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

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General Information

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

This document aims to provide evidence for the inclusion of glecaprevir/pibrentasvir, as a fixed dose combination (FDC) formulation[1], on the core list of the Model List of Essential Medicines for Children (EMLc) for treatment of chronic hepatitis C infection among paediatric patients. The regimen of glecaprevir (GLE) plus pibrentasvir (PIB) represents the combination of two direct-acting antiviral drugs. GLE/PIB tablets 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 extend the indication of the GLE/PIB fixed dose combination (FDC) tablet to the paediatric age groups and weight bands for which this product can be appropriately dosed.

Evidence to support this request is as follows:

- The combination of GLE/PIB provides effective treatment for all common genotypes of HCV. High rates of sustained virologic response (SVR) are measured at 12 weeks after the completion of therapy in children of 3 years of age or older, for whom an appropriate formulation is available.[2; 3]
- Treatment with GLE/PIB is well-tolerated in children and the great majority of patients can complete a treatment course in 8 to 16 weeks.[2]
- The combination of GLE/PIB has a relatively low or manageable risk of drug-drug interactions and can be used in children receiving antiretroviral therapy for HIV infection.[1; 4]
- GLE/PIB 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.[5] GLE/PIB is expected to be added as a treatment for adolescents and 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. The regimen will be recommended as therapy for paediatric patients which fit within dosing recommendations and where an appropriate formulation is available. This will be published in Q2/Q3 2021 as a rapid communication policy brief and will also be included in the overall planned WHO consolidated guidelines on testing, care and treatment of viral hepatitis to be published at the end of 2021.
- Until approval of the granule formulation (pending), the current adult and adolescent regimen consists of three tablets, whilst the children's regimen consists of one or two tablets.[2; 3]
- GLE/PIB is the only pangenotypic formulation approved for use over an 8 week treatment duration.[6]
- In the rare event of failure with NS5B inhibitor therapy, GLE/PIB is can be used as rescue therapy.[7; 8]

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.

Fondazione Penta ONLUS
Corso Stati Uniti 4, 35127 Padova, Italy
Tel +39 049 964 0122 / Mob. +39 348 615 1202
www.penta-id.org

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

INN: glecaprevir pibrentasvir (GLE/PIB)
ATC: J05AP57

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

glecaprevir + pibrentasvir	Tablet: 100 mg + 40 mg Granules: 50 mg + 20 mg in sachet

GLE/PIB is available as an FDC oral tablet containing GLE 100mg/PIB 40mg[1] produced by:

AbbVie, Inc
1400 Sheridan Rd, North Chicago, IL 60064, USA

AbbVie has signed a royalty-free licence agreement with the Medicine Patent Pool for glecaprevir/pibrentasvir that covers 93 low and middle-income countries, worldwide.[9]

The recommended adult dosage of GLE/PIB is three 100mg/40mg tablets (total daily dose: GLE 300 mg and PIB 120 mg) taken orally once daily with food.

The paediatric formulation's regulatory dossier is currently under review by the US-FDA, with approval expected in 2021.

The paediatric formulation developed by AbbVie, Inc comprises of film-coated granules of GLE/PIB, co-packaged in a sachet. The granules are intended to be mixed in a small amount of food for once-daily oral administration. Each sachet contains 50 mg of GLE granules and 20 mg of PIB granules. The proposed dosing is weight-based (not age-based) with 3 sachets for the lowest weight band (≥12 kg to <20 kg), 4 sachets for the ≥20 kg to <30 kg weight band, and 5 sachets for the highest weight band (≥30 kg to <45 kg).[7]

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

We request inclusion of GLE/PIB in the EMLc as an individual essential medicine, as FDC product 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. GLE is a representative of the NS3/4A PI pharmacological class of direct acting antivirals (DAAs) and PIB is a representative of the NS5A inhibitor pharmacological class of DAAs – (GLE/PIB). 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 infection10 and further notes that GLE/PIB is a pan-genotypic DAA combination.[11]

The recommended dose for adults and adolescents 12-17 years old (>45 kg US-FDA) without cirrhosis is GLE 300mg/PIB 120mg for 8 weeks.[12]

The paediatric GLE/PIB formulations dossier has been submitted to FDA, and the review outcome is expected in 2021.

The final proposed dosing recommendations are based on weight bands rather than age groups as indicated above:

- 12 kg to < 20 kg (children 3 years to 6 years of age) GLE 150mg/PIB 60mg
- 20 kg to < 30 kg (children 6 years to 9 years of age) GLE 200mg/PIB 80mg
- 30 kg to < 45 kg (children 9 years to 11 years of age) GLE 250mg/PIB 100mg

For children with compensated cirrhosis the duration of treatment is 12 weeks. For children with HCV genotype 3 infection who are treatment-experienced the duration of treatment is 16 weeks. Dose adjustment is not needed for patients with renal impairment[13], including those requiring dialysis, or for patients with moderate to severe liver impairment. Drug concentrations of both GLE and PIB may be significantly decreased in those receiving strong P-gp and CYP3A enzyme inducers, and concomitant use with these inducers is not recommended.[14]

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 has a 5% risk of transmitting the virus to her infant in pregnancy (about 10% in HIV/HCV co-infected women)[15], however 25-40% of children infected via mother-to-child-transmission of HCV will clear the virus spontaneously in the first 4 years of life.[16] For this reason, treatment is not recommended for children younger than 3 years of age.[17]

Assessment of liver function is recommended at the time of diagnosis and liver transaminases should be monitored throughout treatment. Non-invasive methods for assessment of liver fibrosis have not been validated in children. According to the current knowledge on the natural history of the infection, a minority of children (<5%) will present with advanced liver disease during childhood. The few children found to have cirrhosis generally require more intensive therapy, often including the addition of ribavirin to the DAA regimen.

Undetectable HCV RNA 12 (or 24) weeks after the completion of treatment (SVR) is indicative of treatment success and considered a functional cure. Specialized testing is not required for patient management prior to initiating or while receiving GLE/PIB therapy.[7; 8]

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 (as of 2015) and an estimated 1.75 million new cases per year. China, Pakistan, India, Egypt and Russia are the five countries with the highest numbers of individuals infected, with over 5 million infected people in each country.[18]

The estimated HIV-HCV antibody co-infection prevalence among people with HIV is 6.2% or 2.3 million cases (IQR 1.3–4.3 million), The most common mode of HCV transmission is through direct exposure to blood, such as with injection drug use, parenteral exposure via contaminated medical equipment or transfusion of unscreened blood and blood products.[19]

The HCV risk due to using contaminated medical equipment and transfusions in developed countries is inconsequential due to improved medical practices and routine screening of blood and its products, whereas in developing countries infections due to transfusion and poor medical practice still occur.

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 a 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.[20]

Treatment of chronic HCV in adults in LMICs has improved as availability of DAA treatments has increased. However, little emphasis has been placed on chronic HCV in children and the prevalence, epidemiology, and natural history of infection are not as well understood in children as in adults. A modelling exercise estimated 3.26 million children are living with chronic HCV infection, and 20 countries account for 80% of all cases in patients 0-18 years of age. The countries with the highest number of children with chronic HCV include Pakistan, China, India, Nigeria, and Egypt.[18]

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.[21] As indicated above approximately 5% of infants born to mothers with HCV infection will acquire the infection and up to 10% if the mother is co-infected with HIV. The risk of transmission increases with increasing maternal HCV RNA levels.[15] Fortunately, asymptomatic or minimally symptomatic liver disease is common in paediatric patients, and cirrhosis and hepatocellular carcinoma are rare in this age group.[22] This allows treatment to be deferred in younger children, as per previous treatment guidelines. As suggested in a recent publication, including children and adolescents in national HCV surveillance, testing, and treatment programs can help achieve the goal of HCV elimination.[23]

Many academic and non-governmental organizations suggest that a global HCV 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. Although progression to fibrosis and liver disease is slow in children, in low- and middle-income countries where HIV infection is most prevalent postponing treatment is hazardous, as the follow up of asymptomatic HIV infected children is very uncertain.

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 GLE/PIB in children is based on information gathered from the scientific literature and review of treatment guidelines. A recently published systematic review with meta-analysis assessed the efficacy and safety of DAAs in children and adolescents and supports this request for inclusion in EMLc.24 Sustained virological response at post-treatment week 12 was reported as primary efficacy outcome and adverse events as safety outcome. Among 39 included studies (1796 subjects), the pooled proportion among those receiving all doses of treatment and reaching sustained virologic response at post-treatment week 12 was 100% (95% confidence interval: 100-100). Considering subjects receiving at least one dose of treatment, lowest estimates were reported among children with cirrhosis (83%). Headache and fatigue were the most common adverse events. Serious adverse events were uncommon.

The Maviret® (glecaprevir and pibrentasvir, Abbvie) U.S. package insert[1] provides summaries of:

- description of the registrational trials in adults and adolescents
- information on the metabolism of GLE/PIB
- expected or known drug-drug interactions.

GLE/PIB once daily is the only pan genotypic regimen with a duration approved for 8 weeks unlike other alternative equally potent DAA regimen which require 12 weeks therapy in subjects without decompensated cirrhosis. Given its different resistance profile, GLE/PIB can be offered to patients having failed NS5B inhibitor containing regimens.[25]

Effectiveness of GLE/PIB in children can be extrapolated from larger adult efficacy trials using pharmacokinetic bridging and small confirmatory trials, as accumulated data from interferon-based treatment trials and other DAA treatment trials suggest that children respond to treatment as well or better than adults. Extrapolation of efficacy is an approach endorsed by the U.S. FDA for chronic HCV on the evidence that the course of the infection and the effects of DAAs are considered sufficiently similar between adult and paediatric populations and allows approval of DAAs on the basis of matching pharmacokinetic parameters, provided that the critical parameters are identified in adult patients.[26]

- *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 GLE/PIB to the 2017 EML and these data will not be fully detailed in this document.[11]

In short, GLE/PIB is a second-generation HCV FDC regimen of two DAAs, GLE and PIB, each with potent antiviral activity against HCV GTs 1, 2, 3, 4, 5, and 6, with little or no loss of potency against common HCV NS3 and NS5A resistance associated substitutions, respectively, in vitro. Both drugs have negligible (< 1%) renal excretion, allowing administration of GLE and PIB in patients with any stage of renal function, including patients with severe renal impairment and end-stage renal disease (ESRD).[27; 28]

As the vast majority of adults with HCV are treatment naïve and non-cirrhotic, GLE/PIB is the only pangenotypic regimen with a short, 8-week treatment duration[2] indicated for this patient population (including HIV/HCV co-infected).[29; 30] LE/PIB has also been evaluated in HCV/HIV co-infected subjects.[4]

GLE/PIB provides a re-treatment option for patients failing a prior NS3/4A PI, or a prior NS5A inhibitor containing regimen.[7]

This document focuses on the **use of GLE/PIB in patients younger than 18 years of age**.

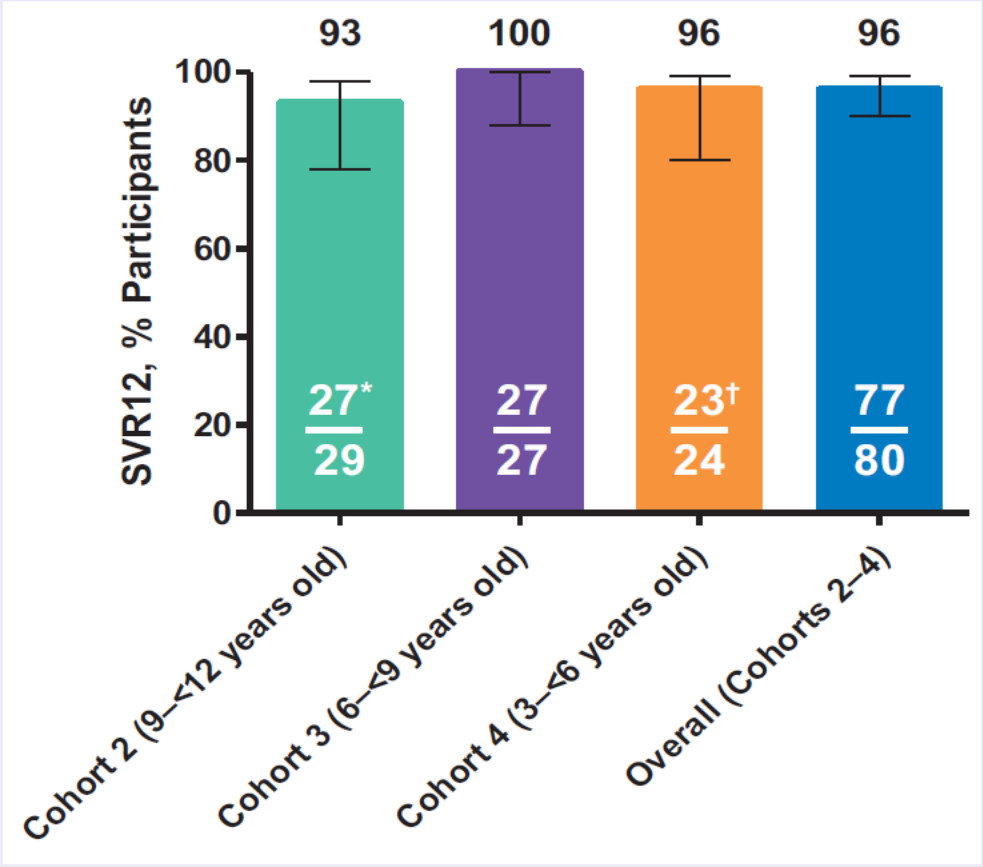
Abbvie is conducting the DORA study, a paediatric trial of GLE/PIB in patients 3 to < 18 years of age as part of their development programs. To date, their registrational study has enrolled children with chronic HCV infection at sites in Belgium, Canada, Germany, Japan, Puerto Rico, Russian Federation, Spain, United Kingdom, United States 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).[2; 3]

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 paediatric weight-based dosing. Results from DORA part 1 were submitted for regulatory review and led to the approval of GLE/PIB for use in the cohort of children 12 years of age and older or weighing at least 45kg. Across the older cohort about 37/47 (%) were infected with genotype 1 HCV, 3/47 (6%), 4/47 (8%) and 3/47 (6%) had genotype 2, 3 and 4, respectively. Adolescents received 300mg/120mg once daily for 8 weeks or for 16 weeks (HCV genotype 3, treatment experience), after which they were monitored for 12 weeks to assess treatment response. Overall, 100% of the study participants achieved SVR. The authors demonstrated that the plasma concentrations of GLE and PIB in the study participants were comparable to those observed in adults receiving the recommended dose.[2]

The DORA part 2 was a phase 2/3, non-randomized, open-label, multinational study that evaluated the efficacy, safety and pharmacokinetics of GLE/PIB paediatric formulation in children aged ≥3 to <12 years with chronic hepatitis C infection (genotype 1-6)_.[3] Participants were divided into 3 age cohorts; in each age cohort they were

first enrolled in parallel into an intense pharmacokinetics (IPK) portion to characterize the PK and safety of each age group, followed by a non-IPK safety/efficacy portion. (Figure 1)

Figure 1. *Percentage of participants achieving SVR 12 by age cohort.*



*One participant with premature discontinuation due to drug-related rash and one participant relapsed by PTW4.
†One participant refused to swallow granule formulation and prematurely discontinued study after being partially dosed on Day 1; the participant did not receive subsequent doses.

Treatment durations were based on adult treatment recommendations in accordance with local prescribing labels.

The data describing the HCV genotype distribution, dose, SVR, virologic failure rates for this cohorts of children younger than 12 years are described in the Table 1 below.

Table 1. *HCV genotype distribution, dose, SVR, virologic failure rates for children younger than 12 years.*

Age cohort (years)	**9-11**	**6-8**	**3-5**
n	29	27	24
SVR; n/total (%)	27/29 (93)	27/27 (100)	23/24 (96)
Relapse	1**	0	0
Treatment discontinuation	1*	0	1§
Dose GLE/PIB (mg)	250/100	200/80	150/60

***One participant prematurely discontinued due to a drug-related rash and **one participant relapsed post-treatment in week 4; **§** one participant refused to swallow the granule formulation and prematurely discontinued the study after being partially dosed on Day 1. This participant did not receive subsequent doses.*

In summary, high rates of SVR12 were seen in children ≥3 to <12 years of age with chronic HCV-infection. No virologic failures were seen on the dose ratio of 50 mg/20 mg GLE/PIB.

- *Summary of available estimates of comparative effectiveness*

In the clinical studies conducted to date, GLE/PIB has not been compared to other DAA regimens. 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.[27]

The standard basis for assessing efficacy across all ages and weights is achieving SVR in a high proportion of participants; > 95% SVR was achieved in almost all reported studies of GLE/PIB across all ages and genotypes studied.[27]

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 GLE/PIB is very small. For children with compensated cirrhosis the duration of treatment is 12 weeks. For children with HCV genotype 3 infection who are treatment-experienced the duration of treatment is 16 weeks.[2; 3]

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

DAAs in general, and GLE/PIB in particular, are well-tolerated and serious adverse events are uncommon. GLE/PIB was generally well-tolerated in the paediatric registrational trial.[2; 3]

In EXPEDITION trials, the adult registrational trials including 2,300 subjects, the most commonly observed adverse reactions (all severity grades) in participants receiving 8 weeks of GLE/PIB treatment included headache and fatigue. Less than 0.1% of subjects treated with GLE/PIB had serious adverse reactions (transient ischemic attack).[12]

The most common adverse events among the 47 adolescents in the older DORA cohort 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.[2] In the youngest DORA cohort, AEs were mild with no serious AEs and 1 AE leading to treatment discontinuation. GLE/PIB was safe and efficacious as a pangenotypic treatment option in children ≥3 years of age with chronic HCV infection. The most common adverse events observed among the 80 patients included headache (14%), vomiting (14%) and diarrhea (10%).[3]

- *Summary of comparative safety against comparators*

There is no comparative safety data in paediatric patients but all DAA regimens included in the Indolfi et al. systematic review were reported to be well-tolerated.[25]

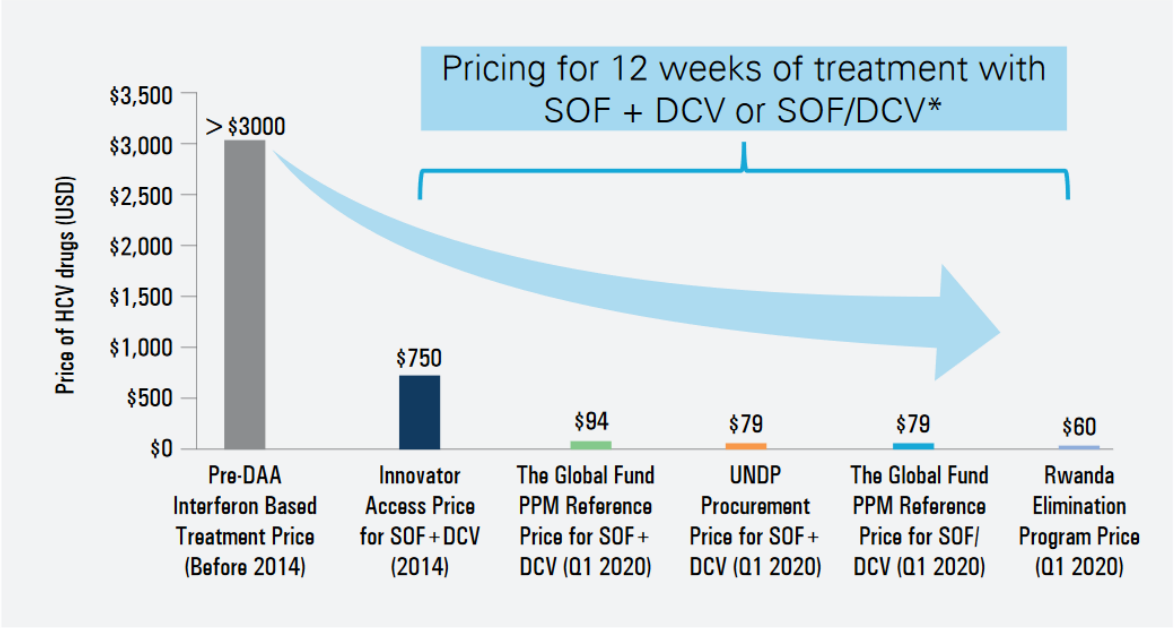
- *Identification of variation in safety that may relate to health systems and patient factors*

There are no specific safety issues associated with GLE/PIB which are expected to pose a differential risk in an 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.

A recent study surveyed the current prices for originator DAAs in 50 countries.[32] The comparison of a standard adult course of GLE/PIB compared well with that of other DAA combinations: median originator prices per standard course were US$41k for sofosbuvir, US$27k for daclatasvir, US$34k for sofosbuvir/velpatasvir, and US$31k for GLE/PIB. 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 less than the originator prices cited above: US$58 for sofosbuvir/velpatasvir, and US$31 for sofosbuvir/daclatasvir. The (API) cost data for GLE/PIB are insufficient to calculate an estimate of the cost of a generic formulation, but the data above would indicate that the price of a generically produced product could be comparable to that of generically produced alternative fixed dose combinations. The figure below shows the evolution of the price of a 12 weeks course of sofosbuvir + daclatasvir as separate tablets and fixed dose combination. It is expected that as GLE/PIB generic products will become available, a similar price evolution will be observed.



*Note: *SOF + DCV refers to a combination of SOF and DCV singles; SOF/DCV refers to FDC.*

Source: CHAI Analysis; The Global Fund Pool Procurement Reference Pricing as of Jan 2020; UNDP procurement support as of Apr 2020.

AbbVie and the Medicines Patent Pool (MPP) have entered a new, royalty-free licensing agreement to accelerate access to GLE/PIB in 99 low- and middle-income countries and territories at affordable prices, enabling access to and treatment scale-up with GLE/PIB. Through this agreement, AbbVie will grant WHO prequalified generic manufacturers to license, manufacture and supply generic versions of GLE/PIB, while maintaining the highest quality and production standards.[33]

Given the high and similar efficacy of the regimen as reported in clinical trials and real-life studies, their cost-effectiveness follows the price ranking cited above.

Country Level Cost Effectiveness Analyses

At the time of submission, no known country level cost-effectiveness studies have been conducted for GLE/PIB granules sachets for children.

Regulatory information

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

SOF with DCV is the most commonly used DAA combination for HCV treatment for adults across LMICs as it is pan-genotypic, has equally efficacious treatment outcomes as other pan-genotypic DAAs recommended by the WHO, SOF/VEL and GLE/PIB and has multiple quality assured generic suppliers. SOF/VEL and GLE/PIB uptake has been limited in LMICs due to their higher price and/ or lack of WHO prequalified generic options available, but with the expected availability of a generic product by Viatris, GLE/PIB will become widely available worldwide.[34]

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

These products are not listed in any of the pharmacopoeia standards.

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