Pharmacotherapeutic report, summary

Simeprevir (Olysio®) for the indication chronic hepatitis C in adult patients

Recommendation by Zorginstituut Nederland dated 22-09-2014, based on an evaluation by the WAR (Scientific Advisory Committee)

The WAR has approved a pharmacotherapeutic report for the medicine simeprevir (Olysio®), hard capsules. Its therapeutic value was determined by comparing simeprevir with sofosbuvir. They reached the following conclusion.
- the therapeutic value of simeprevir, in combination with pegIFN and ribavirin for the treatment of chronic hepatitis C genotype 1 and 4 is equal to that of sofosbuvir in combination with pegIFN and ribavirin, and for genotype 1 it has an added therapeutic value in comparison with telaprevir and boceprevir, both in combination with pegIFN and ribavirin.

Medicine: simeprevir (as sodium), hard capsules, 150 mg

Registered indication. "In combination with other medicinal products for the treatment of chronic hepatitis C in adult patients."

Posology. 150 mg once daily for 12 weeks.

Mechanism of action. Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is essential for viral replication.

Specific details. Simeprevir can be used on HCV genotypes 1 and 4, in combination with pegylated interferon and ribavirin (total treatment duration of 24-48 weeks) or as interferon-free treatment in combination with sofosbuvir (treatment duration 12 weeks).

Summary of the therapeutic value

Intended effects. Only indirect comparisons are possible between simeprevir and sofosbuvir, both in combination with pegIFN and ribavirin, and are, moreover, mostly based on sub-groups. For therapy-naive patients with genotype 1, based on an indirect comparison, there are indications that simeprevir leads to lower response percentages among most patients than sofosbuvir, with the exception of the sub-group of patients with genotype 1b. It should be noted that with regard to HCV genotype 1, unlike simeprevir, sofosbuvir has only been studied in therapy-naive patients and only in a prospective cohort study. The response percentages of simeprevir in therapy-naive patients with genotype 1 are higher than those found in the registration studies of boceprevir and telaprevir.
Patients with HCV genotype 1, who previously relapsed on pegIFN-based therapy, and who were treated with simeprevir have fairly comparable responses with those of therapy-naive patients, while sofosbuvir has not been studied in patients who have been previously treated and an estimate of the efficacy of sofosbuvir is based on extrapolation. In non-responders, simeprevir seems to lead to a similar or better response than boceprevir or telaprevir.
For other patients groups, including HCV genotype 4 and co-infection with HIV, on the basis of indirect comparisons of cohort studies, no definite preference can be indicated for either simeprevir or sofosbuvir, given the fact that in HIV-1 co-infected patients simeprevir has also been studied with patients with relapse, partial responders and non-responders, and sofosbuvir

only with therapy-naive patients. The combination simeprevir-sofosbuvir (genotype 1) seems to lead to a very high rate of response in patients previously treated with pegINF and therapy-naive patients with METAVIR F3/F4, but the quality of the evidence is poor and there is no relevant comparison with sofosbuvir in combination with ribavirin (for patients who do not tolerate peginterferon). The efficacy of simeprevir is greatly reduced in patients with genotype 1a Q80K polymorphism. Taken together, also in combination with the low quality of evidence in some cases, it is not possible to pronounce with sufficient certainty any preference for simeprevir or sofosbuvir based on the response percentages found. There is an advantage for simeprevir in comparison to telaprevir or boceprevir.

Unintended effects. Treatment with simeprevir is associated with increased bilirubin, skin rash, pruritus and increased photosensitivity in comparison to treatment with only pegIFN and ribavirin. The incidence of severe adverse events is limited. Anaemia, a significant and sometimes severe adverse effect of telaprevir and boceprevir, occurs less frequently with simeprevir. Although treatment with simeprevir, but not with sofosbuvir, demands continued treatment with pegIFN and ribavirin for a period of 12-36 weeks, there is no increase in the number of patients who cease treatment with simeprevir within the entire course of treatment or within the first 12 weeks of treatment. Furthermore, in a number of cases patients treated with sofosbuvir need to be treated during an extended 24-week period. There are no signs of genotype-specific differences for simeprevir or sofosbuvir. Taken together, there are no clinically relevant differences, or only minimal ones, in unintended effects between treatment with simeprevir or sofosbuvir, when added to pegIFN and ribavirin. Simeprevir does have a clinically relevant advantage over boceprevir and telaprevir due to the smaller risk of (severe) anaemia. The interferon-free combination of simeprevir/sofosbuvir has clinically relevant advantages in respect of unintended effects in comparison to peginterferon-containing combinations.

Experience. Experience with simeprevir, sofosbuvir, telaprevir and boceprevir is limited.

Applicability. Simeprevir is less broadly applicable than sofosbuvir. Differences in applicability exist between simeprevir and telaprevir/boceprevir, depending on the HCV genotype.

Ease of use. In cases where treatment with simeprevir lasts longer than with sofosbuvir, ease of use of simeprevir is smaller than that of sofosbuvir. In other cases there are no major differences. There are no major differences between simeprevir, telaprevir and boceprevir.

Final conclusion on therapeutic value.
Based on indirect comparisons, where possible, and based on the response percentages found, taking into consideration the methodological limitations, no preference can be pronounced for simeprevir or sofosbuvir in combination with peginterferon and ribavirin. Although treatment with peginterferon and ribavirin is usually longer after simeprevir, than after sofosbuvir, studies

suggest that this is of limited clinical relevance. The efficacy of the combination simeprevir/sofosbuvir has only been demonstrated in patients who have been treated previously and therapy-naive patients with METAVIR F3/F4, and is advantageous for these patients in comparison to interferon-containing alternatives due to a clinically relevant difference in unintended effects. For groups for whom both products are applicable (i.e. genotype 1 or 4, without the presence of genotype 1a Q10K polymorphism), it is impossible to state that one of the two products has a therapeutic added value over the other. In comparison to boceprevir or telaprevir, simeprevir usually leads to higher response percentages and these can be considered clinically relevant advantages also due to the smaller chance of (severe) anaemia.
The therapeutic value of simeprevir in combination with pegIFN and ribavirin for the treatment of chronic hepatitis C genotype 1 and 4 is equal to that of sofosbuvir in combination with pegIFN and ribavirin, and for genotype 1 its therapeutic value exceeds that of telaprevir and boceprevir, both of which are given in combination with pegIFN and ribavirin.

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*The original text of this excerpt from a **WAR-Report** of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's WAR-Report.*
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.