



Treatment of Chronic Hepatitis C - January 2016 Update

(The changes compared to the November 2015 Update are highlighted in yellow)

Swiss Association for the Study of the Liver and Swiss Society for Infectious Diseases

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Introduction

The present document represents an update of the Swiss Association for the Study of the Liver (SASL) Expert Opinion Statement on the treatment of chronic hepatitis C with triple therapy comprising telaprevir (TVR*) or boceprevir (BOC) ¹ as well as the last version of the statement published online in September 2014 which took into consideration the approval of sofosbuvir (SOF) (www.sasl.ch; www.sggssg.ch, www.sginf.ch). It has been elaborated by SASL jointly with the Swiss Society for Infectious Diseases (SSI). Recommendations are based on the results of phase 3 or selected phase 2 clinical studies ²⁻²² and the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C 2015 (www.easl.eu) ²³ 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>) ²⁴. The reader is referred to these documents as well as the 'Fachinformation' approved by Swissmedic (www.compendium.ch or www.swissmedicinfo.ch) and the "Spezialitätenliste" of the Swiss Federal Office of Public Health (FOPH) (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 present update takes into consideration the recent approval in Switzerland of the fixed-dose combination of ledipasvir (LDV) and SOF (Harvoni®) ^{2-5, 19}, the combination of ritonavir-boosted paritaprevir (PTV/r), ombitasvir (OBV) and dasabuvir (DSV) (Viekirax® and Exviera®) ^{6-10, 20-22}, simeprevir (SMV) (Olysio®) ¹¹⁻¹⁵ and daclatasvir (DCV) (Daklinza®) ¹⁶⁻¹⁸. Recommendations will be updated as knowledge gaps are filled and additional indications or new drugs are being approved in Switzerland.

With these advances, robust interferon (IFN)-free combination therapies with short treatment duration (8 to 12 to 24 weeks) are available for all genotypes. We consider Metavir stage 2 or more and extrahepatic manifestations as an indication to treatment of chronic hepatitis C. In

*Abbreviations: TVR, telaprevir; BOC, boceprevir; CYP, cytochrome P450; DAA, directly acting antiviral; DCV, daclatasvir; DSV, dasabuvir; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IFN, interferon; LDV, ledipasvir; LT, liver transplantation; OATP, organic anion transporting polypeptide; OBV, ombitasvir; NAFLD, nonalcoholic fatty liver disease; PEG-IFN- α , pegylated interferon- α ; PTV/r, ritonavir-boosted paritaprevir; RAV, resistance-associated variant; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; TE, treatment-experienced; TN, treatment-naïve.

patients without an urgent treatment indication, a strong patient wish to start therapy should be considered on an individual basis. However, current prices limit access to the new DAAs (see below). Hence, we urge all parties involved to pursue a constructive dialog to facilitate access to treatment to all patients.

Unfortunately, for patients with a strong desire to be treated now who are not included in current reimbursement limitations, combination therapy with pegylated interferon- α (PEG-IFN- α) and ribavirin (RBV) is the only option. However, this should be considered only in those who have good chances of achieving SVR with 24 weeks of conventional treatment.

Reimbursement in Switzerland of the new directly acting antivirals (DAA) is currently limited to prescription by gastroenterologists, infectious diseases specialists, and selected, named other specialists (www.bag.admin.ch/lis-ref). Moreover, reimbursement is limited to certain fibrosis stages, as determined by liver biopsy or FibroScan[®] on two occasions ≥ 3 months apart (Table 1), to patients with symptomatic extrahepatic manifestations of hepatitis C virus (HCV) infection²⁵, and to patients with chronic hepatitis C awaiting liver transplantation (LT) (SOF + RBV for genotypes 1-6 or LDV/SOF for genotype 1) or 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. Extrahepatic manifestations with a well-established indication to antiviral therapy include cryoglobulinemia with end-organ manifestations, non-Hodgkin lymphoma and glomerulonephritis. Debilitating fatigue, porphyria cutanea tarda, lichen planus and other manifestations are associated with chronic HCV infection and may represent indications to antiviral therapy in individual patients.

Background

HCV chronically infects 120-200 million individuals worldwide and an estimated 80,000 (i.e. around 1% of the general population) in Switzerland^{26, 27}. It is believed that about 50% of the latter have not been diagnosed yet. Recommendations for healthcare provider-initiated testing for HCV infection have been issued by the Swiss Experts in Viral Hepatitis (SEVHep) and the FOPH²⁸ and complementary birth cohort-based screening is being discussed²⁹. A national hepatitis C strategy is currently being conceived (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, nonalcoholic 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^{30, 31}.

Practical use of sofosbuvir

SOF (Sovaldi[®], 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 RBV (12-24 wks), PEG-IFN- α /RBV (12 wks), LDV (12-24 wks) or another DAA. SOF in combination with PEG-IFN- α /RBV might still be a very good combination for patients with a genotype 3 infection without contraindications to PEG-IFN- α , whereas it is no longer first choice for patients infected with the other genotypes¹⁹. 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 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). 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).

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®, 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 variants (RAVs) are detected in the majority of patients. The RAVs 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-glycoprotein 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). 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[®], AbbVie, North Chicago, IL) of which two have to be taken in the morning. DSV 250 mg (Exviera[®], AbbVie) has to be taken bid. 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).

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 without cirrhosis^{23, 24}. A recent unpublished study suggests that RBV can even be omitted in cirrhotic genotype 1b patients²². 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. PTV/r and OBV have robust activity also against genotype 4. However, this combination is currently approved only for genotype 1 in Switzerland. Initial data indicate that PTV/r, OBV and DSV can be safely used in patients with advanced renal impairment. However, expert advice is recommended in this situation. This combination is not recommended in patients with decompensated cirrhosis.

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[®], 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. It is active *in vitro* against HCV genotypes 1, 2, 4, 5 and 6. SMV has to be used in combination with PEG-IFN- α 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 and reimbursed in combination with PEG-IFN- α 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 is 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 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) for known drug-

drug interactions and contraindicated drugs. Commonly used drugs that are contraindicated in combination with SMV include, among others, carbamazepin, 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®, 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-glycoprotein. Therefore co-administration with strong inducers of CYP3A4 and/or P-glycoprotein (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). 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- α + RBV, or as IFN-free combination therapy together with SOF or SMV. In Switzerland DCV is approved and reimbursed in combination with PEG-IFN- α 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. The combination of DCV with SOF \pm RBV is a preferred treatment option for genotype 3 infection, as other currently available DAAs have insufficient activity against this genotype.

Table 1. Current reimbursement limitations of approved DAA (CH, January 2016).

DAA	Genotype	Metavir F2 Liver stiffness ≥ 7.5 and ≤ 9.5 kPa ¹	Metavir F3 and F4 Liver stiffness > 9.5 kPa ¹
SOF	1-6	reimbursed	reimbursed
LDV/SOF	1	reimbursed ²	reimbursed ²
PTV/r/OBV + DSV	1	reimbursed	reimbursed
SMV ³	1 and 4	reimbursed	reimbursed
DCV ⁴	3 and 4	reimbursed	reimbursed

¹ As determined by FibroScan® on two occasions ≥ 3 months apart.

² Reimbursement is limited to 8 weeks in TN non-cirrhotic patients with F2 fibrosis and a serum HCV RNA < 6 x 10⁶ IU/ml.

³ SMV is only approved and reimbursed in combination with PEG-IFN- α + RBV (see text).

⁴ DCV is approved and reimbursed in combination with PEG-IFN- α + RBV for patients with HCV genotype 4 infection (24 weeks) and with SOF for patients with genotype 3 infection (12 weeks).

Table 2. Recommended treatment options for patients with chronic hepatitis C.¹

Genotype	Non-cirrhotic	Cirrhotic (Child-Pugh A)
1	<p>LDV/SOF for (8-)12 wks²</p> <p>PTV/r/OBV + DSV ± RBV 12 wks⁵</p> <p>SMV + SOF for 12 wks</p> <p>DCV + SOF for 12-24 wks⁷</p>	<p>LDV/SOF + RBV for 12(-24) wks³</p> <p>LDV/SOF for 24 wks⁴</p> <p>PTV/r/OBV + DSV + RBV 12-24 wks⁶</p> <p>SMV + SOF + RBV for 12 wks</p> <p>SMV + SOF for 24 wks</p> <p>DCV + SOF + RBV for 12 wks</p> <p>DCV + SOF for 24 wks</p>
2	<p>SOF + RBV for 12 wks</p> <p>SOF + PEG-IFN-α + RBV 12 wks</p> <p>DCV + SOF for 12 wks</p>	<p>SOF + RBV for 16-24 wks⁸</p> <p>SOF + PEG-IFN-α + RBV 12 wks</p> <p>DCV + SOF for 12 wks</p>
3	<p>DCV + SOF for 12 wks</p> <p>SOF + PEG-IFN-α + RBV 12 wks</p> <p>SOF + RBV for 24 wks</p>	<p>DCV + SOF ± RBV for 24 wks</p> <p>SOF + PEG-IFN-α + RBV for 12 wks</p>
4	<p>LDV/SOF for 12 wks</p> <p>PTV/r/OBV + RBV for 12 wks</p> <p>SMV + SOF for 12 wks</p> <p>DCV + SOF for 12 wks</p> <p>SOF + PEG-IFN-α + RBV 12 wks</p>	<p>LDV/SOF + RBV for 12(-24) wks</p> <p>LDV/SOF for 24 wks</p> <p>PTV/r/OBV + RBV for 12 wks</p> <p>SMV + SOF + RBV for 12 wks</p> <p>SMV + SOF for 24 wks</p> <p>DCV + SOF + RBV for 12 wks</p> <p>DCV + SOF for 24 wks</p> <p>SOF + PEG-IFN-α + RBV for 12 wks</p>

Color code: **green** = approved and reimbursed (please consult 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; **bordeaux** = off-label use of drugs approved in Switzerland; **orange** = approved in Switzerland but not reimbursed

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; LDV, ledipasvir; OBV, ombitasvir; PEG-IFN-α, pegylated interferon-α; PTV/r, ritonavir-boosted paritaprevir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

¹ Recommendations apply to TN patients and patients who failed previous treatment with PEG-IFN-α and RBV. Please seek expert advice 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, HCC, acute hepatitis C and HCV genotype 5 or 6 infection.

² Treatment may be shortened to 8 wks. in HIV-negative TN patients with Metavir fibrosis stage F2 if their baseline HCV RNA is < 6 x 10⁶ (6.8 log) IU/ml. Patients with fibrosis stage F3 or with a baseline HCV RNA ≥ 6 x 10⁶ (6.8 log) IU/ml should be treated for 12 weeks.

³ The addition of RBV in TN and TE cirrhotic patients is recommended by EASL; this is not foreseen in the current Swiss label and AASLD-IDSA Recommendations. LDV/SOF + RBV for 12 wks is also an appropriate regimen for

TE patients with cirrhosis; this is not foreseen in the current Swiss label. Extension of LDV/SOF + RBV to 24 wks may be considered in TE cirrhotic patients with negative predictors of response, such as platelet count < 75 G/l; this is not foreseen in the current Swiss label.

⁴ Extension to 24 wks without RBV is recommended for cirrhotic patients with contraindications or poor tolerance to RBV. The current Swiss label foresees 24 wks without RBV for TE cirrhotic patients.

⁵ Patients with subtype 1a should receive this regimen with RBV. Noncirrhotic patients with subtype 1b should receive this regimen without RBV.

⁶ 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. Omission of RBV can be considered in cirrhotic genotype 1b patients.

⁷ According to the current Swiss label DCV is approved for the treatment of TN and TE non-cirrhotic genotype 1 patients in combination with SOF for 12 and 24 wks, respectively, but is not reimbursed

⁸ Extension to 16-20 or 16-24 wks in cirrhotic patients is recommended by EASL and AASLD respectively, especially in TE patients; this is not foreseen in the current Swiss label.

HCV RNA monitoring on treatment

On triple therapy with SOF + PEG-IFN- α + RBV, it is recommended to determine HCV RNA at baseline, week 4 and week 12 (end of treatment), and 12 or 24 weeks after the end of treatment.

On IFN-free treatment regimens, it is recommended to determine HCV RNA at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of treatment.

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). Because of the frequent comedication with antiretrovirals and further drugs, it is crucial to check for drug-drug interactions (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.

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