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EMLc

ATC codes: [J05AP07](#) [J05AP08](#)

Indication	Chronic hepatitis C ICD11 code: 1E91.1
INN	Daclatasvir + sofosbuvir
Medicine type	Chemical agent
List type	Core (EML) (EMLc)
Formulations	Oral > Solid > tablet: 60 mg + 400 mg
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Therapeutic alternatives limitations	Pangenotypic direct-acting antiviral combinations
Therapeutic alternatives limitations for EMLc	Pangenotypic direct-acting antiviral combinations
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Daclatasvir + sofosbuvir
DrugBank	Daclatasvir , Sofosbuvir

Expert Committee recommendation

The Expert Committee recommended the addition of the fixed-dose combination of daclatasvir + sofosbuvir, single-agent daclatasvir and single-agent sofosbuvir to the core list of the EMLc for the treatment of children with chronic HCV infection among patients weighting 14 kg or more, based on evidence of pan-genotypic effectiveness and an acceptable safety profile. The Committee noted that the results of a systematic review of trials, including trials involving daclatasvir and sofosbuvir, demonstrated high rates of virological response in children and adolescents, comparable with those observed in adults. The Committee therefore also recommended that listings of daclatasvir and sofosbuvir on the EML be extended to include adolescents. In addition, the Committee recommended the addition to the EML of the fixed-dose combination of daclatasvir + sofosbuvir and single-agent sofosbuvir 200 mg to the EML for treatment of adolescents and adults. The Committee recognized that in paediatric patients with HCV infection and cirrhosis, co-administration of daclatasvir and sofosbuvir with ribavirin may be required. However, the Committee noted that there was limited evidence on the use of ribavirin in children and the number of children requiring ribavirin co-treatment was very small; therefore, the Committee did not recommend the inclusion of ribavirin on the EMLc. The Committee also noted the planned inclusion of daclatasvir + sofosbuvir as one of the recommended regimens for children in the updated WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection, the licensing agreements with the Medicines Patent Pool and the availability of prequalified and generic products.

Background

Sofosbuvir 400 mg tablets and daclatasvir 30 mg and 60 mg tablets were added to the core list of the EML in 2015 for the treatment of chronic hepatitis C virus (HCV) infection in adults based on evidence of significantly improved sustained virological response rates and better side-effect profiles compared with interferon-based regimens (1).

Public health relevance

Chronic HCV infection remains a main 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 a year (2). 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, direct-acting antiviral regimens has led to sustained virological response rates greater than 90% with treatment courses of 12 weeks and greatly improved safety. 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 (3). Treatment of chronic HCV in adults in low- and middle-income countries has been scaled up as availability of direct-acting antiviral treatments has increased. Sofosbuvir combined with daclatasvir has become the preferred pan-genotypic direct-acting antiviral regimen in low- and middle-income countries because low-cost generic products are available. 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 modelling exercise, estimated that 3.26 million children are living with chronic HCV infection, and 20 countries account for 80% of all cases in patients aged 0–18 years. Countries with the highest number of children with chronic HCV include China, Egypt, India, Nigeria and Pakistan (4). The main mode of acquisition of HCV infection in children is mother-to-child transmission, although older children and adolescents may become infected through unsafe injection practices or poor infection control practices. About 5% of infants born to mothers with HCV infection will acquire the infection, up to 10% if the mother is co-infected with HIV. The risk of transmission increases with increasing levels of maternal HCV RNA (5). In one Egyptian study of children aged 8 to 18 years, 77.5% had a family member infected with HCV and 62.5% had an HCV-infected mother (6). Most children with liver disease are asymptomatic or minimally symptomatic and cirrhosis and hepatocellular carcinoma are rare in this age group, which allows treatment to be deferred in younger children according to previous treatment guidelines. As noted in a recent publication, including children and adolescents in national HCV surveillance, testing, and treatment programmes can eventually help achieve the goal of HCV elimination (7).

Benefits

A systematic review and meta-analysis of 39 studies (1796 patients) evaluated the efficacy and safety of direct-acting antiviral medicines in children and adolescents with chronic HCV infection (8). Regimens containing sofosbuvir were given to 1674 patients, including 206 who received sofosbuvir plus daclatasvir, with a small number of these also receiving ribavirin. Sustained virological response ranged from 96.7% to 100% in the 11 studies reporting results for sofosbuvir plus daclatasvir included in the systematic review. Several small observational studies in patients younger than 18 years evaluating sofosbuvir plus daclatasvir have also been done. A prospective, observational study of Indian children aged 10 to 18 years with thalassaemia major evaluated the safety and efficacy of treatment with sofosbuvir 400 mg plus daclatasvir 60 mg for 12 weeks (9). All the children in the study (n = 10) were treatment naïve, did not have cirrhosis and had genotype 3 HCV. They all responded well to therapy with reported improvement in liver aminotransferases and the sustained virological response was 100%. A study of adolescents aged 12 to 18 years infected with HCV in India assessed a decentralized public health approach to management that included optional genotype testing for patients without cirrhosis and the safety of treatment with direct-acting antivirals (10). A total of 45 patients were treated with sofosbuvir and daclatasvir, 43 without cirrhosis and two with cirrhosis. Both the patients with cirrhosis (who also received weight-based ribavirin and a longer course of treatment) and 42 (97.7%) patients without cirrhosis showed a sustained virological response. A study in Egypt reported on the treatment of 40 treatment-naïve children aged 8 to 18 years with HCV infection, genotype 4 or mixed genotypes 4 and 1 (6). Children weighing > 45 kg received sofosbuvir 400 mg plus daclatasvir 60 mg and those weighing 17–45 kg received sofosbuvir 200 mg plus daclatasvir 30 mg. Liver aminotransferases normalized in all children by the end of 12 weeks of treatment and 97.5% showed a sustained virological response. The child who failed to achieve a sustained virological response was lost to follow-up but had undetectable HCV RNA at the end of treatment. Another Egyptian study of 17 adolescents with HCV genotype 4 who received sofosbuvir 400 mg plus daclatasvir 60 mg evaluated the

pharmacokinetics of daclatasvir (11). Weight and serum albumin levels were the main factors influencing pharmacokinetic parameters in this study. These patients had pharmacokinetic profiles comparable to those observed in adults receiving the same dose and had good clinical outcomes. A modelling and simulation study to identify optimal dosing of sofosbuvir and daclatasvir for children weighing between 14 kg and 35 kg was performed as part of the Global Accelerator for Paediatric Formulations collaboration (12). Data from an adolescent pharmacokinetic study were used to estimate pharmacokinetic parameters by weight bands in children between 10 kg and 35 kg receiving either 60 mg or 30 mg of daclatasvir. The simulations showed that the proportion of children with very high daclatasvir exposure increased for children weighing less than 30 kg receiving 60 mg of daclatasvir and for children 10–14 kg receiving 30 mg. It was concluded that daclatasvir 30 mg daily would be expected to provide exposures comparable to adult values in children weighing 14–35 kg. In the clinical studies to date, sofosbuvir plus daclatasvir regimens have not been routinely compared with other regimens regardless of the population being studied. In its guidance for industry on developing direct-acting antiviral medicines, the United States Food and Drug Administration (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 registration package for glecaprevir plus pibrentasvir, sofosbuvir plus daclatasvir compared favourably with glecaprevir plus pibrentasvir in participants with genotype 3 HCV infection, with 97% of participants achieving sustained virological response compared to 95% in the glecaprevir plus pibrentasvir arm with no significant differences in safety profiles (13).

Harms

To date, the number of children treated with sofosbuvir plus daclatasvir is small but increasing. As noted in the previous section, the systematic review of direct-acting antiviral medicines identified published studies that included 1674 children receiving regimens of sofosbuvir and 206 who received sofosbuvir plus daclatasvir (8). Children without cirrhosis receiving their first treatment with sofosbuvir plus daclatasvir were given a 12-week course. Treatment may be extended in those with cirrhosis and/or ribavirin may be added. Direct-acting antiviral medicines in general, and sofosbuvir plus daclatasvir in particular, are well-tolerated and serious adverse events are uncommon. Discontinuation of treatment before completion of the 12-week course was not described in the paediatric groups reviewed. Furthermore, patients rarely discontinued follow-up before assessing sustained virological response at 12 weeks after completion of treatment. The most commonly reported adverse events, occurring in more than 5% of paediatric patients receiving any direct-acting antiviral medicine, included headache (19.9%), fatigue (13.9%), nausea (8.1%) and abdominal pain (7.0%) (8). In the Indian study of 45 children treated with sofosbuvir plus daclatasvir, no serious adverse events, such as anaemia or liver decompensation, and no episodes of headache, diarrhoea or fatigue were reported. Two patients developed transient elevation of liver enzymes which resolved without discontinuing treatment (10). Similarly, one of the Egyptian studies noted adverse events were mild and none required treatment discontinuation (6). In a prospective study of 30 adolescents with HCV infection receiving sofosbuvir plus daclatasvir, the following mild to moderate adverse events were reported in two to four patients each: nausea, abdominal pain, fatigue, headache and pruritus or skin rash. The authors noted no changes in haemoglobin or any other haematological abnormalities throughout the study (14). A study on the effects of sofosbuvir plus daclatasvir treatment on weight and linear growth in adolescents reported no negative impact on linear growth or weight, unlike that reported with interferon-based therapy. Parental reports of increased appetite with treatment and non-statistically significant weight gain were also noted (15). Few comparative safety studies have compared sofosbuvir plus daclatasvir with other direct-acting antiviral regimens in any age group. In the ENDURANCE-3 trial supporting registration of glecaprevir plus pibrentasvir, no significant differences were found in safety profile with a 1% discontinuation rate due to adverse events in the 12-week glecaprevir plus pibrentasvir arm and 1% in the sofosbuvir plus daclatasvir arm (13). The most common adverse reactions reported in the 12-week glecaprevir plus pibrentasvir arm compared with the sofosbuvir plus daclatasvir arm were: headache 17% versus 15%, respectively; fatigue 14% versus 12%; and nausea 12% versus 12%.

Cost / cost effectiveness

The median cost of treating children who can receive the adult dose of sofosbuvir plus daclatasvir, as single products or the single-pill combination, ranges from US\$ 79 to US\$ 120 for a standard 12-week course of treatment according to reference pricing guides (Table 5). The CHAI Hepatitis C market report published in May 2020 identified that the actual in-country prices for 12 weeks of WHO-prequalified sofosbuvir plus daclatasvir varies from US\$ 60 to US\$ 1347 (16). Lack of availability of a low-cost generic version of sofosbuvir 200 mg tablets is likely to result in a higher cost for treating children weighing 14–35 kg compared with adults and adolescents. However, costs for low-dose paediatric sofosbuvir plus daclatasvir will decrease as generic products enter

the global market. Table 5. Cost of treatment of sofosbuvir and daclatasvir for patients weighing 14 kg to 35 kg <Refer to TRS 1035> Innovator brand sofosbuvir is registered by Gilead Sciences as a full-strength 400 mg tablet for adults and adolescents and a half-strength 200 mg tablet for children weighing 17–35 kg. Gilead offers “access pricing” for their branded product to government programmes in 101 selected low- and middle-income countries at a flat price of US\$ 250 per 28-tablet bottle, or US\$ 750 for a full treatment course (19). No pricing information was available for the sofosbuvir 200 mg formulation.

WHO guidelines

Sofosbuvir + daclatasvir is 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 (2). Sofosbuvir + daclatasvir is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the guideline chapter on treatment in adolescents and children. The regimen is expected to be recommended as a first-line therapy for paediatric patients for whom dosing recommendations and an appropriate formulation are available. This update will be published in mid-2021 as a rapid communication policy brief and this recommendation will also be included in the overall WHO consolidated guidelines on testing, care and treatment of viral hepatitis to be published at the end of 2021.

Availability

Sofosbuvir 200 mg and 400 mg (Sovaldi®), registered by Gilead Sciences, is approved by the FDA, European Medicines Agency, and many other regulatory authorities. Gilead Sciences has granted licences directly to a number of generic manufacturers that distribute widely. Fourteen generic suppliers have a license for drugs developed by Gilead Sciences. Eleven Indian generic suppliers are permitted to sell sofosbuvir in 105 countries. Daclatasvir 30 mg and 60 mg (Daklinza®), registered by Bristol Myers Squibb, is approved by the US FDA, European Medicines Agency and other regulatory authorities. Daklinza® was withdrawn from the market in high-income countries in 2019 for commercial reasons and patents were allowed to expire globally. Daclatasvir licences are available through the Medicines Patent Pool in 112 countries and 10 generic suppliers currently have a sublicense for the product. More countries outside the licensed territory to the Medicines Patent Pool will soon have access to generic versions of daclatasvir as Bristol Myers Squibb announced its decision to withdraw or allow market authorization to lapse in countries where the product is no longer routinely prescribed or where other therapeutic options are available. In addition, the WHO prequalification team has designated daclatasvir a reference drug product to allow for the development of future generic products. Many generic suppliers have sofosbuvir, daclatasvir and sofosbuvir + daclatasvir fixed-dose combination products available globally that have been prequalified by WHO or assessed by the Expert Review Panel.

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