CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215110Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRALS: CLINICAL VIROLOGY REVIEW
sNDA: 209394 S-13 **SDN**: 708 **eCTD:** 0168; **NDA:** 215110 **SDN**: 001 **eCTD:** 0001
Clinical Virology Reviewer: Patrick R. Harrington, Ph.D. **Review Completed:** 4/8/2021

Reviewer's Name(s): Patrick R. Harrington, Ph.D.

Sponsor: AbbVie, Inc.
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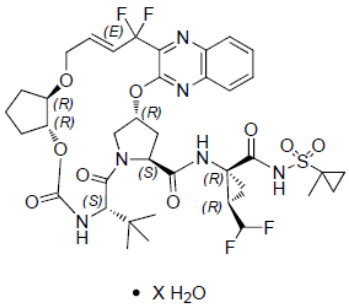
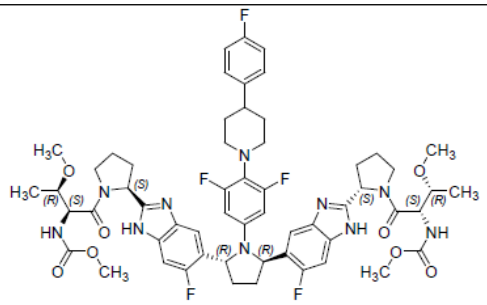
Submission Dates:
Submission Date: 12/10/2020
CDER Receipt Date: 12/10/2020
Assigned Date: 12/14/2020

Proprietary Name	**Mavyret™** **(fixed dose combination product: glecaprevir/pibrentasvir)**	
Individual Drug Names [class]	glecaprevir (GLE, ABT-493) [NS3/4A protease inhibitor]	pibrentasvir (PIB, ABT-530) [NS5A inhibitor]
Parent IND #s	116169 (GLE), 127416 (GLE/PIB)	116170 (PIB), 127416 (GLE/PIB)
Chemical Names	(3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl] cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1*H*,10*H*-9,12-methanocyclopenta[18,19] [1,10,17,3,6]trioxadiazacyclononadecino[11,12-*b*]quinoxaline-10-carboxamide hydrate (IUPAC)	Methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate (IUPAC)
Structures	 • X H_2O **GLECAPREVIR**	 **PIBRENTASVIR**
Molecular Formulas	$C_{38}H_{46}F_4N_6O_9S$ (anhydrate)	$C_{57}H_{65}F_5N_{10}O_8$
Molecular Weights	838.87 (anhydrate)	1113.18

Related/Supporting Documents: 4-month safety update (N209394.746, N215110.011)
Dosage Form and Route of Administration: 100 mg glecaprevir and 40 mg pibrentasvir tablet; 50 mg glecaprevir and 20 mg pibrentasvir coated pellets; oral
Dispensed: Rx x OTC__
Current Indication: Treatment of adult and pediatric patients (b) (4) with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A); also indicated for adult and pediatric patients (b) (4)

with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

Abbreviations: HCV, hepatitis C virus; GT, genotype; GLE, glecaprevir; PIB, pibrentasvir; PK, pharmacokinetics; SVR12, sustained virologic response at follow-up week 12

1. CONCLUSIONS AND LABELING RECOMMENDATIONS

This set of submissions consists of a new sNDA (209394 S-13) to expand the Mavyret indication to include the treatment of pediatric patients 3 years and older (b) (4) and a new NDA (215110) for a new formulation consisting of glecaprevir 50mg and pibrentasvir 20 mg coated pellets.

sNDA 209394 S-13 and NDA 215110 are approvable from a Clinical Virology perspective. No changes to the Mavyret™ prescribing information were proposed for Section 12.4 Microbiology, and we have no recommended additions or edits to the prescribing information to forward to the sponsor.

2. BACKGROUND

Mavyret™ (GLE/PIB) is a fixed-dose combination tablet that includes glecaprevir (GLE, ABT-493; HCV NS3/4A protease inhibitor [PI]) and pibrentasvir (PIB, ABT-530; HCV NS5A inhibitor), and was originally approved in 2017 for the treatment of chronic HCV infection. The current indication includes treatment of adult and pediatric patients (b) (4)

In support of the expanded indication to include pediatric patients as young as 3 years of age, the sponsor provided a clinical study report and datasets from ongoing clinical trial M16-123 ("DORA"), "An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1-6 Chronic Hepatitis C Virus (HCV) Infection." This review covers the submitted clinical virology and drug resistance data from clinical trial M16-123. Due to the high efficacy observed, which was expected, limited independent analyses were conducted.

3. CLINICAL VIROLOGY REVIEW OF M16-123 (Part 2 through Post-Treatment Week 12)

Study Design

Clinical trial M16-123 ("DORA") is an open-label, multicenter study to evaluate the pharmacokinetics (PK), efficacy, and safety of GLE/PIB in HCV-infected pediatric subjects aged ≥3 to <18 years. All HCV GTs were eligible. Subjects could be noncirrhotic or have compensated cirrhosis. Subjects with human immunodeficiency virus type 1 (HIV-1) coinfection were eligible. Both HCV treatment-naïve and treatment-experienced subjects were eligible, although prior treatment experience could not include NS3/4A protease inhibitors or NS5A inhibitors.

The study is divided into two Parts based on the GLE/PIB formulation administered. Part 1 of the study allowed enrollment of adolescent subjects aged ≥12 to <18 years who were willing to swallow the adult formulation of GLE/PIB (Cohort 1). Results from Part 1 through Post-Treatment Week 12 were previously reviewed to support the inclusion of adolescents in the GLE/PIB indication; see the Clinical Virology review of NDA 209394 S-6/SDN 300 for details.

In Part 2, pediatric subjects ≥3 to <12 years of age were split across 3 cohorts (Cohorts 2-4) and treated with a coated pellets pediatric formulation. In each cohort, subjects were enrolled first into an intensive PK portion, followed by the non-intensive PK safety/efficacy portion. Additional intensive PK samples were obtained from subjects in Japan.

The study is ongoing, with Part 2 (Cohorts 2-4) data through Post-Treatment Week 12 (i.e., SVR12 assessment) included in the initial NDA/sNDA package. The final analysis will occur after all subjects have completed the study through Post-Treatment Week 144.

The initial and final doses of GLE/PIB evaluated in Parts 1 and 2 are summarized in Table 1 (CSR, pg. 59). The initial doses in Part 2 were chosen based on PK modeling. The final doses in Part 2 were adjusted based on intensive PK analyses of the first 17 subjects enrolled across all 3 cohorts. A total of 18 subjects received the initial lower doses.

Table 1. GLE and PIB doses evaluated in clinical trial M16-123.

		Initial Doses (mg)		Final Proposed Doses (mg)		
Formulation	Age Group (yrs) & Weight Band (kg)	GLE	PIB	GLE	PIB	Number of sachets[a]
Pediatric formulation	≥ 3 to < 6 yr 12 to < 20 kg	120	45	150	60	3
	≥ 6 to < 9 yr ≥ 20 to < 30 kg	160	60	200	80	4
	≥ 9 to < 12 yr ≥ 30 to < 45 kg	200	75	250	100	5
Adult formulation	≥ 12 to < 18 yr ≥ 45 kg	--	--	300	120	--

GLE = glecaprevir; PIB = pibrentasvir; yr = year

a. Each sachet contains 50 mg/20 mg unit dose of GLE + PIB granules.

The assigned treatment durations were based on HCV GT, cirrhosis status and prior treatment experience, as well as geographic location due to different treatment recommendations in Japan (Table 2; adapted from protocol pg. 40). The treatment durations outside of Japan were consistent with the U.S. prescribing information for adults at the time of trial initiation, although the recommended treatment duration for treatment-naïve subjects with cirrhosis has since been shortened to 8 weeks rather than 12 weeks; this has no bearing on the results from M16-123 as the trial included no subjects with cirrhosis. All subjects administered at least 1 dose of study drug are to be followed through Post-Treatment Week 144 to monitor for safety, viral response, emergence and/or persistence of resistance-associated substitutions, and growth and development.

Table 2. Assigned GLE/PIB treatment durations in M16-123 ("DORA").

Patient Population	Duration
Subjects enrolled outside of Japan	
GT1-6, Non-Cirrhotic, Tx-Naïve GT1, 2, 4, 5 or 6, Non-Cirrhotic, Tx-Experienced	8 Weeks
GT1-6, Cirrhotic, Tx-Naïve GT1, 2, 4, 5 or 6, Cirrhotic, Tx-Experienced	12 Weeks
GT3, Non-Cirrhotic or Cirrhotic, Tx-Experienced	16 Weeks
Subjects enrolled in Japan	
GT1 or 2, Non-Cirrhotic, Tx-Naïve or Interferon ± RBV Tx-Experienced	8 Weeks
GT1 or 2, Cirrhotic, Tx-Naïve or Interferon ± RBV Tx-Experienced GT3-6, Non-Cirrhotic or Cirrhotic, Tx-Naïve or Interferon ± RBV Tx-Experienced GT1-6, SOF + RBV Tx-Experienced	12 Weeks

HCV RNA levels in plasma were measured in a central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0, which has a lower limit of quantification and limit of

detection of 15 IU/mL, regardless of HCV genotype. HCV genotype and subtype were assessed in Screening samples using the Versant® HCV Genotype Inno-LiPA Assay, Version 2.0 or higher. If the LiPA assay could not genotype a sample, its genotype/subtype was to be determined by a Sanger nucleotide sequence analysis assay targeting the HCV NS5B gene. HCV genotype and subtypes were further refined by phylogenetic analysis of baseline NS3/4A and NS5A sequences. Resistance analyses included next generation sequencing (NGS) of NS3/4A and NS5A regions. Independent analysis of resistance data was conducted only for a single subject who experienced virologic failure.

Subject Population, Efficacy and Resistance Results

Baseline disease characteristics are summarized in Table 3 (compiled by reviewer). A total of 127 subjects (80 in Cohorts 2-4) were enrolled and received at least 1 dose of study drug.

Table 3. M16-123 subject disposition and baseline characteristics. All HCV genotype/subtype results shown, except for one GT3 subject, are based on phylogenetic analysis of NS3/4A or NS5A sequences. *Final proposed doses for age and weight groups in Cohorts 2-4.

		Cohort 1 (≥12 to <18) (≥45 kg)	Cohort 2 (≥9 to <12) (≥30 to <45 kg)	Cohort 3 (≥6 to <9) (≥20 to <30 kg)	Cohort 4 (≥3 to <6) (12 to <20 kg)	Total
Number of Subjects		47	29	27	24	127
HCV Genotype	HCV Subtype					
1	1a	24	11	12	14	61
	1b	13	8	10	3	34
	All GT1	37	19	22	17	95
2	2a	1	0	0	0	1
	2b	1	2	0	0	3
	2q	1	0	0	0	1
	All GT2	3	2	0	0	5
3	3	0	0	0	1	1
	3a	4	7	3	5	19
	3b	0	1	0	1	2
	All GT3	4	8	3	7	22
4	4a	0	0	1	0	1
	4d	2	0	0	0	2
	4f	1	0	0	0	1
	4k	0	0	1	0	1
	All GT4	3	0	2	0	5
5	n/a	0	0	0	0	0
6	n/a	0	0	0	0	0
Tx History						
Tx-Naïve		36	27	27	24	114
IFN-based		11	2	0	0	13
Cirrhosis		0	0	0	0	0
GLE and PIB Doses						
GLE 120 MG + PIB 45 MG		0	0	0	6	6
GLE 150 MG + PIB 60 MG		0	0	0	17*	17
GLE 160 MG + PIB 60 MG		0	0	6	0	6
GLE 200 MG + PIB 75 MG		0	6	0	0	6
GLE 200 MG + PIB 80 MG		0	0	20*	1	21
GLE 250 MG + PIB 100 MG		0	23*	1	0	24
GLE 300 MG + PIB 120 MG		47	0	0	0	47

Efficacy based on SVR12 is summarized in Table 4 (FDA analysis). SVR12 rates were at or near 100% for all Cohorts. Excluding the 18 subjects who received the initial lower dose of GLE/PIB, the SVR12 rate in Cohorts 2-4 was 98% (61/62), with no cases of virologic failure.

Table 4. M16-123 SVR12 results.

	Cohort 1 (≥**12** to <18) (≥**45** kg)	Cohort 2 (≥**9** to <12) (≥**30** to <45 kg)	Cohort 3 (≥**6** to <9) (≥**20** to <30 kg)	Cohort 4 (≥**3** to <6) (12 to <20 kg)	Total
SVR12	100% (47/47)	93% (27/29)	100% (27/27)	96% (23/24)	98% (124/127)

A total of 3 subjects in the trial did not achieve SVR12. One subject ([(b) (6)] [Cohort 2]) experienced virologic relapse. Two subjects [(b) (6)] [Cohort 4] and [(b) (6)] [Cohort 2]) prematurely discontinued treatment on Days 1 and 4, respectively, for reasons unrelated to virologic failure.

Subject [(b) (6)] who experienced virologic relapse, was previously treatment-naïve and had an HCV GT3b infection. The subject was in Cohort 2 and received the initial (i.e., lower) GLE/PIB dose of 200 mg/75 mg QD for 8 weeks. Study drug was completed and there were no reports of non-compliance.

Virologic failure in Subject [(b) (6)] could have been attributed to the HCV subtype 3b infection, suboptimal drug exposures with the GLE/PIB dose of 200 mg/75 mg, or both. HCV GT3b is naturally less susceptible to PIB and other NS5A inhibitors (see review of NDA 209394 S-10 for details), which has been attributed to the presence of consensus GT3b NS5A amino acids K30 and M31, both of which were predominant in this subject's Baseline viral population. At the time of virologic relapse, a treatment-emergent NS5A Y93H substitution was also detected, which likely contributed further to reduced HCV susceptibility to PIB. No known GLE resistance-associated substitutions in NS3 were detected at Baseline or at the time of relapse.

According to the 4-month safety update, no subjects in M16-123 have experienced a new HCV infection or late relapse. In Cohort 1, SVR24 was achieved by 100% (47/47) subjects. In Cohorts 2-4, SVR24 was achieved by 91.3% (73/80) subjects. Non-SVR24 subjects include: 1 relapse at Post-Treatment Week 4 (noted above), 2 subjects with premature drug discontinuation (noted above), and 4 subjects without available SVR24 results.

4. LABELING

No changes to the Mavyret™ prescribing information were proposed for Section 12.4 Microbiology. It is acceptable not to include a description of the potential role of HCV subtype 3b in the virologic failure that occurred in Subject [(b) (6)] This subject received a dose of GLE/PIB that is not proposed for marketing for the respective age/weight group, and the reported SVR12 rate in M16-123 described in Section 14 is based only on subjects who received the final recommended dose. Furthermore, data are already described in the prescribing information indicating potentially reduced efficacy of GLE/PIB for HCV subtype 3b.

5. SIGNATURE AND CONCURRENCES

Patrick R. Harrington, Ph.D.
Clinical Virology Reviewer

Date: _____

DAVP/Clin Virol TL/J O'Rear

cc: DAVP/RPM/Hong

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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