Amsterdam, 24 March 2022
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Maviret

International non-proprietary name: glecaprevir/pibrentasvir

Procedure no: EMEA/H/C/004430/P46/011

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	24/01/2022	24/01/2022
☐	CHMP Rapporteur Assessment Report	28/02/2022	23/02/22
☐	CHMP members comments	14/03/2022	n/a
☐	Updated CHMP Rapporteur Assessment Report	17/03/2022	n/a
☒	CHMP adoption of conclusions:	24/03/2022	24/03/2022

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1. Introduction

On 21 December 2021, the MAH submitted the final clinical study report for the completed paediatric study P20-105 for Maviret (glecaprevir/pibrentsavir) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

No SmPC update for Maviret is proposed by the MAH in relation to this study.

2. Scientific discussion

2.1. Information on the development program

No information has been provided by the MAH regarding the context of submission of this final study report for study P20-105 - Real World EviDEnce of the EffecTIveness and Clinical Practice Use of Glecaprevir/Pibrentasvir in Adolescents 12 to < 18 Years of Age with Chronic Hepatitis C Genotypes 1 to 6 in Russian Federation (DETI-2). It is in the Rapporteur's understanding that this study is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The MAH did not provide study drug in this study. It is stated that the drug was used according to the approved product label and reimbursement criteria and was prescribed by the physician under usual, current medical practice and was clearly separated from the decision to include the patient in the study. Therefore, no information has been provided on the pharmaceutical formulation used in the study.

Otherwise, Maviret is available as 100/40mg film-coated tablets and 50mg/20mg coated granules in sachet.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study P20-105 - Real World EviDEnce of the EffecTIveness and Clinical Practice Use of Glecaprevir/Pibrentasvir in Adolescents 12 to < 18 Years of Age with Chronic Hepatitis C Genotypes 1 to 6 in Russian Federation (DETI-2)

2.3.2. Clinical study

Description

Study P20-105 is a prospective, multi-center observational study in patients with CHC genotypes 1 to 6 receiving the oral GLE/PIB regimen. The prescription of a treatment regimen was at the discretion of the physician in accordance with local clinical practice and label, and was made independently from

this observational study and was preceding the decision to offer the patient the opportunity to participate in this study.

Participants

Adolescents 12 to < 18 years of age chronically infected with HCV receiving GLE/PIB were offered the opportunity to participate in this study during a routine clinical visit at the participating sites.

Study design

Patients were observed for the duration of the GLE/PIB therapy and for up to 12 weeks after treatment completion. Follow-up visits, treatment, procedures, and diagnostic methods followed physicians' routine clinical practice. The observational study period entailed the following data collection schemes:

- 8-week treatment regimen: three visits (baseline, end of treatment, sustained virological response at 12 weeks [SVR12])
- 12-week treatment regimen: three visits (baseline, end of treatment, SVR12)
- 16-week treatment regimen: three visits (baseline, end of treatment, SVR12)

Study duration

The inclusion period was approximately 6 months, and the observational period of the study was from baseline visit until 12 weeks post treatment for each patient.

The observational period for patients receiving 8 weeks of GLE/PIB was approximately 20 weeks (8 weeks treatment and 12 weeks post-treatment observation); for patients receiving 12 weeks of GLE/PIB the observational period was approximately 24 weeks (12 weeks treatment and 12 weeks post-treatment observation); and for patients receiving 16 weeks of GLE/PIB the observational period was approximately 28 weeks (16 weeks treatment and 12 weeks post-treatment observation).

Objectives

The primary objective was:

- To describe the effectiveness of GLE/PIB in HCV-infected adolescents 12 to < 18 years of age in routine clinical practice

The secondary objectives of the study were:

- To describe in routine clinical practice the effectiveness of GLE/PIB by subpopulations of interest: mono-HCV infected and co-infected with HCV/HIV adolescents, HCV genotype/subgenotype, cirrhotic and noncirrhotic patients, treatment-experienced (prior treatment with pegIFN (or IFN), and/or RBV and/or sofosbuvir [PRS]) and treatment-naïve, adolescents who use drugs and non-drug users, as evidenced by SVR12 after the end of treatment.
- To document the adherence to the prescribed GLE/PIB regimen overall and by subpopulations of interest
- To describe of Health Care Resource Utilization with the total number of visits/touchpoints
- To collect information on co-morbidities and concomitant medication

- To describe the safety and tolerability of GLE/PIB

Results

Baseline demographics:

A total of 99 patients with CHC enrolled at 7 clinical sites. The core population (CP), defined as all patients enrolled in the study and receiving GLE/PIB, who had started the treatment combination recommended in the current local label for their disease characteristics, was used to describe the main baseline characteristics. One patient was excluded from the CP because GLE/PIB had not been administered in accordance with the local product label. The average age in the CP was 15.08 ± 1.8 years.

A total of 60 female (60/98, 61.22%) and 38 male (38/98, 38.78%) patients were included in the CP. There were 97 Caucasian patients (97/98, 98.98%) and 1 Asian patient (1/98, 1.02%).

Of the 99 enrolled patients, 92 (92.93%) received 8 weeks of therapy, and 7 (7.07%) received 16 weeks of therapy. No patient was assigned to 12 weeks of therapy.

Overall, 45 (45.45%) patients were co-infected HCV/HIV. The majority of patients had HCV genotype 1 (50.51%) or genotype 3 (39.39%). None of the patients were diagnosed with cirrhosis, although patients with cirrhosis were allowed to be enrolled. There were 90 treatment-naïve patients (90.90%) and 9 PRS-experienced patients (9.09%). None of the patients were DAA-experienced. In the study, 2 patients (2/99, 2.02%) used recreational drugs; 1 patient was an active user and 1 patient was a former user. The rest of the patients had never used recreational drugs.

At baseline, the quantitative HCV RNA test was performed in 74 patients (74/98, 75.51%); all 74 were positive. The qualitative HCV RNA test was performed in 60 patients (60/98, 61.22%); 59 of which were positive. One patient had a negative qualitative test, but a positive quantitative test. There were 36 patients who underwent both quantitative and qualitative tests. The analysis of HIV viral load was performed in 43 patients (43/98, 43.88%). The average value was around 1897.72 copies/mL.

Efficacy results:

All 99 enrolled patients completed the study.

The core population with sufficient follow-up data (CPFSU) was chosen to describe the primary endpoint. During the statistical analysis, 6 patients were excluded from the CPFSU: 3 patients due to lack of SVR test result, neither quantitative nor qualitative; 2 patients dropped out of the study before 12 weeks; and 1 patient due to study drug not administered in accordance with the local label during the treatment period.

The effectiveness of therapy, SVR12, with GLE/PIB was 96.77% (90/93 patients from the CPFSU achieved SVR12), among which 8 weeks therapy had been prescribed to 83 patients and 16 weeks therapy to 7 patients. **Virological failure was reported in 3 patients (3/93, 3.23% did not achieve SVR12), all the three patients with virological failure were co-infected with HCV/HIV**:

- All 3 of them were treatment naïve and received therapy for 8-weeks.
- all 3 patients were HIV-positive with stage 4 , of whom 2 patients had stage 4a and 1 patient – Stage 4b, and received therapy a combination of lamivudine + tenofovir + dolutegravir.

- Two patients had HCV genotype 1 (1 patient with genotype 1a, 1 patient with genotype 1 unspecified) and liver fibrosis stage F0 and 1 patient had unknown HCV genotype and liver fibrosis stage F1.
- One patient was an active drug user; others had never used recreational drugs.

Overall, 50 patients with mono-HCV infection (50/50, 100.00%) and 40 patients coinfected with HCV/HIV (40/43, 93.02%) achieved SVR12.

In the CP, 23 patients (23/98, 23.47%) had a concomitant disease. Of the 33 total concomitant diseases reported, the most frequently reported were the following: other specified diseases of the gallbladder (3/33, 9.09%), unspecified anemia (2/33, 6.06%), other specified disorders of the brain (2/33, 6.06%), myopia (2/33, 6.06%) and gastritis and duodenitis (2/33, 6.06%). With the exception of HIV, no patient received concomitant therapy for these conditions.

No data were collected for the adherence to the prescribed GLE/PIB regimen; hence, adherence rates could not be analysed.

In the CP, the number of patients who were using health resources related to HCV during treatment (30/98 patients, 30.61%) decreased compared to baseline (55/98, 56.12%). At the end of treatment, the number of patients who were using health resources related to HCV (51/98, 52.04%) increased to almost that of baseline.

Safety Results

Throughout the study, a total of 7 AEs were reported. There were no SAEs. All 7 AEs were reported as mild in severity with a reasonable possibility of being related to the study drug. All 7 AEs were identified in treatment-naïve patients, who were not drug users. AEs were almost evenly distributed between patients with HCV mono-infection (3/7, 42.86%) and HCV/HIV co-infection (4/7, 57.14%).

The majority of AEs (4/7, 57%) were in nervous system disorders system organ class (SOC): dizziness, dysgeusia, headache, and somnolence. The remainder of the AEs were 2 (2/7, 28.57%) in gastrointestinal disorders SOC (nausea and vomiting), and 1 AE of fatigue (1/7, 14.29%; general disorders and administration site conditions SOC).

MAH's conclusions

The MAH concluded that GLE/PIB treatment HCV was associated with high effectiveness and tolerability. Almost 97% of patients (90/93) achieved SVR12. Overall, 3 HCV/HIV co-infected patients in the study did not achieve SVR12 due to virological failure. According to the MAH, GLE/PIB was well tolerated in adolescent patients and demonstrated a favorable safety profile, consistent with the safety profile established in adults. The benefit-risk of GLE/PIB is unchanged and no update to the Summary of Product Characteristics has been proposed as a result of the data obtained during this study.

2.3.3. Discussion on clinical aspects

The MAH submitted the final clinical study report of an observational paediatric study in adolescents aged to 12 to 18 years of age conducted in Russia Federation to assess the effectiveness of glecaprevir/pibrenstavir (GLE/PIB) in routine clinical practice. In this study, GLE/PIB were prescribed and used according to current local label and patients were observed for the duration of the GLE/PIB therapy and for up to 12 weeks after treatment completion.

A total of 99 patients were enrolled patients in this study. The mean age of enrolled patients was 15.08 ± 1.8 years. Around half of patients were infected with HCV genotype 1 and 39% were infected with genotype 3. None of them had a diagnosis of cirrhosis at baseline. Of interest nearly 45.45 % of them (n=45) were co-infected with HIV. The high majority (90%) were naïve of treatment, 9% were treatment-experienced (with IFN, and/or RBV and/or sofosbuvir), none of them received other DAA-including regimens. There was no available information on the levels of HCV RNA levels at baseline. The average value for HIV viral load for 43/45 co-infected patients was 1897.72 ± 9259.93 copies/mL.

Of the 99 enrolled patients, 92 (92.93%) received 8 weeks of therapy, and 7 (7.07%) received 16 weeks of therapy.

Among the 99 enrolled patients, six patients were excluded from the analysis for the reasons detailed above. The SVR12 was reached in nearly 97% of patients (90/93), which is overall close to what was reported in other studies. In terms of safety, no particular concern was raised in this study, only 7 non serious AEs were collected including dizziness, dysgueusia, headache, somnolence, nausea and fatigue.

Of note, there were three virological failures, all reported in HCV-HIV co-infected patients. All three patients were treatment naïve and had received therapy for 8-weeks. Two were infected with HCV genotype 1, the genotype for the third patient is not known. Among them, one patient was current active user of recreational drugs. Antiretroviral medications were lamivudine/tenofovir/dolutegravir for all three, for which no particular drug-drug interactions with negative impact on exposure to GLE/PIB are expected. It is unknown whether these patients were adherent or not since no data on observance was finally collected in this study. Moreover, data on HCV RNA or any potential substitutions at baseline that could have impacted GLE/PIB efficacy are lacking, making difficult to explore the potential causes of inefficacy. Finally, the absence of any data in terms of adherence and in terms of other sources of PK variability that could have influenced GLE/PIB exposures (other concomitant drugs for example) renders all the more difficult to contextualize the cases of virological failures and reach definitive conclusions.

In the Phase 3 EXPEDITION-2 study conducted in 153 HCV and HIV-1 co-infected adults with or without compensated cirrhosis, it was shown that the presence of HIV-1 co-infection did not impact efficacy, subjects with HCV/HIV-1 co-infection having similar rates of SVR12 as observed in the HCV mono-infected subjects. As a result, the administration scheme recommended for GLE/PIB in HIV co-infected subjects does not differ from that of HCV mono-infection. This approach has been taken up and currently reflected in Therapeutic Guidelines as AASLD or EASL. In DORA-1 and -2 studies performed respectively in 47 adolescent (aged 12 years to less than 18 years) and 80 children aged 3 years to less than 12 years and paediatric studies, there was a limited number of HIV co-infected paediatric patients (4% and 1% respectively). However, it is not expected that HIV co-infection could have an impact on GLE/PIB efficacy in paediatric population that would have not been observed up to date in adult population.

All in all, and taking into account the above considerations and notably the difficulty of contextualizing the three cases of virological failures reported in this real life study, we concur with the MAH's conclusion that the benefit/risk balance of Maviret is unchanged and that no SmPC update is necessary.

3. Rapporteur’s overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Not Applicable