Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

valganciclovir, 450mg tablets, 50mg/ml powder for oral solution (Valcyte®) SMC No. (662/10)

Roche Products Ltd

17 December 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Valganciclovir (Valcyte®) is accepted for restricted use within NHS Scotland.

Indication under review: prevention of cytomegalovirus (CMV) disease in CMV negative patients who have received a solid organ transplant from a CMV positive donor. The marketing authorisation has been amended to allow the duration of CMV prophylaxis in kidney transplant patients to be increased from 100 days to 200 days post-transplantation

SMC restriction: valganciclovir should be initiated by physicians experienced in the care of post-transplant patients.

In a randomised controlled study there was a significant reduction in the incidence of CMV disease at 12 months following 200-day versus 100-day prophylaxis.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Prevention of cytomegalovirus (CMV) disease in CMV negative patients who have received a solid organ transplant from a CMV positive donor. [Change to indication: for **kidney transplant patients**, prophylaxis may be continued until 200 days post-transplantation, previously 100 days.]

Dosing Information

For kidney transplant patients, the recommended dose is 900mg (two valganciclovir 450mg tablets or 18ml of valganciclovir 50mg/ml oral solution) once daily, starting within 10 days of transplantation and continuing until 100 days post-transplantation. Prophylaxis may be continued until 200 days post-transplantation. Dosage adjustment is required in patients with renal impairment according to the calculated creatinine clearance based on the serum creatinine.

Product availability date

11 June 2010

Summary of evidence on comparative efficacy

The submission relates to an extension to the marketing authorisation for valganciclovir in the prevention of cytomegalovirus (CMV) disease in CMV negative patients who have received a solid organ transplant from a CMV positive donor. Valganciclovir, in patients receiving kidney transplantation only, may now be given for 200 days post-transplantation (the marketing authorisation previously specified that prophylaxis may be continued for up to 100 days).

One phase III multi-centre double-blind randomised placebo-controlled study has been conducted and supports this extension to the licence. It compared the safety and efficacy of valganciclovir 900mg orally daily (adjusted for renal function) for 200 days versus valganciclovir 900mg orally daily (adjusted for renal function) for 100 days followed by placebo for 100 days in patients aged ≥ 16 years who were seronegative for CMV disease and at high risk of CMV disease following kidney transplantation from a seropositive donor (D+/R-). Treatment was started as soon as the patient was able to tolerate oral medicines and no later than 10 days post transplant. In patients who were unable to tolerate oral medicines, ganciclovir 5mg/kg intravenously was allowed up until day 10 post transplant or until the patient could tolerate oral medicines (whichever was sooner).

The intent-to-treat (ITT) population, which included all patients randomised and were D+/R- and who received at least one dose of study drug, was used in the efficacy analysis and included 155 and 163 patients in the 200-day and 100-day groups respectively.

The primary endpoint was the proportion of patients who developed CMV disease (CMV syndrome or tissue invasive CMV) within the first 12 months. CMV syndrome was defined as CMV viraemia identified by quantitative polymerase chain reaction (or pp65 antigenaemia and other sponsor-approved CMV assays) and at least one of the following: fever ≥ 38°C, new onset severe malaise, leucopenia on two successive measurements separated by at least 24 hours (defined as a white blood cell [WBC] count of <3500 cells/microlitre if presymptomatic count was ≥ 4000 cells/microlitre or a decrease in WBC of >20% if the presymptomatic count was <4000 cells/microlitre), atypical lymphocytosis of ≥ 5%, thrombocytopenia (defined as a platelet count of <100,000 cells/microlitre if the prior count was ≥115,000 cells/microlitre or a decrease of >20% if the prior count was <115,000 cells/microlitre), or elevation of hepatic transaminases to ≥ 2 × upper limit of normal (ULN). Tissue invasive CMV was defined as evidence of localised CMV infection (CMV inclusion cells, in situ detection of CMV antigen, cell culture or DNA by immunostain or hybridisation, respectively) in a biopsy or other appropriate specimen (e.g. bronchoalveolar lavage, cerebral spinal fluid) and symptoms of organ dysfunction.

The proportion of patients with CMV disease by 12 months post-transplant was 16% (25/155) versus 37% (60/163) in the 200-day and 100-day groups respectively ($p<0.0001$). The between group difference was -20.7%, 95% confidence interval (CI) -30.4% to -10.9%, odds ratio 0.33 (95% CI 0.19 to 0.56). Most patients with CMV disease had CMV syndrome (83/85 [98%]) and it was classed as mild to moderate in severity for 83% versus 76% of cases in the 200-day and 100-day groups respectively. There were three cases of biopsy confirmed tissue invasion; one case at day 215 versus two cases at days 119 and 132 in the 200-day and 100-day groups respectively. All cases were gastrointestinal and resolved with intravenous ganciclovir or valganciclovir.

Secondary endpoints included proportion of patients with CMV disease at 6 and 9 months post transplant, proportion of patients with CMV viraemia, proportion of patients who experienced biopsy-proven acute rejection (BPAR), proportion of patients with graft loss and proportion of patients surviving. The proportion of patients with CMV disease in the 200-day group was significantly lower than the 100-day group at 6 and 9 months. The proportion of patients with CMV viraemia in the 200-day group was significantly lower than the 100-day group at 12 months (37% [58/155 versus 51% [83/163]). BPAR occurred in less patients in the 200-day group than the 100-day group (17 [11%] versus 28 [17%]), although the difference was not statistically significant. Three patients in each group had graft loss. There were no deaths in the 200-day group versus four deaths in the 100-day group (one in the first 100 days of treatment); none were considered related to study treatment.

Follow-up data at 24 months are available and have been published in abstract form. At 24 months CMV disease occurred in 21% (33/155) versus 39% (63/163) of patients in the 200-day and 100-day groups respectively ($p<0.0008$). Tissue invasive CMV occurred in two (1.3%) versus three (1.8%) of patients. There were no statistically significant differences between the groups for rates of acute rejection (12% versus 17%) and graft loss (1.9% versus 4.3%).

Summary of evidence on comparative safety

Most patients reported an adverse event (AE); 97% versus 96% in the 200-day and 100-day groups respectively. The proportion of patients who reported an AE considered to be remotely, possibly or probably related to study treatment was 60% (93/156) versus 52% (86/164) and these were mainly haematological (including leucopenia) in nature. A similar percentage of patients in each group had a drug-related serious AE (8% each).

In terms of haematological AE, there was a similar rate of neutropenia, febrile neutropenia, agranulocytosis, anaemia, thrombocytopenia and pancytopenia between groups with only leucopenia incidence being different between groups (38% versus 26%). Leucopenia was classed as grade 3/4 in 14% of cases and seven patients versus one patient in the 200-day and 100-day groups respectively had leucopenia that led to discontinuation of study medication. Gastrointestinal AE included diarrhoea (31% [49/156] versus 26% [43/164]), nausea (11% [17/156] versus 11% [18/164]) and constipation (9% [14/156] versus 15% [25/164]).

AE from day 100 onwards that occurred more frequently in patients taking valganciclovir for 200 days included leucopenia (19% versus 4%) and upper respiratory tract infection (7% versus 2%). The summary of product characteristics (SPC) for valganciclovir notes that when extending prophylaxis beyond 100 days the possible risk of developing leucopenia and neutropenia should be taken into account. In the study the majority of the myelotoxic laboratory abnormalities were resolved by treatment with granulocyte colony stimulating factor (G-CSF) or interruption of study drug. Although G-CSF was permitted a detailed analysis of its use was not undertaken, however overall the use of G-CSF was similar between the 200-day and 100-day groups (14% [22/156] versus 13% [22/164]).

Summary of clinical effectiveness issues

Patients recruited to the study were seronegative for CMV and received kidney transplantation from a CMV seropositive donor; this study population is comparable to those patients who would be eligible for treatment according to the licensed indication. There was a significant difference in favour of the 200-day group compared to 100-day group for the primary endpoint, the proportion of patients with CMV disease at 12 months.

However there are some limitations and uncertainties with respect to the study. Firstly, immunosuppressive treatments that patients were receiving concurrently were not controlled in the study and no details of immunosuppressive agents used were provided in the published report. Therefore the patients recruited to the study may not reflect Scottish clinical practice in terms of concurrent immunosuppressive treatment. International Consensus Guidelines on “The Management of Cytomegalovirus in Solid Organ Transplantation” note that “the choice of CMV prophylaxis duration may depend on degree of immunosuppression, including the using of antilymphocyte antibodies for induction”. Secondly, endpoints such as the proportion of patients who experienced BPAR, proportion of patients with graft loss and the proportion of patients surviving may have more clinical relevance. For BPAR there was no significant difference between the groups although there was a trend for less BPAR in the 200-day group versus 100-day group (11% versus 17%). An additional post hoc analysis was undertaken by the company. The proportion of patients who had CMV disease and were BPAR positive in the 200-day and

100-day groups was 3.9% versus 8%. Finally, 98% of CMV disease was classed as CMV syndrome which was of mild/moderate severity in 83% versus 76% patients in the 200-day and 100-day groups respectively. Therefore the reduction in CMV disease (primary endpoint) relates mainly to patients with mild to moderate CMV syndrome and there was a slight disparity between the two groups in terms of severity. The clinical relevance of this is uncertain.

With this change to the licence patients may now receive CMV prophylaxis for 200 days post transplantation where previously a treatment duration of 100 days was specified. A 200-day treatment duration is currently being used in the two renal transplant units in Scotland. Adverse events that occurred after day 100 and were higher in the 200-day group included leucopenia and upper respiratory tract infection. No quality of life data are available and therefore the impact of an additional 100 days treatment on quality of life is not known.

A Cochrane review of antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients was published in 2010. The review included 19 studies (n=1981) published between 1989 and 2002 investigating aciclovir, ganciclovir or valaciclovir versus placebo or no treatment. A significant reduction in CMV disease (documented CMV infection with clinical symptoms) and all cause mortality was demonstrated versus placebo. The authors acknowledged that valganciclovir is the antiviral agent most often used in clinical practice and considered that the results of the systematic review of placebo controlled studies were applicable to valganciclovir. However they also noted that further studies are required to determine optimal duration of prophylaxis and dosage, the comparative efficacy and safety of antiviral agents, and efficacy with different immunosuppressive regimens. This systematic review predates the publication of the valganciclovir study supporting the change to licence with respect to the duration to treatment.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility model of the impact of 200 days of valganciclovir compared to 100 days of valganciclovir among D+/R- renal transplant patients over a ten year horizon. This largely modelled the impacts of Acute Rejection (AR) and CMV status on the likelihood of graft rejection. The rates of these were differentiated between the arms in line with a post hoc analysis of the pivotal trial. The daily dose assumed for valganciclovir was based on market research rather than on the pivotal trial.

The likelihood of graft rejection as a function of AR and CMV status was based upon a paper in the literature. This assessed rejection rates over a ten-year time horizon, finding that among AR negative patients CMV status had no real impact, but among AR positive patients CMV positive status increased rejection rates.

Graft rejection led to dialysis, which was associated with higher annual costs, a worse quality of life and a higher annual mortality. Quality of life values were drawn from the literature, as were the main additional cost elements within the analysis.

This resulted in an estimated additional cost of £348 and an additional 0.05 quality adjusted life years (QALYs), to yield a cost effectiveness ratio of £6,785 per QALY. Results were sensitive to the direct drug costs, the ongoing costs of a healthy graft, the ongoing costs of dialysis and the mortality multiplier associated with dialysis.

Additional analysis applying the direct drug costs observed within the trial improved the cost effectiveness of 200 days treatment to £1,868 per QALY.

It should be noted that due to the high costs of dialysis, removing the mortality multiplier associated with dialysis led to 200 days treatment dominating 100 days treatment: i.e. lessening the mortality associated with dialysis improved patient outcomes in the 100 days arm, but given annual dialysis costs of around £32k this improved the cost-effectiveness of 200 days prophylaxis. Increasing the time horizon to 15 years typically also led to 200 days treatment dominating 100 days treatment under a variety of extrapolation scenarios.

Weaknesses included:

- not considering the cost and quality of life impacts from adverse events; and
- potentially too large a disutility being associated with dialysis.

However, the cost-effectiveness result was not particularly sensitive to changes in the above parameters. As such, the cost effectiveness of 200 days valganciclovir has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British Transplantation Society published "Guidelines for the prevention and management of cytomegalovirus disease after solid organ transplantation" in 2004. CMV seronegative recipients who receive a solid organ transplant from a donor who is seropositive should be offered prophylaxis against primary infection. For renal transplant recipients the recommended prophylactic strategy is one of: valaciclovir for 90 days post transplant, oral ganciclovir for 90 days post transplant [no longer available in UK], intravenous ganciclovir for 28 days, oral valganciclovir for 100 days, high dose oral aciclovir for 12 weeks or intermittent intravenous CMV hyperimmune globulin for 12 weeks. Serial measurements of viral load with treatment with intra-venous ganciclovir or oral valganciclovir when levels predict disease or serial measurements of viral load with treatment with oral ganciclovir when levels predict disease are also recommended.

The American Society of Transplantation Infectious Diseases Community of Practice published a paper entitled "Cytomegalovirus in Solid Organ Transplant Recipients" in 2009. In D+/R– kidneys and livers, valganciclovir 900mg/day, oral ganciclovir 3g/day [no longer available in UK], or intravenous ganciclovir 5mgkg/day prophylaxis are effective for prevention of CMV disease. In kidney transplant recipients, valaciclovir 8g/day is an alternative. Prophylaxis should be initiated within 10 days posttransplant and continue until ~3 to 6 months posttransplant.

International Consensus Guidelines on "The Management of Cytomegalovirus in Solid Organ Transplantation" were published on behalf of the Transplantation Society International CMV Consensus Group in 2010.The duration of prophylaxis in D+/R- patients should be generally between 3 months and 6 months (and may depend on degree of immunosuppression, including the using of antilymphocyte antibodies for induction). When a prophylaxis strategy is used for prevention in D+/R- kidney transplant patients the following antiviral medications are

recommended: valganciclovir, IV or oral ganciclovir [no longer available in UK], or valaciclovir. When used for prophylaxis, the usual dose of valganciclovir is 900mg a day, versus treatment dose which is 900mg twice daily; both should be adjusted for renal function.

The guidelines predate the extension to the licensed duration of treatment to 200 days for valganciclovir.

Additional information: comparators

No other antiviral agent is specifically licensed for a duration of 200 days in CMV prophylaxis Valaciclovir has been included in the table below as the SPC notes that treatment may need to be extended (beyond the specified 90 days) for high risk patients.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Valganciclovir tablets or oral solution	**900mg orally once daily for 200 days**	**7,210 to 8,292***
Valaciclovir tablets	2g orally four times daily for 200 days**	6,246

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 22 September 2010.

* Cost will be lower in patients who require dose adjustment due to renal impairment.

** licensed for 90 days treatment duration, although treatment may need to be extended for high risk patients.

Additional information: budget impact

The manufacturer assumed a 100% market share for valganciclovir. Based on an estimated 79 eligible patients receiving 200 days of prophylaxis instead of 100 days in year 1 and 99 patients in year 5, the manufacturer estimated gross drug costs of £457k and £577k respectively. The corresponding net drug costs were £228k in year 1 and, £289k in year 5. SMC experts have indicated that as there is already some use of 200 day prophylaxis the incremental budget impact in practice may be smaller.

References

The undernoted references were supplied with the submission. The one shaded in grey is additional to those supplied with the submission.

Humar A et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. Am J Transplantation 2010; 10: 1228-1237

Roche data on file Final Variation Assessment Report, Valcyte, Valganciclovir, NL/H/323/001-002/II/024)

Humar A et al, Long Term Results of the IMPACT Study: 200 vs 100 Days of Valganciclovir Prophylaxis in Kidney Recipients. American Transplant Congress 2010; abstract 350

Hodson EM, Craig JC, Strippoli GFM, Webster AC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD003774. DOI:10.1002/14651858.CD003774.pub3

This assessment is based on data submitted by the applicant company up to and including 12 November 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.