 copies per ml
    - area under the curve
    - peak and initial viral load

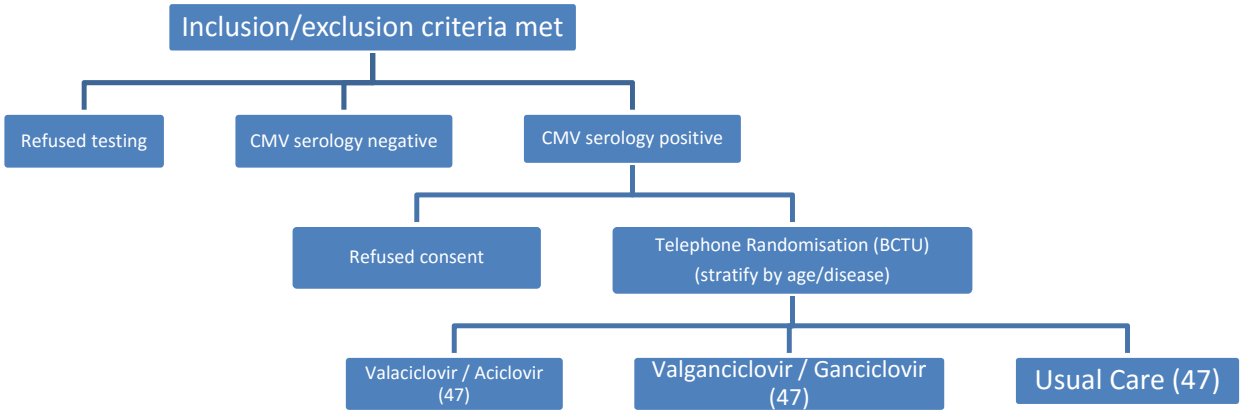
In the event of patient discharge from hospital, death, (or tracheal extubation in the case of NDBL) the results will be censored at the most proximate CMV PCR sample point.

- Markers of inflammation
    - IL6, TNF alpha levels (change between day 0 and day 14/day 28), other herpesviruses (HSV)
- Clinical Outcomes
    - 28 day mortality
    - Organ Failure free (SOFA<2) days, moderate organ dysfunction (SOFA<5) free days by day 28
    - Time to ICU discharge (up to 3 months)
    - Time to hospital discharge (up to 3 months)

5.4.4 Outcome Measures for Safety

- Number of serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs)
- time to neutropenia (count <1.0 $x10^{-9}$/L) over 28 days
- time to thrombocytopenia (plt <50 $x10^{-9}$/L) over 28 days
- Use of GCSF/termination of study drug over 28 days
- Number of platelet transfusions over 28 days
- time to renal insufficiency (Cr Cl <60ml/min, <30ml/min, need for heamodialysis/haemofiltration) over 28 days

5.5 Flow Diagram of Trial



Criteria for premature cessation of study drug:

Withdrawal of consent (patient or NOK) – data collected to point of withdrawal analysed with consent

Requirement for G-CSF to stimulate BM

Neutropenia <1.0 x10-9/L

SAE/SUSAR

5.6 Inclusion Criteria

Total hospital stay of less than 7 days

- This study aims to assess prophylaxis to prevent CMV reactivation. Patients screened for inclusion will include those hospitalised for less than 7 days prior to admission to critical care in order to minimise the inclusion of patients admitted late on in their disease process, with pre-existing critical illness CMV reactivation. Patients deemed clinically well on a rehabilitation/respite ward within the time prior to admission to critical care may be included.

CMV seropositive

- Patients testing CMV positive only will be approached for inclusion in the interventional arm of the study. Patients testing CMV negative will enter the observational arm of the study, and no patient identifiers will be retained.

ICU stay of >24 hours

- Patient recruitment will be deferred until the end of a 24 period on the ICU. This period is essential in order to develop a rapport with the patient and family as part of the consent process, to obtain results of CMV status assays, and to make an assessment regarding suitability of the patient for inclusion in the study.

Mechanically ventilated, anticipated to continue for > 48 hours

- In order to minimise the numbers of patients receiving therapy unnecessarily, and maximise the likelihood of identifying a clinical effect, the study group selects patients with higher risk of reactivation based on previous publications.

5.7 Exclusion Criteria

Age <18 years

Known Pregnancy or breast feeding (negative pregnancy test prior to recruitment in female patients of child bearing age (16-60)

Expected to survive less than 48 hours

Confirmed immunosuppression

- Known or suspected Human Immunodeficiency Virus infection
- Known or suspected underlying immunodeficiency (organ transplantation including stem cell transplantation on immunosuppression, congenital immunodeficiency, in receipt of immunosuppressive medication e.g. azathioprine, methotrexate, tacrolimus, cyclosporine, sirolimus, cyclophosphamide within 30 days)
    - Corticosteroids: Prednisolone chronic administration may be used up to a dose of 10mg/day on average over the preceding 30 days, stress dose hydrocortisone (up to 400mg/day) may be used, topical steroids may be used, short duration of higher

dose steroids for exacerbations of COPD up to 1mg/kg prednisolone or equivalent are permitted for up to 14 days

- Receipt of chemotherapeutic agent within the last 6 months

Use of systemic antiviral medication within the last 7 days. Oseltamivir, frequently used in critically ill patients as empirical or focused therapy for H1N1 has no activity against CMV, and so will not prevent inclusion.

Severe neutropenia (neutophil count <1.0 $x10^{-9}$/L)

Allergy to study drugs

5.8 Informed Consent

Those patients testing positive for CMV will be eligible to enter the interventional part of the trial will undergo a process of consent.

5.8.1 Obtaining informed consent from participants

Once eligibility has been confirmed and, if the patient is competent to give informed consent, authorised staff will describe the proposed study, in both oral and written format. Patients will be made aware of the potential risks and benefits. After the doctor or nurse has checked that the patient has fully understood, the doctor or nurse will invite the patient to sign the form and will then add their own name and countersign it. Previous work on informed consent in critically-ill patients indicated that only a minority (2.5%) may be able to provide informed consent. It will be essential to have robust plans in place for situations in which informed consent is not possible.

5.8.2 Proposed action where fully informed consent is not possible

If the patient is not competent to give informed consent and there is a Personal legal representative (PeLR) present (usually next of kin) to give consent on the presumed wishes on the patient, authorised staff will describe the proposed study to the patient's PeLR. After the doctor or nurse has checked that the PeLR consent form is understood, the doctor or nurse will invite the PeLR to sign the form, and will then add their own name and countersign it. If there is no PeLR present, then the patient will be provided with a Professional Legal Representative (PrLR), which will be the consultant responsible for the care of the patient in critical care (not connected with the conduct of the trial), or a consultant delegated by him/her (not connected with the conduct of the trial). Informed consent for the PrLR will be addressed in the same manner as for the PeLR.

5.8.3 Retrospective Patient Information

If the patient regains capacity, then they will be informed of their inclusion and the details of the trial. The responsible clinician will discuss the study with the patient and the patient will be given a copy of the patient information sheet. The patient will be asked for consent to participate in the trial and to sign the Consent to Continue Form. If the patient does not give consent, data collected about the patient will not be entered into analysis.

5.8.4 Withdrawal of Consent

Patients, or their legal representatives, may withdraw or be withdrawn from the trial at any time. Data recorded until the time of withdrawal will be included in the trial analysis. If patient or legal

representative requests termination of study drug at any point in the trial, it will be stopped, and the patient will continue to be followed up as part of the trial. If consent is withdrawn at any time during the trial, the study drug will be stopped, and permission sought to continue to collect data.

5.9 Randomisation Procedure

Patients meeting criteria for trial inclusion, and testing CMV positive, will undergo randomisation by the Birmingham Clinical Trials unit stratified by age and disease severity. At the time of randomisation, each patient will be allocated a unique patient trial number which will be used throughout the trial for patient identification.

5.10 Trial Treatment Group 1

5.10.1 Randomised to receive Valaciclovir/Aciclovir

Patients will be randomised to receive 2g valaciclovir, four times a day, by enteral route. Treatment will be initiated immediately following inclusion into the study, and continue for a period of 28 days, or until discharge from the ICU, but for a minimum of 14 days. Treatment dosing will be modified in the presence of renal failure to prevent accumulation of study drug using the algorithm below.

5.10.2 Intravenous Aciclovir

Patients unable to receive enteral nutrition (usually because of gastroparesis secondary to critical illness) will receive intravenous aciclovir 10mg/kg three times a day, and changed to enteral valaciclovir when enteral absorption is established.

5.11 Trial Treatment Group 2

5.11.1 Randomised to receive Valganciclovir/Ganciclovir

Patients will be randomised to receive 450mg valganciclovir, once a day, by enteral route. Treatment will be initiated immediately following inclusion into the study, and continue for a period of 28 days, or until discharge from the ICU, but for a minimum of 14 days. Treatment dosing will be modified in the presence of renal failure to prevent accumulation of study drug using the algorithm below.

5.11.2 Intravenous Gancilcovir

Patients unable to receive enteral medication will receive intravenous ganciclovir 2.5mg/kg once a day, and changed to enteral valganciclovir when enteral absorption is established.

5.12 Study Drug Dose Adjustment in Renal Failure

CrCl (ml/min)	Valaciclovir	Aciclovir	Valganciclovir	Ganciclovir
>75	2g qds	10mg/kg tds	450mg od	2.5mg/kg od
51-75	1.5g qds	10mg/kg tds	450mg alt days	1.25mg/kg od
26-50	1.5g tds	10mg/kg bd	450mg twice weekly	0.625mg/kg od
10-25	1.5g bd	10mg/kg od	225mg twice weekly	0.625mg/kg alt days
<10 HD	1.5g od	5mg/kg od	225 mg after HD	0.625mg/kg after HD
<10 CVVH	1.5g od	5mg/kg od	225mg twice weekly	0.625mg/kg od

CVVH = Continuous venovenous haemofiltration, HD = haemodialysis, GFR = Glomerular filtration rate

See summary of product characteristics

5.13 Trial Control Group – Randomised not to receive antiviral therapy

Patients will undergo identical care to those in the treatment arm, other than receipt of trial drugs. Neither arm of the study will have access to CMV viral PCR levels taken as part of the study, which will be block processed in a non-clinically useful timeframe. Antiviral medication may be initiated by the critical care team overseeing the patient care if this is deemed necessary for therapeutic reasons, and the patients will be analysed on an intention to treat basis.

5.14 Monitoring for Drug Related Side Effects

Patients will undergo at least alternate daily blood tests as part of their standard care in the ICU. These tests will be monitored by the study team for evidence of drug related side effects, in particular renal and haematological toxicity. Many of the side effects of the study drug may be confused with pathology caused by critical illness. An open label study design will increase the ability of the study personnel and clinical staff to make reasoned decisions about the likely cause of systemic effects that may be attributable to the study drug. Significant concerns by study personnel or the consultant clinician overseeing the patients care will lead to drug discontinuation, and subsequent analysis on an intention to treat basis.

5.15 Assessments

5.15.1 Patient Details

- Identifiers, Socio-demographics
- Co-morbidities

5.15.2 Recruitment Data

- Date of hospital Admission
- Date of Admission of ICU
- Inclusion/exclusion criteria
- Date met inclusion criteria
- Date Randomised

5.15.3 Critical Care Data

- Diagnosis
- Admission APACHE II score
- Critical care organ support/SOFA score
- Requirement for blood products
- Total ICU days (date of discharge)
- Renal and Haematological blood results

5.15.4 Treatment Data

- Date and time treatment initiated
- Dosing achieved throughout trial period
- Record of any modification to treatment dosing/treatment withdrawal including reason
- Record of systemic antivirals used outside of the study protocol

5.15.5 Monitoring

- Initial CMV serology
- Quantitative CMV PCR at enrolment and every 5 days on blood, urine, and throat swabs for the 28 day study period.
- Non directed bronchiolar lavage (NDBL) sampling for CMV PCR at enrolment and every 5 days whilst intubated on ICU.

- Samples are stored for later assessment for reactivation of other herpesviruses (samples collected at same time as those for CMV PCR) The immune response to herpesviruses, in particular the CD4+ and CD8+ T cell and humoral antibody response will be measured using functional T Cell assays and ELISA. Inflammatory markers will be measured including IL-6, TNF-alpha.

5.15.6 Hospital Data

- Date and time of hospital discharge
- Discharge location
- 28 days from randomisation survival status

5.16 Data Management

Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 1998.

5.17 Trial Monitoring and Adverse Event Management

5.17.1 Adverse Events

Defined as any untoward medical occurrence or effect in a patient treated with the trial drug, which does not necessarily have a causal relationship with trial treatment.

The following are expected adverse events, which may or may not be caused by the trial drugs, and will be included as part of the safety analysis for the trial and do not need to be reported separately:

- Severe thrombocytopenia (<50, <25 $x10^{-9}$/L)
- Neutropenia (<1.0 $x10^{-9}$/L) – Criterion to terminate trial drug
- Requirement for G-CSF – Criterion to terminate trial drug
- Requirement for blood products (other than red blood cells)
- Renal failure – (CrCl <60, CrCl <30, use of haemodialysis/haemofiltration)
- Discontinuation of trial drugs (with reason recorded)

5.17.2 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SAE is defined as an adverse event that fulfils one or more of the following criteria:

1 Results in death
2 Is immediately life threatening
3 Requires hospitalisation or prolongation of existing hospitalisation
4 Results in persistent or significant disability or incapacity
5 Results in congenital abnormality or birth defect
6 Requires medical intervention to prevent one of the above, or is otherwise considered medically significant.

SUSARs are SAEs that are also unexpected (their nature is not consistent with the Summary of Product Characteristics), and considered to be caused by the study drug.

As the recruiting population for the study population are already in a life-threatening situation, it is expected that many study participants will experience SAEs as a result of the underlying medical condition. Events expected in the study population, also collected as outcomes of the trial including death and organ failure, should not be reported as SAEs.

The following events should be reported:

- Unexpected SAEs (SUSARs)
- Side effects of the study drugs sufficiently severe to be fatal or life threatening.

5.17.3 Reporting Procedures of SAEs and SUSARs

The researcher identifying the SAEs and SUSARs will report to the principal investigator within 24 hours of becoming aware of them. The principal investigator will produce a full report using the SAE form, and report the events to the sponsor, ethics committee and MHRA within the required timelines. The principal investigator's assessment of causality of SAEs (i.e. their relationship to trial treatment) will be reported on the Serious Adverse Event form.

5.18 Trial Closure

The end of the trial will be when the final patient 28 day mortality or hospital discharge data has been collected.

6 DATA ANALYSIS

6.1 Primary Outcome

The primary outcome measure for therapeutic efficacy will be the time to reactivation of CMV in blood by quantitative PCR to below the limits of assay detection by day 28. In the event of patient discharge from hospital or death, the results will be censored at the most proximate blood CMV PCR sample point

All analyses will be performed using the intention to treat principle

Baseline covariates will be compared between the two arms to observe balance and the success of randomisation.

The primary analysis will test the hypothesis that there is no difference in time to CMV reactivation between those CMV seropositive patients receiving antiviral prophylaxis compared with those receiving usual treatment.

The primary analysis will be performed unadjusted, and repeated adjusted for baseline covariates using logistic regression. Differences in treatments will be determined using Cox proportional-hazards regression analysis. Values of $p<0.05$ will be considered statistically significant.

6.2 Secondary Outcomes

Secondary outcome measures will be:

- CMV PCR secondary outcome measures in blood urine, throat swab or NDBL over 28 day period of data collection
    - Time to reactivation of CMV PCR defined as above the lower limit of sample assay (blood values used for primary outcome)
    - time to >1000 and >10000 copies per ml
    - area under the curve
    - peak and initial viral load

In the event of patient discharge from hospital, death, (or tracheal extubation in the case of NDBL) the results will be censored at the most proximate CMV PCR sample point.

- Markers of inflammation
    - IL6, TNF alpha levels (change in assay between day 0 and day 14/day 28), other herpesviruses (e.g. HSV)

CLINICAL OUTCOMES

- Mortality at 28 days
- Organ Failure free (SOFA<2) days, moderate organ dysfunction (SOFA<5) free days at day 28
- Time to discharge from the ICU (cut off 3 months)
- Time to discharge from hospital (cut off 3 months)

SAFETY OUTCOMES

- Number of serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs)
- time to neutropenia (count <1.0 $x10^{-9}$/L)
- time to thrombocytopenia (plt <50 $x10^{-9}$/L)
- Use of GCSF/termination of study drug
- Number of platelet transfusions
- time to renal insufficiency (Cr Cl <60ml/min, <30ml/min, need for heamodialysis/haemofiltration)

This study will not be powered to detect a change in mortality or time to discharge, although a larger trial is anticipated following this feasibility study with mortality data as a primary outcome. In view of the heterogeneous nature of intensive care units, it is often difficult to demonstrate mortality differences without unacceptably large sample sizes. For this reason, organ failure free days have been used as a more sensitive way to identify differences between groups. [37] [38] We will use the Sequential Organ Failure Assessment (SOFA) score as a tool to collect organ failure data, using a score of <5 to determine 'relatively good health' as used in other similar methods of analysis, and the absence of any component score >2 to indicate absence of organ failure. Non-survivors will be placed in to the organ failure group for the purposes of analysis. Patients discharged to the ward

will retain their discharge SOFA score for the purposes of analysis. These data, along with mortality data will be collected to ensure accurate data capture methods for the larger trial, and to allow inclusion of pilot data into larger trial.

6.3 Sample Size Calculation

Although this is a pilot study, and so strictly speaking, a sample size calculation is not necessary, it has been performed in order to assess whether the chosen primary outcome variable is likely to reach statistical significance.

The estimated sample size is 141 patients. 47 patients in each treatment arm, and 47 patients in the control arm. This is based on a power of 90%, and a p value of 0.05.

Observational studies have identified that approximately one third of patients in high risk groups reactivate CMV infection in the intensive care. Information on similar dosing regimens for antiviral prophylaxis in immunosuppressed patients have demonstrated over 90% suppression of CMV reactivation. Our sample size is powered to detect a difference in CMV reactivation from 30% in control group to 5% in treatment group.

It is anticipated that this pilot study will lead to a large multicentre trial to detect any clinical benefit of antiviral CMV suppression in critically ill patients. This pilot study will serve to establish drug efficacy and safety in the intensive care population, and facilitate accurate sample size calculation in a large study powered to clinical endpoints.

7 Ethical and Regulatory Compliance

An application has been made to the Integrated Research Application System (IRAS) for ethical approval of the research. The study will not commence until approval has been granted.

8 Risks and anticipated benefits for trial participants and society

Despite increasing evidence confirming the high incidence of and poor outcome in patients with CMV reactivation in the ICU, there is as yet no evidence assessing whether antiviral prophylaxis to prevent reactivation is possible or clinically effective. Testing for CMV reactivation, and consequently treatment with antivirals is currently not usual practice. There is a risk that in the face of lack of evidence, clinicians will begin to initiate antiviral therapy without clinical evidence to back up their decisions, or continue to not treat patients that may potentially benefit. It is for this reason that it essential to perform a clinical trial of this kind, in order to prove or disprove their utility for future patient benefit.

Subjects in this study have the potential for direct benefit from the treatment intervention, although there is always a consequent risk of side effects from administered medications. This risk has been minimised by using the antiviral agent with fewest side effects, with acceptable CMV antiviral activity. Subjects outside of the treatment arm would not under normal circumstances undergo routine testing or treatment for CMV reactivation in this institution, and therefore their treatment will be in no way affected.

9 Drug and CMV PCR Assay Costings

Assumptions: total recruitment 150 patients (70kg) - 47 GCV/VGCV arm, 47 ACV/VACV arm, 47 control arm. Assume no renal dose reduction. Estimate 50% usage of IV preparation. Estimate average of 2 weeks stay on ICU post recruitment. CMV PCR testing twice weekly for three weeks, including on recruitment, and one week post discharge.

Drug Costs

Drug	Dose	Cost per day ex vat	Cost for 2 weeks ex vat	Cost for study ex VAT	Cost inc VAT
Valaciclovir tablet	2g qds	4.64	64.96	3248	3897.6
Aciclovir IV solution	10mg/kg tds	21.6	302.4	15120	18144
Ganciclovir IV solution	2.5mg/kg od	27	378	18900	22680
Valganciclovir (enteral soln)	450mg od	21.14	470	23500	28200
Valganciclovir (tablets)	450mg od	17.91	251		
cost using all oral meds				26748	32097.6
cost using all iv meds				34020	40824
cost assuming 50% iv 50% oral				**30384**	**36460.8**

CMV PCR Costs

	cost each	cost per pt	requested costs
CMV Ig Assay	5	5	2250
blood CMV PCR test	16	128	18816
urine/sputum/throat PCR test (twice weekly)	16	384	56448
total		**517**	**77514**

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11 APPENDICES

11.1 Appendix One - common side effects ganciclovir/valganciclovir

Very common >1/10

Neutropenia, anaemia

Dyspnoea

Diarrhoea

Common >1/100, <1/10

Cr clearance decreased, renal impairment (renal failure uncommon >1:1000, <1/100)

Thrombocytopenia, leucopenia, pancytopenia

Sepsis, cellulitis, uti, oral candida

Anorexia

Depression/anxiety/confusion/abn thinking

Headache, insomnia, taste disturbance, hypoaesthesia, paraesthesia, periph neuropathy, convulsions, dizziness

Macular oedema, retinal detachment, eye pain, vitreous floaters

Ear pain

Cough

N&v, abdo pain

Hepatic function abnormalities

Dermatitis, sweats, pruritis

Back pain, myalgia, arthralgia, cramps

Fatigue, pyrexia, rigors, pain, inj site rxn

11.2 Appendix Two - common and rare side effects of acyclovir/valaciclovir

Very common >1/10

Headache

Common >1/100, <1/10

N&V, diarrhoea

Dizziness

Rashes, pruritis

Uncommon >1/1000, <1/100

Leucopenia, thrombocytopenia (leucopenia mainly in immune-compromised pts)

Confusion, hallucinations, decreased LOC, tremor, agitation

Dyspnoea

Abdominal discomfort

Reversible increase in liver function tests

Urticaria

Renal pain

Rare <1:1000, >1/10000

Renal impairment, ARF (esp elderly or pre-existing renal impt on high doses

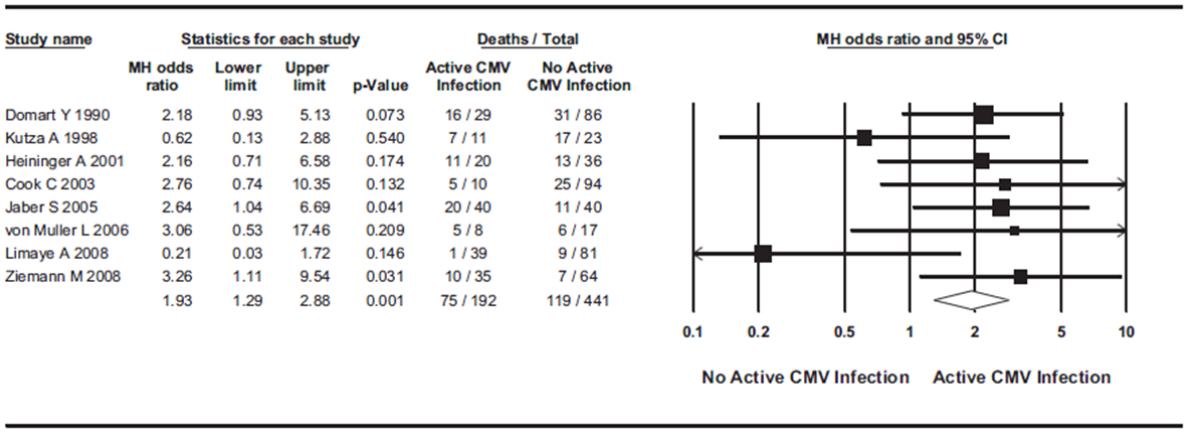
Angioedema

Ataxia, dysarthria, convulsions, encephalopathy, coma, psychosis

anaphylaxis

11.3 Appendix Three

Active CMV infection: All Cause Mortality



Study name	MH odds ratio	Lower limit	Upper limit	p-Value	Active CMV Infection	No Active CMV Infection
Domart Y 1990	2.18	0.93	5.13	0.073	16 / 29	31 / 86
Kutza A 1998	0.62	0.13	2.88	0.540	7 / 11	17 / 23
Heininger A 2001	2.16	0.71	6.58	0.174	11 / 20	13 / 36
Cook C 2003	2.76	0.74	10.35	0.132	5 / 10	25 / 94
Jaber S 2005	2.64	1.04	6.69	0.041	20 / 40	11 / 40
von Muller L 2006	3.06	0.53	17.46	0.209	5 / 8	6 / 17
Limaye A 2008	0.21	0.03	1.72	0.146	1 / 39	9 / 81
Ziemann M 2008	3.26	1.11	9.54	0.031	10 / 35	7 / 64
	1.93	1.29	2.88	0.001	75 / 192	119 / 441

Figure taken from [11]

11.4 Appendix Four - Summary of Product Characteristics –Trial Drugs

11.4.1 Valaciclovir (enteral)

1. NAME OF THE MEDICINAL PRODUCT

Valtrex 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

500 mg tablet

White, biconvex, elongated tablet with a white to off-white core, engraved "GX CF1" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Varicella zoster virus (VZV) infections – herpes zoster

Valtrex is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (see sections 4.4).

Valtrex is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression (see section 4.4).

Herpes simplex virus (HSV) infections

Valtrex is indicated

• for the treatment and suppression of HSV infections of the skin and mucous membranes including

- treatment of first-episode of genital herpes in immunocompetent adults and adolescents and in immunocompromised adults

- treatment of recurrences of genital herpes in immunocompetent adults and adolescents, and in immunocompromised adults

- suppression of recurrent genital herpes in immunocompetent adults and adolescents and in immunocompromised adults

• Treatment and suppression of recurrent ocular HSV infections (see section 4.4)

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1).

Cytomegalovirus (CMV) infections:

Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents (see section 4.4)

4.2 Posology and method of administration

Varicella zoster virus (VZV) infections – herpes zoster and ophthalmic zoster

Patients should be advised to start treatment as soon as possible after a diagnosis of herpes zoster. There are no data on treatment started more than 72 hours after onset of the zoster rash.

Immunocompetent Adults

The dose in immunocompetent patientsis 1000 mg three times daily for seven days (3000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).

Immunocompromised Adults

The dose in immunocompromised patients is 1000 mg three times daily for at least seven days (3000 mg total daily dose) and for 2 days following crusting of lesions. This dose should be reduced according to creatinine clearance (see Renal impairment below).

In immunocompromised patients, antiviral treatment is suggested for patients presenting within one week of vesicle formation or at any time before full crusting of lesions.

Treatment of herpes simplex virus (HSV) infections in adults and adolescents (≥ 12 years)

Immunocompetent Adults and Adolescents (≥ 12 years)

The dose is 500 mg of Valtrex to be taken twice daily (1000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).

For recurrent episodes, treatment should be for three to five days. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately upon appearance of the first signs or symptoms. Valtrex can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.

Herpes labialis

For herpes labialis (cold sores), valaciclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents. The second dose should be taken about 12 h (no sooner than 6 h) after the first dose. This dose should be reduced according to creatinine clearance (see Renal impairment below). When using this dosing regimen, treatment should not exceed one day, since this has been shown not to provide additional clinical benefit. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).

Immunocompromised Adults

For the treatment of HSV in immunocompromised adults, the dosage is 1000 mg twice daily for at least 5 days, following assessment of the severity of the clinical condition and immunological status of the patient. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. This dose should be reduced according to creatinine clearance (see Renal impairment below). For maximum clinical benefit, the treatment should be started within 48 hours. A strict monitoring of the evolution of lesions is advised.

Suppression of recurrences of herpes simplex virus (HSV) infections in adults and adolescents (≥ 12 years)

Immunocompetent Adults and Adolescents (≥ 12 years)

The dose is 500 mg of Valtrex to be taken once daily. Some patients with very frequent recurrences (≥ 10/year in absence of therapy) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg twice daily). This dose should be reduced according to creatinine clearance (see Renal impairment below).Treatment should be re-evaluated after 6 to 12 months of therapy.

Immunocompromised Adults

The dose is 500 mg of Valtrex twice daily. This dose should be reduced according to creatinine clearance (see Renal impairment below). Treatment should be re-evaluated after 6 to 12 months of therapy.

Prophylaxis of cytomegalovirus (CMV) infection and disease in adults and adolescents (≥ 12 years)

The dosage of Valtrex is 2000 mg four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance (see Renal impairment below).

The duration of treatment will usually be 90 days, but may need to be extended in high-risk patients.

Special populations

Children

The efficacy of Valtrex in children below the age of 12 years has not been evaluated.

Elderly

The possibility of renal impairment in the elderly must be considered and the dose should be adjusted accordingly (see Renal impairment below). Adequate hydration should be maintained.

Renal impairment

Caution is advised when administering Valtrex to patients with impaired renal function. Adequate hydration should be maintained. The dose of Valtrex should be reduced in patients with impaired renal function as shown in Table 1 below.

In patients on intermittent haemodialysis, the Valtrex dose should be administered after the haemodialysis has been performed. The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after renal transplantation or engraftment. The Valtrex dosage should be adjusted accordingly.

Hepatic impairment

Studies with a 1000 mg dose of valaciclovir in adult patients show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in adult patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dose adjustment; however, clinical experience is limited. For higher doses (4000 mg or more per day), see section 4.4.

Table 1: DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

Therapeutic Indication	**Creatinine Clearance (mL/min)**	**Valaciclovir Dosage** [a]
Varicella-Zoster Virus (VZV) Infections		
Treatment of herpes zoster (shingles) in immunocompetent and immunocompromised adults	≥ 50	1000 mg three times daily
	30 to 49	1000 mg twice daily
	10 to 29	1000 mg once daily
	10	500 mg once daily
Treatment of HSV infections		
- immunocompetent adults and adolescents	≥ 30	500 mg twice daily
	< 30	500 mg once daily
- immunocompromised adults	≥ 30	1000 mg twice daily
	< 30	1000 mg once daily
Treatment of herpes labialis (cold sores) in immunocompetent adults and adolescents *(alternative 1-day regimen)*	≥ 50	2000mg twice in one day
	30 to 49	1000 mg twice in one day
	10 to 29	500 mg twice in one day
	<10	500 mg single dose
Suppression of HSV infections		
- immunocompetent adults and adolescents	≥ 30	500 mg once daily [b]
	< 30	250 mg once daily

- immunocompromised adults	≥ 30 < 30	500 mg twice daily 500 mg once daily
Cytomegalovirus (CMV) Infections		
CMV prophylaxis in solid organ transplant recipients in adults and adolescents	≥ 75 50 to <75 25 to <50 10 to <25 <10 or on dialysis	2000 mg four times daily 1500 mg four times daily 1500 mg three times daily 1500 mg twice daily 1500 mg once daily

[a] For patients on intermittent haemodialysis, the dose should be given after dialysis on dialysis days.

[b]For HSV suppression in immunocompetent subjects with a history of ≥ 10 recurrences/year, better results may be obtained with 250 mg twice daily.

798
799 **4.3 Contraindications**

Hypersensitivity to valaciclovir or aciclovir or any of the excipients (see section 6.1).

800
801 **4.4 Special warnings and precautions for use**

Hydration status

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Use in patients with renal impairment and in elderly patients

Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side-effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Use of higher doses of valaciclovir in hepatic impairment and liver transplantation

There are no data available on the use of higher doses of valaciclovir (4000 mg or more per day) in patients with liver disease. Specific studies of valaciclovir have not been conducted in liver transplantation, and hence caution should be exercised when administering daily doses greater than 4000 mg to these patients.

Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still possible. Therefore, in addition to therapy with valaciclovir, it is recommended that patients use safer sex practices.

Use in ocular HSV infections

Clinical response should be closely monitored in these patients. Consideration should be given to intravenous antiviral

therapy when response to oral therapy is unlikely to be sufficient.

Use in CMV infections

Data on the efficacy of valaciclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMV-positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy) indicate that valaciclovir should only be used in these patients when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).

802
803 **4.5 Interaction with other medicinal products and other forms of interaction**

The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Following 1000 mg valaciclovir, cimetidine and probenecid reduce aciclovir renal clearance and increase the AUC of aciclovir by about 25% and 45%, respectively, by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC by about 65%. Other medicinal products (including e.g. tenofovir) administered concurrently that compete with or inhibit active tubular secretion may increase aciclovir concentrations by this mechanism. Similarly, valaciclovir administration may increase plasma concentrations of the concurrently administered substance.

In patients receiving higher aciclovir exposures from valaciclovir (e.g., at doses for zoster treatment or CMV prophylaxis), caution is required during concurrent administration with drugs which inhibit active renal tubular secretion.

Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate motefil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co ¯ administered. No changes in peak concentrations or AUCs are observed with co-administration of valaciclovir and mycophenolate mofetil in healthy volunteers. There is limited clinical experience with the use of this combination.

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805 **4.6 Pregnancy and lactation**

Pregnancy

A limited amount of data on the use of valaciclovir and a moderate amount of data on the use of aciclovir in pregnancy is available from pregnancy registries (which have documented the pregnancy outcomes in women exposed to valaciclovir or to oral or intravenous aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy, respectively) and postmarketing experience indicate no malformative or foeto/neonatal toxicity. Animal studies do not show reproductive toxicity for valaciclovir (see section 5.3). Valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Breastfeeding

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. However, at therapeutic doses of valaciclovir, no effects on the breastfed newborns/infants are anticipated since the dose ingested by the child is less than 2% of the therapeutic dose of intravenous aciclovir for treatment of neonatal herpes (see Section 5.2). Valaciclovir should be used with caution during breast feeding and only when clinically indicated.

Fertility

Valaciclovir did not affect fertility in rats dosed by the oral route. At high parenteral doses of aciclovir testicular atrophy and aspermatogenesis have been observed in rats and dogs. No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 to 1000 mg aciclovir.

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807 **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of Valtrex should be borne in mind when considering the patient`s ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

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809 **4.8 Undesirable effects**

The most common adverse reactions (ARs) reported in at least one indication by patients treated with Valtrex in clinical trials were headache and nausea. More serious ARs such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure and neurological disorders are discussed in greater detail in other sections of the label.

Undesirable effects are listed below by body system organ class and by frequency.

The following frequency categories are used for classification of adverse effects:

Very common	≥ 1/10,
Common	≥ 1/100 to < 1/10,
Uncommon	≥ 1/1,000 to < 1/100,
Rare	≥ 1/10,000 to < 1/1000,
Very rare	< 1/10,000

Clinical trial data have been used to assign frequency categories to ARs if, in the trials, there was evidence of an association with valaciclovir.

For ARs identified from postmarketing experience, but not observed in clinical trials, the most conservative value of point estimate ("rule of three") has been used to assign the AR frequency category. For ARs identified as associated with valaciclovir from post-marketing experience, and observed in clinical trials, study incidence has been used to assign the AR frequency category. The clinical trial safety database is based on 5855 subjects exposed to valaciclovir in clinical trials covering multiple indications (treatment of herpes zoster, treatment/suppression of genital herpes & treatment of cold sores).

Clinical Trial Data

Nervous system disorders

Very common:	Headache

Gastrointestinal disorders

Common:	Nausea

Post Marketing Data

Blood and lymphatic system disorders

Uncommon:	Leucopenia, thrombocytopenia

Leucopenia is mainly reported in immunocompromised patients.

Immune system disorders

Rare:	Anaphylaxis

Psychiatric and nervous system disorders

Common:	Dizziness
Uncommon:	Confusion, hallucinations, decreased consciousness, tremor, agitation
Rare:	Ataxia, dysarthria, convulsions, encephalopathy, coma, psychotic symptoms.

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8000 mg daily) of Valtrex for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea

Gastrointestinal disorders

Common:	Vomiting, diarrhoea.
Uncommon:	Abdominal discomfort

Hepato-biliary disorders

Uncommon:	Reversible increases in liver function tests (e.g. bilirubin, liver enzymes).

Skin and subcutaneous tissue disorders	
Common:	Rashes including photosensitivity, pruritus. .
Uncommon:	Urticaria
Rare:	Angioedema
Renal and urinary disorders	
Uncommon:	Renal pain
Rare:	Renal impairment, acute renal failure (especially in elderly patients or in patients with renal impairment receiving higher than the recommended doses).

Renal pain may be associated with renal failure.

Intratubular precipitation of aciclovir crystals in the kidney has also been reported. Adequate fluid intake should be ensured during treatment (see section 4.4).

Additional information on special populations

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised adult patients, particularly those with advanced HIV disease, receiving high doses (8000 mg daily) of valaciclovir for prolonged periods in clinical trials. These findings have also been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

4.9 Overdose

Symptoms and Signs

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB11.

Mechanism of action

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue.

Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as valaciclovir hydrolase.

Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus-infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of UL97. This requirement for activation of aciclovir by a virus-specific enzyme largely explains its selectivity.

The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in

obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic effects

Resistance to aciclovir is normally due to a thymidine kinase deficient phenotype which results in a virus which is disadvantaged in the natural host. Reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

Monitoring of clinical HSV and VZV isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent host and is found infrequently in severely immunocompromised individuals e.g. organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

Clinical studies

Varicella Zoster Virus Infection

Valtrex accelerates the resolution of pain: it reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and, in patients older than 50 years, also post-herpetic neuralgia. Valtrex reduces the risk of ocular complications of ophthalmic zoster.

Intravenous therapy generally is considered standard for zoster treatment in immunocompromised patients; however, limited data indicate a clinical benefit of valaciclovir in the treatment of VZV infection (herpes zoster) in certain immunocompromised patients, including those with solid organ cancer, HIV, autoimmune diseases, lymphoma, leukaemia and stem cell transplants.

Herpes Simplex Virus Infection

Valaciclovir for ocular HSV infections should be given according to applicable treatment guidelines.

Studies of valaciclovir treatment and suppression for genital herpes were performed in HIV/HSV coinfected patients. with a median CD4 count of> 100cells/mm3. Valaciclovir 500 mg twice daily was superior to 1000 mg once daily for suppression of symptomatic recurrences Valaciclovir 1000 mg twice daily for treatment of recurrences was comparable to oral aciclovir 200 mg five times daily on herpes episode duration. Valaciclovir has not been studied in patients with severe immune deficiency.

The efficacy of valaciclovir for the treatment of other HSV skin infections has been documented. Valaciclovir has shown efficacy in the treatment of herpes labialis (cold sores), mucositis due to chemotherapy or radiotherapy, HSV reactivation from facial resurfacing, and herpes gladiatorum. Based on historical aciclovir experience, valaciclovir appears to be as effective as aciclovir for the treatment of erythema multiforme, eczema herpeticum and herpetic whitlow.

Valaciclovir has been proven to reduce the risk of transmission of genital herpes in immunocompetent adults when taken as suppressive therapy and combined with safer sex practices. A double blind, placebo controlled study was conducted in 1,484 heterosexual, immunocompetent adult couples discordant for HSV ‾2 infection. Results showed significant reductions in risk of transmission: 75 % (symptomatic HSV ‾2 acquisition), 50 % (HSV ‾2 seroconversion), and 48 % (overall HSV ‾2 acquisition) for valaciclovir compared to placebo. Among subjects participating in a viral shedding sub-study, valaciclovir significantly reduced shedding by 73 % compared to placebo (see section 4.4 for additional information on transmission reduction).

Cytomegalovirus Infection (see section 4.4)

CMV prophylaxis with valaciclovir in subjects receiving solid organ transplantation (kidney, heart) reduces the occurrence of acute graft rejection, opportunistic infections and other herpes virus infections (HSV, VZV). There is no direct comparative study versus valganciclovir to define the optimal therapeutic management of solid organ transplant patients.

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817 **5.2 Pharmacokinetic properties**

Absorption

Valaciclovir is a prodrug of aciclovir. The bioavailability of aciclovir from valaciclovir is about 3.3 to 5.5-fold greater than that historically observed for oral aciclovir. After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by an enzyme isolated from human liver referred to as valaciclovir hydrolase. The bioavailability of aciclovir from 1000 mg valaciclovir is 54%, and is not reduced by food. Valaciclovir pharmacokinetics is not dose-proportional. The rate and extent of absorption decreases

with increasing dose, resulting in a less than proportional increase in Cmax over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Aciclovir pharmacokinetic (PK) parameter estimates following single doses of 250 to 2000 mg valaciclovir to healthy subjects with normal renal function are shown below.

Aciclovir PK Parameter		250 mg (N=15)	500 mg (N=15)	1000 mg (N=15)	2000 mg (N=8)
C_{max}	micrograms/mL	2.20 ± 0.38	3.37 ± 0.95	5.20 ± 1.92	8.30 ± 1.43
T_{max}	hours (h)	0.75 (0.75–1.5)	1.0 (0.75–2.5)	2.0 (0.75–3.0)	2.0 (1.5–3.0)
AUC	h.micrograms/mL	5.50 ± 0.82	11.1 ± 1.75	18.9 ± 4.51	29.5 ± 6.36

C_{max} = peak concentration; T_{max} = time to peak concentration; AUC = area under the concentration-time curve. Values for C_{max} and AUC denote mean ± standard deviation. Values for T_{max} denote median and range.

Peak plasma concentrations of unchanged valaciclovir are only about 4% of peak aciclovir levels, occur at a median time of 30 to 100 min post-dose, and are at or below the limit of quantification 3 h after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing. Herpes zoster, herpes simplex and HIV infection do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir compared with healthy adults. In transplant recipients receiving valaciclovir 2000 mg 4 times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily AUCs are appreciably greater.

Distribution

Binding of valaciclovir to plasma proteins is very low (15%). CSF penetration, determined by CSF/plasma AUC ratio, is independent of renal function and was about 25% for aciclovir and the metabolite 8-OH-ACV, and about 2.5% for the metabolite CMMG.

Biotransformation

After oral administration, valaciclovir is converted to aciclovir and *L* ‾ valine by first ‾ pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9(carboxymethoxy)methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8 ‾ hydroxy ‾ aciclovir (8 ‾ OH ‾ ACV) by aldehyde oxidase. Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8 ‾ OH ‾ ACV. Neither valaciclovir nor aciclovir is metabolized by cytochrome P450 enzymes.

Elimination

Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the aciclovir metabolite CMMG (about 14% of the recovered dose). The metabolite 8-OH-ACV is detected only in small amounts in urine (< 2% of the recovered dose). Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 h.

Special Populations

Renal impairment

The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).

Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17-31 mL/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, at severe renal impairment compared with normal renal function.

Hepatic impairment

Pharmacokinetic data indicate that hepatic impairment decreases the rate of conversion of valaciclovir to aciclovir but not the extent of conversion. Aciclovir half-life is not affected.

Pregnant women

A study of the pharmacokinetics of valaciclovir and aciclovir during late pregnancy indicates that pregnancy does not affect the pharmacokinetics of valaciclovir.

Transfer into breast milk

Following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (Cmax) in breast milk ranged from 0.5 to 2.3 times the corresponding maternal aciclovir serum concentrations. The median aciclovir concentration in breast milk was 2.24 micrograms/ml (9.95 micromoles/L). With a maternal valaciclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral aciclovir dosage of about 0.61 mg/kg/day. The elimination half-life of aciclovir from breast milk was similar to that for serum. Unchanged valaciclovir was not detected in maternal serum, breast milk, or infant urine.

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819 **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Valaciclovir did not affect fertility in male or female rats dosed by the oral route.

Valaciclovir was not teratogenic in rats or rabbits. Valaciclovir is almost completely metabolised to aciclovir. Subcutaneous administration of aciclovir in internationally accepted tests did not produce teratogenic effects in rats or rabbits. In additional studies in rats, foetal abnormalities and maternal toxicity were observed at subcutaneous doses that produced plasma aciclovir levels of 100 micrograms/mL (>10 ⁻fold higher than 2000 mg single dose valaciclovir in humans with normal renal function).

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821 **6. PHARMACEUTICAL PARTICULARS**

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823 **6.1 List of excipients**

Tablet core

Microcrystalline cellulose

Crospovidone

Povidone

Magnesium stearate

Colloidal silicon dioxide

Film coat

Hypromellose

Titanium dioxide

Macrogol

Polysorbate 80

Carnauba wax

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825 **6.2 Incompatibilities**

Not applicable.

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827 **6.3 Shelf life**

500 mg tablets

Three years

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829 **6.4 Special precautions for storage**

Store below 30°C.

6.5 Nature and contents of container

Polyvinyl chloride / aluminium foil blister packs.

500 mg tablets

Packs of 10, 30, 42, 90 or 112 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

11.4.2 Valganciclovir (enteral)

1. NAME OF THE MEDICINAL PRODUCT

VALCYTE 50 mg/ml powder for oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 5.5 g valganciclovir hydrochloride per 12 g powder for oral solution.

Each ml of the reconstituted solution contains 50 mg valganciclovir (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.

The powder is a granulate with a white to slightly yellow colour.

When the powder is dissolved, it forms a clear, colourless to brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VALCYTE is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

VALCYTE is indicated for the prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.

4.2 Posology and method of administration

Caution – Strict adherence to dosage recommendations is essential to avoid overdose (see sections 4.4 and 4.9).

Valganciclovir is rapidly and extensively metabolised to ganciclovir after oral dosing. Oral valganciclovir 900 mg taken twice daily is therapeutically equivalent to intravenous ganciclovir 5 mg/kg taken twice daily. The ganciclovir systemic exposure following administration of 900 mg valganciclovir oral solution is equivalent to valganciclovir 900 mg tablets.

Standard dosage in adults

Induction treatment of CMV retinitis:

For patients with active CMV retinitis, the recommended dose is 900 mg valganciclovir twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section 4.4).

Maintenance treatment of CMV retinitis:

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg valganciclovir once daily. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

Prevention of CMV disease in solid organ transplantation:

For kidney transplant patients, the recommended dose is 900 mg once daily , starting within 10 days of transplantation and continuing until 100 days post transplantation. Prophylaxis may be continued until 200 days post-transplantation (see sections 4.4, 4.8 and 5.1).

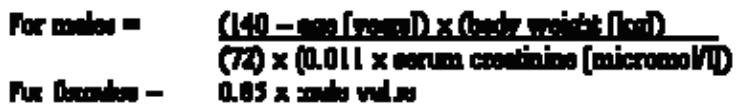
For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg once daily, starting within 10 days of transplantation and continuing until 100 days post transplantation.

Special dosage instructions

Patients with renal impairment

Serum creatinine levels or creatinine clearance should be monitored carefully. Dosage adjustment is required according to creatinine clearance, as shown in the Table below (see sections 4.4 and 5.2).

An estimated creatinine clearance (ml/min) can be related to serum creatinine by the following formulae:



CrCl (ml/min)	Induction dose of valganciclovir	Maintenance/Prevention dose of valganciclovir
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	225 mg once daily
10 – 24	225 mg once daily	125 mg once daily
<10	200 mg three times a week after dialysis	100 mg three times a week after dialysis

Patients undergoing haemodialysis:

Dosage adjustment is necessary for patients on haemodialysis (CrCl <10ml/min) (see sections 4.4 5.2) and a dosing recommendation is given in the Table above.

Patients with hepatic impairment

Safety and efficacy of VALCYTE have not been studied in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents (less than 18 years of age):

Valcyte is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy in this patient population (see section 4.4).

Elderly patients:

Safety and efficacy of VALCYTE have not been established in this patient population.

Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia:

see section 4.4 before initiation of therapy.

If there is a significant deterioration of blood cell counts during therapy with VALCYTE, treatment with haematopoietic growth factors and/or dose interruption should be considered (see section 4.4).

Method of administration

VALCYTE is administered orally, and whenever possible, should be taken with food (see section 5.2).

VALCYTE powder for oral solution requires reconstitution prior to oral administration (see section 6.6). Two oral dosing dispensers with graduations in 25 mg up to 500 mg are provided. It is recommended that patients use the dispenser.

4.3 Contraindications

VALCYTE is contraindicated in patients with hypersensitivity to valganciclovir, ganciclovir or to any of the excipients.

Due to the similarity of the chemical structure of VALCYTE and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible. Therefore, VALCYTE is contraindicated in patients with hypersensitivity to aciclovir and valaciclovir.

VALCYTE is contraindicated during lactation (see section 4.6).

4.4 Special warnings and precautions for use

Owing to the teratogenic character, the VALCYTE powder and reconstituted solution should be handled with caution. Inhalation should be avoided. If the powder or solution make direct contact with skin, the area should be washed thoroughly with soap and water. If the solution gets into the eye, the eye should be thouroghly washed with water immediately.

Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies, ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic, and a suppressor of female fertility. VALCYTE should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 5.3). It is also considered likely that VALCYTE causes temporary or permanent inhibition of spermatogenesis. Women of child bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy (see sections 4.6, 4.8 and 5.3).

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with VALCYTE (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µl, or the platelet count is less than 25000/µl, or the haemoglobin level is less than 8g/dl (see sections 4.2 and 4.8).

When extending prophylaxis beyond 100 days the possible risk of developing leucopenia and neutropenia should be taken into account (see sections 4.2, 4.8 and 5.1).

VALCYTE should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood counts and platelet counts be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment. In patients developing severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see sections 4.2 and 4.8).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections 4.2 and 5.2).

Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir. VALCYTE should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section 4.5).

Patients treated with VALCYTE and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5).

The controlled clinical study using valganciclovir for the prophylactic treatment of CMV disease in transplantation, as detailed in section 5.1, did not include lung and intestinal transplant patients. Therefore, experience in these transplant patients is limited.

For patients on a sodium-controlled diet, this medicinal product contains a total of 0.188 mg/ml sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions with valganciclovir

In-vivo drug interaction studies with VALCYTE have not been performed. Since valganciclovir is extensively and rapidly metabolised to ganciclovir; drug interactions associated with ganciclovir will be expected for valganciclovir.

Drug interactions with ganciclovir

Imipenem-cilastatin

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

Probenecid

Probenecid given with oral ganciclovir resulted in statistically significantly decreased renal clearance of ganciclovir (20%) leading to statistically significantly increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for renal tubular secretion. Therefore, patients taking probenecid and VALCYTE should

be closely monitored for ganciclovir toxicity.

Zidovudine

When zidovudine was given in the presence of oral ganciclovir there was a small (17%), but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage (see section 4.4).

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6g/day, an increase in the AUC of didanosine ranging from 84 to 124% has been observed, and likewise at intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67% has been observed. There was no clinically significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (see section 4.4).

Mycophenolate Mofetil

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co ¯administration of these agents (which have the potential to compete for renal tubular secretion) will result in increases in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid (MPA) pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment to whom MMF and ganciclovir are co ¯administered, the dose recommendation of ganciclovir should be observed and the patients monitored carefully. Since both MMF and ganciclovir have the potential to cause neutropenia and leucopenia, patients should be monitored for additive toxicity.

Zalcitabine

No clinically significant pharmacokinetic changes were observed after concomitant administration of ganciclovir and zalcitabine. Both valganciclovir and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events.

Stavudine

No clinically significant interactions were observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim

No clinically significant pharmacokinetic interaction was observed when trimethoprim and oral ganciclovir were given in combination. However, there is a potential for toxicity to be enhanced since both drugs are known to be myelosuppressive and therefore both drugs should be used concomitantly only if the potential benefits outweigh the risks.

Other antiretrovirals

At clinically relevant concentrations, there is unlikely to be either a synergistic or antagonistic effect on the inhibition of either human immunodeficiency virus (HIV) in the presence of ganciclovir or CMV in the presence of a variety of antiretroviral drugs. Metabolic interactions with, for example, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are unlikely due to the lack of P450 involvement in the metabolism of either valganciclovir or ganciclovir.

Other potential drug interactions

Toxicity may be enhanced when valganciclovir is co ¯administered with, or is given immediately before or after, other drugs that inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, testes and germinal layers of the skin and gastrointestinal mucosa. Examples of these types of drugs are dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulpha combinations, nucleoside analogues and hydroxyurea.

Since ganciclovir is excreted through the kidney (section 5.2), toxicity may also be enhanced during co ¯administration of valganciclovir with drugs that might reduce the renal clearance of ganciclovir and hence increase its exposure. The renal clearance of ganciclovir might be inhibited by two mechanisms: (a) nephrotoxicity, caused by drugs such as cidofovir and foscarnet, and (b) competitive inhibition of active tubular secretion in the kidney by, for example, other

nucleoside analogues.

Therefore, all of these drugs should be considered for concomitant use with valganciclovir only if the potential benefits outweigh the potential risks (see section 4.4).

4.6 Pregnancy and lactation

There are no adequate data from the use of VALCYTE in pregnant women. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir (see section 5.3) there is a theoretical risk of teratogenicity in humans.

VALCYTE should not be used in pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the child.

Women of child-bearing potential must be advised to use effective contraception during treatment. Male patients must be advised to practise barrier contraception during, and for at least 90 days following treatment with VALCYTE unless it is certain that the female partner is not at risk of pregnancy (see section 5.3).

It is unknown if ganciclovir is excreted in breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, breast-feeding must be discontinued (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Convulsions, sedation, dizziness, ataxia, and/or confusion have been reported with the use of VALCYTE and/or ganciclovir. If they occur, such effects may affect the patient's ability to drive and operate machinery.

4.8 Undesirable effects

Valganciclovir is a prodrug of ganciclovir, which is rapidly and extensively metabolised to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir use can be expected to occur with valganciclovir. All of the undesirable effects observed with valganciclovir clinical studies have been previously observed with ganciclovir. The most commonly reported adverse drug reactions following administration of valganciclovir in adults are neutropenia, anaemia and diarrhoea.

Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. In addition, valganciclovir is associated with a higher risk of neutropenia and leucopenia compared to oral ganciclovir.

Severe neutropenia (< 500 ANC/µl) is seen more frequently in CMV retinitis patients undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir.

The frequency of adverse reactions reported in clinical trials with either valganciclovir, oral ganciclovir, or intravenous ganciclovir is presented in the Table below. The adverse reactions listed were reported in clinical trials in patients with AIDS for the induction or maintenance treatment of CMV retinitis, or in liver, kidney or heart transplant patients for the prophylaxis of CMV disease. The term (severe) in parenthesis in the Table indicates that the adverse reaction has been reported in patients at both mild/moderate intensity and severe/life-threatening intensity at that specific frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body System	Very Common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1000, < 1/100)	Rare (≥ 1/10,000, < 1/1000)
Infections and infestations		Oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection		
Blood and lymphatic system disorders	(Severe) neutropenia, anaemia	(Severe) anaemia, (severe) thrombocytopenia, (severe) leucopenia, (severe) pancytopenia, ,	Bone marrow failure	Aplastic anaemia
Immune system disorders			Anaphylactic reaction	
Metabolism and nutrition disorders		De creased appetite, anorexia		
Psychiatric disorders		Depression, anxiety, confusion, abnormal thinking	Agitation, psychotic disorder.	

			hallucination,	
Nervous system disorders		Headache, insomnia, dysgeusia (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness, convulsion	Tremor	
Eye disorders		Macular oedema, retinal detachment, vitreous floaters, eye pain	Visual disturbance, conjunctivitis	
Ear and labyrinth disorders		Ear pain	Deafness	
Cardiac disorders			Arrhythmia	
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Cough		
Gastrointestinal disorders	Diarrhea	Nausea, vomiting, abdominal pain, abdominal pain upper, dyspepsia, constipation, flatulence, dysphagia,	, Abdominal distension, mouth ulceration, pancreatitis	
Hepatobiliary disorders		(Severe) hepatic function abnormal, blood alkaline phosphatase increased, aspartate aminotransferase increased	Alanine aminotrans-ferase increased	
Skin and subcutaneous tissue disorders		Dermatitis, night sweats, pruritus	Alopecia, urticaria, dry skin	
Musculoskeletal and connective tissue disorders		Back pain, myalgia, arthralgia, muscle spasms		
Renal and urinary disorders		Creatinine renal clearance decreased, renal impairment	Haematuria, renal failure	
Reproductive system and breast disorders			Male infertility	
General disorders and administration site conditions		Fatigue, pyrexia, chills, pain, chest pain, malaise, asthenia		
Investigations		Weight decreased, blood creatinine increased		

Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

4.9 Overdose

Overdose experience with valganciclovir

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).

It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see section 4.2 and section 4.4).

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section 5.2)

Overdose experience with intravenous ganciclovir

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

Haematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia

–*Hepatotoxicity*: hepatitis, liver function disorder

Renal toxicity: worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine

–*Gastrointestinal toxicity*: abdominal pain, diarrhoea, vomiting

–*Neurotoxicity:* generalised tremor, convulsion

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05A B14

Mechanism of action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus (HBV).

In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. Triphosphate metabolism has been shown to occur in HSV- and HCMV- infected cells with half-lives of 18 and between 6 and 24 hours respectively, after the removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, further viral DNA elongation.

Antiviral Activity

The *in-vitro* anti-viral activity, measured as IC_{50} of ganciclovir against CMV, is in the range of 0.08µM (0.02µg/ml) to 14µM (3.5µg/ml).

The clinical antiviral effect of VALCYTE has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis. CMV shedding was decreased in urine from 46% (32/69) of patients at study entry to 7% (4/55) of patients following four weeks of VALCYTE treatment.

Clinical efficacy

Treatment of CMV retinitis:

Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either VALCYTE 900 mg (twice daily) or intravenous ganciclovir 5 mg/kg (twice daily). The proportion of patients with photographic progression of CMV retinitis at week 4 was comparable in both treatment groups, 7/70 and 7/71 patients progressing in the intravenous ganciclovir and valganciclovir arms respectively.

Following induction treatment dosing, all patients in this study received maintenance treatment with VALCYTE given at the dose of 900 mg once daily. The mean (median) time from randomisation to progression of CMV retinitis in the group receiving induction and maintenance treatment with VALCYTE was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with VALCYTE was 219 (125) days.

Prevention of CMV disease in transplantation

A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver and kidney transplant patients (lung and gastro-intestinal transplant patients were not included in the study) at high-risk of CMV disease (D+/R-) who received either VALCYTE (900 mg once daily) or oral ganciclovir (1000 mg three times daily) starting within 10 days of transplantation until Day 100 post-transplant. The incidence of CMV disease (CMV syndrome + tissue invasive disease) during the first 6 months post-transplant was 12.1% in the VALCYTE arm (n=239) compared with 15.2% in the oral ganciclovir arm (n=125). The large majority of cases occurred following cessation of prophylaxis (post-Day 100) with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm.

The incidence of acute rejection in the first 6 months was 29.7% in patients randomised to valganciclovir compared with 36.0% in the oral ganciclovir arm, with the incidence of graft loss being equivalent, occurring in 0.8% of patients, in each arm.

A double-blind, placebo controlled study has been conducted in 326 kidney transplant patients at high risk of CMV disease (D+/R-) to assess the efficacy and safety of extending Valcyte CMV prophylaxis from 100 to 200 days post-transplant. Patients were randomized (1:1) to receive Valcyte tablets (900 mg od) within 10 days of transplantation either until Day 200 post-transplant or until Day 100 post-transplant followed by 100 days of placebo.

The proportion of patients who developed CMV disease during the first 12 months post-transplant is shown in the table below.

Percentage of Kidney Transplant Patients with CMV Disease[1], 12 Month ITT Population [A]

	Valganciclovir **900 mg od** **100 Days** **N = 163**	**Valganciclovir** **900 mg od** **200 Days** **N = 155**	**Between Treatment Group Difference**
Patients with confirmed or assumed CMV disease[2]	71 (43.6%) [35.8% ; 51.5%]	36 (23.2%) [16.8% ; 30.7%]	20.3% [9.9% ; 30.8%]
Patients with confirmed CMV disease	60 (36.8%) [29.4% ; 44.7%]	25 (16.1%) [10.7% ; 22.9%]	20.7% [10.9% ; 30.4%]

[1] CMV Disease is defined as either CMV syndrome or tissue invasive CMV. [2] Confirmed CMV is a clinically confirmed case of CMV disease. Patients were assumed to have CMV disease if there was no week 52 assessment and no confirmation of CMV disease before this time point.

[A] The results found up to 24 months were in line with the up to 12 month results: Confirmed or assumed CMV disease was 48.5% in the 100 days treatment arm versus 34.2% in the 200 days treatment arm; difference between the treatment groups was 14.3% [3.2 %; 25.3%].

Significantly less high risk kidney transplant patients developed CMV disease following CMV prophylaxis with Valcyte until Day 200 post-transplant compared to patients who received CMV prophylaxis with Valcyte until Day 100 post-transplant.

The graft survival rate as well as the incidence of biopsy proven acute rejection was similar in both treatment groups. The graft survival rate at 12 months post-transplant was 98.2% (160/163) for the 100 day dosing regimen and 98.1% (152/155) for the 200 day dosing regimen. Up to 24 month post-transplant, four additional cases of graft loss were reported, all in the 100 days dosing group. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100 day dosing regimen and 11.0% (17/155) for the 200 day dosing regimen. Up to 24 month post-transplant, one additional case has been reported in the 200 days dosing group.

Viral Resistance

Virus resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or the viral polymerase gene (UL54). Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas viruses with mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target the viral polymerase.

Treatment of CMV retinitis:

Genotypic analysis of CMV in polymorphonuclear leucocytes (PMNL) isolates from 148 patients with CMV retinitis enrolled in one clinical study has shown that 2.2%, 6.5%, 12.8%, and 15.3% contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment.

Prevention of CMV disease in transplantation:

Active comparator study

Resistance was studied by genotypic analysis of CMV in PMNL samples collected i) on Day 100 (end of study drug prophylaxis) and ii) in cases of suspected CMV disease up to 6 months after transplantation. From the 245 patients

randomised to receive valganciclovir, 198 Day 100 samples were available for testing and no ganciclovir resistance mutations were observed. This compares with 2 ganciclovir resistance mutations detected in the 103 samples tested (1.9%) for patients in the oral ganciclovir comparator arm.

Of the 245 patients randomised to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 127 patients randomised on the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which two resistance mutations were observed, giving an incidence of resistance of 6.9%.

Extending prophylaxis study from 100 to 200 days post-transplant

Genotypic analysis was performed on the UL54 and UL97 genes derived from virus extracted from 72 patients who met the resistance analysis criteria: patients who experienced a positive viral load (>600 copies/mL) at the end of prophylaxis and/or patients who had confirmed CMV disease up to 12 months (52 weeks) post-transplant. Three patients in each treatment group had a known ganciclovir resistance mutation.

867
868 **5.2 Pharmacokinetic properties**

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

Absorption

Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolised in the intestinal wall and liver to ganciclovir. Systemic exposure to valganciclovir is transient and low. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60% across all the patient populations studied and the resultant exposure to ganciclovir is similar to that after its intravenous administration (please see below).

Valganciclovir in HIV positive, CMV positive patients:

Systemic exposure of HIV positive, CMV positive patients after twice daily administration of ganciclovir and valganciclovir for one week is:

Parameter	Ganciclovir (5 mg/kg, IV) n = 18	Valganciclovir (900 mg, p.o.) n = 25	
		Ganciclovir	Valganciclovir
AUC(0 - 12 h) (µg.h/ml)	28.6 ± 9.0	32.8 ± 10.1	0.37 ± 0.22
C_{max} (µg/ml)	10.4 ± 4.9	6.7 ± 2.1	0.18 ± 0.06

The efficacy of ganciclovir in increasing the time-to-progression of CMV retinitis has been shown to correlate with systemic exposure (AUC).

Valganciclovir in solid organ transplant patients:

Steady state systemic exposure of solid organ transplant patients to ganciclovir after daily oral administration of ganciclovir and valganciclovir is:

Parameter	Ganciclovir (1000 mg three times daily) n = 82	Valganciclovir (900 mg, once daily) n = 161
		Ganciclovir
AUC(0 - 24 h) (µg.h/ml)	28.0 ± 10.9	46.3 ± 15.2
C_{max} (µg/ml)	1.4 ± 0.5	5.3 ± 1.5

The systemic exposure of ganciclovir to heart, kidney and liver transplant recipients was similar after oral administration of valganciclovir according to the renal function dosing algorithm.

Following the administration of valganciclovir as an oral solution, equivalent systemic ganciclovir exposures were

obtained compared to the tablet formulation.

Food effect:

Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir in the dose range 450 to 2625 mg was demonstrated only under fed conditions. When valganciclovir was given with food at the recommended dose of 900 mg, higher values were seen in both mean ganciclovir AUC (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%) than in the fasting state. Also, the inter-individual variation in exposure of ganciclovir decreases when taking VALCYTE with food. VALCYTE has only been administered with food in clinical studies. Therefore, it is recommended that VALCYTE be administered with food (see section 4.2).

Distribution:

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir was 1 - 2% over concentrations of 0.5 and 51µg/ml. The steady state volume of distribution (V_d) of ganciclovir after intravenous administration was 0.680 ± 0.161 L/kg (n=114).

Metabolism

Valganciclovir is rapidly and extensively metabolised to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabelled ganciclovir (1000 mg single dose) accounted for more than 1 - 2% of the radioactivity recovered in the faeces or urine.

Elimination

Following dosing with VALCYTE, renal excretion, as ganciclovir, by glomerular filtration and active tubular secretion is the major route of elimination of valganciclovir. Renal clearance accounts for 81.5% ± 22% (n=70) of the systemic clearance of ganciclovir. Post-hoc Bayesian estimates for population mean apparent clearance of ganciclovir in patients with CrCl > 60 ml/min is 14.05 ± 4.13 L/h. In patients with renal impairment, the mean apparent clearance of ganciclovir is 8.46 ± 1.67 L/h (CrCl between 40 and 60 mL/min) and 7.00 ± 1.08 L/h (CrCl between 25 and 40 ml/min).

The half-life of ganciclovir from valganciclovir is 4.1 ± 0.9 hours in HIV- and CMV-seropositive patients.

Pharmacokinetics in special clinical situations

Patients with renal impairment

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see section 4.2 and 4.4).

Patients undergoing haemodialysis

For patients receiving haemodialysis VALCYTE powder for oral solution is recommended to provide an individualised dose (see sections 4.2 and 4.4).

Patients with hepatic impairment

The safety and efficacy of VALCYTE have not been studied in patients with hepatic impairment. Hepatic impairment should not significantly affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made.

5.3 Preclinical safety data

Valganciclovir is a pro-drug of ganciclovir and therefore effects observed with ganciclovir apply equally to valganciclovir. Toxicity of valganciclovir in pre-clinical safety studies was the same as that seen with ganciclovir and was induced at ganciclovir exposure levels comparable to, or lower than, those in humans given the induction dose.

These findings were gonadotoxicity (testicular cell loss) and nephrotoxicity (uraemia, cell degeneration), which were irreversible; myelotoxicity (anaemia, neutropenia, lymphocytopenia) and gastrointestinal toxicity (mucosal cell necrosis), which were reversible.

Further studies have shown ganciclovir to be mutagenic, carcinogenic, teratogenic, embryotoxic, aspermatogenic (i.e. impairs male fertility) and to suppress female fertility.

6. PHARMACEUTICAL PARTICULARS

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874 **6.1 List of excipients**

povidone

fumaric acid

sodium benzoate (E211)

sodium saccharin

mannitol

Tutti-frutti flavour:

maltodextrins (maize)

propylene glycol

arabic gum E414 and natural flavouring substances mainly consisting of banana, pineapple and peach flavour

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876 **6.2 Incompatibilities**

Not applicable.

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878 **6.3 Shelf life**

Powder for oral solution: 2 years.

Reconstituted solution: 49 days. Store in a refrigerator (2°C - 8°C)

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880 **6.4 Special precautions for storage**

This medicinal product does not require any special storage condition.

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

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882 **6.5 Nature and contents of container**

Carton containing a 100 ml amber glass bottle with a child-resistant plastic screw cap, a plastic bottle adapter and a plastic bag containing 2 plastic oral dispensers graduated to 500 mg with graduations of 25 mg.

Each bottle contains 12 g of powder for oral solution. When reconstituted, the volume of the solution is 100 ml, providing a minimal usable volume of 88 ml.

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884 **6.6 Special precautions for disposal and other handling**

Since VALCYTE is considered a potential teratogen and carcinogen in humans, caution should be observed in handling the powder and the reconstituted solution (see section 4.4). Avoid inhalation and direct contact of the powder and solution with skin and mucous membranes. If such contact occurs, wash thoroughly with soap and water. If the powder or solution gets into the eyes, rinse eyes thoroughly with water.

It is recommended that VALCYTE powder for oral solution be reconstituted by the pharmacist prior to dispensing to the patient.

<u>Preparation of oral solution</u>

1. Measure 91 ml of water in a graduated cylinder.

2. Remove the child resistant cap, add the water to the bottle, then close the bottle with the child resistant cap. Shake the closed bottle until the powder is dissolved forming a clear, colourless to brown solution.

3. Remove the child resistant cap and push the bottle adapter into the neck of the bottle.

4. Close the bottle with the child resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.

5. Write the date of expiration of the reconstituted solution on the bottle label (see section 6.3).

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

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11.4.3 Ganciclovir - Intravenous

1. NAME OF THE MEDICINAL PRODUCT

Cymevene® powder for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ganciclovir 500mg (as ganciclovir sodium 546mg).

3. PHARMACEUTICAL FORM

Sterile, freeze-dried powder for reconstitution with Water for Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cymevene is indicated for the treatment of life-threatening or sight-threatening cytomegalovirus (CMV) infections in immunocompromised individuals. These states include acquired immunodeficiency syndrome (AIDS), iatrogenic immunosuppression associated with organ transplantation, or chemotherapy for neoplasia.

Cymevene may also be used for the prevention of CMV disease, specifically in those patients receiving immunosuppressive therapy secondary to organ transplantation.

4.2 Posology and method of administration

For intravenous infusion following reconstitution with 10ml Water for Injection BP. Based on patient weight and therapeutic indication the appropriate calculated dose volume should be removed from the vial (ganciclovir concentration 50mg/ml) and added to an acceptable infusion fluid (typically 100ml) for delivery over the course of 1 hour. Infusion concentrations greater than 10mg/ml are not recommended. (See section *6.6 Instructions for use/handling*).

Adults

Treatment of CMV infection

Initial (induction) treatment: 5mg/kg infused at a constant rate over 1 hour every 12 hours (10mg/kg/day) for 14 to 21 days.

Long-term (maintenance) treatment: For immunocompromised patients at risk of relapse of CMV retinitis a course of maintenance therapy may be given. Intravenous infusion of 6mg/kg once daily 5 days per week, or 5mg/kg once daily 7 days per week is recommended.

Treatment of disease progression: Indefinite treatment may be required in patients with AIDS, but even with continued maintenance treatment, patients may have progression of retinitis. Any patient in whom the retinitis progresses, either while on maintenance treatment or because treatment with Cymevene has been withdrawn, may be re-treated using the induction treatment regimen.

Prevention of CMV disease

Induction regimen: 5mg/kg infused every 12 hours (10mg/kg/day) for 7 to 14 days.

Maintenance regimen: Intravenous infusion of 6mg/kg once daily 5 days per week, or 5mg/kg once daily 7 days per week is recommended.

Special dosage instructions

Patients with renal impairment:

Serum creatinine levels or creatinine clearance should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in the table below (see section *4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties*).

An estimated creatinine clearance (ml/min) can be related to serum creatinine by the following formulae:

$$\text{For males} = \frac{(140 - \text{age (years)}) \times (\text{body weight (kg)})}{(72 \times (0.011 \times \text{serum creatinine (micromol/L)})}$$

$$\text{For females} = 0.85 \times \text{male value}$$

CrCl	Induction dose of ganciclovir
≥ 70ml/min	5.0mg/kg every 12 hours
50 - 69ml/min	2.5mg/kg every 12 hours
25 - 49ml/min	2.5mg/kg/day
10 - 24ml/min	1.25mg/kg/day
< 10ml/min	1.25mg/kg/day after haemodialysis

Elderly patients

No studies on the efficacy or safety of Cymevene in elderly patients have been conducted. Since elderly individuals often have reduced renal function, Cymevene should be administered to elderly patients with special consideration for their renal status (see above).

Paediatric patients

There has been limited clinical experience in treating patients under the age of 12 years (see section *4.4 Special warnings and precautions for use* and *5.2 Pharmacokinetic properties*). Reported adverse events were similar to those seen in adults. However, the use of Cymevene in children warrants extreme caution due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks. Cymevene is not indicated for the treatment of congenital or neonatal CMV infections.

Dosage reductions

For less severe neutropenia or other cytopenias a reduction in the total daily dose should be considered. Cell counts usually normalise within 3 to 7 days after discontinuing the drug or decreasing the dose. As evidence of marrow recovery becomes apparent gradual increases in dose, with careful monitoring of white blood cell counts, may be appropriate.

Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia

See section *4.4 Special warnings and precautions for use* before initiation of therapy.

If there is a significant deterioration of blood cell counts during therapy with Cymevene, treatment with haematopoetic growth factors and/or dose interruption should be considered (see section *4.4 Special warnings and precautions for use* and section *4.8 Undesirable effects*).

Method of administration

Cymevene is a powder for solution for intravenous infusion. For directions on the preparation of the infusion solution, see section *6.6 Instructions for use and handling, and disposal*.

Cymevene must only be given by intravenous infusion, preferably via a plastic cannula, into a vein with adequate blood flow.

Caution - do not administer by rapid or bolus i.v. injection! The toxicity of Cymevene may be increased as a result of excessive plasma levels.

Caution - i.m. or s.c. injection may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.

The recommended dosage, frequency, or infusion rates should not be exceeded.

Caution should be exercised in the handling of Cymevene, see section *6.6 Instructions for use and handling, and*

disposal.

4.3 Contraindications

Cymevene is contra-indicated in patients with hypersensitivity to ganciclovir or valganciclovir or to any of the excipients.

Due to the similarity of the chemical structure of Cymevene and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible. Therefore, Cymevene is contra-indicated in patients with hypersensitivity to aciclovir and valaciclovir.

Cymevene is contra-indicated during pregnancy and lactation (see section *4.6 Pregnancy and lactation)*.

4.4 Special warnings and precautions for use

Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic and a suppressor of female fertility. Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section *5.3 Preclinical safety data*). It is also considered likely that Cymevene causes temporary or permanent inhibition of spermatogenesis. Women of child bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy (see section *4.6 Pregnancy and lactation*, section *4.8 Undesirable effects* and section *5.3 Preclinical safety data*).

The use of Cymevene in children and adolescents warrants extreme caution due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks.

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with Cymevene. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µL, or the platelet count is less than 25000/µL, or the haemoglobin level is less than 8g/dL (see section 4.2 Posology and method of administration, Special dosage instructions and section 4.8 Undesirable effects).

Cymevene should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood counts and platelet counts be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment. In patients developing severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see section *4.2 Posology and method of administration*, Special dosage instructions and section *4.8 Undesirable effects*).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see section*4.2 Posology and method of administration*, Special dosage instructions and section *5.2 Pharmacokinetic properties*,*Pharmacokinetics in special populations*).

Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir. Cymevene should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section*4.5 Interaction with other medicinal products and other forms of interaction*).

Patients treated with Cymevene and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity (see section *4.5 Interaction with other medicinal products and other forms of interaction*).

4.5 Interaction with other medicinal products and other forms of interaction

Imipenem-cilastatin

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section *4.4 Special warnings and precautions for use*).

Probenecid

Probenecid given with oral ganciclovir resulted in statistically significantly decreased renal clearance of ganciclovir (20%) leading to statistically significantly increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for renal tubular secretion. Therefore, patients taking probenecid and Cymevene should be closely monitored for ganciclovir toxicity.

Zidovudine

When zidovudine was given in the presence of oral ganciclovir there was a small (17%), but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage (see section *4.4 Special warnings and precautions for use*).

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6g/day, an increase in the AUC of didanosine ranging from 84 to 124% has been observed, and likewise at intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67% has been observed. There was no clinically significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (see section *4.4 Special warnings and precautions for use*).

Mycophenolate Mofetil

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co-administration of these agents (which have the potential to compete for renal tubular secretion) will result in increases in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid (MPA) pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment to whom MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed and the patients monitored carefully.

Zalcitabine

No clinically significant pharmacokinetic changes were observed after concomitant administration of ganciclovir and zalcitabine. Both valganciclovir and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events.

Stavudine

No clinically significant interactions were observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim

No clinically significant pharmacokinetic interaction was observed when trimethoprim and oral ganciclovir were given in combination. However, there is a potential for toxicity to be enhanced since both drugs are known to be myelosuppressive and therefore both drugs should be used concomitantly only if the potential benefits outweigh the risks.

Other antiretrovirals

At clinically relevant concentrations, there is unlikely to be either a synergistic or antagonistic effect on the inhibition of either HIV in the presence of ganciclovir or CMV in the presence of a variety of antiretroviral drugs. Metabolic interactions with, for example, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are unlikely due to the lack of P450 involvement in the metabolism of ganciclovir.

Other potential drug interactions

Toxicity may be enhanced when ganciclovir is co-administered with, or is given immediately before or after, other drugs that inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, testes and germinal layers of the skin and gastrointestinal mucosa. Examples of these types of drugs are dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulpha combinations, nucleoside analogues and hydroxyurea.

Since ganciclovir is excreted through the kidney (section *5.2*), toxicity may also be enhanced during co-administration of ganciclovir with drugs that might reduce the renal clearance of ganciclovir and hence increase its exposure. The renal clearance of ganciclovir might be inhibited by two mechanisms: (a) nephrotoxicity, caused by drugs such as cidofovir and foscarnet, and (b) competitive inhibition of active tubular secretion in the kidney by, for example, other nucleoside analogues.

Therefore, all of these drugs should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks (see section *4.4 Special warnings and precautions for use*).

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907 **4.6 Pregnancy and lactation**

The safety of Cymevene for use in human pregnancy has not been established. Ganciclovir readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir (see section *5.3 Preclinical safety data*), there is a theoretical risk of teratogenicity in humans. Therefore, Cymevene should not be given to pregnant women as there is a high likelihood of damage to the developing foetus.

Women of childbearing potential must be advised to use effective contraception during treatment. Male patients should be advised to practise barrier contraception during, and for at least 90 days following treatment unless it is certain that the female partner is not at risk of pregnancy (see section *5.3 Preclinical safety data*).

It is unknown if ganciclovir is excreted in breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, breastfeeding must be discontinued.

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909 **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

Convulsion, sedation, dizziness, ataxia and/or confusion have been reported with the use of Cymevene. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

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911 **4.8 Undesirable effects**

In patients who were being treated with ganciclovir the most common haematological side effects were neutropenia, anaemia and thrombocytopenia.

Adverse reactions reported with i.v. ganciclovir, oral ganciclovir and valganciclovir are presented in the table below.Valganciclovir is a pro-drug of ganciclovir, and adverse reactions associated with valganciclovir can be expected to occur with ganciclovir. The frequency groupings of these adverse events are based upon the frequency recorded in clinical trials with CMV retinitis patients with AIDS and in clinical trials with solid organ transplant patients.

Infections and infestations:	
Common (≥ 1/100, < 1/10):	Sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection, oral candidiasis.
Blood and lymphatic disorders:	
Very common (≥ 1/10):	neutropenia, anaemia.
Common (≥ 1/100, < 1/10):	thrombocytopenia, leucopenia, pancytopenia.
Uncommon (≥ 1/1000, < 1/100):	bone marrow depression.
Immune system disorders:	
Uncommon (≥ 1/1000, < 1/100):	anaphylactic reaction.
Metabolic and nutrition disorders:	
Common (≥ 1/100, < 1/10):	appetite decreased, anorexia.
Psychiatric disorders:	
Common (≥ 1/100, < 1/10):	depression, anxiety, confusion, abnormal thinking.
Uncommon (≥ 1/1000, < 1/100):	agitation, psychotic disorder
Nervous system disorders:	
Common (≥ 1/100, < 1/10):	headache, insomnia, dysgeusia (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, convulsions, dizziness (excluding vertigo).
Uncommon (≥ 1/1000, < 1/100):	tremor.
Eye disorders:	
Common (≥ 1/100, < 1/10):	macular oedema, retinal detachment, vitreous floaters, eye pain.
Uncommon (≥ 1/1000, < 1/100):	vision abnormal, conjunctivitis.
Ear and labyrinth disorders:	
Common (≥ 1/100, < 1/10):	ear pain
Uncommon (≥ 1/1000, < 1/100):	deafness.
Cardiac disorders:	
Uncommon (≥ 1/1000, < 1/100):	arrhythmias.

Vascular disorders:	
Uncommon (≥ 1/1000, < 1/100):	hypotension.
Respiratory, thoracic and mediastinal disorders:	
Very common (≥ 1/10):	dyspnoea.
Common (≥ 1/100, < 1/10):	cough.
Gastrointestinal disorders:	
Very common (≥ 1/10):	diarrhoea.
Common (≥ 1/100, < 1/10):	nausea, vomiting, abdominal pain, abdominal pain upper, constipation, flatulence, dysphagia, dyspepsia.
Uncommon (≥1/1000, <1/100):	abdominal distention, mouth ulcerations, pancreatitis.
Hepato-biliary disorders:	
Common (≥ 1/100, < 1/10):	hepatic function abnormal, blood alkaline phosphatase increased, aspartate aminotransferase increased.
Uncommon (≥ 1/1000, < 1/100):	alanine aminotransferase increased.
Skin and subcutaneous tissues disorders:	
Common (≥ 1/100, < 1/10):	dermatitis, night sweats, pruritus.
Uncommon (≥ 1/1000, < 1/100):	alopecia, urticaria, dry skin.
Musculo-skeletal and connective tissue disorders:	
Common (≥ 1/100, < 1/10):	back pain, myalgia, arthralgia, muscle cramps.
Renal and urinary disorders:	
Common (≥ 1/100, < 1/10):	creatinine clearance renal decreased, renal impairment.
Uncommon (≥ 1/1000, < 1/100):	haematuria, renal failure.
Reproductive system and breast disorders:	
Uncommon (≥ 1/1000, < 1/100):	male infertility.
General disorders and administration site conditions:	
Common (≥ 1/100, < 1/10):	fatigue, pyrexia, rigors, pain, chest pain, malaise, asthenia, injection site reaction (intravenous ganciclovir only).
Investigations:	
Common (≥ 1/100, < 1/10):	weight decreased, blood creatinine increased.

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913 **4.9 Overdose**

Overdose experience with intravenous ganciclovir

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

–*Haematological toxicity* - pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia.

–*Hepatotoxicity* - hepatitis, liver function disorder.

–*Renal toxicity* - worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine.

–*Gastrointestinal toxicity* - abdominal pain, diarrhoea, vomiting.

–*Neurotoxicity* - generalised tremor, convulsion.

In addition, one adult received an excessive volume of i.v. ganciclovir solution by intravitreal injection, and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of ganciclovir (see section 5.2 Pharmacokinetic properties, Patients undergoing haemodialysis).

Overdose experience with valganciclovir

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J 05 A B 06 (anti-infectives for systemic use, antivirals for systemic use, direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors).

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine which inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus-6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV) and varicella zoster virus (VZV) and hepatitis B virus. Clinical studies have been limited to assessment of efficacy in patients with CMV infection.

In CMV infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. This has been shown to occur in HSV- and HCMV-infected cells with half-lives of 18 and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to the inhibition of viral DNA synthesis by: (1) competitive inhibition of incorporation of deoxyguanosine triphosphate into DNA by DNA polymerase and (2) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, viral DNA elongation. The *in vitro* anti-viral activity, measured as IC_{50} of ganciclovir against CMV, is in the range of 0.08μM (0.02μg/ml) to 14 μM (3.5μg/ml).

Viral resistance

The possibility of viral resistance should be considered for patients who repeatedly show poor clinical response or experience persistent viral excretion during therapy. CMV resistant to ganciclovir can arise after prolonged treatment or prophylaxis with ganciclovir by selection of mutations in either the viral protein kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or, but less frequently, in the viral polymerase gene (UL54). Virus with mutations in the UL97 gene are resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals with a similar mechanism of action and vice versa.

The working definition of CMV resistance to ganciclovir based on *in vitro* antiviral assays is an IC_{50} value $\geq$ 12.0μM with values > 6.0μM < 12.0μM being considered as indicating intermediate resistance. By these definitions up to 4% of untreated patients have CMV isolates with IC_{50} values that meet the criteria for either resistance or intermediate resistance.

In a prospective study of 76 previously untreated severely immunocompromised AIDS patients with CMV retinitis starting therapy with ganciclovir (i.v. induction / i.v. maintenance or i.v. induction / oral maintenance), the number of patients carrying resistant virus (IC_{50} > 6.0μM) increased with time of treatment; 3.7%, 5.4%, 11.4% and 27.5% of those still on treatment at baseline, 3, 6 and 12 months respectively. Similarly in another study of AIDS patients with CMV retinitis treated for $\geq$ 3 months with i.v. ganciclovir 7.8% of patients carried virus with IC_{50} $\geq$ 12.0μM. Combined data from 4 clinical studies of the treatment of CMV retinitis indicated an incidence of resistance (IC_{50} > 6.0μM) of 3.2% (median exposure 75 days) for i.v. ganciclovir and 6.5% (median exposure 165 days) for oral ganciclovir.

5.2 Pharmacokinetic properties

Systemic exposure

The systemic exposure (AUC_{0-24}) reported following dosing with a single 1-hour i.v. infusion of 5mg/kg ganciclovir in HIV+/CMV+ patients ranged from 21.4 ± 3.1 (N=16) to 26.0 ± 6.06 (N=16) μg.h/ml . In this patient population peak plasma concentration (C_{max}) ranged from 8.27 ± 1.02 (N=16) to 9.03 ± 1.42 (N=16)μg/ml.

Distribution

For i.v. ganciclovir, the volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0.536 ± 0.078 (N=15) to 0.870 ± 0.116 (N=16) L/kg. Cerebrospinal fluid concentrations obtained 0.25 - 5.67 hours post-dose in 2 patients who received 2.5mg/kg ganciclovir i.v. every 8 hours or every 12 hours ranged from 0.50 to 0.68μg/ml representing 24 - 67% of the respective plasma concentrations. Binding to plasma proteins was 1 - 2% over ganciclovir concentrations of 0.5 and 51μg/ml.

Intra-ocular concentrations of ganciclovir range from 40 to 200% of those measured simultaneously in plasma following administration of i.v. ganciclovir. Average intravitreal concentrations following induction and maintenance dosing with i.v. ganciclovir were 1.15 and 1.0 μg/ml respectively. Half-life of ganciclovir within the eye is much longer than that in

plasma with estimates ranging from 13.3 to 18.8 hours.

Metabolism and elimination

When administered i.v., ganciclovir exhibits linear pharmacokinetics over the range of 1.6 - 5.0mg/kg. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, 89.6 ± 5.0% (N=4) of i.v. administered ganciclovir was recovered unmetabolised in the urine. In subjects with normal renal function, systemic clearance ranged from 2.64 ± 0.38ml/min/kg (N=15) to 4.52 ± 2.79ml/min/kg (N=6) and renal clearance ranged from 2.57 ± 0.69ml/min/kg (N=15) to 3.48 ± 0.68ml/min/kg (N=16), corresponding to 90% - 101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from 2.73 ± 1.29 (N=6) to 3.98 ± 1.78 hours (N=8).

Pharmacokinetics in special populations

Renal impairment

Renal impairment leads to altered kinetics of ganciclovir as indicated below.

	Ganciclovir	
Serum creatinine (micromol/l)	**Systemic plasma clearance (ml/min/kg)**	**Plasma half-life (hours)**
< 124 (n = 22)	3.64	2.9
125 - 225 (n = 9)	2.00	5.3
226 - 398 (n = 3)	1.11	9.7
> 398 (n = 5)	0.33	28.5

Patients undergoing haemodialysis

Haemodialysis reduces plasma concentrations of ganciclovir by about 50% after both i.v. and oral administration (see section *4.9 Overdosage*).

During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42 to 92 ml/min, resulting in intra-dialytic half-lives of 3.3 to 4.5 hours. Estimates of ganciclovir clearance for continuous dialysis were lower (4.0 to 29.6 ml/min) but resulted in greater removal of ganciclovir over a dose interval. For intermittent haemodialysis, the fraction of ganciclovir removed in a single dialysis session varied from 50% to 63%.

Paediatric patients

Ganciclovir pharmacokinetics were also studied in 10 children, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir are similar after single and multiple (every 12 hours) i.v. doses (5mg/kg). After the administration of a 5mg/kg single dose, exposure as measured by mean AUC was 19.4 ± 7.1 µg.h/ml, the steady-state volume of distribution reported was 0.68 ± 0.20 l/kg, C_{max} was 7.59 ± 3.21µg/ml, systemic clearance was 4.66 ± 1.72ml/min/kg, and $t_{1/2}$ was 2.49 ± 0.57 hours. The pharmacokinetics of i.v. ganciclovir in children are similar to those observed in adults.

Elderly patients

No studies have been conducted in adults older than 65 years of age.

5.3 Preclinical safety data

Ganciclovir was mutagenic in mouse lymphoma cells and clastogenic in mammalian cells. Such results are consistent with the positive mouse carcinogenicity study with ganciclovir. Ganciclovir is a potential carcinogen.

Ganciclovir causes impaired fertility and teratogenicity in animals (see section 4.4 *Special warnings and precautions for use*).

Based upon animal studies where aspermatogenesis was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir could cause inhibition of human spermatogenesis.

Data obtained using an *ex vivo* human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/ml and occurred by passive diffusion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

The dry powder should not be reconstituted with bacteriostatic water containing parabens, since these are incompatible with ganciclovir sterile powder and may cause precipitation.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Undiluted vials: Do not store above 30°C.

From a microbiological point of view, the product should be used immediately after reconstitution and dilution. If the product is not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user. Following reconstitution and dilution, the following in-use storage times should be followed unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

In-use storage time for the reconstituted vial should not be longer than 12 hours. Do not refrigerate.

In-use storage time for the infusion solution should not be longer than 24 hours when stored in a refrigerator at 2 - 8°C. Freezing is not recommended.

6.5 Nature and contents of container

10ml multidose vials (type I, clear glass) with a grey butyl siliconised stopper in quantities of 5 or 25 vials.

6.6 Special precautions for disposal and other handling

Caution should be exercised in the handling of Cymevene

Since Cymevene is considered a potential teratogen and carcinogen in humans, caution should be exercised in its handling (see section *4.4 Special warnings and precautions for use*). Avoid inhalation or direct contact of the powder contained in the vials or direct contact of the reconstituted solution with the skin or mucous membranes. Cymevene solutions are alkaline (pH approximately 11). If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.

Method of preparation of Cymevene solution

1. Lyophilised Cymevene should be reconstituted by injecting 10ml of sterile Water for Injections into the vial. **Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene sterile powder and may cause precipitation.**

2. The vial should be shaken to dissolve the drug.

3. Reconstituted solution should be inspected for particulate matter prior to proceeding with the admixture preparation.

4. Reconstituted solution in the vial is stable at room temperature for 12 hours. It should not be refrigerated.

Preparation and administration of infusion solution

Based on patient weight the appropriate calculated dose volume should be removed from the Cymevene vial (concentration 50 mg/ml) and added to an acceptable infusion fluid. Normal saline, dextrose 5% in water, Ringer's or lactated Ringer's solution are determined chemically or physically compatible with Cymevene. Infusion concentrations greater than 10mg/ml are not recommended.

Cymevene should not be mixed with other i.v. products.

Because Cymevene is reconstituted with nonbacteriostatic sterile water, the infusion solution should be used as soon as

possible and within 24 hours of dilution in order to reduce the risk of bacterial contamination.

The infusion solution should be refrigerated. Freezing is not recommended.

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

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11.4.4 Aciclovir -Intravenous

1. NAME OF THE MEDICINAL PRODUCT

Aciclovir 25 mg/ml Sterile Concentrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 25 mg aciclovir as aciclovir sodium.

Each vial of 10 ml of solution contains 250 mg aciclovir (sodium salt formed *in situ*)

Each vial of 20 ml of solution contains 500 mg aciclovir (sodium salt formed *in situ*)

Each vial of 40 ml of solution contains 1 g aciclovir (sodium salt formed *in situ*)

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aciclovir 25 mg/ml Sterile Concentrate is indicated for the treatment of severe initial genital herpes in the immunocompromised and the non-immunocompromised.

Aciclovir 25 mg/ml Sterile Concentrate is indicated for the prophylaxis and treatment of Herpes simplex infections in immunocompromised patients.

Aciclovir 25 mg/ml Sterile Concentrate is indicated for the treatment of shingles (Varicella zoster virus) in immunocompetent patients in whom a serious course of the illness can be anticipated.

Aciclovir 25 mg/ml Sterile Concentrate is indicated for the treatment of initial and recurrent Varicella zoster infections in immunocompromised patients.

Aciclovir 25 mg/ml Sterile Concentrate is indicated for the treatment of herpes encephalitis.

Aciclovir 25 mg/ml Sterile Concentrate is indicated for the treatment of Herpes simplex infections in the neonate and infant up to 3 months of age.

4.2 Posology and method of administration

Treatment should be started as early as possible during the course of an active infection.

A course of treatment with Aciclovir 25 mg/ml Sterile Concentrate usually lasts between 5 and 7 days, but the duration of treatment may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis and neonatal Herpes simplex infections usually lasts for at least 10 days.

The duration of prophylactic administration of Aciclovir 25 mg/ml Sterile Concentrate is determined by the duration of the period of risk.

Dosage in adults: Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections (with normal immune response) should be given Aciclovir 25 mg/ml Sterile Concentrate in doses of 5 mg/kg bodyweight every 8 hours.

Immunocompromised patients with Varicella zoster infections or patients with herpes encephalitis should be given Aciclovir 25 mg/ml Sterile Concentrate in doses of 10 mg/kg bodyweight every 8 hours provided renal function is not impaired (see dosage in renal impairment).

The dosage of Aciclovir 25 mg/ml Sterile Concentrate in neonates and infants up to 3 months of age is calculated on the basis of bodyweight.

Neonates and infants up to 3 months of age with Herpes simplex infections should be given Aciclovir 25 mg/ml Sterile Concentrate in doses of 10 mg/kg bodyweight every 8 hours. Treatment for neonatal Herpes simplex infections usually

lasts 10 days.

Dosage in Children: The dose of Aciclovir 25 mg/ml Sterile Concentrate for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children with Herpes simplex (except herpes encephalitis) or Varicella zoster infections (with normal immune response) should be given Aciclovir 25 mg/ml Sterile Concentrate in doses of 250 mg per square metre of body surface area every 8 hours.

In immunocompromised children with Varicella zoster infections or children with herpes encephalitis, Aciclovir 25 mg/ml Sterile Concentrate should be given in doses of 500 mg per square metre body surface area every 8 hours if renal function is not impaired.

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

Dosage in the elderly: In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance. It is recommended that the state of hydration and the creatinine clearance should be evaluated before the administration of high dosages of aciclovir, especially in elderly patients, who may have reduced renal function despite a normal serum creatinine concentration.

Dosage in renal impairment: Caution is advised when administering Aciclovir 25 mg/ml Sterile Concentrate to patients with impaired renal function since the drug is excreted through the kidneys. The following adjustments in dosage are suggested:

Creatinine Clearance Dosage

25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight or 250-500 mg/m^2 in children) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight or 250-500 mg/m^2 in children) should be given every 24 hours.
0 (anuric) to 10 ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg bodyweight or 250-500 mg/m^2 in children) should be halved and administered every 24 hours. In patients receiving haemodialysis half the dose recommended above should be administered immediately after dialysis and thereafter every 24 hours.

Administration

The required dose of Aciclovir 25 mg/ml Sterile Concentrate should be administered by slow intravenous infusion over a one-hour period and adequate hydration should be established.

Aciclovir 25 mg/ml Sterile Concentrate may be administered by a controlled-rate infusion pump.

Refer to Section 6.6 for instructions on use, preparation and handling.

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952 **4.3 Contraindications**

Aciclovir 25 mg/ml Sterile Concentrate is contraindicated in patients known to be previously hypersensitive to aciclovir and valaciclovir.

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954 **4.4 Special warnings and precautions for use**

Solutions of aciclovir are alkaline (pH of approximately 11) and intended for intravenous infusion only and should not be used by any other route.

The dose of Aciclovir 25 mg/ml Sterile Concentrate must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body. Infusions of aciclovir must be given over a period of at least one hour in order to avoid renal tubular damage (see dosage in renal impairment).

Although the aqueous solubility of aciclovir exceeds 100 mg/ml, precipitation of aciclovir crystals in renal tubules and

the consequent renal tubular damage can occur if the maximum solubility of free aciclovir (2.5 mg/ml at 37°C in water) is exceeded. Aciclovir infusions must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first few hours following infusion particular attention should be given to establish sufficient urine flow during that period. Concomitant use of other nephrotoxic drugs, pre-existing renal disease and dehydration increase the risk of further renal impairment by aciclovir.

In patients receiving Aciclovir 25 mg/ml Sterile Concentrate at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.

Contact with eyes or unprotected skin should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

There have been rare reports of Probenecid, cimetidine, theophylline and mycophenolate mofetil linked to increases in the aciclovir mean half-life and area under the plasma concentration-time curve. In these cases an adjustment of the aciclovir dosage is not thought to be necessary given the large therapeutic range of aciclovir.

According to one case report, co-administration of intravenous aciclovir and lithium caused a four-fold increase in lithium serum concentrations. Lithium concentrations should be closely monitored and a reduced lithium dose may be needed.

When aciclovir is administered concomitantly with theophylline, close monitoring of theophylline concentrations and possible theophylline dose reduction is recommended. A study has shown that when theophylline was given as single 320 mg doses before and with the sixth dose of aciclovir 800 mg five times daily for 2 days, the AUC of the theophylline was increased by 45% (from 189.9 to 274.9 micrograms.h/ml) and the total body clearance was reduced by 30%.

Care is also required (with monitoring changes in renal function) if administering Aciclovir 25 mg/ml Sterile Concentrate with drugs that affect other aspects or renal physiology (e,g, cyclosporine, tacrolimus) as they may influence the nephrotoxic effect of aciclovir.

4.6 Pregnancy and lactation

Limited data are available on the use of aciclovir during pregnancy. Aciclovir should not be used during pregnancy unless the potential benefits to the patient outweigh the potential risk to the foetus.

Limited human data show that aciclovir is excreted in human breast milk. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Renal

Rapid increases in blood urea and creatinine levels may occasionally occur in patients given Aciclovir 25 mg/ml Sterile Concentrate. These are usually reversible but progression to acute renal failure can occur in rare cases. The rapid increases in blood urea and creatinine levels are believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect the drug should not be given as an intravenous bolus injection but by slow infusion over a one hour period. Adequate hydration of the patient should be maintained.

The risk of renal damage is increased by concomitant use of other nephrotoxic drugs and pre-existing renal disease.

Renal impairment developing during treatment with Aciclovir 25 mg/ml Sterile Concentrate usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure, however, can occur in exceptional cases.

Skin

Local necrosis and inflammation have occurred when Aciclovir 25 mg/ml Sterile Concentrate has been inadvertently infused into extravascular tissues. Severe local inflammatory reactions or phlebitis have occurred at the injection site sometimes leading to breakdown of the skin. These local effects occur more frequently following inadvertent infusion of aciclovir into extravascular tissues.

Rashes and hives may occur.

Neurological

Reversible neurological reactions such as confusion, lethargy, hallucinations, agitation, tremors, somnolence, psychosis,

convulsions and coma have been associated with Aciclovir 25 mg/ml Sterile Concentrate therapy. Reversible psychiatric effects and headaches have been reported less frequently.

Therefore aciclovir should be used with caution in patients with underlying neurological abnormalities. It should also be used with caution in patients who have manifested neurological reactions to cytotoxic drugs or are receiving concomitant interferon or intrathecal methotrexate.

Haematological

Increases in liver-related enzymes and fever have been reported in patients receiving Aciclovir 25 mg/ml Sterile Concentrate. Haemotological disorders including anaemia, thrombocytopenia and leucopoenia have been rarely reported

Other

Aciclovir should be used with caution in patients with significant hypoxia or serious hepatic or electrolyte abnormalities.

Other less frequent adverse effects reported in patients receiving therapy with Aciclovir 25 mg/ml Sterile Concentrate include, diaphoresis, haematuria, hypotension, nausea and vomiting.

In case of high doses, abdominal pain and thirst have been reported in patients who had been treated previously with aciclovir.

4.9 Overdose

Toxicity and treatment of overdosage

There is little experience concerning overdosage with aciclovir however single doses of Aciclovir 25 mg/ml Sterile Concentrate up to 80 mg/kg bodyweight have been inadvertently administered without adverse effects. Effects of overdosage may be expected to be similar in nature to those described under adverse reactions. Adequate hydration is essential to reduce the possibility of crystal formation in the urine. Aciclovir can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of action: Aciclovir is a synthetic acyclic purine nucleoside analogue (ATC J05A B01) with in vitro and in vivo inhibitory activity against human Herpes viruses, including Herpes simplex virus types 1 and 2 and Varicella zoster virus (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). In cell culture aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV, and CMV.

The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV,VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir needs to be phosphorylated to the active compound aciclovir triphosphate, in order to become active against the virus. Aciclovir triphosphate acts as an inhibitor of, and a substrate for, the herpes specified DNA polymerase preventing further viral DNA synthesis.

5.2 Pharmacokinetic properties

Pharmacokinetics: In adults, the terminal plasma half-life of aciclovir after the administration of Aciclovir 25 mg/ml Sterile Concentrate is about 3 hours. Aciclovir is widely distributed in tissues and body fluids. Approximately 75-80% of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. 9-carboxymethoxymethylguanine is the major significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

In adults, mean steady state peak (Cssmax) plasma concentrations following a one-hour infusion were ;

	2.5 mg/kg	5 mg/kg	10 mg/kg	15 mg/kg
Css max in µmol or in (µg/ml)	22.7 (5.1)	43.6 (9.8)	92 (20.7)	105 (23.6)

Css min, after 7 hours, in µmol or in (µg/ml)	2.2 (0.5)	3.1 (0.7)	10.2 (2.3)	8.8 (2.0)

In children over 1 year of age similar mean peak (Cssmax) and trough (Cssmin) levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg. In neonates (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the Cssmax was found to be 61.2 micromolar (13.8 microgram/ml) and the Cssmin. to be 10.1 micromolar (2.3 microgram/ml).

The terminal plasma half-life in neonates was approximately 4 hours. In the elderly, total body clearance falls with increasing age and is associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life.

In patients with end stage renal failure the plasma half-life is increased, extending to a mean terminal half-life of approximately 20 hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels.

Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement are not anticipated.

971
972 **5.3 Preclinical safety data**

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir is unlikely to pose a genetic risk to man.

Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. Animal studies indicate that at high dose aciclovir is cytotoxic.

In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

There is no experience of the effect of Aciclovir 25 mg/ml Sterile Concentrate on human fertility. Aciclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

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974 **6. PHARMACEUTICAL PARTICULARS**

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976 **6.1 List of excipients**

Sodium hydroxide and water for injections. In the manufacture of the finished product sodium hydroxide and / or hydrochloric acid are used for pH adjustment.

977
978 **6.2 Incompatibilities**

Aciclovir sodium is reported to be incompatible with solutions of amifostine, amsacrine, aztreonam, diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, fludarabine phosphate, foscarnet sodium, idarubicin hydrochloride, meropenem, morphine sulphate, ondansetron hydrochloride, pethidine hydrochloride, piperacillin sodium - tazobactam sodium, sargramostim and vinorelbine tartrate.

Do not use bacteriostatic water for injection containing parabens or benzyl alcohol. Biologic or colloidal fluids (e.g. blood products, protein containing solutions) are incompatible with aciclovir sodium.

979
980 **6.3 Shelf life**

As packaged: 24 months.

After dilution: Chemical and physical in-use stability has been demonstrated for 12 hours at 25 °C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. When dilution is carried out under validated aseptic conditions, the product may be stored for a maximum of 12 hours at room temperature, below 25°C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Glass vials with butyl rubber stopper and an aluminium seal with a plastic 'flip-off' top. Packs of 5 vials (250 mg/10 ml) or (500 mg/20 ml) per carton, and as a single vial (1 g/40 ml) in a carton.

6.6 Special precautions for disposal and other handling

Aciclovir 25 mg/ml Sterile Concentrate contains no preservative. Dilution should therefore be carried out immediately before use under full aseptic conditions and any unused solution should be discarded.

Refrigeration is not recommended as precipitation may occur.

For adults, it is recommended that infusion bags containing 100 ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus one 100 ml infusion bag may be used for any dose between 250 mg and 500 mg aciclovir but a second bag must be used for doses between 500 and 1000 mg. Aciclovir 25 mg/ml Sterile Concentrate should not be diluted to a concentration greater than 5 mg/ml (0.5%w/v) for administration by infusion. After addition of Aciclovir 25 mg/ml Sterile Concentrate to an infusion solution the mixture should be shaken to ensure thorough mixing.

For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is on the basis of 4 ml of solution (100 mg aciclovir) added to 20 ml of infusion fluid.

When diluted in accordance with the recommended schedules, Aciclovir 25 mg/ml Sterile Concentrate is known to be compatible with the infusion fluids listed below:

Sodium Chloride Intravenous Infusion 0.9% w/v;

Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion ;

Sodium Chloride (0.9% w/v) and Glucose (5% w/v) Intravenous Infusion ;

Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion ;

Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution).

Aciclovir 25 mg/ml Sterile Concentrate when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

Aciclovir 25 mg/ml Sterile Concentrate contains no preservative.

Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

UNIVERSITY OF BIRMINGHAM

Anti-viral Prophylaxis for Prevention of Cytomegalovirus (CMV) Reactivation in Immunocompetent Patients in Critical Care

Cytomegalovirus Control in Critical Care - CCCC Statistical Analysis Plan

Version Number	1.0
Author (name and role)	Rebecca Woolley – Statistician
Author Signature and Date	26/01/2015
Reviewer (name and role)	Natalie Ives – Senior Statistician
Reviewer Signature and Date	26/01/2015
Effective Date	26/01/2015
Chief Investigator	Professor Julian Bion

CI Signature and Date	10/08/2015

Revision Chronology		
Version Number	**Issue Date**	**Reason for Change**

ABBREVIATIONS & DEFINITIONS

Abbreviation / Acronym	Meaning
ICU	Critical Care Unit
CMV	Cytomegalovirus
DMC	Data Monitoring Committee
AV	acyclovir/valaciclovir
GV	ganciclovir/valganciclovir
PCR	polymerase chain reaction
NDBL	non-direct bronchiolar lavage
GCSF	granulocyte colony stimulating factor
SOFA	Sequential Organ Failure Assessment
IL-6	interleukin 6
TNFα	tumor necrosis factor alpha
HSV	herpes simplex virus

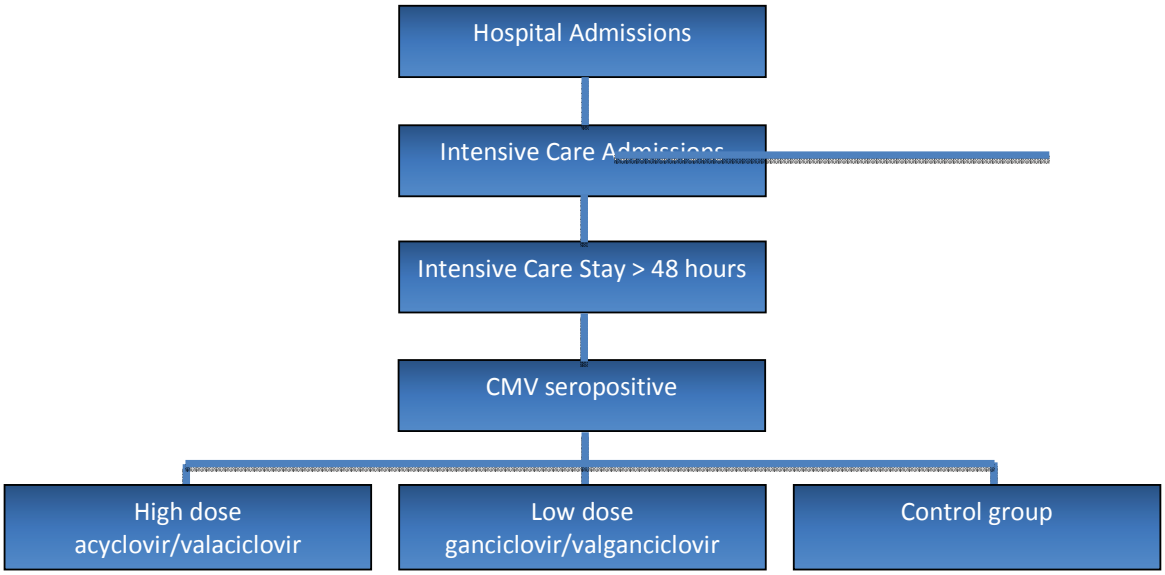
1. Introduction

This document gives a detailed statistical analysis plan for the CCCC trial and should be read in conjunction with the current trial protocol.

2. Study Design

CCCC is a prospective, randomised, open-label single centre pilot phase II trial. Patients admitted to the Birmingham Queen Elizabeth Hospital Critical Care Unit (ICU), and identified by pre-specified criteria to be at high risk of CMV reactivation will be assessed for inclusion into the trial. Blood will be analysed for CMV antibodies to establish past infection, and those patients positive for CMV past infection will be eligible for recruitment into the study. Recruited patients will be randomised into one of three arms: the control arm (no antiviral prophylaxis treatment); to receive high dose acyclovir/valaciclovir (AV); or to receive low dose ganciclovir/valganciclovir (GV). Those randomised to receive the drugs will receive the dosage for the duration of their ICU stay, for a minimum of 14 days, and a maximum of 28 days.

Trial Schema



On the 18th September 2013, the Data Monitoring Committee (DMC) recommended termination of the high dose acyclovir/valaciclovir arm due to a statistically higher mortality in this arm compared to the control arm (p=0.02). The mortality in the control arm was lower than expected, and the opinion of the DMC was that because of the small numbers being recruited into the trial, this would not be corrected over time. Randomisation to the other two trial arms (low dose ganciclovir/valganciclovir and control) continued.

Setting
This is a single centre trial taking place in the ICU at the Queen Elizabeth Hospital, Birmingham.

Interventions
Patients admitted to the ICU and identified as being at high risk of CMV reactivation will be assessed for inclusion in the trial. Blood will be analysed for CMV antibodies to establish past infection, and those patients who test positive for past CMV infection will be eligible for recruitment.

High Dose Acyclovir/Valaciclovir Arm
Following randomisation, patients will commence on 2g valaciclovir, 4 times a day, by entereal route. Treatment will continue until whichever comes soonest – 28 days or until discharge – but will continue for a minimum of 14 days. Treatment dosage will be modified in the presence of renal failure; or if patients are unable to receive enteral nutrition, they will receive intravenous acyclovir 10mg/kg three times a day, and change to enteral valaciclovir when absorption is established.

Low Dose Ganciclovir/Valganciclovir Arm
Following randomisation, patients will commence on 450mg valganciclovir, once a day, by enteral route. Treatment will continue until whichever comes soonest – 28 days or until discharge – but will continue for a minimum of 14 days. Treatment will be modified in the presence of renal failure; or if patients are unable to receive enteral medication, they will receive intravenous ganciclovir 2.5mg/kg once a day, and change to enteral valganciclovir when enteral absorption is established.

Control Arm
Patients will receive care as per normal practice. Antiviral medication may be initiated by the critical care team overseeing the patient care if this is deemed necessary for therapeutic reasons.

Sample Size
A sample size has been calculated in order to see whether the chosen primary outcome variable is likely to reach statistical significance. It has been calculated to detect a proportional difference in CMV reactivation between the AV arm and control arm, and the GV arm and control arm. Recruiting 47 patients to each arm, will give us 90% power with alpha=0.05, to detect a CMV reactivation difference of 30% in the control arm to 5% in the treatment arm of interest. This gives 141 patients required in total.

Note: Since the AV arm has been discontinued, this does not affect the sample size calculation. We still planned to recruit 47 patients to the remaining two arms. This leaves us with 94 patients required in total.

Primary Outcome
The primary outcome measure is defined as the time to reactivation of CMV in blood by quantitative polymerase chain reaction (PCR) to below the limits of assay detection by day 28.

Patients will be followed up for 28 days after randomisation. If hospital discharge or death comes before either CMV reactivation or the 28 days of follow up, then the patient will be censored at the last CMV PCR sample point.

3. General Considerations

Levels of confidence and p-values:
Since this is a pilot study, no hypothesis testing will be performed, so p-values will not be presented. Instead, treatment effect estimates (relative risks, hazard ratios, mean differences etc.) will be presented alongside 95% confidence intervals.

Protocol violations and exclusions from the study:
Primary analyses will be based as much as possible on the intention to treat principle. This states that patients shall be analysed in the treatment arm to which they were randomised, and all patients shall be included whether or not they received the allocated treatment. This is to avoid any potential bias in the analysis.

Missing data:
In the event that there is missing data, primary analyses will concentrate on available data only, with no attempt made to impute missing values. A value will be considered missing if it is not entered at a data collection point entry or the data collection point is itself missing. An assessment of missing data will be made by tabulating missing data by data collection point. (See Appendix for how non-numeric data for CMV will be handled)

Late data:
All data being collected is clinical data that is collected over the 28 day follow up period. Therefore, any data that is not collected on the specified day will be considered as missing.

Timing of interim analyses:
BCTU is only performing the end of trial analyses as described in this Analysis Plan. Interim analyses for presentation of efficacy and safety was performed and presented to an independent DMC, but these analyses were undertaken by personnel outside of BCTU. BCTU were not members of the DMC, so did not see any of the interim analyses.

Timing of first main analyses for dissemination:
The first set of analyses of all trial data for public dissemination will be started once all patients required have been entered into the trial and the last patient has completed follow up (be it at 28 days or hospital discharge or death).

4. Proposed Analyses

The primary comparison groups will be composed of those randomised to acyclovir/valaciclovir or ganciclovir/valganciclovir to those randomised to the control arm (so a combined active treatment group vs. control). This is as per the study protocol. However, in light of the DMC terminating the high dose acyclovir/valaciclovir arm early due to safety issues, it has also been decided to compare the ganciclovir/valganciclovir and control arms. This was decided following discussions with the trial team, and the statisticians at BCTU who were blind to any data at this point. This was decided pre-database lock for final analysis.

All analyses will be based on the intention to treat principle, with all patients analysed in the arms to which they were allocated irrespective of compliance with the randomised allocated treatment, and all patients will be included in the analyses.

The primary analysis will be performed as an unadjusted analysis. As a sensitivity analysis, a second analysis adjusting for the baseline covariates (age, gender and disease severity (defined by SOFA score)) will be performed for the primary outcome.

Primary outcome:

The primary outcome for this study is defined as the time from randomisation to reactivation of CMV in blood by quantitative PCR. A value of greater than or equal to 20 copies is considered to indicate CMV reactivation. Patients who reactivate at baseline will be excluded from the analysis as they have already experienced the outcome of interest

As this is a pilot study, we will not be performing hypothesis testing. However, to provide information to help inform the main trial, the primary outcome will be compared between treatment arms using survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons presented alongside a hazard ratio with respective 95% confidence interval using a simple log-rank test. .

The sample size calculation was based on an assessment of proportions, so the proportion of patients that had a CMV reactivation defined by blood PCR in the treatment and control arms will also be calculated and presented alongside relative risks and respective 95% confidence intervals.

Secondary endpoints:

Secondary endpoints for the study include:

- Time to reactivation of CMV PCR, using lower limits of sample assay (≥20 copies considered a reactivation), in urine, throat swab or NDBL (non-direct bronchiolar lavage)
- Incidence of CMV PCR reactivation using lower limits of assay (≥20 copies considered a reactivation) in blood, urine, throat swab or NDBL
- Time to CMV PCR >1000 and >10000 copies per ml for blood, throat, NDBL and urine samples
- Peak viral load defined as highest CMV PCR over the 28 days for blood, throat, NDBL and urine
- Mean area under the curve by treatment arm for those who had CMV reactivation (excluding baseline reactivations)
- Mean change in IL6 and TNFα levels between day 1 and day 14/28
- Time to reactivation of HSV (herpes simplex virus)
- Incidence of mortality at 28 days
- Organ failure free days (defined as SOFA<2) and moderate organ dysfunction free days (defined as SOFA<5) at day 28. If a patient dies during the 28 day follow up then all remaining days are counted as organ failure days. Similarly, if a patient is discharged before 28 days, then the remaining days are counted as organ failure free days
- Time to discharge from the ICU (3 month endpoint)
- Time to discharge from the hospital (3 month endpoint)
- Time to neutropenia (count $<1.0 \times 10^{-9}$/L) over 28 days

- Time to thrombocytopenia (platelet count <50 x 10^{-9}/L) over 28 days
- Number of platelet transfusions over 28 days
- Time to renal insufficiency. This will be two separate analyses: in the first instance, renal insufficiency is defined as having creatinine clearance <60ml/min; in the second, renal insufficiency is defined as having creatinine clearance <30ml/min or having haemodialysis/haemofiltration. See Appendix for calculation of creatinine clearance.
- Use of GCSF (granulocyte colony stimulating factor) /termination of study drug over 28 days
- Rate of serious adverse events

All of the secondary endpoints as described above will be comparing the treatment arms combined, and the valganciclovir/ganciclovir alone with the control arm. Time to event outcomes will be analysed using Kaplan-Meier curves and presented with their respective hazard ratios and confidence intervals (as per the primary outcome). Incidence rates of CMV reactivation and mortality will be analysed by comparing the proportions between the arms and presenting relative risks with respective 95% confidence intervals. The proportion of patients who have experienced at least one SAE will be presented as risk ratios along with the 95% confidence interval. Number of platelet transfusions and organ-free failure/moderate organ dysfunction days will be compared using Poisson regression analysis and will be reported as mean count differences, with the control arm used as the base comparator, along with 95% confidence intervals.

NB: Since recruitment to the valaciclovir/acyclovir arm was stopped due to high mortality, we will also be presenting the relative risk of mortality in this arm compared to the control arm along with 95% confidence interval.

Planned subgroup analyses:
Not applicable, this is a pilot study with no subgroups analyses planned.

Any deviations from this plan will be described in the final report.

Appendix:

- All blood, NDBL, throat and urine sample assays that are less than 20 are reported as <20 or ND (none detected). For the purpose of the analyses it has been agreed that by default, these will be set to zero.

- Creatinine clearance will be calculated using the Cockcroft Gault formula:

$$eC_{Cr} = \frac{(140 - \text{Age(yrs)})\text{x Mass (kg)x } Constant}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

where *Constant* is 1.23 for male patients and 1.04 for female patients. Ideal body weight will be used as the patient's mass, rather than actual body weight.

This Statistical Analysis Plan has been read and approved by:

	Name	**Signed**	**Date**
Senior Study Statistician:	Natalie Ives		26/01/2015
Chief Investigator:	Julian Bion		10/08/2015
Chair of the DMC (on behalf of the DMC group)	BCTU did not produce the interim DMC analysis report for this study, coming on-board to undertake the final analyses, so NI has agreed that this is not needed for this study.		

The Statistical Analysis Plan will be sent to all members of the DMC for information purposes.