Glecaprevir + pibrentasvir

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.4. Antihepatitis medicines > 6.4.4.2. Medicines for hepatitis C > 6.4.4.2.1. Medicines for hepatitis C > Pangenotypic direct-acting antiviral combinations

EMLc ATC codes: J05AP57

Indication	Chronic hepatitis C ICD11 code: 1E51.1
INN	Glecaprevir + pibrentasvir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 50 mg + 20 mg granules (EMLc) **Oral > Solid > tablet:** 100 mg + 40 mg
EML status history	First added in 2019 (TRS 1021) Changed 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	Glecaprevir + pibrentasvir
DrugBank	Glecaprevir, Pibrentasvir

Expert Committee recommendation

The Expert Committee recommended the addition of the fixed-dose combination of glecaprevir + pibrentasvir 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 from the DORA 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 glecaprevir + pibrentasvir on the EML be extended to include adolescents. The Committee also noted the planned inclusion of glecaprevir + pibrentasvir 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 licensing agreements in place between the manufacturer and the Medicines Patent Pool, which aims to facilitate affordable access to glecaprevir + pibrentasvir in low- and middle-income countries.

Background

The fixed-dose combination of glecaprevir + pibrentasvir was added to the core list of the EML in 2019 for the treatment of adult patients with chronic hepatitis C virus (HCV) infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile. The Expert Committee noted that this combination is one of three pan-genotypic combinations recommended in the current WHO guidelines for treatment of hepatitis C and is suitable for use in patients with or without compensated cirrhosis (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 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).

Benefits

The DORA study is a paediatric trial of glecaprevir + pibrentasvir in patients aged 3 to < 18 years being conducted by Abbvie. To date, the registration study has enrolled children with chronic HCV infection at sites in Belgium, Canada, Germany, Japan, Puerto Rico, Russian Federation, Spain, United Kingdom of Great Britain and Northern Ireland and United States of America across four age groups: 12–17 years (n = 47), 9–11 years (n = 29), 6–8 years (n = 27) and 3–5 years (n = 24) (7,8). Results from DORA part 1 were submitted for regulatory review and led to the approval of glecaprevir + pibrentasvir for use in children 12 years of age and older or weighing at least 45 kg. Across this age group, about 79% were infected with genotype 1 HCV, 6% with genotype 2, 8% with genotype 3 and 6% with genotype 4. Adolescents received 300 mg/120 mg (glecaprevir/pibrentasvir) once daily for 8 weeks or for 16 weeks (HCV genotype 3, treatment experienced), after which they were monitored for 12 weeks to assess treatment response. Overall, 100% of the study participants achieved sustained virological response (95% CI 92.4 to 100.0). The study showed that the plasma concentrations of glecaprevir and pibrentasvir in the participants were comparable to those observed in adults receiving the recommended dose (7). DORA part 2 was a phase II/III, non-randomized, open-label, multinational study that evaluated the efficacy, safety and pharmacokinetics of a glecaprevir + pibrentasvir paediatric granules formulation in children aged ≥ 3 to < 12 years with HCV infection (genotype 1–6) (8). Participants were divided into three age groups. In each group, participants were first enrolled in parallel into an intense pharmacokinetics portion to characterize the pharmacokinetics and safety in each age group, followed by a non-intense pharmacokinetics safety and efficacy portion. Treatment durations were based on adult treatment recommendations in accordance with local

prescribing labels. Data for the three age groups in DORA part 2 are summarized in Table 3. Table 3. Characteristics of the participant groups in the DORA part 2 trial Characteristic Age group (years) Total 9–11 6–8 3–5 Sample size (n) 29 27 24 80 SVR12, no. (%) 27 (93) 27 (100) 23 (96) 77 (96) Relapse, no. 1a 0 0 1 Treatment discontinuation, no. 1b 0 1c 2 Dose glecaprevir/pibrentasvir (mg) 250/100 200/80 150/60 NA SVR12: sustained virological response 12 weeks after the end of the treatment; NA: not applicable. a One participant relapsed after treatment in week 4. b One participant prematurely discontinued the trial due to a drug-related rash. c One participant refused to swallow the granule formulation and prematurely discontinued the trial after having received a partial dose on Day 1. This participant did not receive subsequent doses. Jonas MM, at al., 2020 (8). In summary, high rates of sustained virological response 12 weeks post-treatment were seen in children aged ≥ 3 to < 12 years with chronic HCV infection. No virological failures were seen on the dose ratio of 50 mg/20 mg.

Harms

To date, the number of children treated with glecaprevir + pibrentasvir is very small. Direct-acting antiviral treatments in general, and glecaprevir + pibrentasvir in particular, are well tolerated and serious adverse events are uncommon. Glecaprevir + pibrentasvir was generally well tolerated in the paediatric registration trial (7,8). In the phase II and phase III adult registration trials of glecaprevir + pibrentasvir, the most commonly observed adverse reactions (all severity grades) in participants receiving 8 weeks of glecaprevir + pibrentasvir treatment were headache and fatigue. Less than 0.1% of participants treated with glecaprevir + pibrentasvir experienced serious adverse reactions, e.g. transient ischaemic attack (9). The most common adverse events among the 47 adolescents in the older DORA group included nasopharyngitis (26%), upper respiratory tract infection (19%), headache (17%), fatigue (11%), oropharyngeal pain (11%) and pyrexia (11%). There was no grade 3 or higher aminotransferase or bilirubin elevations, no liver-related toxicities and no cases of drug-induced liver injury (7). In the younger DORA groups, adverse events were mild and no serious adverse events occurred. One adverse event led to treatment discontinuation. The most common adverse events observed in the 80 participants included headache (14%), vomiting (14%) and diarrhoea (10%) (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 glecaprevir + velpatasvir, were well tolerated (10). No specific safety issues associated with glecaprevir + pibrentasvir are known that would be expected to pose a different risk in an international health setting. No special laboratory monitoring is required, so no potential harm is likely to patients if this function is not available in a clinic setting in low and middle income countries.

Additional evidence

Pharmacokinetic characteristics of the 50 mg + 20 mg paediatric formulation of glecaprevir + pibrentasvir were evaluated in the three age groups in part 2 of the DORA study (11). After pharmacokinetic samples were analysed, doses were adjusted from an initial dose ratio of 40 mg + 15 mg to 50 mg + 20 mg to achieve therapeutic exposures similar to adults. The final paediatric weight-based dosages are shown in Table 4. Table 4. Final paediatric dosages of glecaprevir + pibrentasvir based on weight Age group/weight band Dose (glecaprevir + pibrentasvir) 9 to < 12 years/30 kg to < 45 kg 250 mg + 100 mg 6 to < 9 years/20 kg to < 30 kg 200 mg + 80 mg 3 to < 6 years/12 kg to < 20 kg 150 mg + 60 mg The pharmacokinetic exposures of glecaprevir and pibrentasvir in paediatric patients were comparable to exposures in adults and adolescents, and the final doses used achieved target exposure levels.

Cost / cost effectiveness

A recent study surveyed the current prices of originator direct-acting antiviral medicines in 50 countries (12). The cost of a standard adult course of glecaprevir + pibrentasvir compared well with that of other direct-acting antiviral combinations: median originator prices per standard course were US$ 41 000 for sofosbuvir, US$ 27 000 for daclatasvir, US$ 34 000 for sofosbuvir + velpatasvir and US$ 31 000 for glecaprevir + pibrentasvir. The variability of pricing across countries was high. Generic prices estimated based on costs of active pharmaceutical ingredients (API), excipients, manufacturing of finished pharmaceutical product, taxes and a 10% profit margin

were approximately 1000 times lower than the originator prices cited above: US$ 58 for sofosbuvir + velpatasvir and US$ 31 for sofosbuvir + daclatasvir. The API cost data for glecaprevir + pibrentasvir were insufficient to calculate an estimated cost of a generic formulation, but the data above indicate that the price of a generically produced product could be comparable to that of generically produced alternative fixed dose combinations.

WHO guidelines

Glecaprevir + pibrentasvir 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). Glecaprevir + pibrentasvir 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 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 the updated chapter on treatment of adolescents and children will 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

Glecaprevir + pibrentasvir tablets and granules are manufactured by AbbVie. AbbVie and the Medicines Patent Pool have entered into a royalty-free licensing agreement to accelerate access to glecaprevir + pibrentasvir in 99 low- and middle-income countries and territories at affordable prices, enabling treatment scale-up with glecaprevir + pibrentasvir. Through this agreement, AbbVie will grant WHO prequalified generic manufacturers to license, manufacture and supply generic versions of glecaprevir + pibrentasvir, while maintaining the highest quality and production standards.

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