HAUTE AUTORITÉ DE SANTÉ

INFECTIOLOGY
NEW MEDICINAL PRODUCT
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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

HARVONI (sofosbuvir/ledipasvir), fixed combination of of direct-acting antivirals

Minor improvement in the treatment of adults infected with genotype 1, 3 and 4 hepatitis C virus (HCV) by comparison with the other sofosbuvir combination products that are currently available

Main points

- HARVONI has Marketing Authorisation in the treatment of chronic hepatitis C in adults infected with genotype 1, 3 and 4 HCV.
- It may provide a cure for the majority of patients with hepatitis C, with or without extrahepatic manifestations. Treatment with HARVONI should be offered as a priority in all patients whose hepatic disease is at fibrosis stage F3 or F4 and in certain special populations. Patients infected with genotype 3, in whom early treatment is recommended, are specifically mentioned. Patients at fibrosis stage F2 should also receive new treatments promptly. In F0 or F1 patients, treatment may be delayed according to the progression of the disease and the patient's situation.
- It provides a minor improvement in the treatment of chronic genotype 1, 3 and 4 hepatitis C compared with the other sofosbuvir combination products that are currently available, on account of:
  - its high virological efficacy, which is similar to that observed for the other available sofosbuvir combination products (sofosbuvir + daclatasvir and sofosbuvir + simeprevir), but with a better level of evidence,
  - its safety and acceptable level of risk of resistance and drug interactions.

Therapeutic use

The therapeutic strategy for chronic hepatitis C is currently based on combinations of direct-acting antivirals, with or without ribavirin, which allow high levels of efficacy (> 90%) to be achieved, including in patients who had previously been difficult to treat (particularly patients with cirrhosis or HIV co-infection and recipients of liver transplants). Interferon is of next to no use in the majority of patients.

Role of the medicinal product in the therapeutic strategy

For patients of genotype 1: Of the various sofosbuvir combination products, the sofosbuvir/ledipasvir combination is currently the one with the most satisfactory clinical data in terms of level of evidence and is thus the therapeutic option of choice.
For patients of genotype 3 and 4: The sofosbuvir/ledipasvir + ribavirin combination is a treatment option but there are as yet only limited clinical data (phase II studies).

Clinical data

Patients of genotype 1

The efficacy and safety of the ledipasvir/sofosbuvir fixed combination, with or without ribavirin, have been evaluated in three open uncontrolled studies carried out in patients with HCV genotype 1 infection and compensated liver disease (non-cirrhotic and cirrhotic). Two studies included treatment-naïve patients and a third study patients who had failed to respond to previous treatment with peginterferon + ribavirin ± HCV protease inhibitors (boceprevir/telaprevir).
The duration of treatment was 8, 12 or 24 weeks, depending on the study.

In all the studies, the percentage of patients showing a sustained virologic response 12 weeks after the end of treatment, defined as an HCV RNA level < 25 IU/ml (primary endpoint), was high (> 90%) in the different groups treated as per the regimen specified in the Marketing Authorisation.

- Other populations

The efficacy of the ledipasvir/sofosbuvir fixed combination has also been observed in patients with HCV/HIV co-infection, patients with decompensated cirrhosis or transplant patients, and patients with genotype 3 and 4, but these data are still very limited and further studies are needed to validate the preliminary findings.

- Resistance

Data from in-vitro studies and clinical studies show a high genetic barrier for sofosbuvir and low genetic barrier for ledipasvir.

- Adverse effects

The safety profile is satisfactory overall. The available data have not revealed any major concerns.

Benefit of the medicinal product

- The actual benefit* of HARVONI is substantial.
- HARVONI provides minor clinical added value** (CAV IV) by comparison with the other sofosbuvir combination products currently available for the treatment of adults infected with genotype 1, 3 and 4 HCV.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 04 March 2015 (CT-13953) and is available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".