AWMSG Secretariat Assessment Report – Advice no. 0711 Valganciclovir (Valcyte®) powder for oral solution for 200 days prophylaxis of cytomegalovirus (CMV) disease in CMV-negative kidney transplant patients who have received a transplant from a CMV-positive donor

This assessment report is based on evidence submitted by Roche Products Ltd. on 17th December 2010.

1.0 PRODUCT DETAILS

Licensed indication	Valganciclovir (Valcyte®) is indicated for the prevention of cytomegalovirus (CMV) disease in CMV-negative patients who have received a solid organ transplant (SOT) from a CMV-positive donor[1]. This submission considers the licence extension for valganciclovir powder for oral solution for 200 days prophylaxis of CMV disease in CMV-negative kidney transplant patients who have received a transplant from a CMV-positive donor[2]. Please refer to the Summary of Product Characteristics (SPC) for licensed indications not covered in this submission[1].
Dosing	The recommended dose is 900 mg (18 ml solution) once daily, starting within 10 days of transplantation and continuing for 100 days. Prophylaxis may be continued until 200 days post-transplantation[1]. Dosage may need to be adjusted depending on renal function[1].
Marketing authorisation date	11 June 2010[2]
UK launch date	5 July 2010[2]

2.0 DECISION CONTEXT

2.1 Background

CMV is a double-stranded DNA virus of the *Herpesviridae* family. Seroprevalence among the general population is high and increases roughly linearly with age from approximately 40% at age 20 to 80% at age 60[3]. In an immunocompromised or immunosuppressed individual (e.g. following HIV infection or solid-organ or bone marrow transplantation) the normally harmless virus may become active, leading to CMV disease. Symptoms of CMV disease can include malaise, fever and myalgia, with biochemical hepatitis and atypical lymphocytes found on investigation[3]. In SOT recipients, CMV disease is of particular concern as it confers an increased risk of opportunistic infection and allograft rejection[4]. Approximately 8% of renal transplant recipients experience symptomatic CMV disease[3]. Those at highest risk of developing CMV disease are seronegative recipients (R-) of seropositive donor (D+) organs[2,5].

Valganciclovir is a prodrug of ganciclovir and is used as a prophylactic for early-onset CMV disease in SOT patients[2,3]. After oral dosing, valganciclovir is readily metabolised by hepatic and intestinal esterases to ganciclovir. In CMV-infected cells, ganciclovir is phosphorylated to ganciclovir triphosphate, which competitively inhibits deoxyguanosine-triphosphate incorporation into DNA, therefore preventing viral DNA synthesis and elongation[1].

Valganciclovir prophylaxis in SOT recipients has typically been continued for 100 days[6]; however, it has emerged that as many as 30% of all high-risk D+/R- transplant recipients develop CMV disease after this period[7]. An extension of valganciclovir prophylaxis beyond 100 days (or three months) has been suggested to abrogate the occurrence of late-onset CMV disease in D+/R- transplant recipients[2,8–10]. The company submission considers the recent licence extension for 200-day prophylaxis of CMV disease in D+/R- kidney transplant recipients using valganciclovir powder for oral solution[2]. The tablet formulation is the subject of a separate concurrent All Wales Medicines Strategy Group (AWMSG) assessment (advice no. 0611). This submission is specific to recipients of renal transplants only and does not cover other SOT recipients or induction and maintenance treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).

2.2 Comparators

The Welsh Medicines Partnership (WMP) requested 100 days of valganciclovir treatment.

2.3 Guidance and related advice

- British Transplant Society (BTS). Guidelines for the prevention and management of cytomegalovirus disease after solid organ transplantation. Third edition (2011)[3]. The BTS guidelines recommend oral valganciclovir for at least 100 days or for 200 days.
- The Renal Association. Post-operative care of the kidney transplant recipient. 2011[11]. The Renal Association guidelines recommend oral valganciclovir for 3–6 months for prophylaxis of CMV disease.
- The Royal Liverpool and Broadgreen University Hospitals. Protocol for immunosuppression following renal transplantation (2009)[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

As there are no data directly comparing the efficacy of 200- and 100-day prophylaxis with valganciclovir powder for oral solution, the company submission includes results from two studies (WP16302 and NT18435 [IMPACT 200]). Study WP16302 demonstrates the bioequivalence of valganciclovir oral solution and valganciclovir tablets, and NT18435 describes the efficacy of 200- versus 100-day prophylaxis with valganciclovir tablets[2].

3.1 Study WP16302

WP16302 was an adult (≥18 years), multi-centre, open-label, randomised study[2,13]. Patients at risk of CMV disease (n = 23; D+/R-, D+/R+ and D-/R+) undergoing prophylaxis with valganciclovir tablets after their first or second kidney transplant who had adequate haematological and renal function (creatinine clearance [CrCl] ≥60 ml/min) were included in the study. Each patient received 900 mg valganciclovir as both oral solution (18 ml) and tablets (450 mg), each for two consecutive days in a random order. The primary bioequivalence parameters were the area under the plasma concentration–time curve (AUC_{0-24}) and the maximum observed plasma concentration (C_{max}) of ganciclovir. Plasma concentrations were assessed pre-dose

and at intervals between 0.5 and 24 hours after the second dose. Mean AUC_{0-24} and C_{max} values were comparable for both treatments and the 90% confidence intervals for AUC_{0-24} and C_{max} were within the acceptance region for equivalence (80–125%) as per European Medicines Agency (EMA) specifications[14]. Due to the concluded bioequivalence, study NT18435, described below, was used to evidence the efficacy of 200-day versus 100-day treatment with valganciclovir solution[2,13].

3.2 Study NT18435

Study NT18435 (IMPACT 200) was a phase III, randomised, double-blind, multicentre trial which compared the efficacy and safety of 200-day valganciclovir prophylaxis with standard, 100-day prophylaxis in high-risk (D+/R-) kidney allograft recipients using valganciclovir 450 mg tablets[2,4]. Patients (n = 326) aged 17–77 were randomised to two study groups post-transplant. The first arm (intent-to-treat [ITT] population; n = 155) received 900 mg valganciclovir (450 mg tablets) daily for 200 days, and the second arm (ITT population; n = 163) received 900 mg valganciclovir (450 mg tablets) daily until day 100, followed by 100 days of placebo. The primary endpoint measured was the development of CMV disease (including CMV syndrome or tissue invasive disease) within the first 52 weeks post-transplant. Secondary endpoints included CMV viraemia, biopsy-proven acute rejection (BPAR), graft loss, patient survival, opportunistic infection and post-transplantation diabetes mellitus[2,4]. In addition, 24-month follow-up data on CMV disease, BPAR, graft loss, patient survival, seroconversion and genotypic resistance are available[15,16].

At 52 weeks post-transplant, a statistically significant reduction in CMV disease incidence was observed in the 200-day treatment arm compared with the 100-day treatment arm ($p < 0.0001$)[2,4]. CMV disease was observed in 16.1% (25/155) versus 36.8% (60/163) of patients, respectively. These data represent a 56% relative and 21% absolute risk reduction. The vast majority of CMV disease was classified as CMV syndrome (83 out of 85 [97.6%] total disease cases). CMV syndrome was rated as mild to moderate in 83% (20/24) of the 200-day group and 76% (45/59) of the 100-day group. Three patients in total developed tissue-invasive disease; one in the 200-day arm at day 215 and two in the 100-day arm at days 119 and 132[2,4].

The study was not powered to detect differences in the secondary endpoints of graft loss, BPAR or post-transplantation diabetes mellitus[2,4]. There were no significant differences found between the treatment arms for these endpoints; however, there was a trend towards less BPAR following 200 days of valganciclovir therapy versus 100 days (11% vs. 17% respectively, $p = 0.114$). Most patients experienced BPAR before 100 days in both treatment groups (10/17 versus 15/28 in the 200-day and 100-day groups, respectively), and all other cases were spread throughout the remaining time to 12 months. The majority of BPAR cases (13/17 for the 200-day group and 25/28 for the 100-day group) were not associated with measurable CMV viral load, which suggests that CMV viral load was not a major contributor to BPAR. The rate of graft loss was similar for both treatment arms (three grafts were lost in each study arm [out of 155 and 163 patients for 200-day and 100-day arms, respectively]; $p = 0.934$). The incidence of CMV viraemia 12 months post-transplant was significantly lower in the 200-day group (58/155) compared with the 100-day group (83/163) ($p = 0.015$). The proportion of patients with opportunistic infection was significantly lower in the 200-day group ($p = 0.001$); however this difference occurred mainly due to an imbalance in incidence during the first 50 days of treatment. The number of hospitalisations due to CMV was lower in the 200-day group compared with the 100-day group (10% [21/202] versus 21% [45/216]). Long-term data showed the incidence of CMV disease to be 21.3% (n = 33) and 38.7% (n = 63) at 24 months for the 200-day and 100-day arms, respectively ($p < 0.001$)[15]. Quality of Life (QoL) data were not recorded in this study[2,4].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

The SPC states that the most commonly reported drug reactions following administration of valganciclovir are neutropenia, anaemia and diarrhoea[1]. No new safety concerns were highlighted in this submission[2,4,13]. In the IMPACT 200 study, 13 patients in each group reported severe adverse events (AEs) relating to the use of the study drug, predominantly neutropenia. Seventeen patients in the 200-day arm and ten patients in the 100-day arm withdrew from treatment due to drug-related AEs. The overall reported incidence of leucopenia (regardless of whether it was thought to be related to study medication or not) was 38% in the 200-day treatment group versus 26% in the 100-day group; however, median white blood cell counts were similar between the two groups. The incidences of reported neutropenia, agranulocytosis, anaemia, thrombocytopenia and pancytopenia were comparable between treatment groups. No deaths deemed attributable to valganciclovir were reported[2,4].

It should be noted that the SPC states that when extending prophylaxis beyond 100 days the possible risk of developing leucopenia and neutropenia should be taken into account[1].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Unlike valganciclovir tablets, valganciclovir powder for oral solution is licensed for patients with a CrCl <10 ml/min. The availability of an oral dosing method that is suitable for patients (including those on dialysis) with a CrCl <10 ml/min reduces the need for intravenous (IV) ganciclovir. The powder for oral solution enables administration of the lower doses recommended for patients with a CrCl <10 ml/min[1]and is an alternative for patients who cannot swallow tablets.
- The bioequivalence study WP16302 recruited kidney transplant patients from various risk groups (D+/R-, D+/R+ and D-/R+) and only those with adequate renal function (CrCl ≥60 ml/min)[2,13].
- The IMPACT study presented in this submission demonstrates a 21% absolute reduction in incidence, rather than a delayed onset, of CMV disease for D+/R- renal transplant patients receiving 200-day valganciclovir prophylaxis compared with 100-day prophylaxis[2,4].
- In the 200-day arm of the IMPACT study, 123/160 patients completed the treatment course, compared with 94/166 in the 100-day arm. In the 200-day arm, 33/160 withdrew from treatment compared with 70/166 in the 100-day arm; of these, 4 versus 47, respectively, withdrew from treatment due to CMV disease[4].
- During the IMPACT study, the mean daily dose of valganciclovir in the first 100 days of therapy was 9% higher in the 200-day arm of the trial (644.3 mg) compared with the 100-day arm (587.2 mg). The mean daily dose over 200 days was also higher (625.6 mg)[2].
- During the IMPACT study, where a patient was unable to take oral medicine in the first ten days, IV ganciclovir was administered. Use of IV ganciclovir was similar between the two groups (36 [23%] patients in the 200-day arm and 34 [21%] patients in the 100-day arm)[2,4].
- The IMPACT study included patients aged 17–77[4]; however valganciclovir is not recommended for use in children and adolescents <18 years due to insufficient data on safety and efficacy[17].
- Immunosuppressive regimens were not controlled and were administered at the discretion of the investigator[2,4].

- HLA matching was not analysed during the IMPACT study; poor HLA-B and HLA-DR matching has been shown to significantly increase the incidence of CMV infection in SOT recipients. Randomisation procedures undertaken in the study would have minimised HLA-matching bias between the two groups[2,4].
- The usage in South Wales of the valganciclovir powder for oral solution as part of the 100-day treatment regimen is reported as very low[18].

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

6.1.1 Context

The company submission describes a cost utility analysis (CUA) of extended CMV prophylactic treatment using valganciclovir oral solution for 200 days versus 100 days in D+/R-[2]. The analysis is restricted to this patient group and does not inform the use of valganciclovir in recipients who are CMV-positive, or in other SOT patients (for whom the licensed duration of prophylactic therapy remains 100 days[1]).

A simple clinical pathway is modelled. Patients enter the model following transplantation and may continue in a healthy graft state or progress to dialysis (90% haemodialysis and 10% peritoneal dialysis) and/or death. Results of a bioequivalence study are used to support the claim of equivalent efficacy between the tablet and oral solution formulations. Progression to dialysis (i.e. graft failure) is driven by the incidence of CMV disease and acute rejection, as observed in the pivotal phase III IMPACT study of extended prophylactic therapy with valganciclovir tablets[4], and is modelled over ten years using published historical data on the incidence of graft loss based on CMV/acute rejection incidence[19]. Re-transplantation following graft loss is assumed not to be an option. See Appendix 1 for further details.

6.1.2 Results

The results of the base case CUA as presented in the company submission are displayed in Table 1.

Table 1. Company-reported cost utility analysis results[2]

	200 days of treatment	100 days of treatment	Increment
Total costs	£64,499.45	£64,000.57	£498.97
Life-years gained	6.9513	6.9224	0.02892
QALYs gained	5.2486	5.1972	0.0513
ICER	**£9,721 per QALY gained**		
ICER = Incremental cost effectiveness ratio; QALYs = Quality-adjusted life years			

One-way sensitivity analyses indicate that the incremental cost effectiveness ratio (ICER) is sensitive to the proportion of patients receiving haemodialysis or peritoneal dialysis following graft failure, the ongoing costs of healthy grafts after the first year, and the actual dose of valganciclovir received.

The ICER ranges from £7,138 per quality-adjusted life year (QALY) gained when all patients are assumed to receive haemodialysis, to £32,966 per QALY gained if all patients are assumed to receive peritoneal dialysis. When the ongoing costs of healthy graft after the first year are assumed to be equal to those in the first year, the ICER increases to £18,476 per QALY gained. When the dose of valganciclovir is increased from the mean doses observed in the IMPACT trial to the SPC-recommended dose of 900mg once daily, the ICER increases to £30,901 per QALY gained (although this

would be applicable only to patients with CrCl ≥60 ml/min, and the IMPACT trial is reported to have demonstrated a mean daily dose of 625.6 mg over 200 days of treatment).

A further scenario analysis has been conducted to reflect the use of oral solution in patients with delayed graft function (assumed to be around 8% of patients based on expert opinion) that require initial haemodialysis until adequate renal function is achieved. When oral solution is assumed to be used for the first seven days before switching to the tablet formulation, the ICER changes little from the base case analysis, as would be expected.

Analyses have been conducted to explore differential effects among the four different combinations of CMV disease status and acute rejection,which suggest that the overall incremental cost per QALY estimates are driven by the impact of prophylaxis on the incidence of CMV and acute rejection.

The ICER is relatively stable to the assumed utility weights and costs associated with acute rejection, graft failure and CMV disease management. Probabilistic sensitivity analyses to explore the combined uncertainty in several parameter values have not been conducted.

6.1.3 WMP critique of the company's economic evidence

Strengths of the economic evidence include:

- In the absence of alternative sources, the company has made reasonable attempts to model long-term outcomes using a range of data sources.

Limitations to the economic evidence include:

- All analyses may have underestimated the acquisition costs of valganciclovir as, for each 100 ml bottle, up to 12 ml of solution is potentially unavailable for use. The model is very sensitive to the assumed acquisition costs, and the reported ICERs may increase significantly when acquisition costs are corrected (see Appendix 1).
- A simplistic clinical pathway is modelled in which patients that experience graft loss are assumed to remain on dialysis for their modelled lifetime. The historical data used to model graft loss over time is derived from patients who received transplants 15–25 years ago. It is unclear whether or not the risks of graft loss are representative of graft failure rates in clinical practice today, as it is likely that advances have been made in the prevention/treatment of acute rejection and CMV disease.
- The sensitivity and scenario analyses presented in the company submission are limited to one-way analyses and do not address key assumptions employed in the model. A significant contributor to modelled costs and outcomes would appear to be dialysis, but key assumptions surrounding risks of graft loss which drive progression to dialysis have not been subjected to sensitivity analysis. The assumed differential effects of treatment have also not been explored via sensitivity or scenario analysis, and no exploration of the impact of available volume per reconstituted bottle of oral solution has been undertaken. Combined uncertainty across multiple parameters has not been explored.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches have identified one published cost effectiveness analysis of 200-day versus 100-day prophylaxis with valganciclovir in the relevant patient population[20]. This was conducted from the perspective of payers in the USA. As in the company submission, the published economic model uses data from the IMPACT trial

to model probabilities of CMV disease and acute rejection over the first year. However, alternative data sources are used to model longer-term outcomes over five years and ten years, and alternative utility values are assumed for patients experiencing CMV disease and AR, and dialysis. Based on a simulated cohort of 10,000 patients, the model estimates an incremental cost effectiveness ratio of $14,900 per QALY gained over a five-year time horizon (based on a gain of 0.0768 QALYs per patient). Over a ten-year time horizon, the model estimates the 200-day regimen to dominate the 100-day regimen, on the basis of greater effectiveness (a gain of 0.238 QALYs per patient) and lower overall costs[20]. The estimated QALY gains with 200 days of valganciclovir are therefore greater in this published paper than are reported in the model provided in company submission[2]. Sensitivity analyses indicate that the published model was most sensitive to the assumed transition probabilities, which were explored within the range +/-10%[20]. Due to the potential differences in health settings, costings and other factors, it is difficult to extrapolate the results of this study directly to the current decision problem. However, this published paper serves to demonstrate alternative means of modelling outcomes beyond the 12-month IMPACT trial data, which have not been fully explored in the company submission[2].

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and methods

Based on personal communication with University Hospital of Wales, the company reports that there were 120 renal transplants in Wales in 2010, with an assumed 6% year-on-year increase[2]. The proportion of D+/R- patients is assumed to be 25%, reportedly based on serostatus data from NHS Blood and Transplant (not verified)[2].

Uptake of the extended 200-day valganciclovir prophylaxis regimen in these patients is assumed to be 100%. No patients are assumed to die during prophylaxis treatment and the dose of valganciclovir assumed in the budget impact estimate is as observed in the IMPACT study (mean of 587.2 mg per day in the 100-day regimen arm and 625.6 mg per day in the 200-day regimen arm)[2]. The company has assumed that the oral solution (which is licensed for use in patients with CrCl <10 ml/min) would be used for only seven days, post-transplant. Patients are then assumed to switch to the tablet formulation (which is licensed only for use in patients with CrCl ≥10 ml/min).

7.1.2 Results

Table 2. Company-reported budget impact analysis[1]

	2011	2012	2013	2014	2015	2016
Assumed number of eligible D+/R- renal transplant patients	31.8	33.7	35.7	37.8	40.1	42.4
100-day regimen cost	£86,013	£91,152	£96,562	£102,242	£108,463	£114,684
200-day regimen cost*	£160,177	£169,747	£179,853	£190,432	£202,019	£213,607
Incremental costs	**£74,164**	**£78,595**	**£83,291**	**£88,190**	**£93,556**	**£98,923**

D+/R- = Donor positive and recipient negative for CMV infection
* The 200-day costs appear to be calculated incorrectly. Actual budget impact will be £23,000 greater than reported in 2011, rising to £30,800 greater than reported in 2016.

7.1.3 WMP critique of the company's budget impact estimates

The estimated number of renal transplants appears to be limited to those performed at the University Hospital of Wales in Cardiff and does not include those referred to the Royal Liverpool University Hospital and other centres. This would underestimate the potential number of eligible patients and the associated budget impact. The usual recommended dose of valganciclovir is 900 mg daily in patients with CrCl ≥60 ml/min, with reduced doses for those with lower CrCl. The actual budget impact will therefore depend upon doses of valganciclovir used in practice. As observed in the economic model, the acquisition costs of the oral solution may be underestimated by up to 12%. Collectively, the company's estimates of budget impact would appear to be subject to significant uncertainty.

7.2 Comparative unit costs

A range of CMV prophylactic regimens are reported in the literature[3]. Doses of drugs need to be tailored to patients based on renal function, which may be subject to change over time. Table 3 provides example costs of regimens during prophylaxis.

Table 3. Example acquisition costs for CMV prophylaxis in renal transplant patients

Regimen	Drug acquisition cost per regimen[‡]
Valganciclovir (Valcyte®) tablets: 450 mg twice weekly to 900 mg once daily, based on CrCl 10 to ≥60 ml/min[†]*	100 days: £514.98 to £3,604.87 200 days: £1,029.96 to £7,209.73
Valganciclovir (Valcyte®) oral solution: 100 mg three times weekly to 900 mg once daily, based on CrCl <10 to ≥60 ml/min*	100 days: £197.42 to £4,145.76 200 days: £394.84 to £8,291.52
Ganciclovir (Cymevene®) intravenous solution: 1.25 mg/kg/day to 5.0 mg/kg/day, based on CrCl <10 to >70 ml/min*	28 days (assuming 70 kg adult): £833.56
Valaciclovir (non-proprietary) tablets: 1.5 g once daily to 2 g four times daily, based on CrCl <10 to >75 ml/min*	90 days: £516.21 to £2,753.14

CrCl = Creatinine clearance
* Induction doses may be higher. See the individual Summaries of Product Characteristics for specific dosing recommendations[1,17,21,22]
[†] Valganciclovir tablets not licensed for use in haemodialysis patients (CrCl <10 ml/min)[17]. Regimen duration based on British Transplant Society guidelines[3].
[‡] Costs based on British National Formulary list prices assuming vial wastage where applicable[23].
This table does not imply therapeutic equivalence between drugs and doses.

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that valganciclovir is not suitable for shared care within NHS Wales.

8.2 Ongoing studies

There are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

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Appendix 1. Additional health economic analysis information

Table 1A. Health economic analysis detail[2]

	Base case model	Appropriate?
Comparator(s)	100 days of valganciclovir prophylaxis post-transplant versus 200 days of valganciclovir post-transplant.	Yes, as requested by WMP. The economic evidence does not permit comparison against other agents that may be used for CMV prophylaxis.
Population	Adult patients that have undergone kidney transplantation were CMV-negative prior to transplantation and received an organ transplant from a CMV-positive donor. The modelled cohort is stratified into four subgroups according to CMV and AR status, as observed in the 12-month IMPACT study[4] following 100-day or 200-day prophylactic treatment: • CMV-negative and AR-negative (CMV-/AR-) • CMV-positive and AR-negative (CMV+/AR-) • CMV-negative and AR-positive (CMV-/AR+) • CMV-positive and AR-positive (CMV+/AR+).	The modelled population is restricted to a subset of the licensed indication, namely those that have undergone kidney transplantation and were CMV-negative prior to receipt of a kidney from a CMV-positive donor. The company submission notes that it is unknown if the IMPACT study results can be extended to other transplant recipients or other risk categories within renal transplant, such as CMV-positive recipients[2]. The model therefore does not relate to patients who are CMV-positive prior to transplant or have received other solid organ transplants (e.g. heart, liver) or to the use of valganciclovir in the treatment of CMV retinitis in patients with AIDS[1].
Analysis type	CUA based on a Markov model with a one-year cycle. Patients enter the model following transplantation and may continue in a healthy graft state or progress to dialysis (90% heamodialysis and 10% peritoneal dialysis) and/or death.	CUA is the preferred type of analysis. A simple clinical pathway is described for the target population. CMV disease is implicitly assumed to have only renal impacts, and patients who experience graft failure and progress to dialysis are assumed to remain on dialysis for the remainder of their modelled lifetime (i.e. re-transplant is not an option).
Perspective	Considers direct medical costs only, from perspective of NHS Wales.	Yes.
Time horizon	A ten-year time horizon of analysis has been modelled.	A lifetime horizon would be appropriate. Sensitivity analysis appears not to have been undertaken around the time horizon.
Discount rate	3.5% applied to both costs and outcomes.	Yes.
Efficacy	Results of a bioequivalence study between the oral solution and the tablet formulation are used to support the use of the results from the IMPACT study for the oral solution[2]. The probabilities of patient transition from having a healthy graft to a state requiring dialysis are reportedly derived from a US-based retrospective observational study of graft survival and CMV incidence in adults who received a first kidney transplant between 1985 and 1997[19]. Mortality risk for patients with healthy grafts is reportedly derived from NHS Blood and Transplant data and the probability of death in patients with healthy grafts is assumed to be linear over time. Patients on dialysis are assumed to have an elevated risk of death (3.5-fold over one year or more) compared with transplanted patients, based on longitudinal survival data from Scotland[24]. The proportion of patients in each of the four CMV/AR subgroups have reportedly been derived from the incidence of CMV disease and acute rejection episodes observed in each arm of the IMPACT trial at 12 months (Company data on file). The AR- subgroups are assumed to have the same transition probabilities.	There are a number of limitations in the presentation and reliability of the data used to model effectiveness. The proportions of patients within each of the four CMV/AR subgroups in the IMPACT trial, and the assumed mortality rate for patients with healthy grafts, are referenced to data on file and have not been verified by WMP. All are assumed to be constant over time, which implicitly assumes the proportions of patients in each CMV/AR subgroup at 12 months post transplant remains constant over time. This has not been tested in sensitivity analysis and there are no estimates of the proportions of patients in each of the four CMV/AR subgroups at the same time point after cessation of prophylactic therapy. However, abstract-published follow-up data at two years post transplant are consistent with the 12-month data[2]. The data from the retrospective observational study of graft survival and CMV incidence (used to model the risk of graft loss based on CMV/AR status) relates to renal transplants that were carried out 15–25 years ago. It is unclear whether or not these risks of graft loss are representative of graft failure rates in clinical practice today, as it is likely that advances have been made in the prevention/treatment of AR and CMV disease. A Health Technology Assessment (HTA) of immunosuppressive regimens published in 2005 notes that few grafts are lost due to AR now due to advances in immunosuppression therapy[25]. The risk of graft loss would appear to be a key contributor to overall QALY gains and costs, due to the impact of graft loss on the probability of requiring dialysis. However, no sensitivity analyses have been conducted on the assumed risks of graft loss associated with CMV/AR status. Overall rates of graft loss were low and similar at 12 months among the 100-day and 200-day treatment regimens (1.8% and 1.9%, respectively) in the IMPACT study[4].

Table 1A. Continued

	Base case model	Appropriate?
Adverse effects	Assumed to be identical between the two arms and so are effectively excluded from the model.	There are some numerical differences in the incidence of leucopenia and hospitalisation for adverse events noted in the IMPACT study publication; however, safety data from this study are limited[4].
Utility values	Utility values for each modelled health state are derived from a published prospective CUA that employed a time trade-off technique to estimate utility weights over a two-year period post kidney transplant in Canada in the early 1990s[26]. Assumptions have been made regarding the disutility associated with CMV disease and/or AR.	These utility data were derived over 15 years ago, and it is unclear whether or not these reflect current patient experience and QoL. However, the limited sensitivity analyses presented in the submission suggest that the model outputs are relatively insensitive to the actual utility weights assumed[2].
Resource use and costs	Relate to prophylactic drug acquisition costs, management of CMV disease (based on UK expert opinion in the base case analysis), the resource use and management of patients in the first and subsequent years based around published cost data, with appropriate adjustments to avoid double counting.	Valganciclovir is costed on a per mg basis, reportedly using mean doses observed in the IMPACT study (company data on file, not verified by WMP). The mean daily dose of valganciclovir in the first 100 days of therapy was 9% higher in the 200-day arm of the trial (644.3mg) compared with the 100-day arm (587.2mg), and the mean daily dose over 200 days is also higher (625.6mg), which would result in greater drug acquisition costs for the 200-day arm. Valganciclovir dosing is dependent upon renal function, and sensitivity analysis indicates that, when both 100-day and 200-day regimens are dosed as recommended for patients with creatinine clearance ≥60 ml/min (900 mg daily), the ICER increases dramatically to £30,900 per QALY gained, although the IMPACT trial demonstrated that the majority of patients would not have received valganciclovir at a dose as high as 900mg daily. The model assumes that a 100 ml bottle of solution is able to provide 100 ml of solution; however, the SPC notes that the available volume may be as low as 88 ml per 100 ml bottle (presumably due to the dose delivery adaptor fitted to the bottle)[2]. The actual acquisition cost may therefore be underestimated by up to 12%. The model is very sensitive to the assumed valganciclovir acquisition costs and the company has not provided sensitivity analysis around this. It appears from the model that correction of a 12% underestimate in acquisition costs increases the base case ICER (using the reported doses observed in the IMPACT trial) to around £17,800 per QALY gained. Several sensitivity/scenario analyses have been conducted around key assumptions related to non-prophylactic drug costs and sources of resource use. The IMPACT study indicates that the 12-month incidence of CMV-associated hospitalisations was halved in the 200-day group compared with the 100-day group (10.4% versus 20.8%), but the incidence of overall hospitalisations was similar. Sensitivity analyses have not been conducted around these findings[4].
Uncertainty and scenario analyses	Several one-way sensitivity and scenario analyses have been conducted.	One-way sensitivity analyses are mainly limited to cost and utility assumptions applied equally to both arms of the model. No sensitivity/threshold analyses have been conducted to explore differential effects of treatment regimens (such as the incidence of CMV/AR), nor the key parameters of assumed rates of graft loss, etc. Probabilistic sensitivity analysis has not been conducted to explore the impact of combined uncertainty across several parameters.
Model provided?	Yes.	-

AR = Acute rejection; CMV = Cytomegalovirus; CUA = Cost utility analysis; CrCl = Creatinine clearance; HTA = Health Technology Assessment; ICER = Incremental cost effectiveness ratio; QALY = Quality-adjusted life year; QoL = Quality of life; WMP = Welsh Medicines Partnership