Clinical Expert Summary

Valganciclovir (Valcyte®) tablets for 200 days prophylaxis of cytomegalovirus (CMV) disease in CMV-negative kidney transplant patients who have received a transplant from a CMV-positive donor

1. Existing guidelines

One expert cited Cardiff Transplant Unit guidance on the prescribing of valganciclovir for CMV prophylaxis post renal/pancreas transplant, which has been in place for a number of years. The expert highlighted that these guidelines recommend that patients receive CMV prophylaxis with valganciclovir for three months post transplant dependent on the CMV status of organ donor and organ recipient and type of immunosuppression regimen. The British Transplant Society (BTS) Guidelines for the Prevention and Management of CMV Disease after Solid Organ Transplantation[1] were also cited by experts. One expert stated that this recommends using one of the following:

- Oral valganciclovir for at least 100 days
- Oral valganciclovir for 200 days
- Oral valaciclovir for 90 days
- Intravenous ganciclovir (Cymevene®) for 28 days
- Serial measurements of viral load and treatment with oral valganciclovir or intravenous ganciclovir when levels predictive of disease are reached.

2. Disease prevalence

One expert estimated that 100–140 transplants are undertaken per year at the Cardiff Transplant Unit and this activity is increasing. It was suggested that approximately 80% of these (80–112 patients) would be prescribed three months CMV prophylaxis with valganciclovir in line with local guidance. The expert noted that this guidance is not restricted to CMV sero-negative recipients of CMV sero-positive donor organs as described in the manufacturers SPC. It was noted that many CMV-positive recipients of CMV-positive or CMV-negative donors are also prescribed valganciclovir prophylaxis according to their anti-rejection drug regimen. The expert concluded that implementing the license extension would not change the number of patients in Wales receiving CMV prophylaxis with valganciclovir.

Another expert stated that a review of CMV incidence in Cardiff Transplant Unit (01/2004–12/2007) found that 60% of the 339 recipients during this period required CMV prophylaxis. However, the expert suggested that due to the changes in types of donors accepted for organ transplantation (increased age) and intensity of immunosuppression the current percentage of patients needing prophylaxis will need to be re-evaluated and has most likely increased.

One expert estimated that approximately 12 patients per year would require this medication if 200-day prophylaxis was reserved for those undergoing immunological high risk transplantation. If this was extended to include donor positive/recipient negative (D+/R-) transplants (which is the indication covered in the submission), assuming that 20% of transplants fall into this category, approximately 25 patients were estimated to require this treatment. The expert estimated that inclusion of D+/R+ and D-/R+ transplants, assuming 70% of transplants fall in this category, results in approximately 85 patients further per year.

3. Current treatment options

Experts highlighted oral valganciclovir for 100 days post-transplantation as a current treatment strategy for CMV prophylaxis. Other potential options cited by experts include oral valaciclovir, aciclovir or no oral prophylaxis but monitoring of CMV and pre-emptive treatment with valganciclovir or intravenous ganciclovir when necessary. However, one expert stated that only valganciclovir, not other options, were currently used at Cardiff Transplant Unit.

One expert stated that the preferred option would be to continue with 100 days prophylaxis for the majority of at-risk recipients, with the 200-day period being used for those at particularly high risk. The expert considered these to be those recipients who undergo desensitisation to receive an immunologically incompatible transplant, who receive intense induction treatment and multiple blood products. It was highlighted that the recovery of immunological stability, and hence ability to respond to CMV infection, would be expected to be longer in these patients, and thus justify the 200 day period of prophylaxis. The expert stated that any change in prescribing policy will continue to be followed with prospective audit.

4. Unmet needs

One expert suggested that there has been a change to higher intensity immunosuppression regimes and a predicted shift in the type of organs available for transplantation, increasing the age of donors. The expert stated that the incidence of CMV disease and its associated effects will need to be re-evaluated in more recent transplants. Another expert asserted that there were no areas of unmet need locally in relation to CMV prophylaxis.

5. Knowledge of product in given indication

One expert stated that the license extension to 200 days valganciclovir CMV prophylaxis had been discussed by the Cardiff Transplant Unit team and as yet there were no plans to implement any changes to current CMV prophylaxis guidance. The expert also cited local audit data, which indicates that rates of active CMV disease requiring treatment with, for example, intravenous ganciclovir, are relatively low. Additionally, the data cited by the expert demonstrates that where CMV treatment is required it is relatively straightforward (though may involve short stay in hospital to initiate intravenous ganciclovir) and does not appear to adversely impact on patient outcomes such as incidence of acute organ rejection. It was suggested that these issues need to be considered because CMV prophylaxis with valganciclovir is extremely expensive and the drug is not without side effects. The expert stated that the transplant team will continue to review local CMV guidance if new evidence emerges related to complications of CMV infection/disease in solid organ transplant patients.

One expert cited the IMPACT 200 study[2], which was industry-sponsored and demonstrated the efficacy and safety of a 200-day period of CMV prophylaxis with valganciclovir in high risk patients. The expert stated that the cost effectiveness of this approach has been studied in both US and UK renal transplant populations[3,4]. It was highlighted that several other studies have reported the benefits of a 200-day period of prophylaxis, with avoidance of CMV disease and improved renal function, with some clinicians advocating life-long treatment[5]. The expert also noted that the incidence of leucopoenia attributable to valganciclovir is relatively low in the second 100 days, and the risk of development of valganciclovir-resistant CMV strains is also low despite extended prophylaxis[6]. However, the expert highlighted that other studies have reported a high rate of CMV disease despite this extended prophylaxis[7], favouring a policy of

screening and early treatment over continued prophylaxis. It was stated that the interpretation of the IMPACT 200 results has also been criticised; – analysis was univariate, with no correction for confounders, notably treatment of rejection and initial induction treatment[8].

References

1 British Transplantation Society. Guidelines for the prevention and management of CMV disease after solid organ transplantation. 2011. Available at: http://www.bts.org.uk/EasySiteWeb/GatewayLink.aspx?alId=908. Accessed Mar 2011.

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6 Chou S, Marousek G, Boivin G et al. Recombinant phenotyping of cytomegalovirus sequence variants detected after 200 or 100 days of valganciclovir prophylaxis. *Transplantation* 2010; 90 (12): 1409-13.

7 Helantera I, Lautenschlager I, Koskinen P. Prospective follow-up of primary CMV infections after 6 months of valganciclovir prophylaxis in renal transplant recipients. *Nephrol Dial Transplant* 2009; 24 (1): 316-20.

8 Kalil AC, Sun J, Florescu DF. IMPACT trial results should not change current standard of care of 100 days for cytomegalovirus prophylaxis. *Am J Transplant* 2011; 11 (1): 18-21.