Simeprevir in hepatitis C: Added benefit for certain patients

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The drug simeprevir (trade name: Olysio) has been available since May 2014 for the treatment of adult patients with chronic hepatitis C infection. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this new drug offers an added benefit over the appropriate comparator therapy.

The drug manufacturer dossier provided indications and hints of an added benefit of simeprevir when the patients infected with hepatitis C virus (HCV) genotype 1 have been untreated before or have relapsed after initially successful treatment. It is not possible to rate the extent of added benefit, however. IQWiG sees an indication of considerable added benefit for adults with HCV genotype 1 infection in whom previous treatment had no effect (non-responders). There were no evaluable data for further therapeutic indications and thus an added benefit is not proven.

Different virus types cause inflammation

Hepatitis C viruses (HCV) attack the liver and can trigger inflammation there. If this becomes chronic, cirrhosis can develop and liver function progressively deteriorates. Moreover, the risk of liver cancer (hepatocellular carcinoma, HCC) increases. Simeprevir aims to inhibit the reproduction of HCV. Experts assume that if no viruses are

detectable in the blood over a sustained period after treatment (sustained virologic response, SVR), the risk of secondary disease is reduced.

There are six different main types (genotypes) of the hepatitis C virus, which are subdivided into more than 60 subtypes. The effectiveness of different drugs is not the same against all viruses. Genotype 1a is more common in the United States, whereas genotype 1b is more common in Europe.

Comparison with dual therapy or triple therapy

Simeprevir is administered in addition to the drugs peginterferon alfa and ribavirin, which are already on the market; and in certain cases it is administered in addition to sofosbuvir and ribavarin. According to the approval, treatment duration differs for certain patient groups.

Depending on patient characteristics, the options for the comparator therapy are dual therapy with peginterferon alfa (immune-system enhancing drug) and ribavirin (virostatic drug), and triple therapy, in which peginterferon alfa and ribavirin are additionally combined with a protease inhibitor (boceprevir or telaprevir).

For adults with chronic HCV genotype 1 infection without cirrhosis of the liver, the Federal Joint Committee (G-BA) specified both dual therapy and triple therapy as appropriate comparator therapy. In its dossier, the manufacturer differentiated between three groups: untreated (treatment-naive) patients, patients with unsuccessful pretreatment (non-responders), and patients who relapsed after initially successful treatment (relapsed patients).

Simeprevir was only to be compared with dual therapy in treatment-naive patients with cirrhosis of the liver, in patients with chronic HCV genotype 1 infection and additional HCV infection as well as in patients

with chronic HCV genotype 4 infection.

Extent of added benefit cannot be classified on the basis of the surrogate outcome for morbidity

"Sustained virologic response (SVR)" is not in itself a patient-relevant outcome and cannot be equated with "cure". And there are no studies in which SVR is validated as a surrogate outcome in accordance with the usual criteria employed by IQWiG. Nevertheless, the Institute accepts SVR here as a surrogate for the reduced incidence of liver cancer. This is because it is currently accepted that patients with no detectable hepatitis C virus in the blood are at lower risk of liver cancer.

However, it is unclear how many cases of liver cancer can in fact be prevented by simeprevir. It is therefore unclear whether an added benefit is "minor", "considerable" or "major". According to the corresponding legal ordinance, the added benefit is thus "non-quantifiable".

Indication of an added benefit for adults without prior treatment

Data from three studies were available for treatment-naive patients with HCV genotype 1 infection (with or without cirrhosis of the liver) (PILLAR, QUEST-1 and QUEST-2). All study participants received simeprevir or placebo in combination with peginterferon alfa and ribavirin (dual therapy). Age, fibrosis score and two molecular biological factors (Q80K polymorphism and variants of interleukin 28B) are so-called effect modifiers and influenced the study results on morbidity and side effects.

With regard to SVR, there is an advantage of simeprevir: Depending on effect modifiers, there is an added benefit (indication or hint) for certain

patients, which is non-quantifiable.

Simeprevir offers advantages on further aspects of morbidity: In some people, fatigue and global health status improved more than in the comparator group. Certain patients had fewer serious side effects. There were no differences between the treatment groups with regard to mortality; and there were no evaluable data on quality of life. Overall, IQWiG determined an added benefit of simeprevir with the probability "indication" or "hint" for certain patients. In all cases, the extent is non-quantifiable. An added benefit is not proven for patients with a variant of interleukin 28B (IL28B CC genotype).

Indication of added benefit for relapsed patients

Adults with HCV genotype 1 infection who relapsed after initially successful treatment (relapsed patients) participated in the study presented (PROMISE). They received simeprevir or placebo in combination with peginterferon alfa and ribavirin (dual therapy).

Treatment with simeprevir had advantages also in these patients: There was an indication that simeprevir increased the likelihood of being virus-free after the treatment (SVR). However, it remained unclear how often the drug can actually prevent liver cancer. The positive results on further outcomes, such as fatigue, global health status and number of severe side effects (e.g. gastrointestinal and nervous system disorders) are influenced in different ways by effect modifiers: sex, genetic subtype of the virus (genotype 1a or 1b), fibrosis score and Q80K polymorphism.

Overall, there is also an indication of a non-quantifiable added benefit of treatment with simeprevir for this patient group.

Considerable added benefit for non-responders

The manufacturer presented results from a study (ATTAIN), in which simeprevir was compared with telaprevir, for adults with chronic HCV genotype 1 infection with unsuccessful prior therapy (non-responders). Each of the two drugs was used in combination with peginterferon alfa and ribavirin (triple therapy).

There were no differences between the treatment groups with regard to mortality, secondary diseases, fatigue, depression and global health status. Serious side effects and premature treatment discontinuations due to side effects occurred in both groups. Both were less frequent in the simeprevir group, however, including anaemia as serious side effect. Skin and gastrointestinal disorders were also less frequent under simeprevir. Overall, an indication of major added benefit can be derived from the positive effects.

No sufficient data for patients with HIV coinfection and for genotype 4

The manufacturer cited one study each for the assessment of the added benefit of simeprevir in adults with HCV genotype 1 infection and HIV coinfection as well as in patients with HCV genotype 4 infection. However, the dossier lacked a systematic search and appraisal of the available evidence on the comparator therapy so that the data presented were unsuitable. Hence no added benefit of simeprevir is proven for these patients.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and

result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the website gesundheitsinformation.de, published by IQWiG, provides easily understandable and brief German-language information on simeprevir.

The G-BA website contains both general English-language information on benefit assessment pursuant to §35a Social Code Book (SGB) V and specific German-language information on the assessment of simeprevir.

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