HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASES
New medicinal product
April 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

VEMLIDY (tenofovir alafenamide), nucleotide analogue

High clinical benefit in chronic hepatitis B, though no demonstrated clinical advantage over VIREAD (tenofovir disoproxil fumarate)

Main points

- VEMLIDY has been granted marketing authorisation for the treatment of chronic hepatitis B in adults and adolescents aged ≥ 12 years.
- Tenofovir alafenamide (TAF) is a tenofovir prodrug developed to reduce plasma tenofovir levels in order to improve the nephrotoxicity and bone toxicity observed with tenofovir disoproxil fumarate (TDF).
- Overall, its efficacy and safety profile is comparable to that of TDF, though data for patients with a risk of poor response are limited.
- It is a first-line option whose use is justified when BARACLUDE (entecavir) or VIREAD (TDF) cannot be used (particularly in the event of resistance to entecavir, renal impairment or bone risk).
- When used, renal function, phosphate-calcium metabolism and lipid parameters should be monitored.

Therapeutic strategy

- When chronic hepatitis B antiviral treatment is indicated, two first-line strategies can be discussed:
  - Interferon alpha (pegylated or non-pegylated) for up to 1 year,
  - A nucleoside or nucleotide analogue over an extended period of time, or even for life in most cases.
- Nucleoside or nucleotide analogue treatment is primarily indicated in AgHBe-positive patients with no interferon response predictive factors and in the majority of AgHBe-negative patients. It is also recommended in patients with cirrhosis, regardless of their HBe status. The treatment objective is the negativation of HBV DNA by PCR.
- Amongst the various nucleoside or nucleotide analogues, entecavir (BARACLUDE) and TDF (VIREAD) are recommended as first-line treatments for their antiviral activity and for their resistance profile, superior to that of other analogues (adefovir, lamivudine, telbuvidine), with relatively good safety.
- **Role of the medicinal product in the therapeutic strategy**
  VEMLIDY is a first-line option whose use is justified when BARACLUDE (entecavir) or VIREAD (TDF) cannot be used (particularly in the event of resistance to entecavir, renal impairment or bone risk).

Clinical data

- TAF efficacy and safety data are derived from two phase III randomised, double-blind clinical studies whose primary endpoint was to demonstrate non-inferiority relative to TDF in adult patients suffering from chronic HBV infection with compensated liver disease.
- These data highlight a safety profile comparable to that of TDF, with less frequent viral responses in patients with factors predictive of a poor response (high viral load [≥ 7 or 8 log10 IU/ml] upon inclusion, or history of treatment), particularly in AgHBe-positive patients.
- The data are very limited for patients with non-complicated cirrhosis and missing for patients with decompensated liver disease or moderate to severe kidney failure (ClCr < 50 ml/min.).
- The TAF safety and resistance profile is globally comparable to that of TDF, despite lower short-term deterioration (96 weeks) in parameters measuring renal and bone function, whose long-term persistence and

impact on fracture and nephrotoxicity risk reduction remains to be demonstrated. An increase in lipid parameters has been more frequently reported for TAF.
- These data are insufficient to position TAF relative to entecavir (BARACLUDE), particularly in patients with kidney failure or with renal and bone fragility or fracture risk factors.

Special prescription requirements

- Initial quarterly prescription reserved for gastroenterology, hepatology, internal medicine or infectious disease specialists.

Benefit of the medicinal product

- The actual clinical benefit* of VEMLIDY is high
- VEMLIDY provides no clinical added value** (CAV V) over tenofovir disoproxil fumarate (VIREAD and its generic forms) for the management of chronic hepatitis B in adults and adolescents over the age of 12 years.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 18 April 2018 (CT-16449) available at **www.has-sante.fr**

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