EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR ENTECAVIR (ETV)

RMP version to be assessed as part of this application:

Version Number: 15.0

Data-lock Point for this RMP: 23-Jul-2019

Date of Final Sign-off: 04-Nov-2019

Rationale for submitting an updated RMP: To reflect the removal of long-term safety and clinical outcomes, use in the paediatric population (from birth to less than 2 years of age), and use in elderly patients (≥ 65 years of age) as missing information. In addition, the Marketing Authorisation Holder (MAH) has reformatted the RMP in accordance with the revised guideline on Good Pharmacovigilance Practices (GVP) Module V (Rev 2).[1]

Summary of Significant Changes in This RMP

Part/Module	Summary of Major Changes	Version #/Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	Not applicable (N/A)	Version 10.0/28-Oct-2013
SII Nonclinical part of the safety specification	Updated with information on Study AI463080 in regards to the risk of malignant neoplasms.	Version 15.0/Pending
SIII Clinical trial exposure	N/A	Version 14.0/25-Oct-2017
SIV Populations not studied in clinical trials	N/A	Version 13.0/18-Mar-2015
SV Post-authorisation experience	Updated post-authorisation exposure figures.	Version 15.0/Pending
SVI Additional EU requirements for the safety specification	N/A	Version 14.0/25-Oct-2017
SVII Identified and potential risks	Long-term safety and clinical outcomes, use in the paediatric population (from birth to less than 2 years of age), and use in elderly patients (≥ 65 years of age) removed as missing information.	Version 15.0/Pending
SVIII Summary of the safety concerns	Updated to reflect changes in SVII.	Version 15.0/Pending
Part III Pharmacovigilance Plan	N/A	Version 14.0/25-Oct-2017
Part IV Plan for Post-authorisation Efficacy Studies	N/A	Version 14.0/25-Oct-2017
Part V Risk-minimisation Measures	Long-term safety and clinical outcomes, use in the paediatric population (from birth to less than	Version 15.0/Pending

Summary of Significant Changes in This RMP

Part/Module	Summary of Major Changes	Version #/Date of Positive Opinion for Module Update
	2 years of age), and use in elderly patients (≥ 65 years of age) removed as missing information.	
Part VI Summary of the RMP	Updated to reflect changes in Part V.	Version 15.0/Pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	N/A	Version 14.0/25-Oct-2017
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the Pharmacovigilance Plan	N/A	Version 14.0/25-Oct-2017
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	Version 14.0/25-Oct-2017
ANNEX 5 Protocols for proposed and ongoing studies in RMP Part IV	N/A	Version 14.0/25-Oct-2017
ANNEX 6 Details of proposed additional risk-minimisation activities	N/A	Version 10.0/28-Oct-2013
ANNEX 7 Other supporting data	N/A	Version 10.0/28-Oct-2013
ANNEX 8 Summary of changes to the RMP over time	Aligned with changes in current RMP.	Version 15.0/Pending

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number: 14.0

Approved with procedure: EMEA/H/C/00623/II/052

Date of approval (opinion date): 17-Oct-2017

Fanny Pruvot, Qualified Person Responsible for Pharmacovigilance (QPPV):

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the MAH's QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Entecavir
Pharmacotherapeutic group(s) (ATC Code)	J05AF10
Marketing authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Baraclude®
Marketing authorisation procedure	Centralised Procedure in accordance with Regulation (EC) 726/2004
Brief description of the product	Chemical class: ETV is a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) polymerase. Summary of mode of action: It is phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. Intracellular TP levels are directly related to extracellular ETV concentrations, with no significant accumulation beyond initial plateau levels. By competing with the natural substrate deoxyguanosine TP form, ETV-TP functionally inhibits the 3 activities of the viral polymerase: • Priming of the HBV polymerase • Reverse transcription of the negative strand deoxyribonucleic acid (DNA) from the pregenomic messenger ribonucleic acid (RNA) • Synthesis of the positive strand HBV DNA ETV is used to treat adult and paediatric (2 to < 18 years) patients who have chronic hepatitis B virus (CHB).
Hyperlink to the Product Information (PI)	Refer to eCTD sequence number 0124 with procedure EMEA/H/C/000623/N/062
Indication(s) in the EEA	**Current:** ETV is indicated for the treatment of CHB infection (see Summary of Product Characteristics [SmPC] Section 5.1) in adults with: • compensated liver disease and evidence of active viral replication, persistently elevated serum alanine transaminase (ALT) levels, and histological evidence of active inflammation and/or fibrosis. • decompensated liver disease (see SmPC Section 4.4). For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleos(t)ide-naïve patients with hepatitis B e antigen (HBeAg) positive and HBeAg negative HBV infection. With respect to patients with lamivudine (LVD)-refractory hepatitis B (see SmPC Sections 4.4 and 5.1).

Table 1-1: Product Details

	ETV is also indicated for the treatment of chronic HBV infection in nucleoside-naïve paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see SmPC Sections 4.2, 4.4, and 5.1.
Dosage in the EEA	**Current:** ETV should be taken orally, once daily (QD). Adults: *Compensated liver disease* • In nucleoside-naïve patients: the recommended dose is 0.5 mg QD, with or without food. • In LVD-refractory patients (ie, with evidence of viraemia while on LVD or the presence of LVD-resistance [LVDr] mutations) (see SmPC Sections 4.4 and 5.1): the recommended dose is 1 mg QD, which must be taken on an empty stomach (more than 2 hours before or more than 2 hours after a meal) (see SmPC Section 5.2). In the presence of LVDr mutations, combination use of ETV plus a second antiviral agent (which does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy (see SmPC Section 4.4). *Decompensated liver disease* • The recommended dose for patients with decompensated liver disease is 1 mg QD, which must be taken on an empty stomach (more than 2 hours before or more than 2 hours after a meal) (see SmPC Section 5.2). For patients with LVD-refractory hepatitis B (see SmPC Sections 4.4 and 5.1). • Paediatrics: The recommended dose in nucleoside-naïve paediatric patients from 2 to < 18 years of age with compensated liver disease and weighing at least 10 kg is 0.015 mg/kg up to a maximum of 0.5 mg QD, taken with or without food. Doses adjustments (lower) are recommended for patients who have renal impairment for whom the oral solution can be used. As an alternative, in case the oral solution is not available, the dose can be adjusted by increasing the dosage interval of the tablets (see SmPC Section 4.2). The optimal duration of treatment is unknown and is determined according to the patient's response. In patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.

Table 1-1: Product Details

Pharmaceutical form(s) and strength(s)	• **Current:** Film-coated tablets: 0.5 mg and 1.0 mg Oral solution: 0.05 mg/mL
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication and Target Population(s)

Table 2.1-1: Epidemiologic Characteristics of CHB Infection

Epidemiologic Characteristics of CHB Infection	
Incidence	Incidence of HBV infection varies across regions and countries. It has been estimated that worldwide, 10 to 30 million people become infected with HBV each year.[2] The likelihood that newly infected persons will develop CHB infection is dependent on their age at the time of infection. Greater than 90% of those infected at birth, 25% to 50% of children infected between 0 to 5 years of age, and 5% to 10% of older children and adults develop chronic infection.[3,4,5] In Europe, the average annual incidence of reported hepatitis B cases is about 3.4 per 100,000 populations[6] with approximately 15,000 cases per year. This estimate could be an underestimate due to the fact that asymptomatic cases may not be accounted for and, therefore, underreporting of HBV is unlikely.[7] The incidence of hepatitis B among the paediatric population has been decreasing due to the implementation of national hepatitis B vaccination programmes.[8,9,10,11,12,13,14,15] The national coverage of vaccination programmes ranges from as low as 70% to over 90%.[16,17]
Prevalence	Approximately 350 to 400 million people worldwide have CHB infection.[18,19] The world can be divided into 3 different categories based on the prevalence of CHB infection: areas with a high prevalence (> 8%), areas with an intermediate prevalence (2% to 8%), and areas with a low prevalence (< 2%). South and east Asia are high prevalence areas, southern and eastern EU are intermediate prevalence areas, and western EU and the United States (US) are low prevalence areas.[5,18] The prevalence among paediatric populations has been decreasing due to the implementation of national hepatitis B vaccination programmes. In Germany, the prevalence of hepatitis B surface

Table 2.1-1: Epidemiologic Characteristics of CHB Infection

Epidemiologic Characteristics of CHB Infection	
	antigen (HBsAg)-positive children from 3 to 17 years old was 0.2%.[20] The prevalence among 0- to 14-year-olds in 2010 in Poland was < 0.01 per 100,000, the lowest of all age groups.[14] In Turkey, the prevalence of CHB, at 3.5%, was lowest in children < 5 years old.[9] In Greece, post introduction of vaccination programmes, the prevalence of CHB was 0.6%, a decrease from 1.9% in the prevaccination era.[15] In England, the prevalence was 4.6 per 100,000, with approximately half of the cases coming from children born outside of England.[21] In China, similar to Turkey, the lowest prevalence of CHB was in each descending age group with the rate as low as 1% in the 1-year-old category.[10]
Demographics of the population: age, gender, racial and/or ethnic origin	The prevalence of CHB increases with age and tends to be higher in males than in females.[22,23,24]
Risk factors for the disease	The primary risk factors of CHB include high risk sexual activity, occupational exposure (eg, medical worker), male gender, intravenous drug use, and familial exposure (eg, mother-to-child, close household contact with infected individuals).[19,25,26,27]
Main treatment options	Treatment options for CHB in adults include ETV, LVD, adefovir (ADV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF), interferons (standard and pegylated),[2] and clevudine (region specific). In paediatric CHB, treatment options vary by region. In Europe, treatment options are limited to TDF for adolescent patients 12 years and older. In other regions (including the US), treatment options also include interferons (standard and pegylated), LVD, and ADV (12 years and older).
Mortality and morbidity (natural history)	More than 600,000 people die each year from acute or CHB infection.[19] Mortality is significantly increased not only from liver-related causes but also from nonliver causes among HBsAg-positive patients. Crude all-cause mortality was reported to be as high as 1,891 per 100,000 patient-years in males and 772 per 100,000 patient-years in females in Haimen, China. Compared with HBsAg-negative subjects, the age-adjusted relative risk of death was 3.6 and 3.0, respectively, for males and females. For the same HBsAg-positive cohort, the mortality of hepatocellular carcinoma (HCC) was reported to be 1,046 per 100,000 patient-years in males and 319 per 100,000 patient-years in females, and the age-adjusted relative risk, compared with HBsAg-negative subjects, was 23.2 for males and 25.8 for females.[28] A United Kingdom study showed mortality of HCC for HBsAg-positive female blood donors was 33.5 per 100,000 patient-years.[29] This represented a relatively healthy cohort. However, compared with the general population, the standardised mortality ratio was 26.3, which was consistent with the

Table 2.1-1: Epidemiologic Characteristics of CHB Infection

Epidemiologic Characteristics of CHB Infection	
	Haimen study in China. Persons with CHB infection are at high risk of developing cirrhosis and HCC, which are related to high mortality. The annual incidence of cirrhosis has been estimated to be 2% to 6% for HBeAg-positive and 8% to 10% for HBeAg-negative patients.[30] Every year, globally, over a half a million people die of chronic HBV infection, including about 235,000 deaths due to cirrhosis, which may lead to end-stage liver disease and 328,000 deaths due to liver cancer.[4,31] The number of deaths from cirrhosis or HCC attributable to HBV was estimated to be 200 in northwest EU; 2,150 in midwestern EU; 3,000 in southwest EU; and 18,600 in central and eastern EU.[32] The primary treatment for cirrhosis leading to end-stage liver disease is hepatic transplantation. In the US alone, 3% of the 6,000 annual hepatic transplantations are due to HBV-related disease.[33] CHB infection has a serious worldwide impact on individual and public health. Globally, the prevalence of CHB infection is estimated to be 350 million. Between 25% to 30% of untreated adult patients with CHB infection develop sequelae of progressive liver disease, which include cirrhosis, decompensated cirrhosis, HCC, and death related to liver failure and/or HCC. Reported annual incidence data for these sequela vary, in part, secondary to differences in study design and study population. Important patient variables affecting incidence rates include duration of HBV infection (as reflected by geographic region and patient age). Important HBV parameters include activity of viral replication (as reflected by HBeAg status, blood HBV DNA, and liver necroinflammatory index) and HBV genotype. Among patients with HBV viraemia, 15% to 20% develop cirrhosis within 5 years. Cirrhosis is the most important sequelae of progressive liver disease: the annual incidence of both decompensated liver disease and HCC is higher in patients with cirrhosis.[34] The subsequent development of serious complications of CHB during childhood is uncommon and rarely reported. In a long-term retrospective study of 108 children with CHB observed for up to 24 years in a single Italian center, just 1 of 57 subjects (1.7%) with available liver histology was diagnosed with cirrhosis, and no patients had clinical or laboratory evidence of hepatic decompensation.[35] In a large worldwide epidemiology of 1,422 children and adolescents (2 to 18 years) with CHB, 14 (< 1%) had decompensated liver disease.[36]
Important comorbidities	Hepatitis C virus (HCV) coinfection can lead to an increase in the risk of cirrhosis, hepatic decompensation and liver injury when compared with mono-infection alone.[37] A higher risk of HCC is present in HCV/HBV coinfected patients.[37,38] Patients coinfected with HCV and HBV have a rate of death nearly 10-fold higher than either infection alone.[39]

Table 2.1-1: Epidemiologic Characteristics of CHB Infection

Epidemiologic Characteristics of CHB Infection	
	Although hepatitis D virus (HDV) may be associated at first with suppression of HBV virus, coinfection leads to an increase in severe or fulminant hepatitis compared with monoinfection.[40] The development of HCC may also be exacerbated in CHB/HCV coinfected patients but this is not yet fully elucidated.[40,41] The risk of developing cirrhosis is 3 times higher than in CHB mono-infection.[41] CHB patients in Italy with HDV had poorer survival experience based on an increased standardised mortality ratio than patients with HBV monoinfection.[42] Human immunodeficiency virus (HIV) coinfection can lead to an increase in the risk of cirrhosis and end-stage liver disease.[43] A higher risk of HCC may also be present in HIV/HBV coinfected patients.[38] HIV coinfection may lead to flares of hepatic transaminases due to immune reconstitution after treatment.[38] Liver-related mortality was higher among HIV/HIV coinfected patients than either HIV or HBV monoinfected patients.[44] The risk of death increased 3-fold in HIV[45] coinfected patients compared with the monoinfected patients.[39]

2.2 Nonclinical Part of the Safety Specification

Table 2.2-1: Summary of Significant Nonclinical Safety Findings

Key Safety Findings	Relevance to Human Usage
Genotoxicity ETV was clastogenic in human lymphocytes at high, cytotoxic concentrations. In contrast, ETV was not clastogenic in a repeat-dose oral micronucleus assay in rats, even at toxic doses. In a battery of other genetic toxicology tests, ETV showed no evidence of DNA reactivity. Mechanistic studies suggest that the clastogenicity of ETV in human lymphocytes may result from perturbations in deoxyribonucleoside triphosphate pools.	The significance of clastogenicity of ETV in vitro in human lymphocytes is unknown.
Carcinogenicity Lung tumour in male mice at low-exposure multiples and in females at high-exposure multiples relative to those in humans. Liver carcinomas in male mice, benign vascular tumours in female mice, brain gliomas in male and	Data from a long-term clinical study (AI463080) showed that ETV was not associated with an increased risk of malignant neoplasms as compared with other standard of care HBV nucleos(t)ide analogues in subjects with chronic HBV infection.

Table 2.2-1: Summary of Significant Nonclinical Safety Findings

female rats, and liver adenomas and carcinomas in female rats.	
Reproductive toxicity	
In reproductive studies in rats, ETV demonstrated no effects on reproductive function or fertility and no adverse findings in a perinatal/postnatal study at exposures ≥ 21 times that in humans at 1.0 mg daily.	Overall, adequate safety margins relative to the exposures in humans were evident for ETV.
Developmental toxicity	
Except for a decrease in acoustic startle response observed at high multiples of human exposure in juvenile rats (≥ 92 times than in paediatric patients administered ETV at 0.015 mg/kg), no new toxicities were observed in juvenile animals relative to those seen in adult animals.	The significance of a decrease in acoustic startle response in juvenile rats and its relevance to humans is unclear.

2.2.1 Conclusions on Nonclinical Data

Table 2.2.1-1: Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

2.3 Clinical Trial Exposure

Clinical investigation of ETV has been underway since 27-Jan-1997. Approximately 16,904 subjects have been randomised in clinical trials, with 10,789 subjects exposed to ETV. This calculation is based on trials that have been unblinded or in which all treatment arms receive ETV (including single-arm trials) and ongoing, blinded trials based on the randomisation schemes for those trials.

Tables presenting cumulative ETV clinical trial exposure data by duration, dose, age group and gender, ethnic origin, region, and special populations are presented in Appendix 2, using a cutoff date of 03-May-2017.

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2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The main exclusion criteria involve the properties of ETV and exclusion criteria that are applied generally to clinical trials and real-world practice.

Hypersensitivity reactions to ETV or any components of the product or known history of allergy to nucleos(t)ide analogues continue to be contraindicated in clinical trials.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale (If Not Included as Missing Information)
Hypersensitivity to ETV or any components of the product or known history of allergy to nucleos(t)ide analogues	Involves the properties of ETV	No	This is an exclusion criterion applied generally to clinical trials and real-world practice.

There are no additional exclusion criteria that are proposed to remain as contraindications.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

There is no current clinical trial development programme for ETV.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	There are no adequate and well-controlled studies of ETV in pregnant women.
Breastfeeding women	ETV is excreted in the milk of rats. It is not known whether ETV is excreted in human milk. Breastfeeding is not recommended during treatment with ETV.
Liver transplant	65 subjects treated with ETV in Study AI463109,[46] and 9 subjects treated in AI463015,[47] for a total of 74 persons and 104.17 person-years (see Table 4 in Appendix 2).
Patients with relevant comorbidities:	
Patients with hepatic impairment	32 subjects total treated with ETV in Study AI463032: 16 healthy subjects and 16 subjects with hepatic impairment.[48] 102 subjects treated with ETV in AI463048.[49]
Patients with renal impairment	34 subjects total treated with ETV in Study AI4163011: 6 healthy subjects and 28 subjects with varying degrees of renal impairment.[50]

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Patients with HIV/HBV coinfection	ETV has not been evaluated in HIV/HBV coinfected patients not currently receiving effective HIV treatment. Selection of an HIV variant containing the M184V resistance substitution was documented during ETV treatment for CHB infection in an HIV/HBV coinfected patient who was not simultaneously receiving highly active antiretroviral therapy (HAART). Therefore, therapy with ETV is not recommended for HIV/HBV coinfected patients who are not receiving HAART. [51] ETV has not been studied as a treatment for HIV infection and is not recommended for this use. ETV has been studied in 68 adults with HIV/HBV coinfection receiving a LVD-containing HAART regimen. The purpose was to study add on ETV in patients receiving a LVD-containing HAART regimen in whom HIV was successfully controlled (stable HIV RNA < 400 copies/mL), but whose HBV DNA was not suppressed by the LVD component of the HAART. This study was initiated before the use of TDF and emtricitabine (FTC) had become widespread, and these drugs were excluded from the ongoing HAART that was maintained while under study observation. The design requirement that patients enter this study with controlled HIV viraemia made it impossible to detect an incremental increase in HIV suppression due to the addition of ETV. Results confirmed that 1) ETV is effective for the treatment of LVD-refractory HBV in HIV coinfected patients simultaneously receiving HAART; and 2) the coadministration of ETV together with a HAART regimen is safe and does not result in any loss of ARV activity. [52,53]
Patients with a disease severity different from inclusion criteria in clinical trials	ETV has not been evaluated in CHB patients with normal aminotransferases (ALT or aspartate transaminase [AST]) or inactive HBV and in children < 2 years of age or those who were immune tolerant. Patients in these groups would generally not qualify to be treated under current treatment guidelines.
Population with relevant different ethnic origin	Results from Study AI463085 confirmed that the efficacy and safety of ETV in the 40 treated Black/African Americans with CHB was consistent with the experience in the Phase 3 programme. While enrollment of the Hispanic cohort was limited due to the inability to recruit patients (6 subjects), the data were consistent with clinical use of ETV in the Black/African American and overall Phase 3 populations and did not identify any evidence that extrapolation from the broad consistency of data across the entire Phase 3 global programme was inappropriate.
Subpopulations carrying relevant genetic polymorphisms	ETV is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) isoenzymes, and the pharmacokinetics (PK) of ETV in humans is unlikely to be affected by the coadministration of agents that are either metabolised by, inhibit, or induce the CYP450 system. Likewise, the PK of known CYP450 substrates is unlikely to be affected by the coadministration of ETV.
Children	The safety and effectiveness of ETV in paediatric patients from 2 to < 18 years of age has been assessed based on 2 clinical trials in patients with CHB (AI463028 and AI463189). These trials provided experience in

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
	219 HeBeAg-positive nucleos(t)ide treatment-naïve patients treated with ETV for a median duration of 99 weeks. The adverse reactions observed in paediatric population treated with ETV were consistent with those observed in clinical trials of ETV in adults. To date, no safety signal has been identified specific to the paediatric population in postmarketing data.
	Paediatric studies of ETV did not include subjects < 2 years old or those who were immune tolerant. Patients in these groups would generally not qualify to be treated under current treatment guidelines.
Elderly	Clinical studies of ETV did not include sufficient numbers of subjects aged ≥ 65 years to determine if they respond differently from younger subjects. The PK profile of ETV does not differ by age. No dosage adjustment of ETV based on age is required. ETV is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. To date, no safety signal has been identified specific to the elderly population in postmarketing data.

2.5 Post-authorisation Experience

2.5.1 Post-authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

There is no readily available information on the actual number of patients treated with ETV during the reporting period. However, an estimate of the number of treated patients is derived from sales figures as described below.

2.5.1.2 Exposure

Sales figures for ETV were received from approved vendors from 01-Jan-2005 through 31-Dec-2018. Based on these sales data, an estimated 699,916,300 mg were sold from 01-Jan-2005 through 31-Dec-2018.

Using the average dose and duration of treatment as described in the prescribing information for ETV, the estimated 699,916,300 mg sold can be used to calculate an estimated number of patients treated. The estimated sales and average dose and duration of treatment, based on the prescribing information, are used to calculate the estimated number of patients treated (patient-years). Keeping in mind that the dose and duration of therapy may depend on several factors (eg, age [adult, paediatric], body weight, renal function, specific treatment indication, therapeutic response), the following assumptions were used to arrive at an estimation of the number of patients treated with ETV during the period referenced above:

- Each patient was an adult who received 0.5 mg of ETV for the treatment of CHB infection with evidence of active liver inflammation.
- Each patient received this dose for 1 year (365 days).
- Each patient received a total dose of 182.5 mg.
- Taking into account the available sales data and the assumptions as described above, the number of patients exposed (in patient-years) to commercial ETV from 01-Jan-2005 through 31-Dec-2018 is estimated to be:

    - 699,916,300 mg ÷ 182.5 mg = 3,835,158 patients treated

- Given the above-mentioned limitations and assumptions, this estimate of the cumulative number of patients treated from 01-Jan-2005 through 31-Dec-2018 should be interpreted with caution.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

ETV is not a controlled substance and has no additive potential. Therefore, the potential for misuse as a recreational drug is quite low.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarised in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Exacerbation of hepatitis
	Development of ETV resistance (ETVr)
Important potential risks	Carcinogenicity
	Potential mitochondrial toxicity
Missing information	Long-term safety and clinical outcomes data
	Paediatric population
	Decompensated patients

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

At the time of the initial RMP submission, safety risks that were not included in the RMP did not meet the criteria to be designated as an important, identified, or potential risk. ETV's well-characterised safety profile has been consistent across approved indications and reflected in the SmPC under Sections 4.4 and 4.8.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks considered important for inclusion in the list of safety concerns for the first approved RMP are provided in Table 2.7.1.2-1.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the Initial RMP

Risk Type	Risk-Benefit Impact
Important Identified Risks	
Exacerbation of hepatitis	Acute exacerbation of hepatitis following withdrawal of therapy, while often asymptomatic, can be associated with severe complications, particularly in patients with advanced cirrhosis. In patients treated with LVD or ADV, these complications occasionally have resulted in death. During the clinical development of ETV, symptoms associated with withdrawal of ETV therapy have generally been benign. However, the frequency of severe complications following withdrawal of ETV may be greater in the postmarketing period than during clinical studies, as a broader population of patients, including those with severe comorbidities, is exposed to the drug.
Development of ETVr	Antiviral resistance may result in a loss of clinical effect and potential transmission of resistant HBV. In LVD-refractory patients, mutations in the HBV polymerase that encode LVDr substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with ETVr. Patients with LVDr HBV are at higher risk of developing subsequent ETVr HBV than patients not previously treated with LVD. In addition, virological breakthrough can be associated with serious clinical complications of the underlying liver disease, especially in decompensated patients. Subsequent rebound in viraemia may be associated with ALT flares and disease progression to cirrhosis, hepatic decompensation, and HCC.
Important Potential Risks	
Carcinogenicity	Analyses of malignancies that have occurred during the clinical studies do not show an increase in human malignancies over the expected rate in patients with CHB or in the comparator group from clinical studies. The major limitation of the clinical studies' analyses is that the lag period for detection of a malignancy following exposure to a carcinogen may exceed the observation period of the ETV studies to date. The majority of patients have been observed up to 52 weeks. Additionally, relatively rare events are difficult to assess during clinical development related to the size of programmes. Long-term observational studies, specifically Study 080, with larger populations enrolled will overcome these limitations.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the Initial RMP

Risk Type	Risk-Benefit Impact
Mitochondrial toxicity	Mitochondrial toxicity is a recognised class effect of nucleos(t)ides. Within the class, the frequency of this event and its numerous manifestations are highly variable. This variability is partially related to the degree of binding to host (G analog) DNA polymerase by the nucleos(t)ide. Other factors influencing frequency are female gender, obesity, pregnancy, and specifically for HIV-infected patients with low CD4 count. The characteristics of ETV, ie, its low binding affinity for DNA polymerase and no effect on oxidative metabolism in HepG2 cells, predict that mitochondrial toxicity related to ETV will be low compared with other nucleos(t)ide. The human experience to date is consistent with these models; mitochondrial toxicity is rare.
Missing Information	
Long-term safety and clinical outcomes	Three ETV studies (AI463049, AI463080, and AI463901) allow for long-term follow-up of ETV-treated patients to assess for potential risk of malignant neoplasms and other long-term complications. Studies AI463080, AI463049, and AI463901 have been completed; the final clinical study reports have been submitted.
Paediatric population	The safety and efficacy of ETV in paediatric patients from 2 to < 18 years of age has been assessed based on 2 clinical trials in patients with CHB (a Phase 2b pharmacokinetic study [AI463028] and a Phase 3 study [AI463189]). These trials provided experience in 219 HBeAg- positive nucleoside treatment-naïve patients treated with ETV for a median duration of 99 weeks. The adverse reactions observed in paediatric population treated with ETV were consistent with those observed in clinical trials of ETV in adults.
Decompensated patients	At the time of initial RMP submission, ETV was not indicated for use in decompensated patients.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Reclassification	Reasons for the Reclassification
Removal of use in the paediatric population (from birth to less than 2 years of age) as missing information	As per the revised GVP Module V guidance (March 2017), "Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications."[1] Paediatric patients less than 2 years of age are not part of the on-label indications in the Company Core Data Sheet (CCDS)[54] and are therefore not relevant to list among missing information. The MAH has accordingly removed "use in the paediatric population (from birth to less than 2 years of age)" from the list of missing information.
Removal of use in elderly patients (≥ 65 years of age) as missing information	As per the revised GVP Module V guidance, "missing information" refers to use in a particular patient population, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far.[1] Data on use in elderly patients are available in Sections 3.5 and 9.2.4.3 of the CCDS, which state no dosage adjustment of ETV based on age is required and that the pharmacokinetic profile of ETV does not differ by age. The MAH has accordingly removed "use in elderly patients (> 65 years of age)" from the list of missing information.[54]

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Important Identified Risk 1 - ETVr

Antiviral resistance may result in a loss of clinical effect and potential transmission of resistant HBV. In LVD-refractory patients, mutations in the HBV polymerase that encode LVDr substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with ETVr. Patients with LVD-resistant HBV are at higher risk of developing subsequent ETVr HBV than patients not previously treated with LVD. Virologic breakthroughs due to resistance to ETV require the existence of primary LVDr substitutions (M204I/V ± L180M) along with an additional substitution at residues T184, S202, or M250 of the polymerase protein. In addition, virological breakthrough can be associated with serious clinical complications of the underlying liver disease, especially in decompensated patients. Subsequent rebound in viraemia may be associated with ALT flares and disease progression to cirrhosis, hepatic decompensation, and HCC. Development of ETVr in treatment-naïve patients is extremely uncommon when ETV is taken as prescribed.

Table 2.7.3.1-1 summarises the characteristics of ETVr in ETV-treated patients.

Table 2.7.3.1-1: Important Identified Risk: ETVr

Important Identified Risk ETVr	
Potential mechanisms	Compared with activity against wild-type HBV, there is an 8-fold reduction in susceptibility to ETV in cell-based studies when LVD and LdT resistance-associated substitutions rtM204I/V ± rtL180M (LVDr) are present. High-level ETVr requires preexisting LVDr substitutions plus additional changes at primary positions rtT184, rtS202, or rtM250 ± a secondary change at rtI169 in the HBV reverse transcriptase.
Evidence source and strength of evidence	Scientific literature, CCDS[54]
Characterisation of risk	*Frequency:* **Adult Data:** Adult patients in pivotal clinical trials initially treated with ETV 0.5 mg (nucleoside-naïve) or 1.0 mg (LVD-refractory) and with an on-therapy polymerase chain reaction HBV DNA measurement at or after Week 24 were monitored for resistance. Nucleoside-naïve studies: 663 patients were treated and monitored for resistance in Year 1, 278 patients in Year 2, 149 patients in Year 3, 121 patients in Year 4, and 108 patients in Year 5. The cumulative probability of emerging genotypic ETVr substitutions in nucleoside-naïve studies was 0.2%, 0.5%, 1.2%, 1.2%, and 1.2% through Years 1, 2, 3, 4, and 5, respectively. Two patients experienced a virologic rebound due to emergence of an ETVr substitution through the first 5 years of therapy. Results reflect a switch from the 0.5 mg dose to the 1 mg dose of ETV for 147 of 149 patients in Year 3 and all patients in Years 4 and 5, and of combination ETV-LVD therapy (followed by long-term ETV therapy) for a median of 20 weeks for 130 of 149 patients in Year 3 and for 1 week for 1 of 121 patients in Year 4 in a rollover study. LVD-refractory studies: The cumulative probability of emerging genotypic ETVr substitutions in LVD-refractory studies was 6.2%, 15.0%, 36.3%, 46.6%, and 51.45% through Years 1, 2, 3, 4, and 5, respectively. **Paediatric Data:** Nucleoside-naïve HBeAg-positive children from the 2 ETV paediatric studies (AI463028 and AI463189) were assessed for the frequency of ETVr through 96 weeks of treatment. A total of 183 patients (21 from AI463028 and 162 from AI463189) were treated and monitored for resistance in Year 1 and 180 patients (22 from AI463028 and 158 from AI463189) in Year 2. None of the patients evidenced emergent ETVr in Year 1, and 2 patients evidenced emergent ETVr in Year 2, giving a cumulative probability of 0% and 1.1% through Years 1 and 2, respectively. *Impact on the individual patient* Antiviral resistance may result in loss of clinical effect; subsequent rebound in viraemia may be associated with ALT flares and disease progression to cirrhosis, hepatic decompensation, and HCC. *Duration of treatment, risk period:* Patients are at risk during the entire course of treatment and for a brief time after treatment discontinuation while serum levels of ETV are still detectable. Patients with LVDr HBV are at higher risk of developing subsequent ETVr. *Reversibility:* The development of resistance is not reversible.

Table 2.7.3.1-1: Important Identified Risk: ETVr

Important Identified Risk ETVr	
Risk factors and risk groups	*LVD-refractory patients:* Mutations in the HBV polymerase that encode LVDr substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with ETVr. Patients with LVDr HBV are at higher risk of developing subsequent ETVr HBV than patients not previously treated with LVD. Virologic response should be closely monitored in the LVD-refractory population, and appropriate resistance testing should be performed. In patients with decompensated liver disease, virologic breakthrough may be associated with serious clinical complications of the underlying liver disease. Therefore, in patients with both decompensated liver disease and LVDr HBV, combination use of ETV plus a second antiviral agent (that does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy. Reduction of HBV DNA to < 300 copies/mL correlated strongly with maintenance of the HBV DNA response during continued treatment and with an absence of resistance.
Preventability	No factors/means identified. The treatment paradigm for patients with LVDr HBV is changing, and use of combination therapy is increasing in order to address the long-term risks for progressive, sequential resistance. Study AI463111 was a comparative study of the efficacy and safety of combination therapy versus ETV monotherapy in CHB subjects with LVDr. Although combination therapy failed to demonstrate superiority over ETV monotherapy for the primary endpoint (proportion of subjects with HBV DNA < 50 IU/mL at Week 48), the study confirmed the expectation that combination therapy provides a meaningful resistance benefit over ETV monotherapy in CHB subjects with LVDr.
Impact on the risk-benefit balance of the product	The risk of ETVr is well-known and appropriately described in the label. There are no additional pharmacovigilance activities or risk-minimisation measures for ETVr.
Public health impact	Potential transmission of resistant HBV is a theoretical possibility but not well-documented in the literature for any current HBV nucleos(t)ide therapy.

Important Identified Risk 2 - Exacerbation of Hepatitis

Acute hepatitis occurring during or following withdrawal of nucleos(t)ide treatment of chronic HBV infection, for which no cause other than HBV or treatment of HBV is identified, is a recognised complication of HBV therapy. Synonyms for this event are exacerbation of hepatitis, hepatic flare, and ALT flare. ALT flare is often an asymptomatic occurrence manifesting as an isolated elevation in serum ALT with/without an accompanying increase in serum AST. Uncommonly, there are concurrent abnormalities in one or more laboratory measures of hepatic function (eg, increased total bilirubin, prothrombin time/international normalised ratio, and/or decreased albumin). Rarely, patients may manifest clinical signs of hepatic decompensation (eg, new onset or worsening preexisting ascites), including frank hepatic failure, which in some cases is followed by death. The latter occurs principally in patients with preexisting advanced liver disease (cirrhosis or decompensated cirrhosis).

Table 2.7.3.1-2 summarises the characteristics of exacerbation of hepatitis in ETV-treated patients.

Table 2.7.3.1-2: Important Identified Risk: Exacerbation of Hepatitis (ALT Increase/Hepatic Flare)

Important Identified Risk: Exacerbation of Hepatitis (ALT Increase/Hepatic Flare)	
Potential mechanisms	ALT flares related to viral rebound during ETV treatment should be differentiated from early on-treatment host-induced flares, as described above. The former may occur either on-treatment, as a consequence of emergence of ETVr viral mutants, or ensue following interruption or discontinuation of therapy. Accordingly, this type of ALT flare is commonly referred to in the literature as "viral induced" to distinguish the pathogenesis from that of a host-induced event. Differential diagnosis: ALT flares in patients with CHB infection may also be spontaneous in nature, resulting from a spontaneous bout of viral activity or following exposure of a patient to concurrent potent immunosuppressive therapy. In addition, concurrent infection or superinfection with another hepatotropic virus (hepatitis A virus or HDV, respectively) may result in hepatobiliary laboratory abnormalities, which mimic those characteristic of an ALT flare. Finally, other events that need to be considered in the differential diagnosis of an HBV-associated ALT flare are drug- or toxin-induced increases in serum ALT, hepatitis due to nonhepatic viruses (eg, herpes group viruses, adenovirus), and shock liver. Risk of off-treatment hepatic flare with currently approved nucleoside reverse transcriptase inhibitor (NRTI) HBV therapeutics, including ETV, has been well-documented in the literature and is also outlined in the product labels. Events of hepatic flares have been closely monitored in the ETV clinical and postmarketing surveillance programme.
Evidence source and strength of evidence	Scientific literature[38,55,56,57,58,59,60,61]
Characterisation of risk	*Frequency:* The frequency of ALT flares in ETV-treated patients in the Phase 2/3 studies was less than that experienced with LVD for both the nucleoside-naïve and LVD-refractory populations. Approximately 6% of nucleoside-naïve patients and 12% of LVD-refractory patients in these studies had a posttreatment flare, and none were associated with hepatic decompensation. Acute exacerbation of hepatitis following withdrawal of therapy, while often asymptomatic, can be associated with severe complications, particularly in patients with advanced cirrhosis. In patients treated with LVD or ADV, these complications occasionally have resulted in death. During the clinical development of ETV, symptoms associated with withdrawal of ETV therapy have generally been benign. To date there has not been a change in the severity or frequency of this event that has warranted an update in the product safety information. Among ETV-treated patients, the median times to off-treatment ALT flare were 23, 24, and 17 weeks in Studies AI463022, AI463027, and AI463026, respectively. These intervals were substantially longer than those for the LVD-treatment group (12 weeks in Study AI463022, 9 weeks in Study AI463027, and no events in Study AI463026). The longer time to off-treatment ALT flare among ETV-treated patients is consistent with more profound on-treatment viral suppression, which results in a longer period before the recurrence of viraemia achieves a sufficient threshold level to trigger an ALT flare. Data are limited with respect to the time to onset of ALT flare and the frequency of flares in decompensated patients. *Impact on the individual patient:*

Table 2.7.3.1-2: Important Identified Risk: Exacerbation of Hepatitis (ALT Increase/Hepatic Flare)

Important Identified Risk: Exacerbation of Hepatitis (ALT Increase/Hepatic Flare)	
	ALT flare is often an asymptomatic occurrence, manifesting as an isolated elevation in serum ALT with or without elevated AST. Uncommonly, events may be associated with other laboratory abnormalities and/or clinical manifestations indicative of hepatic decompensation, including hepatic failure, which in some cases is followed by death. The latter occurs principally in patients with preexisting advanced liver disease. *Duration of treatment, risk period:* Patients are at risk during their entire course of therapy and after discontinuation of therapy. *Reversibility:* On-treatment ALT flares occurring in ETV-treated patients have generally occurred early following initiation of therapy and been associated with a preceding decline from baseline in HBV DNA levels. These observations suggest an immune-mediated pathogenesis, such as boosting of HBV-specific host effector responses as a consequence of the decreased viral antigen burden; hence, these flares are often referred to in the literature as "host-induced." Early on-treatment ETV-associated ALT flares generally resolve without a need for treatment interruption or discontinuation.
Risk factors and risk groups	Underlying cirrhosis (hepatic decompensation), HBV pre-S deletion precore mutations before treatment (with LVD), higher pretreatment ALT (HBeAg-positive), LVD-resistant virus with rebound viraemia, HCV/ HDV coinfection during treatment with interferon and ribavirin, expansion of HBV-specific memory cells (CD8 T-cells), robust immune response, decreased CD4 T-cell count in HIV coinfected patients, concurrent chemotherapy, and emergence of precore mutants in late HBV infection.
Preventability	After LVDr has developed, maintaining an individual on LVD therapy can prevent flares. Add-on therapy or a change to a drug combination with adequate coverage of LVDr HBV is presumed to prevent flares, and this assumption is embodied in current treatment guidelines.
Impact on the risk-benefit balance of the product	The risk of exacerbation of hepatitis (ALT increase/hepatic flare) is well-known and appropriately described in the label. There are no additional pharmacovigilance activities or risk-minimisation measures for exacerbation of hepatitis (ALT increase/hepatic flare).
Public health impact	Manifestations of exacerbation of hepatitis may require hospitalisation or may be life-threatening.

Important Identified Risk 3 - Emergence of Resistant HIV in HIV/HBV Coinfected Patients Not Receiving Concurrent Effective HIV Treatment

Emergence of HIV resistance has been observed when ETV was used to treat CHB infection in patients with untreated HIV infection. Therefore, therapy with ETV is not recommended for HIV/HBV coinfected patients who are not receiving HAART. ETV has not been studied as a treatment for HIV infection and is not recommended for this use. Events of decreased HIV RNA

with or without HIV drug resistance occurred in a subset of HIV/HBV coinfected patients receiving ETV who demonstrated increasing percentages of HIV RNA clones harbouring the M184V mutation. This resistance substitution is considered to have important clinical implications because it limits future HIV treatment options (specifically, it confers resistance to LVD and FTC, which are standard components of first-line HIV therapy). Long-term outcome information is not available.

Table 2.7.3.1-3 summarises the characteristics of emergence of resistant HIV in HIV/HBV coinfected patients not receiving concurrent effective HIV treatment in ETV-treated patients.

Table 2.7.3.1-3: Important Identified Risk: Emergence of Resistant HIV in HIV/HBV Coinfected Patients

Important Identified Risk: Emergence of Resistant HIV in HIV/HBV Coinfected Patients	
Potential mechanisms	The Company began pharmacologic investigations to understand the differences between findings reported from the Johns Hopkins laboratory and the original Company observations, which did not demonstrate anti-HIV activity.[62] Briefly, these nonclinical investigations assessed the activity of ETV against an expanded set of HIV-1 isolates under various assay conditions. Results indicated that ETV potency (EC50) was particularly influenced by experimental conditions, and that the inhibitory concentrations ranged from 0.026 μM, depending on the viral strain and the level of virus used to initiate infection in the assay system. In addition, under comparable assay conditions, HIV pseudovirus variants containing the M184V substitution have reduced susceptibility to ETV relative to the comparable virus without this substitution. Finally, ETV can select for a M184I substitution *in vitro* at micromolar concentrations, which confirms that ETV has the potential to exert inhibitory pressure on HIV replication. The CCDS states that therapy with ETV is not recommended for HIV/HBV coinfected patients who are not also receiving effective HIV therapy.
Evidence source and strength of evidence	*In vitro* assessment of ETV against HIV,[64] Clinical Overview, [63] scientific literature[64]
Characterisation of risk	*Frequency:* In HIV/HBV coinfected patients, ETV has only been studied clinically in patients receiving concomitant effective HIV therapy and has not been assessed in clinical trials for anti-HIV clinical activity. As of 28-Mar-2008, Bristol-Myers Squibb (BMS) had received a total of 22 cases of decreased HIV RNA, including 12 in which patients demonstrated increasing percentages of HIV RNA clones harbouring the M184V mutation, in HIV/HBV coinfected patients receiving ETV. The incidence of such cases has shown a marked and continuous decline over the following reporting periods, a pattern which is considered to be a result of the positive impact of the Dear Health Care Professional letters issued and changes to the prescribing information regarding the avoidance of use of ETV in HIV/HBV coinfected patients who are not currently receiving effective anti-HIV therapy. *Impact on the individual patient:* The emergence of HIV resistance at M184 can appear when ETV is used to treat HBV in HIV/HBV coinfected patients who are not receiving concurrent effective HIV treatment. This resistance substitution is considered to have important clinical implications because it limits future HIV treatment options (specifically, it confers

Table 2.7.3.1-3: Important Identified Risk: Emergence of Resistant HIV in HIV/HBV Coinfected Patients

Important Identified Risk: Emergence of Resistant HIV in HIV/HBV Coinfected Patients	
	resistance to LVD and FTC, which are standard components of first-line HIV therapy). *Duration of treatment, risk period:* Patients with HIV are at risk of developing resistant HIV whenever ETV is administered without concomitant HAART. *Reversibility:* HIV resistance is not reversible.
Risk factors and risk groups	HIV/HBV coinfected patients not receiving effective concomitant HAART.
Preventability	Avoidance of use of ETV without concomitant HAART in this subset of HIV/HBV coinfected patients.
Impact on the risk-benefit balance of the product	The risk of emergence of resistant HIV in HIV/HBV coinfected patients not receiving concurrent effective HIV treatment is well-known and appropriately described in the label. There are no additional pharmacovigilance activities or risk-minimisation measures for emergence of resistant HIV in HIV/HBV coinfected patients not receiving concurrent effective HIV treatment.
Public health impact	Limited HBV-infected patients with unrecognised HIV infection. Relevant to all current nucleos(t)ide HBV therapies.

Important Potential Risk - Mitochondrial Toxicity (Including Lactic Acidosis)

Mitochondrial dysfunction is a recognised concern for all nucleos(t)ide analogues, manifesting clinically as lactic acidosis (LA) or a symptomatic hyperlactacidaemia, pancreatitis, neuropathies, myopathies, lipoatrophy, and hepatic events. Nonclinical screening can identify drugs with a particularly high potential for interference with γ-polymerase and mitochondrial toxicity. The *in vitro* data from the preclinical mitochondrial toxicity evaluation of ETV, which was consistent with the standard approach recommended for such screening, indicated that ETV would be expected to have little or no potential for mitochondrial toxicity. Given the absence of ETV effects of mitochondrial polymerase γ and oxidative metabolism, clinical adverse events (AEs) related to mitochondrial dysfunction are generally not considered expected with ETV; however, the Company is committed to monitoring these categories of events over the long term.

Table 2.7.3.1-4 summarises the characteristics of mitochondrial toxicity in ETV-treated patients.

Table 2.7.3.1-4: Important Potential Risk: Mitochondrial Toxicity (Including LA)

Important Potential Risk: Mitochondrial Toxicity (Including LA)	
Potential mechanisms	Capacity of phosphorylated NRTIs to inhibit host mitochondrial DNA polymerase-γ through a mechanism similar to their therapeutic activity.
Evidence source and strength of evidence	Scientific literature[65,66,67,68,69,70]
Characterisation of risk	*Frequency:* Mitochondrial toxicity is a recognised class effect of nucleos(t)ides (ie, those that are HBV or HIV related). Within the class, the frequency of this event and its numerous manifestations are highly variable. This variability is partially related to the degree of binding to host γ-DNA polymerase by the nucleos(t)ide analogue. Other factors influencing frequency are female gender, obesity, pregnancy, and, specifically for HIV-infected patients, low absolute CD4 T-cell count. The characteristics of ETV (ie, its low binding affinity for DNA polymerase and no effect on oxidative metabolism in HepG2 cells) predict that mitochondrial toxicity related to ETV will be low compared with other nucleos(t)ides. The human experience to date is consistent with these models; mitochondrial toxicity is rare. Serum lactate levels have poor predictive value for relevant clinical events and were not prospectively monitored in ETV studies. AEs related to LA syndrome may be reported less frequently in patients with HBV than in patients with HIV, where this is a well-recognised syndrome. Underreporting bias cannot be ruled out. *Impact on the individual patient:* Mitochondrial dysfunction is a recognised concern for all nucleos(t)ide analogues manifesting clinically as LA or symptomatic hyperlactacidaemia, pancreatitis, neuropathies, myopathies, lipoatrophy, and hepatic events. The proposed mechanism for this (as well as other mitochondrial toxicity syndromes) is thought to be nucleos(t)ide interference with γ-polymerase. In the case of lactate disorders, the primary organ dysfunction involves the liver, with decreased mitochondrial DNA synthesis leading to a disruption of normal hepatocyte metabolic activity and compromised lactate metabolism; however, underlying host factors may also predispose towards LA, and even transient or reversible conditions (such as the third trimester of pregnancy) can be of clinical importance. Patients with impaired hepatic function at baseline, regardless of the etiology, appear to be at increased risk for lactate complications. *Duration of treatment, risk period:* Patients are at risk for the duration of treatment. *Reversibility:* Mitochondrial toxicity may be reversible or partially reversible when the inciting agent is discontinued.
Risk factors and risk groups	Adult "mitochondrial disease" syndromes occur most likely in genetically susceptible individuals, brought out by the stress of NRTI therapy; such patients may also have a positive family history for similar events. Neither the prevalence of relevant genetic changes nor their potential impact is completely understood. In patients with chronic liver disease, LA may result from both increased lactate production and decreased hepatic lactate clearance in patients with cirrhosis; increased lactate production may result from tissue hypoperfusion or compromised cellular oxygen metabolism, while decreased lactate clearance may result from a

Table 2.7.3.1-4: Important Potential Risk: Mitochondrial Toxicity (Including LA)

Important Potential Risk: Mitochondrial Toxicity (Including LA)	
	lack of functioning hepatocytes. Individuals with advanced hepatic cirrhosis are expected to maintain a fragile acid-base balance and to experience impaired ability for lactate disposal because of a relative lack of functioning hepatocytes. In addition, most of the identified patients also had significant relevant comorbidities. It is therefore considered likely that the severity of the underlying hepatic disease, as well as the relevant comorbidities, may have had a causal role and/or could provide an alternative explanation for the development of LA in the majority of cases. The relatively high frequency of underlying cirrhosis, hepatic decompensation, or acute liver failure observed in the patients described in the postmarketing case reports of LA or increased lactic acid received to date suggests that patients with these conditions may be at specific increased risk for lactate-associated AEs. Many cases were also noted to be confounded by relevant comorbidities (eg, diabetes) and/or concomitant medications (eg, metformin).
Preventability	There are no established methods for preventing mitochondrial toxicity in patients receiving NRTI therapy. Micronutrients may have a role, but further study is needed.
Impact on the risk-benefit balance of the product	The risk of emergence of mitochondrial toxicity (including LA) is well-known and appropriately described in the label. There are no additional pharmacovigilance activities or risk-minimisation measures for mitochondrial toxicity (including LA).
Public health impact	Although rare, manifestations of mitochondrial dysfunction may require hospitalisation or may be life-threatening.

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source
Population in Need of Further Characterisation	
Use in pregnancy	There are no adequate and well-controlled studies in pregnant women. ETV should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.[71]
Use in patients with severe acute exacerbation of CHB	In a retrospective analysis, a higher 1-year mortality rate with ETV was identified when compared to LVD in a specific subset of patients in whom therapy was initiated during a spontaneous severe acute exacerbation of CHB infection.[72] Although this analysis suggested that ETV was associated with an increased mortality at 1 year, the excess mortality was accounted for by deaths in the first 30 days of treatment. In contrast, 3 other retrospective analyses of ETV versus LVD-treated patients with an acute spontaneous exacerbation of CHB revealed a similar response with both treatments and no increases in mortality during treatment at specific time points of 4 weeks and 6 months.[73,74,75]

2.8 Summary of the Safety Concerns

Safety concerns are summarised in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	ETVr
	Exacerbation of hepatitis (ALT increase/hepatic flare)
	Emergence of resistant HIV in HIV/HBV coinfected patients
Important potential risks	Mitochondrial toxicity (including LA)
Missing information	Use in pregnancy
	Use in patients with severe acute exacerbation of CHB

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

See Annex 4 for forms, as applicable, summarised in Table 3.1-1.

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires	
Postmarketing questionnaires for: • ALT flare • HCC • LA • Liver injury • Malignancies	Questionnaires record events including signs and symptoms, diagnostic test results, actions taken, event resolution, and relevant medical history (see Annex 4)
Other Forms of Routine Pharmacovigilance Activities	
Not applicable	

3.2 Additional Pharmacovigilance Activities

There are no ongoing additional pharmacovigilance activities for ETV. A tabulated summary of completed pharmacovigilance activities is provided in Annex 2.

3.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing additional pharmacovigilance activities for ETV.

4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

There are no protocols for imposed postauthorisation efficacy studies.

5 PART V: RISK-MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMISATION ACTIVITIES)

The current ETV SmPC provides information on the identified and potential risks discussed in Section 2.7.3. These include warnings regarding the potential for exacerbations of hepatitis both during and posttreatment, class labelling regarding the potential risk for LA, and information regarding nonclinical safety findings, particularly the rodent carcinogenicity studies. Use during pregnancy is not recommended unless clearly necessary.

As described in the Pharmacovigilance (PhV) Plan, further measures are being undertaken to monitor the risk of development of HIV resistance with ETV use in HIV/HBV coinfected patients not concurrently receiving effective HIV treatment, to monitor exacerbation of hepatitis and mitochondrial toxicity, including LA, to evaluate the occurrence of ETVr, and to continue to assess the efficacy and safety in paediatric patients (2 to < 18 years).

As new data become available, these will be assessed and reported to the health authorities. The RMP and the PI will be updated accordingly and any other necessary actions taken. The Company assesses the currently available data and important identified or potential risks as being adequately addressed through the proposed marketing authorisation conditions, including information provided in the ETV SmPC and through the actions described in the PhV Plan. No other risk-minimisation measures are considered necessary at this point.

5.1 Routine Risk-minimisation Measures

Table 5.1-1: Description of Routine Risk-minimisation Measures by Safety Concern

Safety Concern	Routine Risk-minimisation Activities
ETVr	**Routine risk communication:** The SmPC warns about ETVr in Section 4.4 and recommends dosing in Section 4.2 **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on preventing ETVr in ETV-treated patients is described in SmPC Section 4.4, Special warnings and precautions for use. **Other routine risk-minimisation measures beyond the Product Label:** None.
Exacerbation of hepatitis	**Routine risk communication:** The SmPC warns of exacerbation of hepatitis in Sections 4.4 and 4.8. Package Leaflet (PL) Section 2. **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on the symptoms and monitoring of hepatitis in patients treated with ETV is provided in SmPC Section 4.4, Special warnings and precaution for use, and Section 4.8, Undesirable effects.

Table 5.1-1: Description of Routine Risk-minimisation Measures by Safety Concern

	Other routine risk-minimisation measures beyond the Product Label: None.
Emergence of resistant HIV in HIV/HBV coinfected patients not concurrently receiving effective HIV treatment	**Routine risk communication:** The SmPC Section 4.4 warns that ETV should not be used for HIV/HBV coinfected patients who are not receiving HAART and that ETV has not been studied as a treatment for HIV infection and is not recommended for this use. PL Section 2. **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on treatment of patients coinfected with HIV with ETV is provided in SmPC Section 4.4, Special warnings and precautions for use. **Other routine risk-minimisation measures beyond the Product Label:** None.
Mitochondrial toxicity	**Routine risk communication:** • The SmPC Section 4.4 warns of the risk of mitochondrial toxicity. • PL Section 2. • **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on the symptoms and monitoring of LA is provided in SmPC Section 4.4, Special warnings and precautions for use. **Other routine risk-minimisation measures beyond the Product Label:** None.
Use in pregnancy	**Routine risk communication:** The SmPC Section 4.6 describes use in pregnancy. PL Section 2. **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on use of ETV in pregnant women is provided in SmPC Section 4.6, Fertility, pregnancy, and lactation. **Other routine risk-minimisation measures beyond the Product Label:** None.

Table 5.1-1: Description of Routine Risk-minimisation Measures by Safety Concern

Use in patients with severe acute exacerbation of CHB	**Routine risk communication:** The SmPC Section 4.4 and 4.8 warns of use in severe acute exacerbation of CHB. **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on the monitoring of patients for severe acute exacerbation of CHB following discontinuation of therapy in patients treated with ETV is provided in SmPC Section 4.4, Special warnings and precautions for use, and Section 4.8, Undesirable effects. **Other routine risk-minimisation measures beyond the Product Label:** None.

5.2 Additional Risk-minimisation Measures

Not applicable. There are no additional risk-minimisation measures for ETV.

5.3 Summary of Risk-minimisation Measures

A summary of risk-minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk-minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk-minimisation Measures	Pharmacovigilance Activities
ETVr	**Routine risk-minimisation measures:** SmPC Section 4.4, Special warnings and precautions for use, and Section 4.2, Posology and method of administration **Additional risk-minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted letter/questionnaire for ETVr. **Additional pharmacovigilance activities:** None.
Exacerbation of hepatitis	**Routine risk-minimisation measures:** SmPC Sections 4.4, Special warnings and precautions for use and Section 4.8, Undesirable effects. PL Section 2. **Additional risk-minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Table 5.3-1: Summary of Risk-minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk-minimisation Measures	Pharmacovigilance Activities
Emergence of resistant HIV in HIV/HBV coinfected patients not concurrently receiving effective HIV treatment	**Routine risk-minimisation measures:** SmPC Section 4.4, Special warnings and precautions for use. PL Section 2. **Additional risk-minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Mitochondrial toxicity	**Routine risk-minimisation measures:** SmPC Section 4.4, Special warnings and precautions for use. PL Section 2. **Additional risk-minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Use in pregnancy	**Routine risk-minimisation measures:** SmPC Section 4.6, Fertility, pregnancy, and lactation. PL Section 2. **Additional risk-minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Use in patients with severe acute exacerbation of CHB	**Routine risk-minimisation measures:** SmPC Section 4.4, Special warnings and precautions for use. **Additional risk-minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BARACLUDE (entecavir)

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

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

This summary of the RMP for BARACLUDE 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 BARACLUDE's RMP.

I. The medicine and what it is used for

BARACLUDE is authorised for CHB infection (see SmPC for the full indication). It contains entecavir as the active substance and it is given orally.

Further information about the evaluation of entecavir's benefits can be found in BARACLUDE's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/baraclude.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 health care professionals
- Important advice on the medicine's packaging
- The authorised 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 patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk-minimisation* measures.

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

II.A List of important risks and missing information

Important risks of BARACLUDE are risks 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 BARACLUDE. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	ETV resistance
	Exacerbation of hepatitis (ALT increase/hepatic flare)
	Emergence of resistant HIV in HIV/HBV coinfected patients
Important potential risks	Mitochondrial toxicity (including lactic acidosis)
Missing information	Use in pregnancy
	Use in patients with severe acute exacerbation of CHB

II.B Summary of important risks

Important identified risk

ETV Resistance	
Evidence for linking the risk to the medicine	Scientific literature, CCDS[54]
Risk factors and risk groups	*LVD-refractory patients:* Mutations in the HBV polymerase that encode LVDr substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with ETVr. Patients with LVDr HBV are at higher risk of developing subsequent ETVr HBV than patients not previously treated with LVD. Virologic response should be closely monitored in the LVD-refractory population, and appropriate resistance testing should be performed. In patients with decompensated liver disease, virologic breakthrough may be associated with serious clinical complications of the underlying liver disease. Therefore, in patients with both decompensated liver disease and LVDr HBV, combination use of ETV plus a second antiviral agent (that does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy. Reduction of HBV DNA to < 300 copies/mL correlated strongly with maintenance of the HBV DNA response during continued treatment and with an absence of resistance.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4 and recommended dosing in Section 4.2.
Exacerbation of Hepatitis (ALT Increase/Hepatic Flare)	
Evidence for linking the risk to the medicine	Scientific literature.[38,55,56,57,58,59,60,61]
Risk factors and risk groups	Underlying cirrhosis (hepatic decompensation); HBV pre-S deletion precore mutations before treatment (with LVD); higher pretreatment ALT (HBeAg-positive); LVD-resistant virus with rebound viraemia; HCV/HDV coinfection during treatment with interferon and ribavirin; expansion of HBV-specific memory cells (CD8 T-cells); robust immune

Important identified risk

	response; decreased CD4 T-cell count in HIV coinfected patients; concurrent chemotherapy; and emergence of precore mutants in late HBV infection.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Sections 4.4 and 4.8.
Emergence of Resistant HIV in HIV/HBV Coinfected Patients	
Evidence for linking the risk to the medicine	In vitro assessment of ETV against HIV,[63] Clinical Overview, scientific literature[64]
Risk factors and risk groups	HIV/HBV coinfected patients not receiving effective concomitant HAART.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4.

Important potential risk

Mitochondrial Toxicity (Including Lactic Acidosis)	
Evidence for linking the risk to the medicine	Scientific literature[65,66,67,68,69,70]
Risk factors and risk groups	Adult "mitochondrial disease" syndromes occur most likely in genetically susceptible individuals, brought out by the stress of NRTI therapy; such patients may also have a positive family history for similar events. Neither the prevalence of relevant genetic changes nor their potential impact is completely understood. In patients with chronic liver disease, LA may result from both increased lactate production and decreased hepatic lactate clearance in patients with cirrhosis; increased lactate production may result from tissue hypoperfusion or compromised cellular oxygen metabolism, while decreased lactate clearance may result from a lack of functioning hepatocytes. Individuals with advanced hepatic cirrhosis are expected to maintain a fragile acid-base balance and to experience impaired ability for lactate disposal because of a relative lack of functioning hepatocytes. In addition, most of the identified patients also had significant relevant comorbidities. It is therefore considered likely that the severity of the underlying hepatic disease, as well as the relevant comorbidities, may have had a causal role and/or could provide an alternative explanation for the development of LA in the majority of cases. The relatively high frequency of underlying cirrhosis, hepatic decompensation, or acute liver failure observed in the patients described in the postmarketing case reports of LA or increased lactic acid received to date suggests that patients with these conditions may be at specific increased risk for lactate-associated AEs. Many cases were also noted to be confounded by relevant comorbidities (eg, diabetes) and/or concomitant medications (eg, metformin).
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4

Missing information

Use in Pregnancy	
Evidence for linking the risk to the medicine	There are no adequate and well-controlled studies in pregnant women. ETV should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.[71]
Risk-minimisation measures	Routine risk-minimisation measures: SmPC description in Section 4.6.
Use in Patients with Severe Acute Exacerbation of CHB	
Evidence for linking the risk to the medicine	In a retrospective analysis, a higher 1-year mortality rate with ETV was identified when compared with LVD in a specific subset of patients in whom therapy was initiated during a spontaneous severe acute exacerbation of CHB infection.[72] Although this analysis suggested that ETV was associated with an increased mortality at 1 year, the excess mortality was accounted for by deaths in the first 30 days of treatment. In contrast, 3 other retrospective analyses of ETV- versus LVD-treated patients with an acute spontaneous exacerbation of CHB revealed a similar response with both treatments and no increases in mortality during treatment at specific time points of 4 weeks and 6 months.[73,74,75]
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BARACLUDE.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for BARACLUDE.

7 LIST OF ABBREVIATIONS

Term	Definition
ADV	adefovir
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMS	Bristol-Myers Squibb
CCDS	Company Core Data Sheet
CHB	chronic hepatitis B
CY	cytochrome
DNA	deoxyribonucleic acid
EEA	European Economic Area
EPAR	European Public Assessment Report
ETV	entecavir
ETVr	entecavir resistance
EU	European Union
FTC	emtricitabine
GPV	Good Pharmacovigilance Practices
HAART	highly active antiretroviral therapy
HBeAG	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HPS	High Pure System
LA	lactic acidosis
LdT	telbivudine
LVD	lamivudine
LVDr	lamivudine resistance
MAH	Marketing Authorisation Holder
N/A	not applicable
NRTI	nucleoside reverse transcriptase inhibitor
PI	Product Information
PK	pharmacokinetics

Term	Definition
PL	Package Leaflet
QD	once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RNA	ribonucleic acid
SmPC	Summary of Product Characteristics
TDF	tenofovir disoproxil fumarate
TP	triphosphate
US	United States

APPENDIX 1 REFERENCES

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