Pharmacotherapeutic report, summary

Sofosbuvir (Sovaldi®) for the indication chronic hepatitis C in adult patients

Recommendation by Zorginstituut Nederland, dated 14 April 2014, based on an evaluation by the WAR (Scientific Advisory Committee).

The WAR has approved a pharmacotherapeutic report for the medicine sofosbuvir (Sovaldi®) in film-coated tablets. In determining its therapeutic value, it was compared to various treatment regimens with interferon, ribavirin, boceprevir and telaprevir. They reached the following conclusion.
- sofosbuvir for the treatment of chronic hepatitis C in adult patients has added therapeutical value in comparison to relevant existing standard treatments.

Medicine. Sofosbuvir, film-coated tablets 400 mg (Sovaldi®)

Registered indication. "In combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults".
Posology. 400 mg 1X daily during a period of 12 or 24 weeks.
Mechanism of action. Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the SN5B polymerase and acts as a chain terminator. GS-461203 is not an inhibitor of human DNA and RNA polymerase nor an inhibitor of mitochondrial RNA polymerase.
Specific details. Sofosbuvir is the first drug of a new class of antiviral medicines against hepatitis C and it is also the first drug that facilitates interferon-free treatment. Sofosbuvir can be used as a pan-genotypic inhibitor.

Summary of the therapeutic value

Intended effects.
The quality of most of the available evidence on the efficacy of sofosbuvir in comparison to relevant standard treatments is low due to indirect comparisons involving prospective cohorts of various studies of variable sizes and the need to carry out sub-group analyses. On the other hand, confidence in the results can be increased because the outcomes found on sustained virologic response (SVR) are consistent and responses are mainly larger, based on indirect comparisons with the current standard treatments. Furthermore, there are no concrete indications that the difference in effect between treatments with sofosbuvir and standard treatments can be related to differences in prognostic factors of the patients included in the studies.

Taking into consideration the methodological limitations of the indirect comparison, using sofosbuvir, pegylated interferon alpha 2a or 2b (pegIFNα) and ribavirin to treat patients with genotype 1 leads to higher response percentages than treatment with pegIFNα, ribavirin and telaprevir/boceprevir. The effects found can be extrapolated to the rarer HCV genotypes 4 to 6 incl. and to treatment experienced patients. For therapy-naive patients with HCV genotype 2 and 3, the response percentages with sofosbuvir and ribavirin are higher in comparison to standard treatment, pegIFNαa and ribavirin. Patients who failed after at least 12 weeks of interferon-based therapy achieved response percentages with sofosbuvir that were comparable to those achieved with the standard treatment for therapy-naive patients (pegIFNα and ribavirin) for these genotypes. The study provides insufficient evidence for establishing the efficacy of sofosbuvir on patients with co-infections, or patients who are eligible for a liver transplant or who have undergone a liver transplant. However, this is a very small number of patients with an unknown (very unfavourable) natural course. The assumption for these patients is that the evidence of efficacy as noted among other patient groups can be extrapolated to these groups.

Unintended effects.
In comparison to the existing treatments, sofosbuvir does not generally result in more side effects, or more severe side effects. Reported adverse effects are generally associated with the known side effects profiles of pegIFNα and/or ribavirin. Because for a number of groups the existing medication can be replaced (boceprevir or telaprevir for HCV genotype 1 and pegIFNα for HCV genotypes 2 or 3), and the duration of treatment with sofosbuvir is generally shorter than with existing therapies, the incidence of side effects may be reduced and/or the side effects profile may be more favourable in comparison to existing treatments.

Experience. Ample experience has been gained with pegIFNα and ribavirin, while experience with sofosbuvir, boceprevir and telaprevir is limited.

Applicability. Treatment to which sofosbuvir has been added can be put to broader use than treatment to which telaprevir or boceprevir has been added. Furthermore, treatment with sofosbuvir can be put to a broader use than treatment with pegIFNα. Due to the fact that sofosbuvir always has to be administered at least in combination with ribavirin, the applicability of ribavirin will form the most limiting factor for the applicability of the therapy as a whole.

Ease of use. Treatment with sofosbuvir is considerably shorter than the treatments usually used and – in cases where it replaces treatment with pegIFNα – it makes the weekly subcutaneous injection superfluous. In view of the need of to take ribavirin twice daily, it can be claimed that the addition of sofosbuvir to treatment with ribavirin will lead to hardly any extra limitations in ease of use. This makes the ease of use of treatment with sofosbuvir greater than that of treatment based on pegIFNα, ribavirin and, where applicable, telaprevir and boceprevir.

Final conclusion on therapeutic value.
In indirect comparisons, sofosbuvir leads to consistently higher virus clearance than the treatments used to date. This, plus the observation that there are no concrete indications that the differences in effects can be ascribed to differences in patient characteristics in the clinical studies, means that – despite the moderate evidence brought forward – nevertheless sufficient confidence exists regarding the demonstrated effects of sofosbuvir. There are no indications that viral resistance can occur against sofosbuvir due to previous treatments with either interferon or boceprevir and telaprevir. The assumption is that the evidence on efficacy of sofosbuvir in therapy-naive patients can be extrapolated to treatment-experienced patients.