HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASE
New medicinal product
September 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

PREVYMIS (letermovir), antiviral

High clinical benefit and minor clinical improvement in the prevention of CMV reactivation and CMV disease after allogeneic haematopoietic stem cell transplantation

Main points

- PREVYMIS has MA for the prevention of cytomegalovirus (CMV) reactivation and CMV disease in adult CMV-seropositive allogeneic haematopoietic stem cell transplantation (HSCT) recipients [R+].
- It has demonstrated its efficacy, particularly in terms of the reduction of pre-emptive treatment initiation, with no blood toxicity.
- Its clinical impact on mortality, the incidence of CMV disease or the onset of graft-versus-host disease (GvHD) has yet to be demonstrated.

Therapeutic strategy

- The initiation of treatments to prevent infection (prophylaxis) or disease (pre-emptive treatment) in the months following transplantation reduces the frequency and severity of CMV disease.
- CMV disease prevention is essentially based on regular (weekly or monthly) viral load measurements in the months following transplantation resulting in the initiation of a pre-emptive antiviral treatment over a threshold considered to be associated with a high risk of onset of clinical signs (generally 3 to 4 log copies/mL). The antivirals used for pre-emptive treatment are: CYMEVAN (ganciclovir), ROVALCYTE (valganciclovir), FOSCAVIR (foscarnet), associated if possible with a reduction in the immunosuppressant treatment.
- **Role of the medicinal product in the therapeutic strategy**
  PREVYMIS is the only antiviral indicated for the prevention of CMV reactivation and CMV disease in adult CMV-seropositive allogeneic haematopoietic stem cell transplantation recipients [R+]. Its use should commence no later than 28 days post-transplantation and should be the subject of a detailed assessment after 100 days post-transplantation in the absence of a demonstrated benefit.

Clinical data

- A double-blind, randomised study assessed the efficacy and safety of letermovir (n=373) versus placebo (n=192) in CMV-positive adults.
- The rate of clinically significant CMV infection at week 24 post-transplantation (primary endpoint combining the onset of CMV disease and the initiation of pre-emptive treatment due to viraemia) was 37.5% (122/325) in the letermovir versus 60.6% (103/170) in the placebo group; therefore a reduction of 23.5% (CI95% [14.6%, 32.5%]; p<0.0001). At week 48 post-transplantation, the rate of CMV disease was 3% (8/325) in the letermovir group and 4% (6/170) in the placebo group. The all-cause mortality was 19% (61/325) in the letermovir group and 24% (40/170) in the placebo group. The rate of GvHD 48 weeks post-transplantation was 59% (190/325) in the letermovir group and 61% (103/170) in the placebo group.

- Care should be taken when interpreting these findings particularly due to the population at a low risk of CMV reactivation included in the study (68% in the letermovir group and 73% in the placebo group), the high number of premature discontinuations of treatment (28% in the letermovir group and 58% in the placebo group) and concomitant antiviral treatments (5% of the patients in the letermovir group were treated with foscarnet during the study, 4% with ganciclovir and 4% with valganciclovir).

- The adverse effects reported most frequently and at a higher frequency than that of the placebo were: nausea, diarrhoea and vomiting. No blood toxicity was observed.

Special prescription requirements

- Medicinal product subject to hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of PREVYMIS is high
- PREVYMIS provides an improvement in actual clinical benefit** (IACB IV, minor) in the prevention of CMV reactivation and CMV disease in adult CMV-seropositive allogeneic haematopoietic stem cell transplantation recipients [R+].
- Approved for non-hospital pharmacy reimbursement for tablet forms and for hospital treatment for all dosage forms.

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This document was drafted on the basis of the Transparency Committee opinion dated 5 September 2018 (CT-16715)
available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"