



## Treatment of Chronic Hepatitis C - **June 2017 Update** SASL-SSI Expert Opinion Statement

**(The main changes compared to the March 2017 Update are highlighted in yellow)**

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### Introduction

This document represents an update of the last version of the Swiss Association for the Study of the Liver (SASL) and Swiss Society for Infectious Diseases (SSI) Expert Opinion Statement (EOS) on the Treatment of Chronic Hepatitis C virus (HCV) infection published online in **March 2017** ([www.sasl.ch](http://www.sasl.ch); [www.sggssg.ch](http://www.sggssg.ch), [www.sginf.ch](http://www.sginf.ch)). It has been elaborated jointly by SASL and SSI. Recommendations are based on the results of phase 3 or selected phase 2 clinical studies<sup>1-26</sup> and the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C ([www.easl.eu](http://www.easl.eu))<sup>27</sup> as well as the Recommendations by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (<http://hcvguidelines.org>)<sup>28</sup>. The reader is referred to these documents as well as the 'Fachinformation' approved by Swissmedic ([www.compendium.ch](http://www.compendium.ch) or [www.swissmedicininfo.ch](http://www.swissmedicininfo.ch)) and the "Spezialitätenliste" of the Swiss Federal Office of Public Health (FOPH) ([www.spezialitaetenliste.ch](http://www.spezialitaetenliste.ch)) for further information, including key references and sustained virological response (SVR) rates that can be expected with the different treatment regimens as well as current reimbursement. The HCV Advisor App ([www.hcvadvisor.com](http://www.hcvadvisor.com)) is based on this EOS and has been endorsed by SASL and SSI. It provides rapid information on recommended treatment regimens, costs and reimbursement.

Treatment of chronic hepatitis C is a fast evolving field with rapidly changing recommendations. An exhaustive discussion in all aspects of HCV treatment is beyond the scope of this EOS. The aim of this EOS is rather to provide a practical and concise guidance for treating physicians with regular updates upon approval of new compounds. Expert advice should be sought for patients with direct acting antiviral (DAA) failure, decompensated cirrhosis, renal insufficiency, pre- or post-liver transplantation, other organ transplants (e.g. bone marrow, lung, heart, kidney), acute hepatitis C and HCV genotype 5 or 6 infection which will not be covered. Treatment indications and priorities are not discussed in detail in this EOS.

The EOS update in March 2017 took into consideration the recent approval of the fixed-dose combination of velpatasvir (VEL) and sofosbuvir (SOF) (Epclusa<sup>®</sup>)<sup>29-31</sup>, and considered the label extension for ritonavir-boosted paritaprevir (PTV/r) and ombitasvir (OBV) for the treatment of HCV genotype 4 infections. It took also into account new data on the influence of resistance associated substitutions (RASs) on cure rates, particularly among treatment-experienced patients<sup>32</sup>. Accordingly, distinct recommendations are provided for treatment-naïve and -experienced patients. Guidance for pre- and post-treatment assessments was also included.

The current update includes the expanded reimbursement limitations by the FOPH of May 1<sup>st</sup> 2017. In addition, the combination of sofosbuvir and ribavirin is no longer recommended for the treatment of HCV genotype 2 infection due to suboptimal response rates (see Tables 3A and 3B).

### Reimbursement in Switzerland of the new DAAs is currently limited to:

1. prescription by gastroenterologists, infectious diseases specialists, and selected, named other specialists ([www.bag.admin.ch/lis-ref](http://www.bag.admin.ch/lis-ref)) and
2. one of the following:
  - a. Metavir stage  $\geq 2$  as determined by liver biopsy or FibroScan<sup>®</sup> on two occasions  $\geq 3$  months apart (Table 2) or
  - b. patients with clinically significant extrahepatic manifestations of hepatitis C virus (HCV) infection<sup>33</sup> or
  - c. patients with HIV and/or HBV coinfection irrespective of liver fibrosis stage or
  - d. patients with intravenous drug consumption irrespective of fibrosis stage, if:
    - i. they receive an opioid substitution or if they would qualify for such a substitution and directly observed DAA disposal is ensured by a physician or by a pharmacist at least during 5 days/week or
    - ii. they consume substances other than opioids while in addiction medicine care and directly observed DAA disposal is ensured by a physician or by a pharmacist at least during 5 days/week or
  - e. patients with Metavir stage  $\geq 2$  with previous HCV treatment failure or
  - f. patients before or after liver transplantation (LT) (SOF + RBV for genotypes 1-6 or LDV/SOF for genotype 1) or
  - g. patients with recurrent hepatitis C post-LT (LDV/SOF for genotype 1).

For all other indications reimbursement has to be negotiated with health insurances on an individual basis. There is growing evidence that extrahepatic manifestations of HCV infection (reviewed in <sup>34, 35</sup>) contribute considerably to morbidity and mortality and, therefore, justify to treat chronic hepatitis C regardless of fibrosis stage.

In recent years, many patients chose to buy DAAs using internet resources due to high costs and reimbursement restrictions. It is important that these patients contact a specialized physician for guidance on diagnosis and treatment of HCV infection. If patients chose to buy DAAs abroad, it is crucial that treatment monitoring is performed according to national and international recommendations. A guidance for the use of DAAs purchased abroad is provided at [www.hepatitis-schweiz.ch/de/medikamente-online-kaufen](http://www.hepatitis-schweiz.ch/de/medikamente-online-kaufen).

Universal treatment irrespective of fibrosis stage is recommended by the current AASLD-ISDA guidance (<http://hcvguidelines.org>). Hence, we urge all parties involved to pursue a constructive dialogue to enable universal access to treatment for all patients.

## Background

HCV chronically infects **60-80 million** individuals worldwide<sup>36</sup>. Detailed information on HCV prevalence and on diagnosis rates are not yet available in Switzerland. Recommendations for healthcare provider-initiated testing for HCV infection have been issued by the Swiss Experts in Viral Hepatitis (SEVHep) and the FOPH<sup>37</sup> and complementary birth cohort-based screening is being discussed<sup>38</sup>. A national hepatitis C strategy has been conceived ([www.hepatitis-schweiz.ch](http://www.hepatitis-schweiz.ch)).

The clinical course of chronic hepatitis C depends on a number of modifiable (alcohol, coinfections with hepatitis B virus or HIV, non-alcoholic fatty liver disease) and unmodifiable factors (age at the time of infection, sex, genotype 3, host genetics); 2-20% may develop cirrhosis over the first 20 years of infection, and disease progression may be accelerated in a non-linear fashion thereafter, with an estimated 15-30% developing cirrhosis after 30 years. It is expected that the peak of the disease burden (decompensated liver cirrhosis, hepatocellular carcinoma [HCC], LT and mortality) will be reached in Switzerland only around 2030, unless more efficient means of screening and treatment for those in need of therapy are implemented<sup>39, 40</sup>.

## Pre-treatment assessment

Before starting antiviral treatment, other causes that contribute to the progression of liver disease should be carefully evaluated. All patients should be tested for hepatitis B virus (HBV) (HBsAg, anti-HBc, anti-HBs), as well as human immunodeficiency virus (HIV) infection. In patients who are HBsAg positive as well as in HBsAg-negative, anti-HBc-positive patients, a HBV DNA test should be obtained, whereas all patients without previous HBV exposure should be vaccinated.

Hepatitis B reactivation has been **rarely** observed in HBsAg-and/or anti-HBc-positive patients during antiviral treatment for HCV. The FDA identified 24 cases of HBV reactivation in HCV/HBV coinfecting patients treated with DAAs including 2 deaths and 1 patient who required transplantation. FDA issued a boxed warning on April 2016 ([www.fda.gov/Drugs/DrugSafety/ucm522932.htm](http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm)). Therefore, concurrent antiviral treatment with an HBV nucleoside/nucleotide analogue is recommended in HBsAg-positive patients or if HBV DNA is detectable in HBsAg-negative, anti-HBc-positive patients, while patients with negative HBsAg and HBV DNA but positive anti-HBc ± anti-HBs should be monitored closely<sup>27</sup>.

Alcohol consumption should be determined and quantified. Specific counseling to stop any harmful alcohol use should be given. In addition, components of the metabolic syndrome (weight, BMI, diabetes mellitus, hypertension, hyperlipidemia) should be determined and appropriate counseling and/or treatment initiated, as indicated. Other causes of chronic liver diseases such as hemochromatosis and others should also be excluded.

As current treatment regimens are determined by the fibrosis stage and previous treatments, a detailed treatment history has to be obtained. The stage of fibrosis can be determined with either a liver biopsy or transient elastography (FibroScan®). In patients with cirrhosis, determination of liver function (Child-Pugh score) and assessment of portal hypertension are essential. DAA protease inhibitor-based treatment regimens should only be considered in patients with well compensated liver function (Child-Pugh A) and without prior history of liver decompensation.

Before deciding on the treatment regimen and treatment duration, it is crucial to know the HCV genotype and the current serum HCV RNA load. If the viral genotype has not been determined recently, HCV genotyping should be repeated. Testing for the presence of RAS prior to starting treatment should be performed as indicated in Tables 3A and 3B.

In order to gather important real-life data on the natural history and treatment outcomes of HCV infection in Switzerland, we suggest to include HCV-infected patients in the Swiss Hepatitis C Cohort Study (SCCS), and (for HIV-coinfected patients) in the Swiss HIV Cohort Study (SHCS).

### **Practical use of sofosbuvir**

SOF (Sovaldi<sup>®</sup>, Gilead Sciences, Foster City, CA) is a uridine nucleotide inhibitor of the HCV NS5B RNA-dependent RNA polymerase, with potent pangenotypic activity and a high barrier to resistance. It is administered at a dose of one 400-mg tablet per day, with or without food. It is reimbursed, with limitations (see above), since August 2014.

SOF is generally well tolerated and has to be combined with another DAA and/or RBV (see Tables 3A and 3B for specific recommendations). The combination with PEG-IFN- $\alpha$ /RBV is no longer recommended due to the availability of very safe and efficient interferon-free combinations in all genotypes. The most commonly reported adverse effects are headache, fatigue and nausea.

The risk of drug-drug interactions, notably with most antirejection and antiretroviral treatments, is low. However, coadministration of potent P-glycoprotein (P-gp) inducers, such as rifampicin, carbamazepine, phenytoin or St. John's wort should be avoided, as they significantly decrease the plasma concentration of SOF ([www.hep-druginteractions.org](http://www.hep-druginteractions.org)). The combination of SOF and another DAA with amiodarone has been linked to instances of severe bradycardia and is therefore contraindicated.

SOF and its main metabolite GS-331007 are eliminated predominantly by the kidney. Therefore, SOF should not be administered to patients with severe renal impairment (estimated glomerular filtration rate < 30 ml/min) or with end-stage renal disease until more data is available; expert advice is recommended. SOF exposure is not significantly changed in patients with mild liver function impairment, but it is increased about 2- to 2.5-fold in those with moderate to severe hepatic impairment. However, dose adaptations are not recommended in this situation. Therapeutic drug monitoring for SOF and GS-331007 is available at the Division of Clinical Pharmacology of the CHUV ([www.chuv.ch/pcl](http://www.chuv.ch/pcl)).

### **Practical use of the ledipasvir/sofosbuvir fixed-dose combination**

LDV is a NS5A inhibitor with potent activity against genotypes 1a, 1b, 4, 5 and 6 but lower activity against genotypes 2a and 3a. It is administered with or without food once daily at a dose of 90 mg in combination with SOF 400 mg as a fixed-dose combination single tablet (Harvoni<sup>®</sup>, Gilead Sciences, Foster City, CA). It is reimbursed, with the limitations above, since February 2015.

LDV/SOF is generally well tolerated over 8-12-24 weeks of administration. The most commonly reported adverse effects are fatigue and headache. In patients who fail LDV/SOF NS5A resistance-associated substitutions (RASs) are detected in the majority of patients. The RASs can persist for many years, maybe forever. Expert advice is recommended before retreating these patients.

The risk of drug-drug interactions, notably with most antirejection and antiretroviral treatments, is low. However, coadministration of potent P-gp inducers, such as rifampicin, carbamazepine, phenytoin or St. John's wort should be avoided (see above). Proton pump inhibitors (PPI) at a dose equal to 20 mg omeprazole can be safely co-administered with LDV/SOF. Higher doses should be avoided, as this may decrease LDV levels, and PPI should not be taken before LDV/SOF. LDV/SOF should also not be combined with tipranavir boosted with ritonavir and rosuvastatin ([www.hep-druginteractions.org](http://www.hep-druginteractions.org)). LDV/SOF increases exposure to tenofovir which warrants close monitoring for renal toxicity when LDV/SOF and tenofovir are co-administered. For the combination with amiodarone, see recommendations above.

As discussed above, LDV/SOF should not be administered to patients with severe renal impairment (estimated glomerular filtration rate < 30 ml/min) or with end-stage renal disease until more data is available; expert advice is recommended. LDV/SOF in combination with ribavirin has been evaluated in patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C 10-12 points) and no additional safety issues were reported.

### **Practical use of the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir**

PTV/r, a ritonavir-boosted, first-generation, second-wave protease inhibitor, OBV, an NS5A inhibitor, and DSV, a non-nucleosidic polymerase inhibitor are reimbursed in Switzerland for the treatment of chronic hepatitis C of genotype 1 since February 2015, with the limitations discussed above. PTV/r (75/50 mg) and OBV (12.5 mg) are coformulated in a single tablet (Viekirax<sup>®</sup>, AbbVie, North Chicago, IL) of which two have to be taken in the morning. DSV 250 mg (Exviera<sup>®</sup>, AbbVie) has to be taken twice daily. It is recommended to take these medications with food. There is a significant potential for drug-drug interactions. Hence, it is recommended to consult continuously updated databases such as the drug interactions database from the University of Liverpool ([www.hep-druginteractions.org](http://www.hep-druginteractions.org)).

Treatment with PTV/r, OBV and DSV is combined with RBV for patients with genotype 1a infection or cirrhosis. According to current recommendations RBV can be omitted for patients with genotype 1b infection with and without cirrhosis<sup>19, 28, 27</sup>. Standard treatment duration is 12 weeks. The current Swiss label foresees extension to 24 weeks only for genotype 1a-infected cirrhotic patients with a previous null response. However according to EASL and AASLD guidelines treatment should be extended to 24 weeks in treatment naïve and PEG-IFN- $\alpha$ -RBV experienced genotype 1a patients with compensated cirrhosis. PTV/r and OBV have robust activity also against genotype 4<sup>19, 20, 26</sup>. This combination has recently been approved in Switzerland also for patients with genotype 4 infection. PTV/r, OBV and DSV can be used in patients with advanced renal impairment. However, expert advice is recommended in this situation.

This combination is contraindicated in patients with decompensated cirrhosis (Child-Pugh B or C; <http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm>).

Combination therapy with PTV/r, OBV and DSV is generally well tolerated. Unconjugated hyperbilirubinemia due to inhibition of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 may be observed occasionally. The adverse effects of RBV are well known.

## Practical use of simeprevir

SMV (Olysio<sup>®</sup>, Janssen Therapeutics, Titusville, NJ) is a first generation, second wave protease inhibitor which is administered at a dose of 150 mg (one capsule) once daily. Importantly, in Switzerland SMV is no longer reimbursed, irrespective of the fibrosis stage. It is active *in vitro* against HCV genotypes 1, 2, 4, 5 and 6. SMV has to be used in combination with PEG-IFN- $\alpha$  and RBV or in combination with another DAA (e.g. SOF or DCV) with or without RBV as part of an IFN-free regimen. In Switzerland SMV is only approved in combination with PEG-IFN- $\alpha$  and RBV for patients with genotype 1a (without NS3 Q80K polymorphism), genotype 1b or genotype 4 infection. SMV in combination with SOF  $\pm$  RBV for 12-24 weeks would be a well-tolerated, effective IFN-free regimen, which is licensed in the US and Europe for use in patients with genotype 1 and 4 infection, but is off-label in Switzerland.

SMV is well tolerated and the most common side effects are rash, photosensitivity, pruritus and nausea. SMV is a known inhibitor of OATP1B1 and multidrug resistance-associated protein 2 (MRP2) and, therefore, mild, transient hyperbilirubinemia can be observed in approximately 10% of patients.

There is a significant potential for drug-drug interactions. See package inserts and continuously updated online databases (e.g., [www.hep-druginteractions.org](http://www.hep-druginteractions.org)) for known drug-drug interactions and contraindicated drugs. Commonly used drugs that are contraindicated in combination with SMV include, among others, carbamazepine, phenytoin, phenobarbital, clarithromycin, rifampicin, fluconazole, voriconazole, milk thistle, St. John's wort, some antiretroviral drugs including any protease inhibitor irrespective of boosting with ritonavir, efavirenz, delavirdine, etravirine, nevirapine and ritonavir.

In patients with renal impairment no dosage adjustments are necessary. SMV should not be used in patients with decompensated cirrhosis (Child-Pugh B and C).

## Practical use of daclatasvir

DCV (Daklinza<sup>®</sup>, Bristol-Myers Squibb, New York, NY) is an inhibitor of the HCV NS5A protein with pangenotypic activity. It is administered as an oral tablet of 60 mg once daily. DCV is approved in Switzerland since August 2015. It is metabolized by cytochrome P450 isoenzymes, predominantly 3A4 (CYP3A4) and P-gp. Therefore co-administration with strong inducers of CYP3A4 and/or P-gp (e.g. rifampicin, dexamethasone, St. John's wort) is contraindicated. The dosage has to be reduced to 30 mg when combined with some inhibitors of CYP3A4 (e.g. atazanavir/ritonavir), and increased to 90 mg when combined with moderate inducers of CYP3A4 (e.g. efavirenz; see [www.compendium.ch](http://www.compendium.ch)). However, DCV is dosed 60 mg daily when combined with darunavir/ritonavir. Dose modification is not required in the elderly or in patients with renal or hepatic impairment.

DCV is in general well tolerated. The most common adverse effects are headache, fatigue, nausea and diarrhea. DCV has been studied together with PEG-IFN- $\alpha$  + RBV, or as IFN-free combination therapy together with SOF or SMV.

In Switzerland DCV is approved and reimbursed in combination with PEG-IFN- $\alpha$  and RBV for patients with genotype 4 infection and in combination with SOF for patients with genotype 3 infection for a maximal treatment duration of 24 and 12 weeks, respectively.

## Practical use of the grazoprevir/elbasvir fixed-dose combination

GZR/EBR is a fixed-dose combination (Zepatier®, Merck, New Jersey, NJ) consisting of 100 mg GZR and 50 mg EBR. GZR inhibits the NS3-4A protease and EBR the HCV NS5A protein. This combination shows activity against HCV genotypes 1 and 4. It is approved and reimbursed in Switzerland for genotype 1 and 4 infections.

GZR is a substrate of the OATP1B transporter and strongly interacts with OATP1B inhibitors (e.g. rifampicin) which are contraindicated. GZR and EBR are both substrates of CYP3A4 and P-gp. Therefore, co-medications which significantly inhibit (e.g. ketoconazole) or induce (e.g. carbamazepine, phenytoin, flucloxacillin, St. John's wort) CYP3A4 and P-gp are also contraindicated. The same applies for the class of HIV protease inhibitors, for efavirenz and etravirine. For co-medications with a moderate inhibition of CYP3A or P-gp liver enzymes need to be monitored. Dose modification in the elderly or in the patients with renal impairment is not necessary. GZR/EBR can be used in patients with advanced renal impairment. However, expert advice is recommended in this situation. In case of significant liver impairment (Child-Pugh B and C) GZR/EBR is contraindicated.

The most common adverse effects are fatigue, headache, insomnia, nausea and diarrhea. Liver enzymes should be measured before treatment initiation and at week 8 during treatment because in 1% of the study patients an elevation has been observed.

In patients with HCV genotype 1a baseline resistance testing has to be performed to identify potential NS5A polymorphisms (M28T/A, Q30E/H/R/G/K/L/D, L31M/V/F, H58D and Y93C/H/N) as these significantly reduce rates of SVR12 with a 12-week course of GZR/EBR. If such a polymorphism has been detected the total GZR/EBR treatment duration is 16 weeks in combination with weight-based RBV (1000 mg [ $< 75$  kg] to 1200 mg [ $\geq 75$  kg]). Resistance testing is reimbursed by the manufacturer of GZR/EBR. Prolongation of GZR/EBR treatment to 16 weeks in combination with RBV is also indicated for patients with genotype 4 infection who failed a previous treatment with PEG-IFN- $\alpha$  and RBV (relapse excluded) (see Table 1).

**Table 1. Recommended regimens and durations of GZR/EBR  $\pm$  RBV.**

Genotype	Patient population	Treatment	Duration
1a	Treatment-naïve or PEG-IFN- $\alpha$ /RBV-experienced <sup>1</sup> <b>without</b> baseline NS5A polymorphisms <sup>2</sup>	GZR/EBR	12 wks
1a	Treatment-naïve or PEG-IFN- $\alpha$ /RBV-experienced <sup>1</sup> <b>with</b> baseline NS5A polymorphisms <sup>2</sup>	GZR/EBR +RBV	16 wks
1b	Treatment-naïve or PEG-IFN- $\alpha$ /RBV-experienced <sup>1</sup>	GZR/EBR	12 wks
4	Treatment-naïve or relapse after PEG-IFN- $\alpha$ /RBV	GZR/EBR	12 wks
4	PEG-IFN- $\alpha$ /RBV-experienced <sup>3</sup>	GZR/EBR +RBV	16 wks

<sup>1</sup> Patients who have failed treatment with PEG-IFN- $\alpha$ /RBV in combination with a NS3-4A protease inhibitor (boceprevir, telaprevir, SMV, PTV/r) should be discussed with an expert.

<sup>2</sup> Resistance testing to identify/exclude NS5A polymorphisms (28, 30, 31, 58, 93) prior to the initiation of therapy is mandatory.

<sup>3</sup> 'Experienced' includes previous 'virological breakthrough', 'partial response' and 'null response'. Non-cirrhotic patients who had a 'relapse' are treated like TN patients, i.e. with GZR/EBR for 12 wks.

### Practical use of the velpatasvir/sofosbuvir fixed-dose combination

Velpatasvir (VEL) is an NS5A inhibitor with pangenotypic activity. It is administered once daily independently of food intake in a fixed-dose combination single pill containing 100 mg of VEL and 400 mg of SOF (Epclusa®, Gilead Sciences, Foster City, CA). It is reimbursed since January 2017 with the limitations outlined below. The most common side effects include sleep disturbances, headache and fatigue.

VEL is metabolized by CYP2B6, CYP2C8 and CYP3A4 and is transported by P-gp, BCRP and OAT-transporters. Most drug-drug interactions are mild, but some drugs are contraindicated together with VEL (see [www.hep-druginteractions.org](http://www.hep-druginteractions.org)); potent P-gp inducers such as rifampicin, some antiepileptic drugs or St John's worth) or cytochrome-inducing drugs such as efavirenz significantly reduce VEL drug levels and should not be co-administered. With regard to co-administration of PPIs or amiodarone, the same restrictions apply as for LDV/SOF (see above). VEL/SOF is not recommended in patients with severe renal impairment (estimated glomerular filtration rate < 30 ml/min) because of the substantially higher concentration of the SOF metabolites GS-331007 (see above). VEL/SOF has been studied in patients with decompensated cirrhosis<sup>29</sup> and was generally well tolerated in this setting. Safety and efficacy of VEL/SOF were assessed in the phase III Astral studies<sup>29-31</sup>. This combination therapy achieved cure rates > 95% across all genotypes. Suboptimal SVR were only observed in genotype 3 infected cirrhotic or treatment-experienced patients with pre-existing NS5A RASs (particularly the Y93H substitution). Accordingly, AASLD and EASL recommendations foresee to either exclude this variant or to add RBV in this situation (see also Tables 3A and 3B).

**Table 2. Current reimbursement limitations of approved DAA according to Metavir stage** (criteria for reimbursement independently of Metavir are listed above, p.2).

DAA	Genotype	Metavir F2-F4 Liver stiffness $\geq 7.5^1$
SOF	1-6	reimbursed
LDV/SOF	1	reimbursed <sup>2</sup>
PTV/r/OBV + DSV	1	reimbursed
PTV/r/OBV	4	reimbursed
SMV <sup>3</sup>	1 and 4	not reimbursed
DCV <sup>4</sup>	3 and 4	reimbursed
GZR/EBR	1 and 4	reimbursed
VEL/SOF	3	reimbursed
	2, 3, 5, 6	reimbursed in decompensated cirrhosis



- <sup>1</sup> As determined by FibroScan<sup>®</sup> on two occasions  $\geq 3$  months apart.
- <sup>2</sup> Reimbursement is limited to 8 weeks in treatment-naïve non-cirrhotic patients with F2 fibrosis and a serum HCV RNA  $< 6 \times 10^6$  IU/ml.
- <sup>3</sup> SMV is only approved but no longer reimbursed (irrespective of fibrosis stage) in combination with PEG-IFN- $\alpha$  + RBV (see text).
- <sup>4</sup> DCV is approved and reimbursed in combination with PEG-IFN- $\alpha$  + RBV for patients with HCV genotype 4 infection (24 weeks) and with SOF for patients with genotype 3 infection (12 weeks).

## HCV RNA monitoring on treatment

It is recommended to determine HCV RNA at baseline, week 2 or 4 (assessment of adherence, optional), week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of treatment (SVR12 or SVR24, respectively).

## Follow-up after SVR

EASL recommends to retest HCV RNA 48 weeks after the end of treatment. Given the extremely high probability of permanent cure in patients with SVR, physicians may choose to omit this control. If HCV RNA is still negative, these patients can be considered as definitively cured. HCV RNA determination is no longer necessary, unless the patient has an ongoing or new risk behavior for HCV reinfection (illicit drug use, sexual practices that involve exchange of blood).

Patients with an indication for HCC screening as recommended by international guidelines should remain under HCC surveillance every 6 months with ultrasound and alpha-fetoprotein (the role of alpha-fetoprotein is controversial). EASL recommends HCC screening for all patients with Metavir stage  $\geq$  F3 or FibroScan  $> 9.5$  kPa, other guidelines (e.g. EACS) recommend HCC screening for cirrhotic patients only. Patients with cirrhosis should undergo screening for esophageal varices as recommended in the Baveno VI consensus statement<sup>41</sup>. Patients without advanced liver disease (F0-F2; FibroScan  $\leq 9.5$  kPa) but with cofactors for liver disease progression (alcohol use, metabolic syndrome, non-alcoholic fatty liver disease etc.) should be periodically (once a year) assessed for liver disease progression. Patients without significant liver fibrosis (Metavir F0-F1; FibroScan  $< 7.5$  kPa) and without risk factors for disease progression can be released from specialized care.

## Special patient populations

Response rates to DAAs are similar in HCV-HIV-coinfected as compared to HCV-monoinfected patients. Therefore, treatment indications and regimens for HCV-HIV-coinfected patients should in general follow those of HCV-monoinfected patients. Specific recommendations for the management of HCV infection in HIV-infected patients are updated regularly by the European AIDS Clinical Society ([www.eacsociety.org](http://www.eacsociety.org)). Because of the frequent co-medication with antiretrovirals and further drugs, it is crucial to check for drug-drug interactions ([www.hep-druginteractions.org](http://www.hep-druginteractions.org)) before starting DAA treatments. However, in the large majority of patients, drug-drug interactions are manageable and should not be a barrier to starting DAA therapy.

Expert advice should be sought for patients with previous failure of a regimen comprising a DAA as well as patients with decompensated cirrhosis, renal insufficiency, pre- or post-liver transplantation, other organ transplants (e.g. bone marrow, lung, heart, kidney), HCC, acute hepatitis C and HCV genotype 5 or 6 infection.

### **Recommended treatment options for patients with chronic hepatitis C**

Recommended treatment options are summarized in Table 3. The recommendations were adapted according to new data on the influence of RASs on SVR. For example, a pooled analysis of 35 studies demonstrated the impact of LDV-specific RASs on SVR<sup>32</sup>. Cure rates were suboptimal in patients with NS5A RASs before starting LDV/SOF, particularly in treatment-experienced patients. Accordingly, the updated tables provide separate recommendations for treatment-naïve and treatment-experienced patients. The updated SASL-SSI EOS is mostly in line with the EASL Recommendations of September 2016<sup>27</sup>; differences are outlined in the footnotes to Tables 3A and 3B. In some instances, the recommended treatment regimens depend on the presence or absence of NS5A RASs. Of note, the reimbursement of resistance tests in Switzerland is uncertain with the exception of resistance tests before starting GZR/EBR (see above for further information).

**Table 3. Recommended treatment options for patients with chronic hepatitis C.**

**A. Treatment-naïve patients**

Genotype	Non-cirrhotic	Cirrhotic (Child-Pugh A)
1a	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF for 8-12 wks<sup>1</sup></p> <p>GZR/EBR ± RBV for 12-16 wks<sup>2</sup></p> <p>PTV/r/OBV+DSV+RBV 12 wks</p> <p>DCV + SOF for 12 wks</p>	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF ± RBV for 12(-24) wks<sup>3</sup></p> <p>GZR/EBR ± RBV for 12-16 wks<sup>2</sup></p> <p>PTV/r/OBV+DSV + RBV 12-24 wks<sup>4</sup></p> <p>DCV + SOF ± RBV for 12(-24) wks<sup>3</sup></p>
1b	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF for 8-12 wks<sup>1</sup></p> <p>GZR/EBR for 12 wks</p> <p>PTV/r/OBV + DSV 8-12 wks<sup>5</sup></p> <p>DCV + SOF for 12 wks</p>	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF ± RBV for 12(-24) wks<sup>3</sup></p> <p>GZR/EBR for 12 wks</p> <p>PTV/r/OBV + DSV 12 wks</p> <p>DCV+SOF ± RBV for 12(-24) wks<sup>3</sup></p>
2	VEL/SOF for 12 wks <sup>6</sup>	VEL/SOF for 12 wks <sup>6</sup>
3	<p>VEL/SOF for 12 wks</p> <p>DCV + SOF for 12 wks</p>	<p>VEL/SOF ± RBV for 12(-24) wks<sup>7</sup></p> <p>DCV + SOF + RBV for 24 wks</p>
4	<p>GZR/EBR for 12 wks</p> <p>VEL/SOF for 12 wks</p> <p>PTV/r/OBV + RBV for 12 wks</p>	<p>GZR/EBR for 12 wks</p> <p>VEL/SOF for 12 wks</p> <p>PTV/r/OBV + RBV for 12 wks</p>

Color code: **green** = approved and reimbursed (please consult [www.spezialitaetenliste.ch](http://www.spezialitaetenliste.ch) for eventual updates); **blue** = according to the current Swiss label, but with potential modifications of treatment duration and/or the addition of RBV; **orange** = approved in Switzerland but not reimbursed.

<sup>1</sup> Treatment may be shortened to 8 wks in treatment-naïve (TN) patients with Metavir fibrosis stage ≤ F2 if their baseline HCV RNA is < 6 x 10<sup>6</sup> (6.8 log) IU/ml. Patients with fibrosis stage ≥ F3 or with a baseline HCV RNA ≥ 6 x 10<sup>6</sup> (6.8 log) IU/ml should be treated for 12 weeks.

<sup>2</sup> 12 wks without RBV in patients without baseline NS5A polymorphisms, 16 wks with RBV in those with NS5A polymorphisms (see Table 1).

<sup>3</sup> The current EASL Recommendations foresee LDV/SOF or SOF+DCV for 12 wks without RBV in treatment-naïve cirrhotics with genotype 1a or 1b infection. In cirrhotic patients with negative predictors of response such as platelet counts < 75 G/l and RASs that confer high-level resistance to NS5A inhibitors, addition of RBV can be considered. If these patients do not tolerate ribavirin, extension to 24 weeks can be considered. This is not foreseen in the current Swiss label.

<sup>4</sup> Extension to 24 wks is by the current Swiss label foreseen only for cirrhotic patients with subtype 1a and a previous null response. EASL recommends to treat all cirrhotic patients with subtype 1a for 24 weeks.

<sup>5</sup> EASL recommends 8 wks for treatment-naïve patients with ≤ F2; this is not foreseen in the current Swiss label.

<sup>6</sup> SOF + RBV is no longer recommended due to suboptimal response rates. This is in line with the EASL and AASLD recommendation. However, in Switzerland SOF + RBV is currently the only reimbursed IFN-free regimen for patients with genotype 2 infection and compensated liver function.

<sup>7</sup> Patients with cirrhosis should be treated with VEL/SOF + RBV for 12 weeks or with VEL/SOF for 24 wks if RBV-intolerant. Extension to 24 weeks in patients who cannot tolerate RBV requires approval by health insurances. If NS5A resistance testing is performed and demonstrates the absence of NS5A RAS Y93H, treatment can be performed with VEL/SOF for 12 weeks without RBV.

## B. Treatment-experienced patients ([PEG-]IFN- $\alpha$ /RBV-experienced, DAA-naïve)

Geno-type	Non-cirrhotic	Cirrhotic (Child-Pugh A)
1a	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF <math>\pm</math> RBV for 12(-24) wks<sup>8</sup></p> <p>GZR/EBR <math>\pm</math> RBV for 12-16 wks<sup>9</sup></p> <p>PTV/r/OBV + DSV + RBV 12 wks</p> <p>DCV + SOF <math>\pm</math> RBV for 12(-24) wks<sup>8</sup></p>	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF <math>\pm</math> RBV for 12(-24) wks<sup>8</sup></p> <p>GZR/EBR <math>\pm</math> RBV for 12-16 wks<sup>9</sup></p> <p>PTV/r/OBV+DSV+RBV 12-24 wks<sup>10</sup></p> <p>DCV + SOF <math>\pm</math> RBV for 12(-24) wks<sup>8</sup></p>
1b	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF for 12 wks</p> <p>GZR/EBR for 12 wks</p> <p>PTV/r/OBV + DSV 12 wks</p> <p>DCV + SOF for 12 wks</p>	<p>VEL/SOF for 12 wks</p> <p>LDV/SOF <math>\pm</math> RBV for 12(-24) wks<sup>11</sup></p> <p>GZR/EBR for 12 wks</p> <p>PTV/r/OBV + DSV 12 wks</p> <p>DCV+SOE <math>\pm</math> RBV for 12(-24) wks<sup>11</sup></p>
2	VEL/SOF for 12 wks <sup>12</sup>	VEL/SOF for 12 wks <sup>12</sup>
3	<p>VEL/SOF <math>\pm</math> RBV for 12(-24) wks<sup>13</sup></p> <p>DCV + SOF <math>\pm</math> RBV for 12(-24) wks<sup>8</sup></p>	<p>VEL/SOF <math>\pm</math> RBV for 12(-24) wks<sup>13</sup></p> <p>DCV + SOF + RBV for 24 wks</p>
4	<p>GZR/EBR + RBV for 12-16 wks<sup>14</sup></p> <p>VEL/SOF for 12 wks</p> <p>PTV/r/OBV + RBV for 12 wks</p>	<p>GZR/EBR + RBV for 16 wks<sup>14</sup></p> <p>VEL/SOF for 12 wks</p> <p>PTV/r/OBV + RBV for 12 wks</p>

<sup>8</sup> EASL recommends adding RBV or extension to 24 wks (if RBV-intolerant) in patients with RASs that confer high-level resistance to NS5A inhibitors. Only the extension to 24 weeks (for LDV/SOF in cirrhotics; for DCV + SOF in non-cirrhotics) is foreseen in the current Swiss label. The addition of RBV is not foreseen in the current Swiss label.

<sup>9</sup> 12 wks without RBV in patients without baseline NS5A polymorphisms, 16 wks with RBV in those with NS5A polymorphisms (see Table 1).

<sup>10</sup> Extension to 24 wks is by the current Swiss label foreseen only for cirrhotic patients with subtype 1a and a previous null response. EASL recommends to treat all cirrhotic patients with subtype 1a for 24 weeks.

<sup>11</sup> The current EASL recommendations foresee LDV/SOF or SOF+DCV for 12 wks without RBV in treatment-experienced cirrhotics with 1b infection. In cirrhotic patients with 1b infection with negative predictors of response such as platelet counts < 75 G/l and RASs that confer high-level resistance to NS5A inhibitors, addition of RBV can be considered. This is not foreseen in the current Swiss label. If these patients do not tolerate ribavirin, extension to 24 weeks can be considered.

<sup>12</sup> SOF + RBV is no longer recommended due to suboptimal response rates. This is in line with the EASL and AASLD recommendation. However, in Switzerland SOF + RBV is currently the only reimbursed IFN-free regimen for patients with genotype 2 infection and compensated liver function.

<sup>13</sup> Treatment experienced patients without or with cirrhosis should be treated with VEL/SOF + RBV for 12 weeks or with VEL/SOF for 24 wks if RBV-intolerant. Extension to 24 weeks in patients who cannot tolerate RBV requires approval by health insurances. If NS5A resistance testing is performed and demonstrates the absence of NS5A RAS Y93H, treatment can be performed with VEL/SOF for 12 weeks without RBV.

<sup>14</sup> The current Swiss label foresees GZR/EBR for 12 wks without RBV in previous [PEG-]IFN- $\alpha$ /RBV relapsers (see Table 1).

## References

1. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection. *N Engl J Med* 2014;370:1483-1493.
2. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. *N Engl J Med* 2014;370:1889-1898.
3. Bourlière M, Bronowicki J-P, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis* 2015;15:397-404.
4. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. *N Engl J Med* 2014;370:1879-1888.
5. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV Genotype 1b Infection. *Gastroenterology* 2014;147:359-365.e1.
6. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin. *N Engl J Med* 2014;370:1594-1603.
7. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r–Ombitasvir and Dasabuvir with or without Ribavirin for HCV. *N Engl J Med* 2014;370:1983-1992.
8. Poordad F, Hezode C, Trinh R, et al. ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. *N Engl J Med* 2014;370:1973-1982.
9. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin. *N Engl J Med* 2014;370:1604-1614.
10. Fornis X, Lawitz E, Zeuzem S, et al. Simeprevir With Peginterferon and Ribavirin Leads to High Rates of SVR in Patients With HCV Genotype 1 Who Relapsed After Previous Therapy: A Phase 3 Trial. *Gastroenterology* 2014;146:1669-1679.e3.
11. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014;384:403-413.
12. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014;384:414-426.
13. Reddy KR, Zeuzem S, Zoulim F, et al. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. *Lancet Infect Dis* 2015;15:27-35.
14. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet* 2014;384:1756-1765.
15. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. *N Engl J Med* 2014;370:211-221.
16. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015;61:1127-1135.
17. Hézode C, Hirschfield GM, Ghesquiere W, et al. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naïve chronic hepatitis C genotype 1 or 4 infection: a randomised study. *Gut* 2015;64:948-956.
18. Foster GR, Pianko S, Brown A, et al. Efficacy of Sofosbuvir Plus Ribavirin With or Without Peginterferon-Alfa in Patients With Hepatitis C Virus Genotype 3 Infection and Treatment-Experienced Patients With Cirrhosis and Hepatitis C Virus Genotype 2 Infection. *Gastroenterology* 2015;149:1462-1470.
19. Asselah T, Hézode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. *Lancet Gastroenterol Hepatol* 2016;1:25-35.
20. Waked I, Shiha G, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without

- compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. *Lancet Gastroenterol Hepatol* 2016;1:36-44.
21. Feld JJ, Moreno C, Trinh R, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. *J Hepatol* 2015;64:301-307.
  22. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015;385:1075-1086.
  23. Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015;385:1087-1097.
  24. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. *Ann Intern Med* 2015;163:1-13.
  25. Kwo P, Gane E, Peng CY, et al. Efficacy and safety of grazoprevir/elbasvir plus +/- RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-EDGE treatment-experienced trial. *J Hepatol* 2015;62:S674-S675.
  26. Hézode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet* 2015;385:2502-2509.
  27. European Association for the Study of the Liver Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017;66:153-194.
  28. Aasld Idsa Hcv Guidance P. Hepatitis C guidance: AASLD-IDSa recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015;62:932-954.
  29. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. *N Engl J Med* 2015;373:2618-28.
  30. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *N Engl J Med* 2015;373:2599-607.
  31. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med* 2015;373:2608-17.
  32. Zeuzem S, Mizokami M, Pianko S, et al. NS5A Resistance-Associated Substitutions in Patients with Genotype 1 Hepatitis C Virus: Prevalence and Effect on Treatment Outcome. *J Hepatol* 2017.
  33. Cacoub P, Gragnani L, Comarmond C, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. *Digestive and Liver Disease* 2014;46 Suppl 5:S165-S173.
  34. Negro F, Forton D, Craxi A, et al. Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology* 2015;149:1345-60.
  35. Younossi Z, Park H, Henry L, et al. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology* 2016;150:1599-608.
  36. WHO Global Hepatitis Report 2017 (<http://www.who.int>).
  37. Fretz R, Negro F, Bruggmann P, et al. Hepatitis B and C in Switzerland - healthcare provider initiated testing for chronic hepatitis B and C infection. *Swiss Med Wkly* 2013;143:w13793.
  38. Bruggmann P, Richard J-L. Birth year distribution in reported hepatitis C cases in Switzerland, *Eur J Public Health* 2015;25:141-143.
  39. Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis C virus infection with today's treatment paradigm. *J Viral Hepat* 2014;21:34-59.
  40. Müllhaupt B, Bruggmann P, Bihl F, et al. Modeling the Health and Economic Burden of Hepatitis C Virus in Switzerland. *PLoS One* 2015;10:e0125214.
  41. De Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743-752.