Application for Inclusion of Sofosbuvir/Daclatasvir on the WHO Model List of Essential Medicines for Children (EMLc)

Table of Contents

General Information

1. Summary statement of the proposal for inclusion, change or deletion.

This document proposes the inclusion of sofosbuvir/daclatasvir, either as a fixed dose combination (FDC) product or as the single drug products, for treatment of chronic hepatitis C infection among pediatric patients on the core list of the Model List of Essential Medicines for Children (EMLc). The regimen of sofosbuvir (SOF) plus daclatasvir (DAC) represents the combination of two direct-acting antiviral drugs. Both SOF and DAC tablets as single drug products are currently included in the WHO Model List of Essential Medicines (EML) for treatment of chronic hepatitis C virus (HCV) in adults. This application proposes to add the recently approved SOF/DAC FDC tablet as well as the individual SOF and DAC products to the Model List of Essential Medicines for Children (EMLc) to span the pediatric ages and weight bands for which these products provide appropriate dosing.
The principal reasons for requesting this inclusion are as follows:

- The combination of SOF and DAC provides effective treatment for all common genotypes of HCV, with high rates of sustained virologic response (SVR) measured at 12 weeks after the completion of therapy.
- Treatment with SOF/DAC is well-tolerated and the great majority of patients are able to complete a treatment course of 12 weeks (for non-cirrhotic patients).
- The combination of SOF/DAC has a relatively low or manageable risk of drug-drug interactions and can be used in patients receiving antiretroviral therapy for HIV infection with some dose modification.
- SOF/DAC was already included as one of the three recommended pan-genotypic regimens for adults in the 2018 WHO Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection. SOF/DAC is expected to be added as a treatment for children with chronic HCV infection in the planned update to the chapter on treatment in adolescents and children in the 2018 WHO Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection, and the regimen will be recommended as a first line therapy for pediatric patients for whom dosing recommendations and an appropriate formulation are available. This update will be published in Q2/Q3 2021 as a rapid communication policy brief, and will also be included in the overall WHO consolidated guidelines on testing, care and treatment of viral hepatitis to be published end 2021.
- SOF/DAC has become the regimen of choice in low- and middle-income countries (LMIC) for treatment of adults with chronic HCV infection, with WHO-prequalified products available from multiple suppliers at the lowest prices of any DAA regimens. Alignment of the adult and pediatric regimens for LMIC markets provides significant opportunity to advance the treatment and cure of chronic HCV among children.

2. Relevant WHO technical department and focal point (if applicable).

Philippa Easterbrook, WHO Global Hepatitis Program

3. Name of organization(s) consulted and/or supporting the application.

Clinton Health Access Initiative, Inc.
Boston, MA USA

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: sofosbuvir, daclatasvir
ATC: J05AP08 (SOF), J05AP07 (DAC)

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

SOF/DAC is available as an FDC oral tablet containing SOF 400mg/DAC 60mg.
SOF is available as oral tablets of two strengths, either 400mg or 200mg.
DAC is available as oral tablets of two strengths, either 60mg or 30mg.
SRA, WHO-prequalified, or ERP-reviewed product manufacturers include:

- Gilead Sciences Ireland UC, – SOF, currently only source of 200mg tablets
  IDA Business & Technology Park
  Carrigtohill, County Cork, Ireland
- Viatris Inc. (formerly Mylan Laboratories Limited) – SOF, DAC, and SOF/DAC
  Plot No. 564/A/22
  Road No. 92
  Jubilee Hills, Hyderabad – 500096, India
- Hetero Labs Ltd – SOF and DAC
  7-2-A2, Industrial Estates,
  Sanath Nagar, Hyderabad, Ranga Reddy District, Telangana, 500 018, India
- Cipla Ltd – SOF, DAC, and SOF plus DAC co-packaged
  Cipla House
  Peninsula Business Park
  Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India
- Laurus Labs Ltd – DAC
  2nd Floor, Serene Chambers
  Road No. 7
  Banjara Hills, Hyderabad, Telangana, 500 034, India
- European Egyptian Pharmaceuticals Industries Co (Pharco) – SOF
  PO Box 111, El Manshia Alex
  Cairo Desert Road KM 25
  Amriya, Alexandria, Egypt
- Strides Pharma Science Ltd – SOF
  Strides House, Opp. IIMB
  Bilekahali, Bannerghatta Road
  Bangalore, Karnataka, 560 076, India

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We request inclusion of SOF and DAC in the EMLc as single-component products in the "Medicines for Hepatitis C" category (6.4.4.2), in the sub-category: "Pangenotypic direct-acting antiviral combinations" (6.4.4.2.1) without a square box. The single drug products SOF and DAC should be annotated as in the EML, "pangenotypic when used in combination with.…" the other drug. We also request similar addition of SOF/DAC to the EMLc as an FDC product in the same category as the FDC is now available as a prequalified product in LMIC. There are other direct acting antivirals listed for the treatment of chronic HCV, but these are not considered therapeutic equivalents.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

The current EML listing for DAAs recommends genotype-specific treatment for adolescents aged 12-17 years or weighing at least 35 kg with chronic HCV infection and further notes that both SOF and DAC have pan-genotypic activity when used in combination. The recommended dose for adults and adolescents (>35kg) without cirrhosis is SOF 400mg plus DAC 60mg or SOF/DAC 400mg/60mg given once daily for 12 weeks. Dose adjustment is not needed for patients with renal or hepatic impairment but the dose of DAC should be decreased to 30mg in patients also receiving strong CYP450 3A4 inhibitors and increased to 90mg in those receiving CYP450 3A4 inducers.[1]

Dosing recommendations for children between 14kg and 35kg are planned for the the 2021 update to the chapter on treatment in adolescents and children in the 2018 WHO Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection, based on a meta-analysis of recent clinical trials conducted in children and pharmacokinetic modeling and simulation exercises. The dose to be recommended in children weighing greater than 30kg without cirrhosis will be SOF 400mg plus DAC 60mg (or SOF/DAC) based on currently available data and supplemental modeling. For children 14kg to 35kg the rcommended dose will be SOF 200mg plus DAC 30mg given once daily for 12 weeks (see Section 9). An FDC of the lower-strength doses is not available at this time.

Identification of children with chronic HCV infection is frequently made on the basis of diagnosis of an infected parent and subsequent testing of the child. Diagnosis of chronic HCV requires testing to identify viral RNA by PCR in the blood, as antibody testing may indicate past or cleared infection. An HCV-infected woman may transmit the virus to her infant in about 5% of affected pregnancies (about 10% in HIV/HCV co-infected women) but 25-40% of children infected via mother-to-child-transmission of HCV will clear virus spontaneously in the first 4 years of life.[2] For this reason, treatment is not recommended for children younger than 3 years of age. Assessment of liver function is recommended at the time of diagnosis and liver transaminases should be monitored throughout treatment. A combined assessment of AST and platelet count, the AST to platelet ratio index (APRI) can provide an indication of the degree of liver fibrosis and liver biopsy is not routinely recommended in children. Transient elastography (FibroScan®) can also be considered to assess stage of fibrosis but is not widely available for children in LMIC. Undetectable HCV RNA 12 (or 24) weeks after the completion of treatment (SVR) is indicative of treatment success and considered a functional cure. However, specialized testing is not required for patient management prior to initiating or while receiving SOF/DAC therapy.

8. Information supporting the public health relevance.

Chronic HCV infection remains a major cause of liver disease globally, with an estimated 71 million people living with chronic HCV overall as of 2015 and an estimated 1.75 million new cases per year.[3] Previously, interferon-based therapy was long and difficult to tolerate, had a low success rate, and required extensive clinical and laboratory monitoring during treatment. The introduction of multiple all-oral, DAA regimens has led to SVR rates > 90% with treatment courses of 12 weeks and greatly improved safety profile. With these improved characteristics acknowledged, in 2016, the World Health Assembly adopted targets for the elimination of chronic HCV as a public health threat by 2030.[4] Treatment of chronic HCV in adults in LMIC has scaled up as availability of DAA treatments has increased. Of the approved DAA regimens, SOF/DAC has become the preferred regimen in LMIC due to the availability of low-cost generic products.

Little emphasis has been placed on chronic HCV in children and the prevalence, epidemiology, and natural history of infection are less well understood in children than in adults. A recently-published modeling exercise, estimated 3.26

million children are living with chronic HCV infection; 20 countries account for 80% of all cases in patients 0-18 years of age. Countries with the highest number of children with chronic HCV include: Pakistan, China, India, Nigeria, and Egypt.[5] The predominant mode of acquisition of HCV infection in children is mother-to-child transmission, although older children and adolescents may become infected via unsafe injection practices or poor infection control practices. About 5% of infants born to mothers with HCV infection will acquire infection, up to 10% if the mother is co-infected with HIV. The risk of transmission increases with increasing maternal HCV RNA levels. In one Egyptian cohort of children 8 to 18 years of age, 77.5% had an infected family member and 62.5% had an HCV-infected mother.[6] Fortunately, asymptomatic or minimally symptomatic liver disease is common in pediatric patients and cirrhosis and hepatocellular carcinoma are rare in this age group, allowing treatment to be deferred in younger children according to previous treatment guidelines. However, many academic and non-governmental organizations have noted that a global elimination strategy cannot succeed unless it includes treatment of children and, increasingly, countries with a high burden of HCV infection are developing case finding strategies and treatment programs for children as well as adults. As noted in a recent publication, including children and adolescents in national HCV surveillance, testing, and treatment programs can eventually help achieve the goal of HCV elimination.[7]

9. Review of benefits: summary of evidence of comparative effectiveness.

Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Evidence of effectiveness of SOF/DAC in children is based on information gathered from the scientific literature and review of treatment guidelines discussions. A recently published systematic review with meta-analysis assessed the efficacy and safety of DAAs in children and adolescents and was used to justify this EMLc request.[8] In addition, based on accumulated data from interferon-based treatment trials and other DAA treatment trials to date suggesting that children responded to treatment as well or better than adults, it is also expected that effectiveness of SOF/DAC in children can be extrapolated from larger adult efficacy trials using pharmacokinetic bridging, small confirmatory trials, and modeling and simulation exercises. Extrapolation of efficacy is an approach endorsed by the U.S. Food and Drug Administration for chronic HCV because the course of the infection and the effects of DAAs are considered sufficiently similar between adult and pediatric populations to allow approval of DAAs on the basis of matching pharmacokinetic parameters after the critical parameters are identified in adult patients.[9] Finally, modeling and simulation to identify optimal dosing of SOF and DAC for children between 14kg and 35kg was performed as part of the Global Accelerator for Pediatric Formulations (GAPf) collaboration.

Summary of available data (appraisal of quality, outcome measures, summary of results)

A review of the available clinical trials data in adults was submitted to the Expert Committee with the request for addition of DAC and SOF to the 2017 EML and these data will not be repeated in this dossier. SOF, as Sovaldi® (Gilead Sciences, USA) and DAC, as Daklinza® (Bristol-Myers Squibb, USA) have been shown to be pan-genotypic when given together but innovator-sponsored clinical trials of the two drugs in combination were limited in high-income countries (HIC). The combination of SOF and DAC has become the preferred regimen in LMIC because of its effectiveness against all common genotypes and the increasing availability of low-cost generic products. This dossier will focus on what is known regarding the use of SOF and DAC in patients less than 18 years of age. Although use of a medication in adolescents is usually included in the EML, discussion of dosing in this age group is necessary in this dossier in order to support pediatric weight-based dosing.

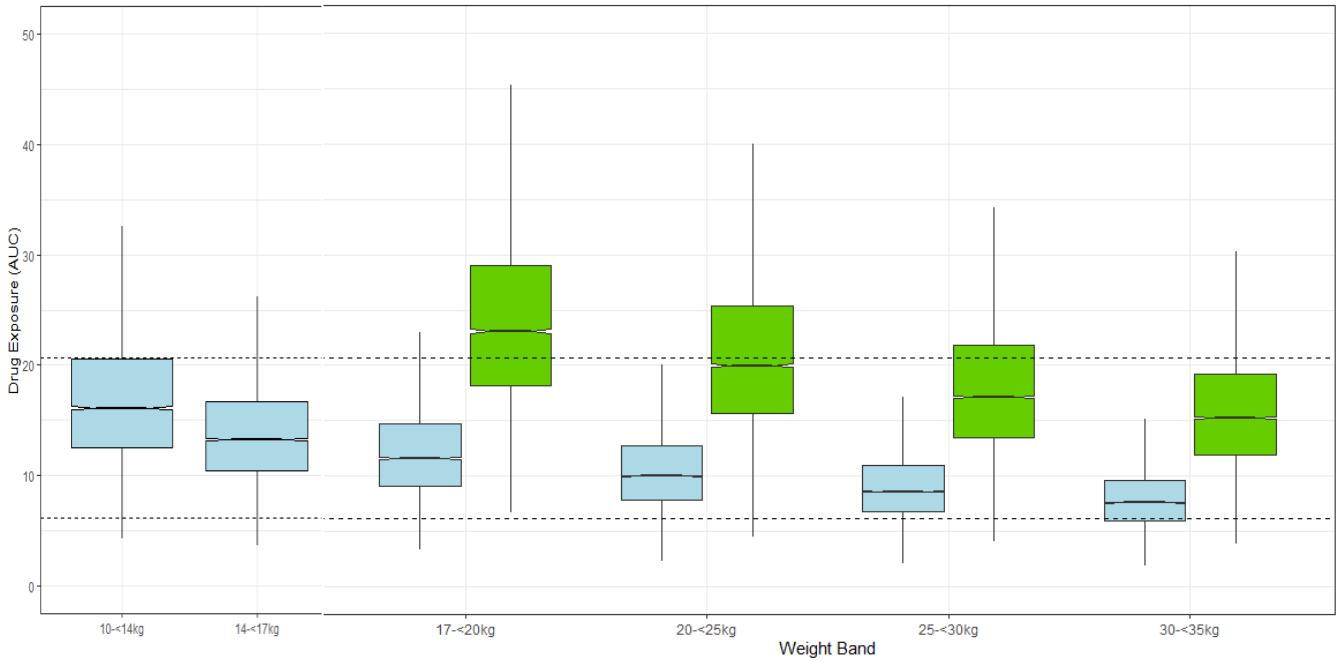
Bristol-Myers Squibb has not conducted clinical trials of DAC in patients < 18 years of age and has no ongoing pediatric development program. Gilead Sciences has conducted pediatric trials of SOF in patients < 18 years of age as part of the development programs for Sovaldi®, Harvoni® (sofosbuvir/ledipasvir), and Epclusa® (sofosbuvir/velpatasvir). They have received FDA and EMA approval for use of SOF in combination with another DAA at a dose of 400mg for

children ≥ 35kg and 200mg for those 17 to <35kg (for patients receiving SOF/velpatasvir, the weight cut-off for 400mg is 30kg).

Multiple small observational studies in patients younger than 18 years of age evaluating SOF plus DAC have been reported. In one study, a cohort of Indian children 10 to 18 years of age with thalassemia major were treated with SOF 400mg plus DAC 60mg for 12 weeks. All children in the cohort were treatment naïve, not cirrhotic, and had genotype 3 HCV; they responded well to therapy with reported improvement in liver transaminases and SVR of 100%.[10] Another group of HCV-infected adolescents in Punjab, India, were managed using a "public health" approach that included decentralized care and optional genotype testing for patients without cirrhosis. Twelve of 57 adolescents in the cohort who opted to have genotyping performed had genotypes 1, 4 or 5 and were treated with a different regimen while 45 were treated with SOF and DAC with good results, including 43 non-cirrhotic and 2 cirrhotic patients. Among those treated with SOF and DAC, SVR was achieved in 97.7% of the non-cirrhotic group and 100% in the cirrhotic group (who also received weight-based ribavirin and a longer course of treatment).[11] Investigators in Egypt reported on their treatment of 40 treatment-naïve children ages 8 to 18 years, all with genotype 4 or mixed genotypes 4 and 1. Children > 45kg received SOF 400mg plus DAC 60mg; those 17kg to 45kg received SOF 200mg plus DAC 30mg. Liver transaminases normalized in all children in the cohort by the end of 12 weeks of treatment and 97.5% achieved SVR. The child who failed to achieve SVR was lost to follow-up but had undetectable HCV RNA at the completion of treatment.[12] Another cohort of 17 Egyptian adolescents with HCV genotype 4 receiving SOF 400mg plus DAC 60mg was evaluated with intensive pharmacokinetic sampling for DAC. Weight and serum albumin levels were the main factors influencing PK parameters in this study. These patients had PK profiles comparable to those observed in adults receiving the same dose and good clinical outcomes.[13]

While these studies are small, they are representative of many similar studies reporting on implementing DAA treatment regimens in children and adolescents with excellent results. Many of the studies have been conducted in LMIC where the burden of disease is high. The systematic review and meta-analysis conducted by Indolfi et al identified near 100% success in achieving SVR with SOF-containing regimens administered to a total of 1674 patients, 206 receiving SOF plus DAC (plus ribavirin in a small number).[8]

Figure 1: Predicted daclatasvir exposure (AUC0-24) in children receiving DAC 30 vs 60 mg OD over the weight range 10 to <35 kg



The horizontal dashed lines in the graph above represent the adult DAC exposure 5th to 95th percentiles (6.15 to 20.63 μg.hr/mL)

In addition to the small clinical cohorts, pharmacokinetic modeling and simulation can be used to support and refine dosing recommendations. In a modeling and simulation exercise (results to be presented in early 2021) performed for the GAP-f consortium, Cressey et al used data from the adolescent PK study to estimate PK parameters by weight bands in children between 10kg and 35kg receiving either 60mg or 30mg of DAC. Their simulations demonstrated that the proportion of children with very high DAC exposures increased for children less than 30kg receiving 60mg and for children 10kg-14kg receiving 30mg (see Figure 1). It was therefore concluded that DCV 30 mg OD would be expected to provide exposures comparable to adult values in children 14-35 kg. The use of currently available low-cost DCV formulations together with approved doses of pediatric SOF formulations would expand considerably access to HCV treatment in chiildren. [14]

Summary of available estimates of comparative effectiveness

In the clinical studies to date, SOF/DAC regimens have not been routinely compared to other regimens regardless of the population being studied. In its guidance for industry on developing DAAs, the U.S. FDA notes that a development plan containing at least one comparative trial is preferred but non-comparative studies using historical controls may be acceptable. In the ENDURANCE-3 trial conducted as part of the registrational package for glecaprevir/pibrentasvir (G/P)(Mavyret®, AbbVie Inc), SOF/DAC compared favorably to G/P in patients with genotype 3 HCV, achieving SVR in 97% compared to 95% in the G/P arm with no significant differences in safety profile.[15] The standard basis for assessing efficacy across all ages and weights is achieving SVR in a high proportion of participants, > 95% in almost all reported studies of SOF plus DAC across all ages. There are no comparative pediatric trials available, but SVR ranged from 96.7% to 100% in the 11 abstracts and publications reporting SOF plus DAC that were included in the systematic review of DAA use in children.[8]

10. Review of harms and toxicity: summary of evidence of safety.

Estimate of total patient exposure to date

To date, the number of children treated with SOF/DAC is small but increasing. As noted above, the systematic review identified published studies that included 1674 children receiving SOF-containing DAA regimens and 206 who received SOF plus DAC. Non-cirrhotic children receiving their initial treatment with SOF/DAC received a 12-week course. Treatment may be extended in those with cirrhosis and/or ribavirin may be added.

Description of the adverse effects/reactions and estimates of their frequency

DAAs in general, and SOF plus DAC in particular, are well-tolerated and serious adverse events are uncommon. Discontinuation of treatment prior to completion of the 12-week course was not described in the pediatric cohorts reviewed, and patients rarely discontinued follow-up prior to assessing SVR at 12 weeks following completion of treatment. According to the systematic review, the most commonly reported adverse events occurring in more than 5% of pediatric patients receiving any DAA included headache (19.9%), fatigue (13.9%), nausea (8.1%), and abdominal pain (7.0%).[8] Among the 45 patients in the Indian cohort, the authors specifically note no serious adverse events such as anemia or liver decompensation and no events of headache , diarrhea, or fatigue were reported. Two of their patients developed transient elevation of liver enzymes which resolved without discontinuing treatment.[11] Similarly, in one Egyptian cohort side effects were noted to be mild and none required discontinuing treatment.[12] Another Egyptian cohort of 30 patients reported mild to moderate events of nausea, abdominal pain, fatigue, headache, and pruritus or skin rash in 2 to 4 patients each. The authors noted in this publication no changes in hemoglobin or any other hematological abnormalities throughout the study.[16] In a later publication, Yakoot et al report on the effects of SOF plus DAC treatment on weight and linear growth in their expanded cohort of adolescents. They noted no negative impact on linear growth or weight, unlike that reported with interferon-based therapy, and noted parental reports of increased appetite with treatment and non-statistically significant weight gain.[17]

Summary of available data (appraisal of quality, summary of results)

Overall, the quality and quantity of data supporting the safety of SOF/DAC in adults is good and includes both clinical trials and observational cohorts in a variety of settings. SOF/DAC has become the preferred regimen in LMIC for adults with chronic HCV because of its favorable safety/tolerability profile, high success in achieving SVR, and availability of low-cost generic products. Small pediatric trials have included patients down to 17kg and modeling and simulation supports use down to 14kg.

Summary of comparative safety against comparators

There is little comparative safety data evaluating SOF/DAC against other DAA regimens in any age group. In the ENDURANCE-3 trial supporting registration of G/P, SOF/DAC compared favorably to G/P in patients with genotype 3 HCV, as noted above. There were no significant differences in safety profile with 1% discontinuations due to adverse events in the 12-week G/P arm and 1% in the SOF/DAC arm. The most common adverse drug reactions reported in the 12-week G/P arm compared to the SOF/DAC arm were headache (17% vs 15%, respectively), fatigue (14% vs 12%), and nausea (12% vs 12%).[15] There is no comparative safety data in pediatric patients but all DAA regimens included in the Indolfi systematic review were reported to be well-tolerated.

Identification of variation in safety that may relate to health systems and patient factors

No specific safety issues associated with SOF/DAC are expected to pose a differential risk in the international health setting. No special laboratory monitoring is required that might result in potential harm to patients if not available in LMIC clinic setting.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

As noted in the table below, the median cost of treating children who can receive the adult dose of SOF plus DAC, as single products or the FDC, ranges from $79.00 to $120.00 for a standard 12-week course of treatment according to reference pricing guides. CHAI's Hepatitis C Market Report published in May, 2020 identified that the actual in-country prices for 12 weeks of WHO-prequalified SOF plus DCV varies from $60 to $1,347.[18] Lack of availability of a low-cost generic version of SOF 200mg tablets is likely to result in a higher cost for treating children weighing 14kg to 35kg

compared to adults and adolescents. However, costs for low-dose pediatric SOF/DAC will decrease as generic products enter the global market.

Cost of Treatment with SOF 400mg plus DAC 60mg, SOF 400mg/DAC 60mg, or SOF 200mg plus DAC 30mg for patients 14kg to ≥ 35kg

	SOF 400mg + DAC 60mg Tablets – 28 Pack		SOF/DAC FDC Tablets – 28 Pack		SOF 200mg + DAC 30mg Tablets – 28 Pack	
Reference Price	Price per 28 Tablet Pack	Median cost 12-wk course	Price per 28 Tablet Pack	Median cost 12-wk course	Price per 28 Tablet Pack	Median cost 12-week course
Global Fund Reference Price, Q1 2020	SOF $18.20 DAC $12.99	$94.00	$26.25	$79.00	--- DAC $10.00	---
MSF Access Price, Q4 2017	--	$120.00	---	---	---	---
UNDP Health Procurement Mechanism, Q1 2020	--	$90.00	---	---	---	---
Global Fund Transaction Summary*	SOF $15.00 DAC $6.40	$64.20	---	---	--- DAC $8.00	---

All prices in USD. Reference price source information:
Global Fund Reference Pricing: https://www.theglobalfund.org/media/7500/ppm_strategicmedicineshivreferencepricing_table_en.pdf
MSF Access Price: https://msfaccess.org/msf-secures-generic-hepatitis-c-treatment-120-compared-147000-launch-price-tag
UNDP Health Procurement Mechanism: https://www.clintonhealthaccess.org/chai-releases-first-ever-hepatitis-c-market-report/
*Represents weighted average cost per pack.

Sovaldi® is registered by Gilead Sciences as a full-strength 400mg tablet for adults and adolescents and a half-strength 200mg tablet for children weighing from 17kg to 35kg. Gilead offers "access pricing" for their branded Sovaldi® to government programs in 101 selected LMIC at a flat price of $250/28-tablet bottle, or $750 for a full treatment course.[19] While there is currently no SOF 200mg product available through either Gilead's access or a generic and, therefore, no pricing information available, it is a similar composition formulation and should cost slightly less than the full-strength product because of lower amount of active ingredient, if both products are being sold (or used) at similar volumes.

Special Pricing Arrangements

The Rwanda HCV Elimination Program was launched in December 2018. As part of the program, the Rwanda Ministry of Health negotiated a price of $60 per 12-week patient course with WHO-prequalified SOF 400mg plus DCV 60mg. No other special pricing arrangements are known to the authors of this dossier.

Country Level Cost Effectiveness Analyses

At the time of submission, no known country level cost-effectiveness studies have been conducted for SOF, DAC or SOF/DAC tablets for children.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

Sovaldi® (sofosbuvir), registered by Gilead Sciences, is approved by FDA, EMA, and multiple other regulatory authorities; Gilead has granted licenses directly to multiple generic manufacturers that distribute widely. Fourteen generic suppliers have a license for Gilead's drugs. Eleven Indian generic suppliers are permitted to sell SOF across 105 countries.

Daklinza® (daclatasvir), registered by Bristol-Myers Squibb, was approved by FDA and EMA. Daklinza was withdrawn from the commercial market in HIC in 2019 for reasons not related to a safety issue (i.e., for business reasons) and patents were allowed to expire globally. DAC licenses are available through MPP across 112 countries and ten generic suppliers currently have a sublicense for the product. Additional countries outside the licensed territory to the Medicines Patent Pool will soon have access to generic versions of daclatasvir as BMS announced its decision to withdraw or allow market authorization to lapse in countries where the product no longer is routinely prescribed or where there are other therapeutic options available. In addition, the WHO Prequalification team has designated a DAC reference drug product to allow for development of future generic products.

Multiple generic suppliers have WHO-prequalified or ERP-reviewed SOF, DAC, and SOF/DAC products available in the international setting, see listing in Section 5.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

These products are not yet listed in the pharmacopoeia standards.

References: Comprehensive reference list and in-text citations.

1. U.S. Food and Drug Administration. Daklinza (daclatasvir) tablets, for oral use, package insert. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206843s008lbl.pdf
2. Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C, Bulterys M, Siberry G, Walsh N, Chang M-H, Meyers T, Giaquinto C, Wirth S, Chan P-L, and Penazzato M. 2019. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol Hepatol, Published Online, April 11, 2019, http://dx.doi.org/10.1016/ S2468-1253(19)30046-9
3. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018. https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1
4. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021: towards ending viral hepatitis, June 2016. https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1
5. Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M, Estes C, Gamkrelidze I, Jerabek K, Ma S, Montoya S, Razavi-Shearer D, Razavi-Shearer K, Robbins-Scott S, Razavi H, and El Sayed MH. Global prevalence of hepatitis C virus in children in 2018: a modelling study. Lancet Gastroenterol Hepatol 2020; 5: 374–92.
6. Abdel Ghaffar TY, El Naghi S, Abdel Gawad M, Helmy S, Abdel Ghaffar A, Yousef M, and Moafy M. Safety and efficacy of combined sofosbuvir/daclatasvir treatment of children and adolescents with chronic hepatitis C Genotype 4. J Viral Hepat 2019;26:263–270. https://doi.org/10.1111/jvh.13032
7. El-Sayed MH and Indolfi G. Hepatitis C virus treatment in children: a challenge for hepatitis C virus elimination. *Semin Liver Dis* 2020; 40:213-224.
8. Indolfi G, Giometto S, Serranti D, Bettiol A, Bigagli E, De Masi S, Lucenteforte E. Systematic review with meta-analysis: the efficacy and safety of direct-acting antivirals in children and adolescents with chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2020;52:1125–1133.
9. U.S. Food and Drug Administration. Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry. Nov 2017. https://www.fda.gov/media/79486/download
10. Mehta R, Kabrawala M, Nandwani S, Desai P, Bhayani V, Patel S, and Parekh V. Safety and Efficacy of Sofosbuvir and Daclatasvir for Hepatitis C Virus Infection in Patients with β-Thalassemia Major. J Clin Exp Hepatol 2018 Mar;8(1):3-6. doi: 10.1016/j.jceh.2017.06.002. Epub 2017 Jun 23.
11. Dhiman RK, Grover GS, Premkumar M, Taneja S, Duseja A, Rathi S, and Satsangi S. Direct-acting antiviral Therapy Is Safe and Effective in Pediatric Chronic Hepatitis C: The Public Health Perspective. J Pediatr Gastro Nutr 2019;68: 74–80.
12. Abdel Ghaffar TY, El Naghi S, Abdel Gawad M, Helmy S, Ghaffar AA, Yousef M, and Moafy M. Safety and efficacy of combined sofosbuvir/daclatasvir treatment of children and adolescents with chronic hepatitis C Genotype 4. J Viral Hepat 2019; 26:263-270. DOI: 10.1111/jvh.13032
13. Al-Nahari MM, Abbassi MM, Se Ebeid F, Hassany M, El-Sayed MH, and Farid SF. Pharmacokinetics of daclatasvir in Egyptian adolescents with genotype-4 HCV infection. Antivir Ther 2020;25(2):101-110. doi: 10.3851/IMP3357.
14. Cressey TR, Abbrassi M, Lallemant M, Indolfi G, Al-Nahari M, Farid S, Easterbrook P, Penazzato M, and El-Sayad MH. Adequate daclatasvir exposures in children 14-35kg with available adult formulations. Abstract submitted to Conference on Retroviruses and Opportunistic Infections/virtual, 2021.
15. S. Zeuzem, G.R. Foster, S. Wang, A. Asatryan, E. Gane, J.J. Feld, T. Asselah, M. Bourlière, P.J. Ruane, H. Wedemeyer, S. Pol, R. Flisiak, F. Poordad, W.-L. Chuang, C.A. Stedman, S. Flamm, P. Kwo, G.J. Dore, G. Sepulveda-Arzola, S.K. Roberts, R. Soto-Malave, K. Kaita, M. Puoti, J. Vierling, E. Tam, H.E. Vargas, R. Bruck, F. Fuster, S.-W. Paik, F. Felizarta, J. Kort, B. Fu, R. Liu, T.I. Ng, T. Pilot-Matias, C.-W. Lin, R. Trinh, and F.J. Mensa. Glecaprevir–pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med, 2018;378:354-69. DOI: 10.1056/NEJMoa1702417

16. Yakoot M, El-Shabrawi MH, Abdel Gawad MM, Mahfouz AA, Helmy S, Abdo AM, and El-Khayat HR. Dual Sofosbuvir/Daclatasvir Therapy in Adolescent Patients with Chronic Hepatitis C Infection. J Pediatr Gastro Nutr 2018; 67: 86-89.
17. Yakoot M, El-Shabrawi MH, Abdel Gawad MM, Mahfouz AA, Khalil AF, Kamal NM, Helmy S, Abdo AM, Kamal EM and El-Khayat HR. Effects of dual sofosbuvir/daclatasvir therapy on weight and linear growth in adolescent patients with chronic hepatitis C virus infection. Pediatr Inf Dis J 2019, 38(7): e154-e157.
18. Clinton Health Access Initiative. Hepatitis C Market Report. May 2020. https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/05/Hepatitis-C-Market-Report_Issue-1_Web.pdf
19. Gilead Sciences. HCV Access Fact Sheet: Expanding Chronic Hepatitis C Treatment in Low- and Middle-Income Countries. 2019. https://www.gilead.com/-/media/files/pdfs/other/hcv-access-fact-sheet-061219.pdf?la=en&hash=ECF6F2AE73040656D7313C2D1BB27812