EU Risk Management Plan for Vemlidy® (Tenofovir Alafenamide)

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
12.0	25 April 2024	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP:	To update the milestone for Category 3 Study GS-US-320-1092.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part II Safety Specification	Section Part II: Module SI: Epidemiology of the indication and target populations(s)	Post marketing exposure updated
	Section Part II: Module SII: Non-clinical part of the safety specification	
	Section Part II: Module SIII: Clinical study exposure	
	Section Part II: Module SIV: Populations not studied in clinical studies	
	Section Part II: Module SV: Postauthorization experience	
	Section Part II: Module SVI: Additional EU requirements for the safety specification	
	Section Part II: Module SVII: Identified and potential risks	
	Section Part II: Module SVIII: Summary of the safety concerns	
Part III Pharmacovigilance Plan		Updated milestone for Category 3 Study GS-US-320-1092.
Part IV Plan for postauthorization efficacy studies		None.

Part	Module/Annex	Significant changes to RMP
Part V Risk Minimization Measures		None.
Part VI Summary of RMP		Updated to reflect changes in Part II and III Safety Specification.
Part VII Annexes		Updated to reflect changes in Parts II and III.

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
11.0	EMEA/H/C/004169/II/0043/G	11 January 2024

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	Lamivudine
ABC	Abacavir
ADR	adverse drug reaction
ALT	alanine aminotransferase
APR	Antiretroviral pregnancy registry
ART	antiretroviral treatment
ATC	anatomical therapeutic chemical (classification system)
B	bictegravir
BMD	bone mineral density
CES1	carboxylesterase 1
CHB	chronic hepatitis B
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum observed concentration of drug
COBI, C	cobicistat (Tybost®)
CrCl	creatinine clearance
CPT	Child- Pugh-Turcotte classification
CYP	cytochrome P450 enzyme
DLP	data-lock point
DNA	deoxyribonucleic acid
DTG	dolutegravir
DVY	emtricitabine/ tenofovir alafenamide (coformulated; Descovy®)
EASL	European Association for the Study of the Liver
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDC	fixed-dose combination
FTC, F	emtricitabine (Emtriva®)
GEN	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
GVP	Good Pharmacovigilance Practices
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether- à-go-go related gene
HIV (HIV-1)	human immunodeficiency virus (type-1)

IC50	concentration required to produce 50% inhibition
IFN	interferon
INN	international nonproprietary name
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
NA	nucleos(t)ide analogue
N/A	not applicable
NOAEL	no observed adverse effect level
NtRTI	nucleotide reverse transcriptase inhibitor
OAT	organic anion transporter
ODE	emtricitabine/ rilpivirine/tenofovir alafenamide (coformulated; Odefsey®)
PBRER	periodic benefit-risk evaluation report
PEG-IFN	pegylated interferon alpha
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PL	package leaflet
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PRAC	Pharmacovigilance Risk Assessment Committee
PRT	proximal renal tubulopathy
PSUR	periodic safety update report
PV	pharmacovigilance
QD	once daily
QPPV	Qualified Person for Pharmacovigilance
RMP	risk management plan
RPV; R	rilpivirine
SmPC	Summary of Product Characteristics
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TVD	tenofovir disoproxil fumarate/emtricitabine (Truvada®)
UGT	uridine glucuronosyltransferase
WHO	World Health Organization

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Tenofovir alafenamide (TAF)
Pharmaco-therapeutic group(s) (ATC Code):	Nucleoside and nucleotide reverse transcriptase inhibitors (J05AF13)
Marketing Authorization Holder	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	Tenofovir alafenamide film-coated tablets
Invented name(s) in the European Economic Area (EEA)	Vemlidy®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: TAF is a phosphonamidate prodrug of tenofovir (2' deoxyadenosine monophosphate analogue) and is a nucleotide reverse transcriptase inhibitor (NtRTI).
	Summary of mode of action: TAF enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. TAF is primarily hydrolyzed to form tenofovir by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular tenofovir (TFV) is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate (TFV-DP). TFV-DP inhibits HBV replication through incorporation into viral DNA (deoxyribonucleic acid) by the HBV reverse transcriptase, which results in DNA chain- termination.
	Important information about its composition: None
Hyperlink to the Product Information	Vemlidy Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Vemlidy is indicated for the treatment of chronic hepatitis B (CHB) in adults and paediatric patients 6 years of age and older weighing at least 25kg.
	Proposed: Not applicable
Dosage in the EEA	Current: One 25 mg tablet, taken orally, once daily.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablet containing 25 mg TAF.
	Proposed: Not applicable
Is/Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. HBV Infection

SI.1.1. Incidence

The incidence of hepatitis B virus (HBV) infection varies by geographical region, with the highest incidence found in regions and countries with high prevalence (see section SI.1.2). Incidence of HBV infection has decreased considerably due to the widespread use of the HBV vaccine in infancy, wherein an estimated global coverage of 84% was estimated in 2015. However, transmission from mother-to-child and from exposure during early childhood remains common in geographies wherein HBV is endemic and accounts for the majority of new infections {Voiculescu 2015, World Health Organization (WHO) 2017}. In geographies of low incidence, such as the European region and region of the Americas, transmission mainly occurs among adolescents and adults via sexual contact and injection drug use {MacLachlan 2015, Trepo 2014}. The implementation of universal precautions and improved methods of blood donor screening significantly reduced HBV transmission in healthcare settings, contributing to the decrease of incidence in these regions {Trepo 2014}. Some key illustrative figures for the incidence of infection in Europe are as follows {Roure 1995}:

- The lowest rate of infection was in Northern European countries at less than 1/100,000 per year
- Southern European countries had an incident rate of around 6/100,000 per year
- Central European countries had a markedly higher incidence of infection at approximately 20/100,000 per year

SI.1.2. Prevalence

Worldwide, 257 million (95% CI: 199-368 million) people were estimated to be living with HBV infection in 2015, accounting for 3.5% (95% CI: 2.7-5.0%) of the total population. Global prevalence varies widely, with the largest burden of disease in the Western Pacific and Africa regions (6.2% and 6.1%, respectively). These two regions alone comprise 68% of the total infected population. Regions with intermediate prevalence are the Eastern Mediterranean and South-East Asia regions (3.3% and 2.0%, respectively); and the lowest prevalence is found in the European region and region of the Americas (1.6% and 0.7%, respectively). Overall, the majority of those currently living with HBV were infected before 5 years of age and were born prior to the widespread use of the HBV vaccine in infancy (between 1980 and early 2000's). (Table SI.1); {Schweitzer 2015, World Health Organization (WHO) 2017})

Since the introduction of the HBV vaccine, worldwide prevalence among children (5 years old and below) decreased from 4.7% to 1.3%, contributing to the overall decline in prevalence {World Health Organization (WHO) 2017}. However, some developing countries, where implementation of vaccination programs is challenging, have not experienced as significant a decline. For example, although the European region has an overall low prevalence of 1.6% (95% CI: 1.2-2.6%), Eastern European countries have been found to have higher prevalence compared to Western European countries {Duffell 2015, Ott 2017, Schweitzer 2015, Zampino 2015}. Additionally, prevalence in some low endemic geographies is increasing due to migration from areas of high or intermediate prevalence {MacLachlan 2015}.

Table SI.1. Regional Prevalent Cases of HBV Infection in 2015

	Number of Prevalent Cases (n; 95% CI) Overall	Prevalent Cases (%; 95% CI) Overall	Prevalent Cases (%; 95% CI) Children[a]
Africa Region	60 million (45-84 million)	6.1 (4.6-8.5)	3.0 (2.0-4.7)
Region of the Americas	7 million (4-16 million)	0.7 (0.4-1.6)	0.2 (0.1-0.5)
Eastern Mediterranean Region	21 million (17-28 million)	3.3 (2.6-4.3)	1.6 (1.2-2.1)
European Region	15 million (11-23 million)	1.6 (1.2-2.6)	0.4 (0.2-0.8)
South-East Asia Region	39 million (29-77 million)	2.0 (1.5-4.0)	0.7 (0.5-1.6)
Western Pacific Region	115 million (93-140 million)	6.2 (5.1-7.6)	0.9 (0.6-1.3)
Total	**257 million (199-368 million)**	**3.5 (2.7-5.0)**	**1.3 (0.9-2.2)**

a Prevalence of Hepatitis B Surface Antigen (HBsAg) among children aged 5 years and younger.
Source: {World Health Organization (WHO) 2017}

SI.1.3. Demographics of the Population in the Authorized Indication

SI.1.3.1. HBV Infection by Age

Age at the time HBV is contracted is a major predictor of chronic infection. Perinatal transmission rates range from 10% to 90%, with 40% to 90% of infants infected at birth developing chronic infection {Kew 2010}. Infection during childhood (5 years old and below) is also likely to develop into chronic infection (50%), and is considered a major indicator by World Health Organization (WHO) for measuring success in abating HBV infection worldwide {Kew 2010, World Health Organization (WHO) 2017}. Horizontal transmission between children or other close contacts is the primary source of infection at this age. Prevalence among children is highest in the Africa region (3.0% [95% CI: 2.0-4.7%]) and the Eastern Mediterranean region (1.6% [95% CI: 1.2-2.1]) (Table SI.1{World Health Organization (WHO) 2017}).

Contracting HBV in adulthood is less likely to result in chronic infection and is more common in areas where HBV prevalence is low. Major modes of transmission include high-risk behaviors including sexual contact with multiple partners, men who have sex with men, and injection drug use, and to a lesser degree, hospital acquired infection {Kew 2010, Trepo 2014}. In the EU, 33.4% of all HBV cases (acute and chronic) were among adults 25-34 years old from 2006 to 2012. The prevalence of reported chronic HBV cases among adults in this age group was the highest (approximately 30 per 100,000), while the prevalence among age groups greater than 45 years old were all below 10 per 100,000. The age distribution of reported acute cases was similar to that of chronic cases, though prevalence of acute cases is much lower compared to chronic (less than 5 per 100,000 among all age groups) {Duffell 2015}.

SI.1.3.2. HBV Infection by Gender

Worldwide, HBV prevalence among men (3.9%) was slightly higher compared to women (3.5%) in 2005 {Ott 2012}.

SI.1.4. Main Existing Treatment Options

The goal of therapy for chronic hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and death {European Association for the Study of the Liver (EASL) 2017}. This goal can be achieved if HBV replication can be suppressed in a sustained manner. Drugs available for the treatment of chronic hepatitis B include interferon alpha (IFN), pegylated interferon alpha (PEG-IFN) and nucleoside/ nucleotide analogues (NAs). NAs for HBV therapy directly inhibit the HBV reverse transcriptase polymerase and can be classified into nucleosides (i.e., lamivudine, telbivudine, and entecavir) and nucleotides (i.e., adefovir dipivoxil, tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide [TAF]). For treatment-naïve patients, current treatment guidelines recommend the long-term administration of a potent NA with high barrier to resistance (e.g., entecavir, TDF, TAF) {European Association for the Study of the Liver (EASL) 2017}.

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

The course of HBV infection is highly variable and depends on several factors, including age at infection, immune status and how quickly the infection is recognized. Two distinct phases can be described; acute and chronic. The acute phase of HBV infection begins between 6 and 24 weeks post infection. Much acute infection is asymptomatic, but this phase may be accompanied by nausea, vomiting, anorexia, headache, jaundice and increased aminotransferase levels. In a small proportion of cases, fulminant hepatitis occurs, but the acute phase of infection is very rarely fatal. Patients who successfully recover from the acute phase of illness develop permanent immunity to future infection, detectable in serum by the presence of anti-hepatitis B antibodies. Table SI.1 summarizes the main features of acute HBV infection in adults and neonates {World Health Organization (WHO) 2002}.

Table SI.2. Course of Acute HBV Infection in Adults and Neonates

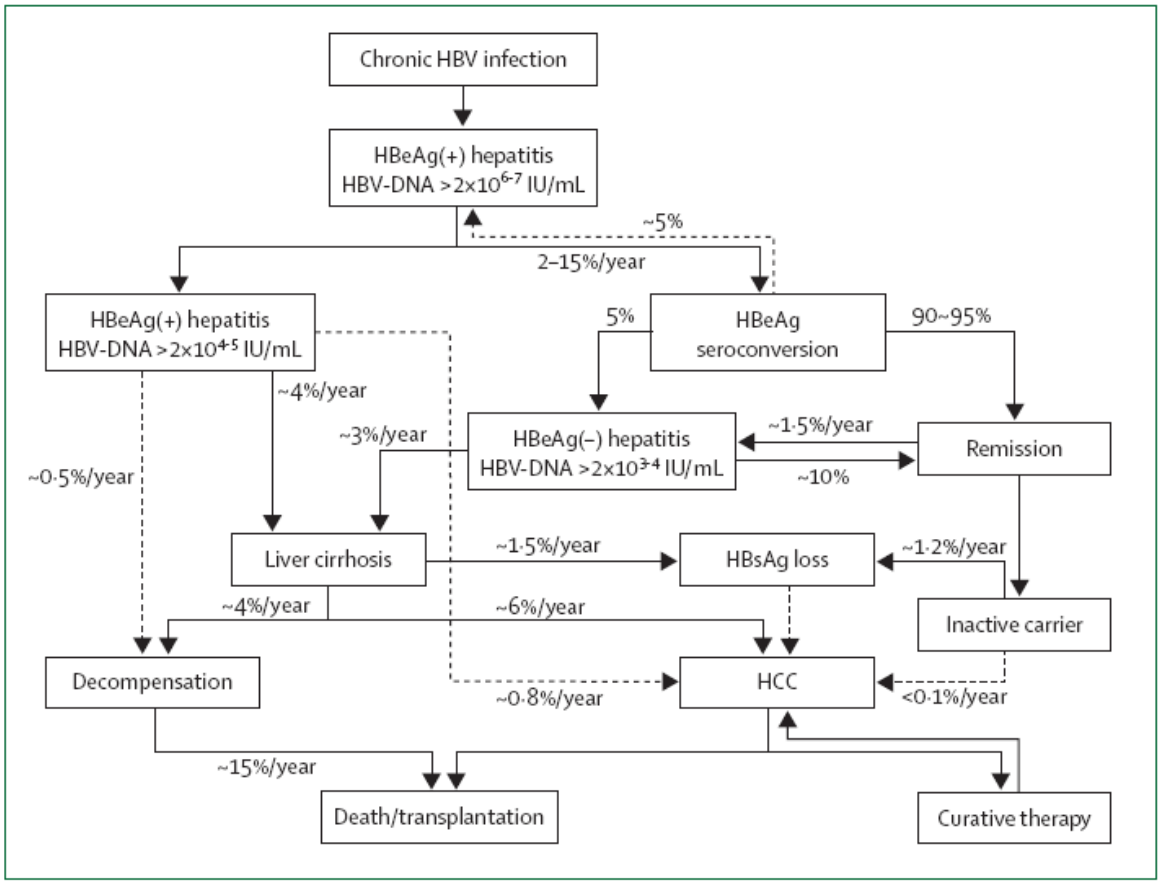
Feature	Adults	Neonates
Asymptomatic	50-70%	~90%
Symptomatic	30-50%	~10%
Fulminant hepatitis	<1%	<1%
Full recovery with permanent immunity (anti-HBs antibodies)	~90%	~10%

Patients who do not fully recover from the acute phase will go on to experience the chronic phase of HBV infection. This is characterized by progressive inflammation of the liver and it can take decades for symptoms to develop. During this period, distinct immunological features include the serum presence of the hepatitis B surface antigen (HBsAg). All patients with serum HBsAg are potentially infectious and all patients with chronic HBV are HBsAg positive. Every year, ~ 2% of chronic HBV patients terminate active infection and become HBsAg negative. Patients who remain infected experience gradually declining liver function and frequently develop liver cirrhosis and HCC.

SI.1.5.1. Morbidity and Mortality

Liver cirrhosis and HCC are serious complications associated with chronic HBV infection in its more advanced stages, accounting for 96% of deaths due to viral hepatitis in 2015 {World Health Organization (WHO) 2017}. Cirrhosis, liver failure, and/or HCC are expected to develop in 15% to 40% of HBV infected individuals {Lavanchy 2004}. Approximately 2% to 10% of chronic hepatitis B (CHB) patients progress to cirrhosis each year, and 5% to 10% of cirrhotic patients develop evidence of hepatic decompensation or HCC each year {Sherman 2007}. In patients with CHB, the 5 year cumulative incidence of developing cirrhosis is 8% to 20%. The 5 year cumulative incidence of decompensation is 20%. The 5 year survival rate is 80% to 86% for compensated cirrhosis and 14% to 35% for decompensated cirrhosis {European Association For The Study Of The Liver 2009}. A schematic showing the possible outcomes of HBV infection is shown in Figure SI.1.

Figure SI.1. Possible Outcomes of Chronic Hepatitis B



Source: {Liaw 2009}

SI.1.5.1.1 Cirrhosis

Progression to cirrhosis is more frequent in older patients, men, alcohol abusers, and those with hepatitis B e antigen (HBeAg) negative disease. After cirrhosis develops, the yearly risk of decompensation (manifested as ascites, jaundice, portal hypertension, and/or variceal bleeding) is approximately 6% {The Institute of Hepatology 2004}. Typical changes in laboratory values after progression to cirrhosis include decreased serum albumin, prolonged prothrombin time, and decreased platelet counts {European Association For The Study Of The Liver 2009}. Approximately 10% to 30% of patients with CHB have acute alanine aminotransferase (ALT) flares due to destruction of infected hepatocytes by the immune system {The Institute of Hepatology 2004}.

SI.1.5.1.2 Hepatocellular Carcinoma

Patients with CHB are 100 times more likely to develop HCC than those who resolve an acute HBV infection. HCC is likely to develop 25 to 30 years after the acute infection, when hepatocytes damaged through the immune response regenerate. The mortality rate for HCC is very high; the 5-year survival rate is only 5% to 6% {The Institute of Hepatology 2004}.

The worldwide prevalence of HCC largely reflects the distribution of HBV infection, and the incidence has increased, primarily due to new viral infections, and is the sixth most common cancer worldwide {MacLachlan 2015}. Among cirrhotic patients with CHB, the annual incidence of HCC is 2% to 5% {European Association For The Study Of The Liver 2009}. HBV accounts for up to 80% of primary liver cancers, and it is second only to tobacco as a leading cause of human cancer {The Institute of Hepatology 2004, Zuckerman 2007}.

SI.1.5.1.3 Liver Transplantation

Cirrhosis and HCC are among the leading indications for liver transplantation {Kim 2009}. According to the US Organ Procurement and Transplantation Network, 1 year survival rates following liver transplantation for cirrhosis or HCC are 85% to 90%. At 3 years, survival rates range from 68% for HCC to 77%–85% for cirrhosis, and at 5 years drop to 54% for HCC and 70%–80% for cirrhosis {Organ Procurement and Transplantation Network 2009}. Without prophylaxis, >80% of patients who receive liver transplants for HBV related illness will have recurrent infection. However, decreases in transplant waiting lists and post-transplant mortality have been observed since the 2000's, after the introduction of vaccination programs and more potent and effective NAs, such as entecavir and TDF {Young 2017}. During this time, the likelihood of liver transplant has also decreased, suggesting the improved efficacy of these therapies in delaying progression of the HBV to decompensated cirrhosis {Al-Hamoudi 2015, Young 2017}.

SI.1.6. Important Co-morbidities

Below is a list of important conditions that have evidence of higher risk among HBV patients and/or those accessing antiviral treatment for HBV:

- Renal Disorders {di Belgiojoso 2002, Liu 2018, Worobetz 2000}
- Membranous glomerulonephritis (GN)
  - Membranoproliferative GN
  - IgA nephropathy
  - Hepatorenal syndrome
  - Fanconi syndrome
- Bone Disorders
  - Fractures (in patients with severe liver disease) {Biver 2017}
  - Reduced bone mineral density {Gallego-Rojo 1998, Gill 2011, Gonzalez-Calvin 2004, Schiefke 2005, Tsuneoka 1996}
  - Osteoporosis {Chen 2015, Fung 2011, Gallego-Rojo 1998, Gonzalez-Calvin 2004}

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1. Table of Key Safety Findings from Non-Clinical Studies

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Safety pharmacology, genotoxicity, carcinogenic potential and reproductive toxicity No specific concerns were identified in the safety pharmacology, genotoxicity and reproductive toxicity studies with TAF. Per agreement with the EMA, carcinogenicity studies, and a perinatal and postnatal study were not required for TAF registration due to the lack of TAF exposure in rats and TgRasH2 mice and lower TFV exposure in rats and mice compared to the same studies in which tenofovir disoproxil fumarate (TDF) was administered. Long-term oral carcinogenicity studies of TDF in mice and rats at exposures up to 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg TDF therapeutic dose (M990205; R990204), showed a low incidence of liver adenomas at the highest dose of 600 mg/kg/day in female mice and no carcinogenic potential in the long-term study in rats.	Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity, carcinogenic potential, and reproductive toxicity.
Renal toxicity The repeat-dose oral toxicity of TAF has been studied in mice, rats, dogs and monkeys. In chronic studies, kidneys (karyomegaly, tubular degeneration), and bone (atrophy of metaphyseal cancellous bone) were the primary target organs. Renal tubular karyomegaly was observed in rats and dogs orally administered TAF. Focal areas of minimal renal cortical tubular basophilia and associated minimal nuclear karyomegaly were present in rats administered 400 mg/kg/day for 4 weeks and 100 mg/kg/day for 26 weeks. Renal tubular karyomegaly and/or basophilia were observed in dogs administered 3 and 10 mg/kg/day for 4 weeks and dogs administered 6 or 18/12 mg/kg/day for at least 13 weeks. Renal cortical tubular degeneration/regeneration findings were limited to animals administered 6 or 18/12 mg/kg/day for at least 13 weeks in the 39-week dog toxicity study. Similar findings of renal cortical tubular degeneration/regeneration and karyomegaly were present in dogs administered at 6 or 18/12 mg/kg/day for 39 weeks. These changes were minimal to slight in affected males and females at 6 mg/kg/day. In high-dose males (18/12 mg/kg/day) the severity ranged from mild to moderate. Similar lesions (karyomegaly and tubular degeneration) but of only minimal severity were also present in 2 males administered 2 mg/kg/day of TAF for 39 weeks. After a 13-week recovery period, treatment-related histology changes were still observed in the kidney but were of reduced incidence and severity.	The estimated safety margin for use of 25 mg/day TAF in humans based TFV exposure at the no observed adverse effect level (NOAEL) in the animal studies is 12 for rats, 4 for dogs and > 18 for monkeys when considering renal toxicity.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Loss of bone mineral density (BMD) Atrophy of metaphyseal cancellous bone was observed in rats administered TAF at 100 mg/kg/day for 26 weeks. TAF also increased biochemical markers of bone turnover and decreased serum 1,25-dihydroxy- and 25-hydroxyvitamin D_3 in rats (≥ 25 mg/kg/day) and dogs (≥ 37.5 mg/kg/day for 6 days). In a 39-week dog study, BMD changes at 18/12 mg/kg/day were most likely due to body weight loss, but these changes were accompanied by a slight but significant decrease in serum 1,25-dihydroxyvitamin D_3 in males only and a significant increase in 25-hydroxyvitamin D_3 in females only.	The estimated safety margin for use of 25 mg/day TAF in humans based on TFV exposure at the NOAEL in the animal studies is 12 for rats, 4 for dogs and > 18 for monkeys when considering BMD loss.
Nasal inflammation in mice TAF administered by oral gavage for up to 13 weeks to mice at ≥ 10 mg/kg/day resulted in adverse degenerative (olfactory) and acute inflammatory (infiltrate neutrophil) changes in the nasal mucosa (TX-120-2007). These changes were not observed in rats, dogs or monkeys for longer durations of administration.	Because these changes were not observed in rats, dogs or monkeys for longer durations of administration, the risk of nasal inflammation in humans is considered to be very low.
PR and QT prolongation The IC_{50} for the inhibitory effect of TAF on hERG potassium current was estimated to be greater than 10 µM, far above human exposure (PC-120-2005). In the 39-week dog study (TOX-120-002), there was some evidence at 6 and 18/12 mg/kg/day for an effect to slightly prolong PR intervals (approximately 13% to 24%). TAF appeared to reversibly reduce heart rate with an associated mild QT interval prolongation in the high-dose group only. These changes were associated with decreases in serum triiodothyronine {Kienle 1994, Tribulova 2010}. No PR prolongation or any change in ECG results occurred in the safety pharmacology study in dogs that evaluated a TAF dose up to 100 mg/kg (D2000006).	No PR or QT prolongation or any change in ECG results occurred in a thorough QT study of TAF (GS-US-120-0107).
Histiocyte infiltrate in dogs At 18/12 mg/kg/day in dogs, the highest dose tested, a minimal infiltration of histiocytes was present in some organs (eye [choroid plexus, ciliary body], lung, and spleen) in some animals. In-life ophthalmologic examinations of all dogs were normal. The histiocytic infiltration observed in multiple organs was most likely an indirect drug effect due to general debilitation and was not observed in other repeat dose toxicity studies. There were no drug-related effects on ophthalmic exams or microscopic exams of ocular tissue observed in repeat dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), nonhuman primates (4 weeks) or in the 4-week dog toxicology study. The minimal to slight infiltration of mononuclear cells in the ocular posterior uvea occurred only in dogs administered the highest dose of TAF where compound-related toxicities occurred on clinical condition, weight gain, serum chemistry, BMD, and other organ histopathology. In addition to the toxicology data, distribution of ^{14}C-TAF to eyes has been assessed in mice, rats, and dogs (AD-120-2011, AD-120-2020, and D990173-BP). Melanin binding has specifically been assessed by comparing distribution in pigmented and non-pigmented mice (C57 black and CD-1, respectively) and rats	Based on the evidence from tissue distribution and toxicology studies, the risk of posterior uveitis in humans is considered to be very low.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
(Long Evans and Sprague-Dawley, respectively). [^{14}C]-TAF-related radioactivity distributed poorly to the eyes of rats and dogs (C_{max} in eyes <8% that observed in plasma). Transient exposure to low levels of [^{14}C]-TAF-related radioactivity was observed in the eyes of rats decreasing to undetectable levels at 8 hours post dose. No difference in distribution was observed between Sprague-Dawley and Long Evans rats, including in the skin and eyes, suggesting no binding to melanin. The distribution of [^{14}C]-TAF to eyes in mice was higher than other species studied (C_{max} in eyes 15%-20% that observed in plasma). More persistent exposures in eye lens, eye uveal tract, and eyes were observed in C57 black mice compared to CD-1 mice. However, no difference in distribution between pigmented and nonpigmented skin was observed illustrating that [^{14}C]-TAF-related radioactivity was not selectively associated with melanin-containing tissues. The posterior uveitis in dogs administered the highest dose of TAF occurred at 9- and 42-fold higher exposure to TAF and TFV, respectively, than that observed in human participants administered a 25 mg dose of TAF and does not correlate with the tissue distribution where TAF was found to poorly penetrate across the blood brain and blood retinal barrier in dogs. Because TAF has poor penetration across the blood brain and blood retinal barrier in dogs, it is unlikely that TAF directly caused the observed histiocytic infiltration in the posterior uvea.	
<u>TAF metabolism and transport</u> TAF is a substrate for intestinal efflux transporters P-gp and BCRP.	Since TAF is a substrate for intestinal efflux transporters P-gp and BCRP, TAF exposure may be affected by P-gp and/or BCRP inhibitors and/or P-gp inducers of the intestinal efflux transporters.

PART II: MODULE SIII - CLINICAL STUDY EXPOSURE

SIII.1. Clinical Study Exposure

The tables in this section present exposure data for TAF (up to 09 November 2022) in participants with HBV from the following studies:

- Completed studies GS-US-320-0101, GS-US-320-4018, GS-US-320-4035, GS-US-389-2025, GS-US-320-3912, GS-US-464-4437, GS-US-320-0108, and GS-US-320-0110

- Ongoing blinded study GS-US-320-1092

Table SIII.1. Duration of TAF Exposure in Participants with HBV

	Ongoing Blinded Studies (All participants exposed to blinded treatment)		Completed Studies or Ongoing Unblinded Studies (Participants exposed to TAF)	
Duration of Exposure	**Persons**	**Person-days**	**Persons**	**Person-days**
≥ 1 day	106	123,072	2438	3,661,910
> 30 days	106	123,072	2377	3,660,430
> 90 days	106	123,072	2368	3,659,878
> 180 days	104	122,817	2354	3,657,875
> 1 year	101	122,121	1887	3,503,258
> 2 years	89	114,894	1482	3,239,291
> 3 years	64	92,010	1369	3,131,426
> 4 years	29	48,331	1291	3,027,735
> 5 years	4	7521	997	2,545,240

Table SIII 2. TAF Exposure by Age Group and Gender in Participants with HBV

Age Group	Ongoing Blinded Studies (All participants exposed to blinded treatment)				Completed Studies or Ongoing Unblinded Studies (Participants exposed to TAF)			
	Persons		Person-days		Persons		Person-days	
	Male	Female	Male	Female	Male	Female	Male	Female
<18 yrs	61	45	71,093	51,979	0	0	0	0
18-30 yrs	0	0	0	0	245	124	446,827	198,208
31-40 yrs	0	0	0	0	445	171	755,304	289,301
41-50 yrs	0	0	0	0	416	200	635,815	340,742
51-65 yrs	0	0	0	0	430	269	515,824	362,431
> 65 yrs	0	0	0	0	91	47	70,772	46,686

Table SIII 3. TAF Exposure by Racial Origin in Participants with HBV

Racial Group	Ongoing Blinded Studies (All participants exposed to blinded treatment)		Completed Studies or Ongoing Unblinded Studies (Participants exposed to TAF)	
	Persons	Person-days	Persons	Person-days
White	28	32,687	344	570,716
Black or African American	5	3942	43	31,743
Asian	69	82,136	2006	3,001,448
Native Hawaiian or Pacific Islander	2	1987	37	46,609
Other	2	2320	8	11,394

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL STUDIES

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV 1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Children (aged < 18 years)	Children aged < 18 years were excluded from TAF Phase 3 clinical studies for the treatment of HBV.	Yes (long-term safety in children 6 years of age and older weighing at least 25 kg) No (children < 6 years of age and ≥ 6 years of age weighing less than 25 kg) TAF is currently indicated in children 6 years of age and older weighing at least 25 kg based on data from Study GS-US-320-1092 (Cohort 1 and Cohort 2 Group 1). TAF is not proposed for use in children < 6 years of age or in children ≥ 6 years of age weighing less than 25 kg and, therefore, the safety of TAF in younger children is not considered missing information.
Pregnant females	Limited information on the use in this patient population.	Yes
Females who are breastfeeding	Limited information on the use in this patient population. Based on published reports, TAF and TFV were present in human breast milk at very low levels in women administered TAF.	Yes
HIV type 1 (HIV-1) infected patients	To investigate the safety and efficacy of TAF in HBV monoinfected patients, without additional complications from HIV infection. In addition, TAF and TDF monotherapy were administered in the TAF Phase 3 clinical studies, which is not appropriate for treatment for HIV-1.	No Rationale: Safety in patients with HBV/HIV coinfection has been monitored through routine pharmacovigilance (PV) activities and data have been presented in the Vemlidy periodic safety update report (PSUR)/ periodic benefit-risk evaluation report (PBRER). No safety concerns have been identified regarding use of TAF in this patient population. In addition, no new safety concerns were identified in a study of participants with HBV/HIV coinfection treated with the TAF-containing product, Genvoya (GEN; elvitegravir/cobicistat/emtricitabine/TAF), (GS-US-292-1249). The safety profile in the coinfected population was similar to that in patients with HIV-1 monoinfection.

Criterion	Reason for Exclusion	Considered to be Missing Information
Hepatitis C infected patients	To investigate the safety and efficacy of TAF in HBV monoinfected patients, without additional complications from HCV infection.	No Rationale: Safety in patients with HBV/HCV coinfection has been monitored through routine PV activities and data have been presented in the Vemlidy PSUR/PBRER. No safety concerns have been identified regarding the use of TAF in this patient population. In addition, no new safety concerns were identified in a study of 148 participants with HIV/HCV coinfection receiving TAF containing products for the treatment of HIV-1 (Study GS-US-366-1992).
HBV infected patients with renal impairment (creatinine clearance [CrCl] < 50 mL/min).	Participants received blinded TAF versus TDF. TDF requires dose interval adjustment in patients with CrCl < 50 mL/min. Limiting to patients with CrCl ≥ 50 mL/min would ensure 1 tablet once daily dosing of either blinded TAF or TDF.	No Rationale: Safety in patients with renal impairment has been monitored through routine PV activities and data have been presented in the Vemlidy PSUR/PBRER. No new safety concerns for TAF were identified through 192 weeks of treatment in patients with CHB and Stage 2 or greater CKD who have previously received a liver transplant (Study GS-US-320-3912).

SIV.2. Limitations to Detect Adverse Reactions in Clinical Study Development Programs

Table SIV 2. Ability of the Clinical Study Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program[a]	Discussion of Implications for Target Population
Which are rare	2438 HBV infected patients have been exposed to TAF in the TAF clinical program.	The clinical trial program is large enough to detect at least uncommon adverse drug reactions (ADRs). ADRs with a frequency greater than 1 in 459 could potentially be detected if there were no background incidence.
Due to prolonged exposure	1887 HBV infected participants have been exposed to TAF for more than 1 year and 1369 HBV infected participants have been exposed to TAF for more than 3 years in the TAF clinical trial program.	No ADRs specifically associated with prolonged exposure to TAF have been identified in the TAF clinical trial program.
Due to cumulative effects	1887 HBV infected participants have been exposed to TAF for more than 1 year and 1369 HBV infected participants have been exposed to TAF for more than 3 years in the TAF clinical trial program.	No cumulative effects to TAF have been identified in the TAF clinical trial program.

Ability to Detect Adverse Reactions	Limitation of Trial Program[a]	Discussion of Implications for Target Population
Which have a long latency	1887 HBV infected participants have been exposed to TAF for more than 1 year and 1369 HBV infected participants have been exposed to TAF for more than 3 years in the TAF clinical trial program.	No ADRs to TAF with a long latency have been identified in the TAF clinical trial program.

a Table includes the number of participants exposed to TAF in completed and ongoing unblinded studies (participant exposure in ongoing blinded studies is not included)

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Study Development Programs

Table SIV 3. Exposure of Special Populations Included or not in Clinical Study Development Programs

Type of special population	Exposure	Considered to be Missing Information
Elderly patients	138 participants (117,458 person-days) aged above 65 years have been treated with TAF in the HBV clinical trial program[a].	No Rationale: Population pharmacokinetics of patients with CHB in Phase 1 and Phase 3 trials of TAF showed that within the age range studied (18 to 78 years), age did not have a clinically relevant effect on exposures of TAF. Safety in elderly patients has been monitored through routine PV activities and data have been presented periodically in the Vemlidy PSUR. No safety concerns have been identified regarding the use of TAF in this patient population.
Pregnant women	Pregnant women were excluded from enrolling in clinical studies. As of 09 May 2018, there were 17 cases of pregnancy during treatment with TAF in Gilead-sponsored clinical studies.	Yes
Breastfeeding women	Breastfeeding women were excluded from enrolling in clinical studies. As of 09 November 2021, there were no cases of breastfeeding during treatment with TAF in Gilead-sponsored clinical studies.	Yes

Type of special population	Exposure	Considered to be Missing Information
Safety in HBV infected patients with renal impairment (CrCl < 50 mL/min)	Patients with CrCl < 50 mL/min were excluded from the pivotal Phase 3 studies (GS-US-320-0108 and GS-US-320-0110). In the Phase 1 study GS-US-120-0108, a total of 14 non-HBV/HIV-infected participants with severe renal impairment (defined as participants with CrCl between 15 to less than 30 mL/min who were not on dialysis) were administered a single 25 mg dose of TAF. In the Phase 2 study GS-US-320-3912, a total of 26 adults with CHB, Stage 2 or greater CKD, who had a liver transplant were administered TAF 25 mg once daily.	No Rationale: Safety in patients with renal impairment has been monitored through routine PV activities and data have been presented in the Vemlidy PSUR/PBRER. No new safety concerns for TAF were identified through 192 weeks of treatment in patients with CHB and Stage 2 or greater CKD who have previously received a liver transplant (Study GS-US-320-3912).
Safety in severe hepatic impairment (Child-Pugh-Turcotte [CPT] score C)	In study GS-US-320-1615, a total of 10 participants with CPT class C severe hepatic impairment caused by non-hepatitis B-induced liver cirrhosis were administered a single 25 mg dose of TAF.	No Rationale: TAF is primarily hydrolyzed by CES1 in primary hepatocytes. A Phase 1 study (GS-US-320-1615) which evaluated the pharmacokinetics of TAF in participants with severe hepatic impairment demonstrated lack of clinically important changes in TAF exposure across the range of hepatic function. This contributes to the conclusion that no dose adjustment is required in hepatic impairment.
Safety in children < 18 years	In study GS-US-320-1092 a total of 88 CHB infected pediatric participants received TAF 25mg dose: 70 adolescents aged 12 to < 18 years weighing at least 35 kg and 18 children aged 6 to <12 years weighing at least 25 kg.	Yes (long-term safety in children 6 years of age and older weighing at least 25 kg) No (children < 6 years of age and ≥ 6 years of age weighing less than 25 kg) Rationale: See Table SIV 1
Safety in HBV/HCV coinfected patients	Not included in the TAF HBV clinical development program.	No Rationale: See Table SIV 1
Safety in HBV/HIV coinfected patients	Not included in the TAF HBV clinical development program. In HIV study GS-US-292-1249, 74 HBV/HIV coinfected participant received a TAF-containing product, GEN.	No Rationale: See Table SIV 1

a Number of participants exposed to TAF in completed studies and ongoing unblinded studies (participant exposure in ongoing blinded studies is not included)

PART II: MODULE SV - POSTAUTHORIZATION EXPERIENCE

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Sales Data

Patient exposure to marketed Vemlidy is estimated from sales data. The number of bottles sold was multiplied by 30 to provide the number of tablets sold (with the exception of Japan where the numbers of bottles were multiplied by 14 to provide the number of tablets, as 14-tablet bottles are available). As of November 2019, only 30-tablet bottles are available from Japan (14- tablet bottles have been discontinued). As Vemlidy is taken as a once daily dose; the total number of tablets was divided by 365.25 to provide patient-years of treatment.

It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors and wastage.

Prescription Data

Insufficient prescription data are available to estimate the demographics of HBV infected patients exposed to Vemlidy in the EU. Estimates of the demographics of HBV infected patients exposed to Vemlidy in the United States (US) were obtained from prescription data from the following sources:

IQVIA Retail and Non-Retail: The retail and mail data (prescriptions and volumes) captured by IQVIA includes prescriptions dispensed at pharmacies or through mail channels as well as projections for prescriptions not captured within these channels. The non-retail data (volume only) captures product not included in the retail data that has been sold to clinics, hospitals, long-term care, or other institutions.

Compliance Data based on SHA Claims: Measure for patient compliance based on the Symphony Health patient claims data. Examines the average number of pills dispensed for patients on Vemlidy compared to number of expected pills if the patients were fully compliant.

IQVIA National Prescription Audit (NPA) Extended Insights: This is retail prescription data dispensed at pharmacies that includes patient demographics, such as age and sex.

SHA PTD: This is prescription data dispensed at pharmacies combined with prescription claims data that is registered through switches. This is a longitudinal database tracking patient prescriptions filled over time in the retail and mail order channels.

SV.1.2. Exposure

SV.1.2.1. Exposure Based on Sales Data

Cumulative patient exposure to Vemlidy since first marketing approval in United States on 10 November 2016 to 09 November 2023 is estimated to be 1,934,211 patient-years.

SV.1.2.2. Exposure Based on Prescription Data

Estimates of the demographics of HBV infected patients exposed to Vemlidy in the US, based on prescription data, are presented in Table SV 1.

Table SV 1. Demographic Data of Patients Exposed to Vemlidy in the US

		Number or Percentage of Patients	Source
Estimates of Peak Number of Patients Exposed to Vemlidy Each Year[a]	2016	2400	IQVIA Retail and Non-Retail Compliance Data Based on SHA Claims
	2017	18,435	
	2018	28,816	
	2019	35,697	
	2020	39,864	
	2021	41,294	
	2022	43,879	
	2023	44,432	
Patient Age (years)[a]	0-19	0%	IQVIA NPA Extended Insights
	20-39	13%	
	40-59	47%	
	60-64	12%	
	65-74	19%	
	75-84	7%	
	85+	1%	
Patient Sex[a]	Female	41%	IQVIA NPA Extended Insights
	Male	59%	
Treatment Naïve/Experienced[a]	Naïve	55%	SHA PTD
	Experienced	45%	

a November 2016 to August 2023

PART II: MODULE SVI-ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for TAF to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

Not applicable

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new important identified risks, important potential risks or missing information have been identified for TAF since the submission of the last RMP.

Missing information modified or removed from the list of safety concerns, including reasons for removal are presented in Table SVII 1.

Table SVII 1. Missing Information: Reason for Modification or Removal

Safety Concern Removed	Reason for Modification or Removal from List of Safety Concerns
Missing Information	
Long-term safety in adults	'Long-term safety in adults' is proposed for removal. Long-term data in HBV infected patients are available up to Week 384 from Studies GS-US-320-0108 and GS-US-320-0110. No new safety concerns for Vemlidy were identified from these long-term data. Due to the completion of Studies GS-US-320-0108 and GS-US-320-0110, no additional pharmacovigilance activities are being conducted to assess long-term safety in adults.
Development of resistance in long-term use	'Development of resistance in long-term use' is proposed for removal. Long-term resistance data in HBV infected patients are available up to Week 384 from Studies GS-US-320-0108 and GS-US-320-0110. No new safety concerns regarding development of resistance for Vemlidy were identified from these long-term data. Due to the completion of Studies GS-US-320-0108 and GS-US-320-0110, no additional pharmacovigilance activities are being conducted to assess development of resistance in long-term use.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for TAF.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for TAF.

SVII.3.1.3. Presentation of the Missing Information

Table SVII 2. Missing Information

Missing Information:	Evidence source
Long-term safety information in children 6 years of age and older weighing at least 25 kg	Safety data for TAF in HBV infected children 6 years of age and older weighing at least 25 kg is currently limited to 96 weeks of treatment (Study GS-US-320-1092).
Safety in pregnancy and lactation	No adequate and well-controlled studies of TAF have been conducted in pregnant women. A moderate amount of data on pregnant women receiving TAF (300-1000 pregnancy outcomes) indicate no malformations or fetal/neonatal toxicity. Current labeling recommends that TAF may be considered during pregnancy, if necessary. Limited information is available on the use of TAF in breastfeeding women. In animal studies it has been shown that TFV is excreted into milk. Based on published reports, TAF and TFV were present in human breast milk at very low levels in women administered TAF.

PART II: MODULE SVIII- SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety information in children 6 years of age and older weighing at least 25 kg
	Safety in pregnancy and lactation

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
GS-US-320-1092 A randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of TAF in children and adolescent participants with CHB virus infection	*Safety concern(s) addressed:* Missing information: Long-term safety information in children 6 years of age and older weighing at least 25 kg *Objectives:* To evaluate the safety and efficacy of TAF in adolescents with CHB and to evaluate the PK, safety and efficacy of TAF in children with CHB	*Study design:* Randomized, double-blind, placebo-controlled clinical study with an open-label extension phase with TAF *Study population:* Treatment-naïve and treatment-experienced, adolescents and children, males and females, with CHB who are HBeAg--positive or HBeAg-negative	Submission of final report	Q2 2027
Antiretroviral Pregnancy Registry	*Safety concern(s) addressed:* Missing information: Safety in pregnancy and lactation *Objectives:* To collect information on the risk of birth defects in patients exposed to TAF during pregnancy	*Study design:* Prospective, observational, exposure-registration, and follow-up study *Study population:* Pregnant patients exposed to antiretroviral drugs	Submission of interim reports	In the Vemlidy PSUR (data lock point [DLP] and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
A randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of TAF in children and adolescent participants with chronic hepatitis B virus infection GS-US-320-1092 Ongoing	To evaluate the safety and efficacy of TAF in adolescents with CHB and to evaluate the PK, safety and efficacy of TAF in children with CHB	*Missing information:* Long-term safety information in children 6 years of age and older weighing at least 25 kg	Submission of final report	Q2 2027
Antiretroviral Pregnancy Registry Ongoing	To collect information on the risk of birth defects in patients exposed to TAF during pregnancy	*Missing information:* Safety in pregnancy and lactation	Submission of interim reports	In the Vemlidy PSUR (data lock point [DLP] and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorization efficacy studies.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine risk minimization measures

The routine risk minimization measures for Vemlidy in the EU comprise of the SmPC, the package leaflet (PL) and the legal status of the product. Vemlidy is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of chronic hepatitis B (SmPC section 4.2).

The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V.1. The legal status can be considered a general measure applicable to all of the individual safety concerns.

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Missing Information	
Long-term safety information in children 6 years of age and older weighing at least 25 kg	No routine risk minimization measures are considered necessary.
Safety in pregnancy and lactation	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2

V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary risk minimization measures

Vemlidy has the legal status of medicinal product subject to restricted medical prescription in the EU, whereby therapy should be initiated by a physician experienced in the management of chronic hepatitis B (SmPC section 4.2). This routine risk minimization measure beyond the product information can be considered a general measure applicable to all of the safety concerns summarized below.

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Long-term safety information in children 6 years of age and older weighing at least 25 kg	No risk minimization measures are considered necessary.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Clinical study in children and adolescents with CHB (GS-US-320-1092)
Safety in pregnancy and lactation	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. Summary of risk management plan for Vemlidy (Tenofovir Alafenamide)

This is a summary of the risk management plan (RMP) for Vemlidy. The RMP details important risks of Vemlidy, how these risks can be minimized, and how more information will be obtained about Vemlidy's risks and uncertainties (missing information).

Vemlidy's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Vemlidy should be used.

This summary of the RMP for Vemlidy should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vemlidy's RMP.

II. The Medicine and What is it Used for

Vemlidy is authorized for treating chronic hepatitis B (CHB), an infectious disease that affects the liver, in patients aged 12 years and older weighing at least 35 kg. It contains tenofovir alafenamide (TAF) as the active substance and it is given orally.

Further information about the evaluation of Vemlidy's benefits can be found in Vemlidy's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/vemlidy

III. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Vemlidy, together with measures to minimize such risks and the proposed studies for learning more about Vemlidy's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Vemlidy is not yet available, it is listed under 'missing information' below.

III.A. List of important risks and missing information

Important risks are those that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vemlidy. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety information in children 6 years of age and older weighing at least 25 kg
	Safety in pregnancy and lactation

III.B. Summary of Important Risks

Vemlidy has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby Vemlidy therapy should be initiated by a doctor experienced in the management of chronic hepatitis B (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Missing information	**Long-term safety information in children 6 years of age and older weighing at least 25 kg**
Risk Minimization Measure(s)	No risk minimization measures
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study in children and adolescents with CHB (study GS-US-320-1092) See Section III.C of this summary for an overview of the postauthorization development plan.

Missing information	Safety in pregnancy and lactation
Risk Minimization Measure(s)	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry See Section III.C of this summary for an overview of the post-authorization development plan.

III.C. Post-authorization Development Plan

III.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Vemlidy.

III.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
GS-US-320-1092 A randomized, double-blind evaluation of the pharmacokinetics (PK), safety, and antiviral efficacy of TAF in children and adolescent participants with CHB	*Objectives:* To evaluate the safety and efficacy of TAF in adolescents with CHB and to evaluate the PK, safety and efficacy of TAF in children with CHB *Safety concern(s) addressed:* Missing information: Long-term safety information in children 6 years of age and older weighing at least 25 kg
Antiretroviral Pregnancy Registry	*Objectives:* To collect information on the risk of birth defects in patients exposed to TAF during pregnancy *Safety concern(s) addressed:* Missing information: Safety in pregnancy and lactation

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table Part VII.1. Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concern addressed	Protocol link Milestones
Planned studies			
None	Not applicable	Not applicable	Not applicable
Ongoing studies			
A randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of TAF in children and adolescent participants with chronic hepatitis B virus infection GS-US-320-1092 Category 3	To evaluate the safety and efficacy of TAF in adolescents with CHB and to evaluate the PK, safety and efficacy of TAF in children with CHB	*Missing information:* Long-term safety information in children 6 years of age and older weighing at least 25 kg	See Annex 3 for full protocol Week 24 interim report: Q2 2022 (Cohort 1, and Cohort 2 Group 1) (submitted Q2 2022) Week 96 interim report: (Cohort 1, and Cohort 2 Group 1) (submitted Q3 2023) Final report: Q2 2027
Antiretroviral Pregnancy Registry Category 3	To collect information on the risk of birth defects in patients exposed to TAF during pregnancy	*Missing information:* Safety in pregnancy and lactation	See Annex 3 for full protocol Interim reports to be included in TAF PSURs/PBRERs (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs/PBRERs)

Table Part VII.2. Completed Studies

Study	Summary of Objectives	Safety Concern addressed	Date of Final Study Report Submission
Phase 1, multiple dose study to evaluate the pharmacokinetic drug-drug interaction potential between sofosbuvir/velpatasvir/ GS-9857 (SOF/VEL/VOX) fixed-dose combination (FDC) and HIV antiretrovirals in healthy participants GS-US-367-1657 Category 3	To evaluate the PK of sofosbuvir (SOF), its metabolites GS-566500 and GS-331007, velpatasvir (VEL) and voxilaprevir (VOX) upon administration of SOF/VEL/VOX FDC with FTC/RPV/TAF FDC, EVG/COBI/FTC/TAF FDC + FTC/TDF FDC. To evaluate the safety and tolerability of SOF/VEL/VOX and FTC/RPV/TAF, EVG/COBI/FTC/TAF, DRV+RTV+FTC/TDF administered alone or in combination	*Missing information:* Safety in patients with HCV coinfection	17 November 2017
Phase 3, randomized, double blind study to evaluate the efficacy and safety of switching from TDF 300 mg QD to TAF 25 mg QD in participants with CHB who are virologically suppressed GS-US-320-4018 Category 3	To compare the safety and tolerability and evaluate efficacy in virologically suppressed participants with chronic HBV	*Missing information:* Long-term safety information in adults; Development of drug resistance in long-term use	21 January 2021
Phase 2, randomized, open-label study to evaluate the efficacy and safety of TAF versus TDF-containing regimens in participants with chronic HBV infection and stage 2 or greater chronic kidney disease who have received a liver transplant GS-US-320-3912 Category 3	To evaluate the safety and efficacy of TAF in participants with chronic HBV infection and Stage 2 or greater chronic kidney disease who have received a liver transplant	*Missing information:* Safety in HBV infected patients with renal impairment (CrCl < 50 mL/min)	25 March 2022
Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF versus TDF in HBeAg-negative participants with CHB GS-US-320-0108 Category 3	To evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative participants with CHB	*Missing information:* Long-term safety information in adults; Development of drug resistance in long-term use	28 June 2023
Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF versus TDF in HBeAg-positive participants with CHB GS-US-320-0110 Category 3	To evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive participants with CHB	*Missing information:* Long-term safety information in adults; Development of drug resistance in long-term use	28 June 2023

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Table Part VII.3. Overview of Included Protocols

Study Number and Title	Version of Protocol	Date of Protocol Version
Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None	Not applicable	Not applicable
Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None	Not applicable	Not applicable
Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.		
Final protocols not reviewed or not approved:		
GS-US-320-1092 A randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of TAF in children and adolescent participants with chronic hepatitis B virus infection	Amendment 5	06 February 2018
Antiretroviral Pregnancy Registry	Version 4	17 September 2013

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None.

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None.

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None.

Annex 7. Other Supporting Data (Including Referenced Material)

Annex 8. Summary of Changes to the Risk Management Plan over Time

Table Part VII.4. Summary of Changes to the Risk Management Plan Over Time

Version	Approval date/Procedure	Change
2.0	09 November 2017 (CHMP Opinion) EMEA/H/C/4169/II/0004	Relevant Week 96 data from Studies GS-US-320-0108 and GS-US-320-0110 were included. No new safety concerns were identified from the Week 96 data.
3.0	20-April-2018 (CHMP Opinion) EMEA/H/C/004169/IB/0012	Update to clinical study report submission date for Study GS-US-320-3912

Version	Approval date/Procedure	Change
4.0	04 October 2018 (CHMP Opinion) EMEA/H/C/WS/1441	MAH name was changed from Gilead Sciences International Ltd. to Gilead Sciences Ireland UC. The RMP was updated to meet the requirement of the revisions to GVP Module V (EMA/838713/2011; Rev 2) and the RMP template (EMA/PRAC/613102/2015 Rev 2) including proposed revisions to the safety concerns associated with Vemlidy. As a result of review of the safety concerns, the following risks and missing information have been removed from the RMP: Important identified risks: Post-treatment hepatic flares Important potential risks: Renal toxicity Bone events due to potential proximal renal tubulopathy/loss of BMD Ocular effects Overdose of tenofovir occurring through accidental concurrent use of TAF with a TDF- or TAF-containing product Missing Information: Safety in elderly patients Safety in patients with HCV co-infection Safety in patients with HIV co-infection Safety in children aged 2 years to < 12 years The completed Category 3 study GS-US-367-1657 was removed from the Pharmacovigilance Plan and the Category 3 additional PV activity “Planned clinical studies in TAF PIP” was removed from the Pharmacovigilance Plan as safety in children aged 2 years to < 12 years is no longer considered missing information.
5.0	12 December 2019 (CHMP Opinion) EMEA/H/C/004169/II/0020	Relevant Week 48 data from Study GS-US-320-4018 was included, involving virologically suppressed participants with chronic hepatitis B infection switching from TDF to TAF. No new safety concerns were identified from the Week 48 data. Minor administrative updates included.
6.0	28 January 2020 (CHMP Opinion) EMEA/H/C/004169/II/0021	Inclusion of an interim milestone (Week 24) for Study GS-US-320-1092, investigating the safety and efficacy of TAF in HBV infected children and adolescents.
7.0	21 May 2021 (CHMP Opinion) EMEA/H/C/004169/IB/0031	Update to the milestone submission due dates for Category 3 Studies GS-US-320-1092 (Week 24) (investigating the safety and efficacy of TAF in HBV infected children and adolescents) and GS-US-320-3912 (Final) (investigating the safety and efficacy of TAF versus TDF-containing regimens in participants with CHB infection and Stage 2 or greater chronic kidney disease who have received a liver transplant).

Version	Approval date/Procedure	Change
8.0	08 July 2021 (CHMP Opinion) EMEA/H/C/004169/II/0030	Removal of the completed Category 3 additional pharmacovigilance activity, Study GS-US-320-4018, evaluating the efficacy and safety through Week 96 of switching from TDF 300 mg once daily (QD) to TAF 25 mg QD in participants with CHB who are virologically suppressed.
9.0	01 September 2022 (CHMP Opinion) EMEA/H/C/004169/II/0038	Removal of the completed Category 3 additional pharmacovigilance activity, Study GS-US-320-3912, evaluating the efficacy and safety of TAF versus TDF-containing regimens in participants with chronic HBV infection and Stage 2 or greater chronic kidney disease who have received a liver transplant. Removal of the Missing Information of "safety in HBV infected patients with renal impairment (CrCl < 50 mL/min)" from the EU-RMP following completion of Study GS-US-320-3912.
10.0	26 April 2023 (CHMP Opinion) EMEA/H/C/004169/II/0040	Completed milestone for submission of interim Week 24 data for clinical study GS-US-320-1092, evaluating the pharmacokinetics, safety, and antiviral efficacy of TAF in children and adolescents. Updated missing information 'Long-term safety in adults and adolescents' to 'Safety in adults and children 6 years of age and older weighing at least 25 kg'. Included published data on TAF and tenofovir excretion in human milk. Pregnancy data updates based on the APR report (Data lock point:31 July 2021).
11.0	11 January 2024 EMEA/H/C/004169/II/0043/G	To update the milestone for Category 3 Study GS-US-320-1092.Removal of completed Category 3 additional pharmacovigilance activities, GS-US-320-0108 and GS-US-320-0110, evaluating the safety and efficacy of TAF versus TDF in HBeAg-negative and HBeAg-positive participants, respectively. Updated missing information 'Long-term safety in adults and children 6 years of age and older weighing at least 25 kg' to 'Long-term safety in children 6 years of age and older weighing at least 25 kg'. Removal of missing information 'Development of resistance in long-term use'. To add the date of the final study report submission for GS-US-320-0108 and GS-US-320-0110.
12.0	Currently under review	To update the milestone for Category 3 Study GS-US-320-1092.

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