Sofosbuvir + velpatasvir

Statut de médicament essentiel ✓

EMLc | Codes ATC: J05AP55

Indication	Chronic hepatitis C Code ICD11: 1E91.1
INN	Sofosbuvir + velpatasvir
Type de médicament	Chemical agent
Type de liste	Liste de base (EML) (EMLc)
Formulations	Oral > Solid > tablet: 200 mg + 50 mg (EMLc) ; 400 mg + 100 mg
Historique des statuts LME	Ajouté pour la première fois en 2017 (TRS 1006) Modifié en 2019 (TRS 1021) Modifié en 2021 (TRS 1035)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	Des médicaments appartenant à la même classe pharmacologique peuvent être utilisés
Limites de l'équivalence thérapeutique	Pangenotypic direct-acting antiviral combinations
Limites d'équivalence thérapeutique pour l'EMLc	Pangenotypic direct-acting antiviral combinations
Renseignements sur le brevet	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Sofosbuvir + velpatasvir
DrugBank	Sofosbuvir Velpatasvir

Recommandation du comité d'experts

The Expert Committee recommended the addition of the fixed-dose combination of sofosbuvir + velpatasvir to the core list of the EMLc for the treatment of children aged 3 to 12 years with chronic HCV infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile. The Committee noted that the results of the paediatric trial demonstrated high rates of virological response in children and adolescents, comparable with those observed in adults. The Committee therefore also recommended that listing of sofosbuvir + velpatasvir on the EML should be extended to include adolescents. The Committee recognized that in paediatric patients with HCV infection and cirrhosis, co-administration of sofosbuvir + velpatasvir 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 sofosbuvir + velpatasvir 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, and the availability of prequalified and generic products in some settings.

Contexte

The single-pill combination of sofosbuvir + velpatasvir was added to the core list of the EML in 2017 for the treatment of chronic hepatitis C virus (HCV) infection in adults based on evidence of a favourable benefit–risk ratio. Efficacy outcomes from phase II and III studies of sofosbuvir + velpatasvir showed sustained virological response rates greater than 90% in all studies and for all genotypes. Safety data indicated few discontinuations due to adverse events and a rate of serious adverse events similar to that observed with other regimens (1).

Pertinence pour la santé publique

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 many all-oral, direct-acting antiviral treatments has led to rates of sustained virological response 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. 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). 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 (6).

Bénéfices

An innovator-sponsored trial of sofosbuvir + velpatasvir in children younger than 18 years is ongoing. To date, the trial has enrolled children with chronic HCV infection in three age groups: 12–17 years (n = 102), 6–11 years (n = 73) and 3–5 years (n = 41) from sites in Belgium, Italy, United Kingdom of Great Britain and Northern Ireland and United States of America. In the two older age groups, about 75% of the children were infected with genotype 1 HCV, 13% had genotype 3 and smaller numbers had genotypes 2, 4 and 6. Children aged 6–11 years received 200 mg + 50 mg and those aged 12–17 years received 400 mg + 100 mg once daily for 12 weeks, after which they were monitored for 12 weeks to assess treatment response. Overall, 93.7% of the study participants achieved sustained virological response. Of the 11 children who did not achieve sustained virological response, only two experienced virological failure; in the others, the lack of sustained virological response was due to participants being lost to follow-up or spitting up or being unable to swallow the study drug. Plasma concentrations of sofosbuvir and velpatasvir in study participants were comparable to those observed in adults receiving the recommended dose (7). The children aged 3–5 years received 200 mg + 50 mg once daily (weight ≥ 17 kg) or 150 mg + 37.5 mg daily, administered using an investigational granule formulation (weight < 17 kg). Mean weight in this age group was 19 kg (range 13–35 kg). It was not clear whether all children received the investigational granule formulation. The distribution of HCV genotypes in this group was: genotype 1 (78%), genotype 2 (15%), genotype 3 (5%) and genotype 4 (2%). Sustained virological response was achieved in 83% (34/41) of the children. No virological failures were documented, and the seven treatment failures were non-virological failures, either early treatment discontinuation or loss to follow-up (8). An observational study evaluated sofosbuvir + velpatasvir in five children with relapsed and refractory leukaemia and active genotype 1b HCV infection undergoing allogeneic haematopoietic cell transplant. All the children achieved virological response and normalization of liver enzymes without significant adverse events during treatment. After a median of 15 months of follow-up, four of the children remained disease free and with a sustained virological response. No major drug interactions were observed with either cyclosporine or sirolimus (9).

Torts

To date, the number of children treated with sofosbuvir + velpatasvir is very small. In general, sofosbuvir + velpatasvir has been shown to be well tolerated and serious adverse events are uncommon. In the ASTRAL-1 placebo-controlled registration trial in adults, the most commonly observed adverse reactions (all severity grades) in participants receiving 12 weeks of sofosbuvir + velpatasvir treatment included headache (22%), fatigue (15%), nausea (9%), asthenia (5%) and insomnia (5%). Most adverse reactions (79%) were mild and, with the exception of asthenia, occurred at a similar or lower frequency than placebo-treated patients. Participant's with cirrhosis receiving sofosbuvir + velpatasvir plus ribavirin were more likely to have haematological abnormalities during treatment but these laboratory abnormalities occurred in less than 1% of study participants (10). Sofosbuvir + velpatasvir was generally well tolerated in the paediatric trials (7,8). The most common adverse events among the 175 participants in the two older age groups included headache (23%), fatigue (18%), nausea (13%), vomiting (12%) and cough (11%). Four patients had serious adverse events reported during the trial: auditory hallucinations and constipation (two children in the younger age group), and suicidal ideation, exacerbation of bipolar disorder and suicide attempts (two adolescents in the older age group). Additional assessment of the psychiatric events showed that 27% of the study participants had some relevant psychiatric medical history (7). The most common adverse events observed in the 41 patients in the youngest age group were vomiting (27%), cough (15%), pyrexia (15%), rhinorrhoea (15%), fatigue (12%), nasal congestion (12%) and diarrhoea (12%). One patient in this age group discontinued treatment due to an adverse event but there were no serious adverse events. In addition, no negative effects on weight gain, height, body mass index, radiographic bone age, or sexual maturation were reported from treatment initiation to 24 weeks post-treatment in either boys or girls aged 3–17 years (8). No comparative safety data with other direct-acting antiviral regimens in paediatric patients are available. A systematic review of 39 studies that evaluated the efficacy and safety of direct-acting antiviral treatments in 1796 children and adolescents reported all regimens studied, including sofosbuvir + velpatasvir, were well tolerated (11).

Rapport coût/efficacité

Gilead Sciences offers "access pricing" for Epclusa® 400 mg + 100 mg tablets to government programmes in 101 selected low- and middle-income countries at a flat price of US$ 900 for a 12-week treatment course (12). At present, there is a single generic formulation of sofosbuvir + velpatasvir 400 mg + 100 mg tablet now widely available. The United Nations Development Programme's Health Procurement Mechanism lists the price as US$ 270 for a 12-week course (13). The introduction of additional generic products has the potential to substantially lower the cost of sofosbuvir + velpatasvir, as in India and Pakistan where local generic products are available. A 2020 study on the variability in cost of originator direct-acting antiviral products, reported on the availability of generic direct-acting antivirals globally and estimated the cost of production of some direct-acting antivirals (14). No pricing information was available for the sofosbuvir + velpatasvir 200 mg + 50 mg formulation.

Directives de l'OMS

Sofosbuvir + velpatasvir 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 + velpatasvir is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the guidelines chapter on treatment in adolescents and children. The regimen is expected be recommended as 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.

Disponibilité

Sofosbuvir + velpatasvir 400 mg + 100 mg and 200 mg + 50 mg tablets, registered by Gilead Sciences, are approved by the US Food and Drug Administration and European Medicines Agency; voluntary licences are available in some low- and middle-income countries through the company. To date, WHO-prequalified generic sofosbuvir + velpatasvir 400 mg + 100 mg tablets are available from Viatris (formerly Mylan Laboratories Ltd). India and Pakistan are reported to have locally manufactured generic products.

Autres considérations

The recommended dose of sofosbuvir + velpatasvir for adults and adolescents 12–17 years weighing more than 35 kg, and children

6–12 years weighing at least 30 kg (without cirrhosis) is 400 mg + 100 mg daily for 12 weeks. The approved dose for children 6–12 years weighing 17–30 kg is 200 mg + 50 mg daily for 12 weeks. Weight-based ribavirin is added to these regimens for children with cirrhosis. Regulatory submissions to extend the weight-band dosing recommendations to children 3–5 years weighing less than 17 kg, using a dose of 150 mg + 37.5 mg daily, are currently pending.

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