Module 1.8.2

European Union Risk Management Plan (EU-RMP) for DOVATO (dolutegravir/lamivudine fixed-dose combination)

STATEMENT REGARDING LICENSE AGREEMENTS

This Risk Management Plan has been prepared by GlaxoSmithKline (GSK) on behalf of ViiV Healthcare (VH) and reviewed and endorsed by VH. GSK provide pharmacovigilance (PV) services under contract to VH from within their own PV system, details of which are settled in a pharmacovigilance agreement. GSK definitions, processes and/or systems are therefore referred to in this report. The integration of the data necessary for the management of safety for all products in VH is achieved via use of the GSK PV system; in GSK this is achieved by sharing an electronic global safety database. All adverse event (AE) reports for all VH marketed products and SAEs for investigational assets are collected into this GSK database, from which the information necessary for reporting to various competent authorities is obtained and constitutes a key body of data for signal management, risk management plans and aggregate safety report generation which is undertaken by GSK under the oversight of VH.

Whilst GSK are the providers of all operational PV services for VH marketed products, as product owner, sponsor of clinical trials and Marketing Authorisation Holder (MAH) of Medicinal Products, VH is accountable for safety governance of each of its products. This includes the decisions on product safety issues and the action to be taken following identification and assessment of safety issues by the product review team, such as suspension of trials, updates to the product label, and other risk management actions.

RMP version to be assessed as part of this application	
RMP Version number	6.0
Data lock point for this RMP	28 February 2025
Date of final sign off	19 May 2025
Rationale for submitting an updated RMP	
The RMP has been updated to include the 2024 Antiretroviral Pregnancy Registry data. Post-authorisation exposure data updated to the latest available data.	

Summary of significant changes in this RMP		
PART	**MODULE**	**Changes made in EU-RMP version 6.0**
Part I: Product(s) Overview		Minor administrative changes
Part II: Safety Specification	Module SI: Epidemiology of the Indication(s) and target population(s).	No change
	Part II: Module SII : Non-Clinical part of the Safety Specification	No change
	Module SIII: Clinical trial exposure	No change
	Module SIV: Populations not studied in clinical trials.	No change
	Module SV : Post authorisation experience	Update to post-authorisation exposure data.
	SV.1: Additional EU requirements for the safety specification	No change
	Module SVII: Identified and Potential Risks. Module SVIII Summary of Safety Concerns	Updated to add 2024 Antiretroviral Pregnancy Registry data. No change

Part III: Pharmacovigilance Plan (including post authorisation safety studies).		Updated information on 2024 APR data.
Part IV: Plans for post-authorisation efficacy studies		No change
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities).		No change
Part VI: Summary of RMP		No change
Part VII: Annexes		No change

Other RMP versions under evaluation N/A (Not applicable)		
RMP Version number	Submitted on	Procedure number
N/A	N/A	N/A
Details of the currently approved RMP Not applicable		
Version number	Approved with procedure	Date of approval (opinion date)
5.0	EMEA/H/C/xxxx/WS/2620	31 October 2024
QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV	
QPPV Signature	Electronic signature on file	

ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse drug reaction
AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
APR	Antiretroviral Pregnancy Registry
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC	Area under the concentration curve
c/ml	Viral copies per ml
CAR/cART	Current antiretroviral regimen
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical study report
CVW	Confirmed virological withdrawal
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DHPC	Direct Health Care Professional communication
DLP	Data lock point
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EEA	European Economic Area
EFV	Efavirenz
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed dose combination
FTC	Emtricitabine
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HSR	Hypersensitivity
INN	International Nonproprietary Name
INI/INSTI	Integrase strand transfer inhibitor
IRIS	Immune reconstitution inflammatory syndrome
m 2.7.4	Summary of Clinical Safety

MAA	Marketing authorization application
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for regulatory activities
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NTD	Neural tube defect
NVP	Nevirapine
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PDCO	Paediatric committee
PhV	Pharmacovigilance
PI	Protease inhibitor
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PT	Preferred term
RAL	Raltegravir
aRMM	Additional Risk Minimisation Measure
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse transcriptase
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TBDR	Texas Birth Defects Registry
TBR	Tenofovir alafenamide fumarate-based regimen
TDF	Tenofovir disoproxil fumarate
TdP	Torsades de Pointes
TFQ	Targeted follow up questionnaire
UGT	Uridine diphosphate glucuronosyl transferase
VHL	ViiV Healthcare UK Limited
VL	Viral Load

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Dolutegravir and lamivudine
Pharmacotherapeutic group(s) (ATC Code)	J05AR25
Marketing Authorisation Holder/ Applicant	ViiV Healthcare Limited
Medicinal products to which this RMP refers	Dolutegravir/lamivudine fixed-dose combination
Invented name(s) in the European Economic Area (EEA)	DOVATO
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Dolutegravir/lamivudine 50/300 mg fixed dose combination (DTG/3TC FDC) is a single tablet containing one integrase strand transfer inhibitor (DTG) and one nucleoside analogue (3TC). DTG inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle. 3TC is a reverse transcriptase inhibitor (NRTI) and is metabolised sequentially by intracellular kinases to the lamivudine triphosphate (TP), which is the active moiety. Lamivudine-TP is the substrate for and competitive inhibitor of HIV reverse transcriptase (RT). The main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination and interruption of the viral replication cycle.
Reference to the Product Information	Please refer to product information (section 1.3.1. of the eCTD)

Indication(s) in the EEA	DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine
Dosage in the EEA	The recommended dose of DOVATO (containing 50mg DTG / 300mg 3TC) in adults and adolescents is one tablet once daily. DOVATO should not be administered to adults or adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced. A separate preparation of dolutegravir is available where a dose adjustment is indicated due to drug- drug interactions. In these cases, the physician should refer to the individual product information for dolutegravir. There are limited data available on the use of DOVATO in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients. Special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters. DOVATO is not recommended for use in patients with a creatinine clearance < 30 mL/min. No dose adjustment is required in patients with mild or moderate renal impairment. However, the lamivudine exposure is significantly increased in patients with a
Pharmaceutical form(s) and strengths	Film-coated tablet (tablet). White, film-coated, oval, biconvex tablets debossed with “SV 137” on one face.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

As dolutegravir/lamivudine fixed-dose combination (DTG/3TC FDC) does not contain a new active substance this module has not been populated as there is no new epidemiology information specific to the DTG/3TC FDC. Please refer to the latest approved EU-RMP for DTG for the latest epidemiology information.

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

This module has not been populated as no new non-clinical data was generated for the DTG/3TC FDC. Please refer to the latest approved DTG and ABC/3TC EU RMPs for the latest non-clinical information for the single entities.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Phase I studies

The Sponsor has undertaken a bioequivalence study (204994) to confirm that the DTG/3TC FDC tablets (formulated as either a monolayer or bilayer) were equivalent to DTG and 3TC given as two separate tablets together as well as a relative bioavailability study (204993) in healthy adult volunteers.

The Phase I bioequivalence study (204994) evaluated the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.

The Phase I bioavailability study (204993) evaluated the relative bioavailability of a single dose of DTG 50mg and 3TC 300mg when administered together in each of two FDC tablet formulations compared to the co-administration of a single dose of the single entity DTG and 3TC products.

In the Phase I studies, 183 healthy volunteers were exposed to co-administered DTG and 3TC as follows:

- In 204994 (Phase I bioequivalence study), 154 subjects received a single dose of study drug in each of three treatment periods (DTG/3TC FDC or DTG + 3TC single tablets)
- In 204993 (Phase I bioavailability study), 29 subjects received single doses of the study drug in each of 3 treatment periods (DTG + 3TC in one period and the DTG/3TC FDC in two periods)

Since the initial MAA, two Phase I studies have been initiated in pediatric subjects:

- Study 216149 is a Phase I Randomized, 2-Cohort, 2-Period, Single Dose, Crossover Clinical Study to Assess the Effect of Food on the Pediatric Dispersible Tablet Formulations of TRIUMEQ (Dolutegravir/Abacavir/Lamivudine) and DOVATO (Dolutegravir/Lamivudine) in Healthy Adult Participants. This study is ongoing.
- Study 205894 was a 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric TRIUMEQ Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared With Adult Tablets in Healthy Volunteers. This study is now completed.

Phase III studies

The safety specification for the DTG/3TC FDC in adult subjects supporting the marketing authorization application involved 2 ongoing identical Phase III clinical trials using DTG 50 mg + 3TC 300 mg co-administered as individual tablets.

Data up to Week 48 (data cut-off date: 22 May 2018) was included from two ongoing identical Phase III clinical trials (204861 (GEMINI-1) and 205543 (GEMINI-2))

investigating the efficacy, safety, and tolerability of DTG plus 3TC compared to DTG plus tenofovir (TDF)/emtricitabine (FTC) in HIV-1-infected treatment-naïve adults. Eligible subjects are randomised 1:1 to receive a two-drug regimen of DTG plus 3TC once daily or DTG plus the FDC tablet of TDF/FTC once daily until Week 148.

Data up to Week 144 is now available and subject exposure is shown in Table 1 below.

Table 1 Cumulative Number of Subject Exposure to Dolutegravir and Lamivudine Given as the Single Entities from Ongoing ViiV Healthcare- Sponsored Interventional Studies 204861 and 205543 (GEMINI 1 and 2) by Age, Sex and Racial Group

	GEMINI-1 and GEMINI-2 (DTG + 3TC)
Total	716
Age (yrs)	
<18	0
18 – 64	712
65 – 74	4
>=75	0
Sex	
Male	603
Female	113
Racial Group	
African American/African Heritage	99
American Indian or Alaskan Native	49
Asian - Central/South Asian Heritage	0
Asian - East Asian Heritage	61
Asian - Japanese Heritage	0
Asian - South East Asian Heritage	10
Native Hawaiian or Other Pacific Islander	2
White - Arabic/North African Heritage	8
White - White/Caucasian/European Heritage	472
White – Mixed race	0
Missing	0
Mixed race	15

a. Data as of 16 July 2021

Since the initial MAA, 4 additional Phase III ViiV Healthcare sponsored interventional trials were initiated where subjects received the DTG/3TC FDC. A brief description of these studies is included below:

Study 204862 (TANGO)

A Phase 3, randomised, multicentre, parallel-group, non- inferiority study evaluating the efficacy, safety, and tolerability of switching to DTG+3TC in HIV-1 infected adults who are virologically suppressed. Study recruited ART-experienced virologically suppressed adult subjects on a stable tenofovir alafenamide (TAF) based regimen (TBR) with no evidence or history of NRTI or INSTI drug resistance. Data to week 96 is now available.

Study 212355 (STAT)

An open-label, single arm, 52-week pilot study with the primary objective to evaluate the feasibility, efficacy and safety of a rapid 'test and treat' intervention at Week 24 in adult participants with a new diagnosis of HIV 1 initiating treatment with the DTG/3TC FDC immediately as first line regimen. This study is now complete.

Study 208090 (SALSA)

A Phase IIIb, randomised, multicentre, open-label, non-inferiority study evaluating the efficacy, safety and tolerability of switching to DTG/3TC in HIV-1 infected adults who are virologically suppressed. Data up to 24 weeks have now been analysed for this study.

Study 205861 (DANCE)

A Phase IIIb, single arm study evaluating the efficacy and safety of DTG/3TC FDC in ART-naive HIV-1-infected adolescents, ≥12 to <18 years of age, who weigh at least 25 kg.

Cumulative subject exposure to dolutegravir/lamivudine FDC from phase I-III ongoing and completed VH-sponsored interventional studies is shown in the tables below.

Table 2 Cumulative Number of Dolutegravir/lamivudine FDC Subjects from Ongoing and Completed VH-Sponsored Interventional Studies

Phase / Study / Treatment	Number of Subjects Exposed		
	Ongoing Studies	Completed Studies	Total
Phase 1 and 2a - Total (including comparator and placebo)	**16[b]**	**201[b]**	**217[b]**
204993			
Dolutegravir/ lamivudine FDC	0	29[b]	29
204994			
Dolutegravir/ lamivudine FDC	0	78[b]	78
Dolutegravir+lamivudine FDC	0	76[b]	76
205894			
Dolutegravir/ lamivudine FDC	0	18[b]	18
216149			
Dolutegravir/ lamivudine FDC	16[b]	0	16
Phase 2b/3/3b/4 - Total (including placebo/comparator)	**1265**	**131**	**1396**
204862			
Dolutegravir/ lamivudine FDC[e]	667	0	667
Tenofovir alafenamide fumarate-based regimen (TBR)	371	0	371
205861[d]			
Dolutegravir/lamivudine FDC	32	0	32
212355			
Dolutegravir/lamivudine FDC	0	131	131
208090			
Dolutegravir/lamivudine FDC	246	0	246
Continue current regimen	247	0	247
TOTAL Dolutegravir/ lamivudine FDC	**961[b]**	**332[b]**	**1293[b,c]**

Abbreviations: FDC – fixed dose combination, SE- single entity, DTG – dolutegravir, 3TC – lamivudine, VH – ViiV Healthcare

a. Data as of 16 July 2021.
b. Subjects also received DTG SE or DTG/ABC/3TC FDC.
c. Total exposures for studies using DTG/3TC FDC
d. Subjects from 205861 are paediatric patients
e. 298 subjects are late switchers from TBR to DTG/3TC FDC

Table 3 Cumulative Subject Exposure to dolutegravir/lamivudine FDC in Completed VH-Sponsored[b,c] Interventional Studies by Age, Sex and Racial Group

	Number of Subjects
Total[d]	947
Age (years)	
<18	12
18 – 64	920
65 – 74	15
>=75	0
Sex	
Male	682
Female	265
Racial Group	
African American/African Heritage	209
American Indian or Alaskan Native	33
Asian – Central/South Asian Heritage	7
Asian - East Asian Heritage	29
Asian - Japanese Heritage	5
Asian - South East Asian Heritage	9
Native Hawaiian or Other Pacific Islander	6
White - Arabic/North African Heritage	13
White - White/Caucasian/European Heritage	631
Mixed Race	5

Abbrevations: VH – ViiV Healthcare, FDC – fixed dose combination, DTG – dolutegravir, 3TC – lamivudine

a. Data as of 16 July 2021

b. The completed VH-sponsored interventional studies included in this table are 205894, 204993 and 204994

c. The ongoing VH-sponsored interventional study included in this table that have met primary endpoint completion is 204862, 212355 and 208090.

d. The table excludes 298 subjects from ongoing study 204862 who are late switchers from Tenofovir alafenamide fumarate-based regimen (TBR) to DTG/3TC FDC

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

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in the Phase III DTG+3TC clinical trials are shown in the table below.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
History or presence of allergy or intolerance to the study drugs or their components or drugs of their class	Hypersensitivity is a rare but recognized risk for ART containing DTG, regardless of dose. and is contraindicated in patients receiving DTG.	No	DTG/3TC is contraindicated in anyone with hypersensitivity to DTG, 3TC or to any of the excipients and a warning around Hypersensitivity reactions (HSR) is included in module 4.4 of the SmPC.
Concomitant use of dofetilide	Dofetilide is prohibited as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity	No	The use of DTG and dofetilide is contraindicated in the SmPC
Anticipated need for HCV therapy during the study	HCV therapy at present includes the use of interferon, which is an immune modulator and thus may affect CD4+ cell count or other responses to treatment	No	Patients with HIV infection receiving DTG/3TC may have a HCV co-infection. Safety data across all patient populations supports the administration of DTG/3TC in HIV infected patients co-infected with HCV Treatment with DTG/3TC will be guided by established guidance and medical practice

Subjects positive for HBV at screening (+HbsAg)	Hepatitis B surface antigen positivity was an exclusion criterion for 204861 (GEMINI-1) and 205543 (GEMINI-2) due to the blinded use of DTG/3TC. Treatment guidelines (e.g., EACS guidelines) recommend ART initiation with TDF-based therapy for HBV- co-infected patients in need of anti-HBV therapy and/or with CD4+ cell counts <500.	No	Patients with HIV infection receiving DTG/3TC may have a HBV co-infection. Safety data across all patient populations with DTG or 3TC supports the administration of DTG/3TC in HIV infected patients co-infected with HBV. Treatment with DTG/3TC will be guided by established guidance and medical practice. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting therapy with DTG/3TC in hepatitis B co-infected patients.
Severe hepatic impairment as determined by Child- Pugh	No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C);	No	As part of routine risk minimisation the SmPC states that DTG/3TC should be used with caution in patients with severe hepatic impairment
ALT >5 times the upper limit of normal (ULN) ALT 3xULN and bilirubin 1.5xULN (with >35% direct bilirubin) Any verified Grade 4 laboratory	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study.	No	Patients with HIV infection receiving DTG/3TC may have other conditions which result in laboratory abnormalities. On review of safety data across all patient populations with DTG or 3TC, there is no reason

abnormality			to suggest that there are additional risks in these patients. Treatment with DTG/3TC will be guided by established guidance and medical practice
Subject has estimated creatinine clearance <50 mL/min via Cockroft-Gault method	Studies with 3TC show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose reduction of 3TC is therefore required for patients with creatinine clearance of < 50 ml/min. These patients were therefore excluded from the DTG/3TC studies.	No	In a phase I, open-label, parallel-group study to evaluate the PK and safety of a single 50 mg dose of DTG in HIV-negative subjects with severe renal impairment (CrCl <30 mL/min, not on dialysis), compared to healthy controls; severe renal impairment had a relatively moderate effect on DTG PK, reducing Cmax and AUC by around 23-40%, which is not considered clinically significant. Based on the 3TC data, DTG/3TC is not recommended for patients with creatinine clearance of < 50 ml/min. Treatment with DTG/3TC will be guided by established guidance and medical practice.

Ongoing malignancy (204861 and 205543)	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Patients with HIV infection receiving DTG/3TC may have concurrent malignancy. On review of safety data across all patient populations, there is no reason to suggest that there are additional risks in these patients. Treatment with DTG/3TC will be guided by established guidance and medical practice.
Women who are pregnant, breast feeding or plan to become pregnant or breastfeed	Pregnant and breast-feeding women are not routinely enrolled into clinical trials to avoid exposing the foetus, baby or infant to the study medication.	Yes	There is an increasing amount of data from the use of DTG in pregnant women (see SVII.1.2). There are limited data on use of DTG/3TC use in pregnancy. A large amount of data on the use of 3TC in pregnant women (more than 3000 outcomes from first trimester) indicates no malformative toxicity.
Subjects who in the investigator's judgment pose a significant suicidality risk	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition is exacerbated during the study.	No	Section 4.8 of the DTG/3TC FDC SmPC lists depression, including suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness) as an adverse reaction.
Evidence of an active CDC Category C disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm3	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	On review of safety data across all patient populations, there is no reason to suggest that DTG/3TC should be contraindicated in these patients. Treatment with DTG/3TC will be guided by established guidance and medical practice.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The DTG/3TC FDC clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

To date no long-term toxicities have been noted in clinical trials or post-marketing for DTG or 3TC single entities, which have been approved since 2013 and 1996 in the EU, respectively. There is no evidence from experience with DTG and 3TC single entities to suggest that the long-term safety profile of the DTG/3TC FDC would be any different.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant and breast feeding women	Pregnant women were excluded from DTG/3TC clinical studies. Subjects that became pregnant (intrauterine) were required to discontinue from the studies. Clinical experience of DTG/3TC use during pregnancy is therefore limited (see SVII.3.2). Breastfeeding women were not included in the clinical development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with severe hepatic impairment (Child Pugh score C) were excluded from the phase III clinical studies.
Patients with renal impairment	Subjects with estimated creatinine clearance (CrCl) <50 mL/min (Cockroft-Gault method), indicative of moderate and severe (<30 mL/min) renal impairment, were excluded from DTG+3TC clinical studies. This is due to the renal excretion of 3TC and the previous need for dose adjustment when CrCl <50mL/min. This has subsequently been amended in the SmPC and dose adjustment is now only required when CrCl <30mL/min.
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical programme included treatment- naïve HIV-1-infected patients with a viral load (VL) cap of ≤500,000 c/mL However, data on a small number of subjects who did enter the study with VL of >500,000 copies (due to changes in VL between screening and baseline assessment) does not suggest a difference in efficacy. The majority of subjects who enrolled into the Phase III DTG+3TC clinical trials were CDC Category HIV infection stage 1 or 2, but there were a number of subjects who were CDC category HIV infection stage 3 at baseline (approximately 9% in DTG+3TC arm and 8% the DTG+TDF/FTC arm)).

Type of special population	Exposure
Population with relevant different ethnic origin	All clinical studies were conducted internationally. Although the majority of patients in the clinical studies were white, no ethnicities were excluded (Table 3). Data from the individual components does not suggest any notable differences in the safety profile between different ethnic or racial groups.
Subpopulations carrying relevant genetic polymorphisms	Subjects with genetic polymorphisms were not examined in the study population.
Paediatrics	An MAA has been approved for DTG in the EU with an indication in children above 6 years of age, supported by data from study ING112578 (Pediatric Study P1093). DTG is in development for use in children ≥ 4 weeks to <18 years of age. 3TC is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children. Children and adolescents were not included in the DTG+3TC clinical development programme. However, data from the individual components supports adolescent dosing of DTG+3TC in those weighing >40kg as the single entities do not require dose reduction in adolescents weighing >40kg.
Elderly	There was no upper restriction of age in the Gemini studies. However, elderly individuals that are HIV treatment-naïve are less common and therefore there is limited information regarding the use of DTG/3TC in the elderly (≥65 years old). Only 4 (<1%) of subjects on DTG/3TC across the pivotal studies were ≥65 years of age or older at the time of the initial MAA Table 3. Based on the individual components, there is no evidence that the safety profile will be different in elderly patients.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for DTG/3TC.

For DTG/3TC the best estimates of total post-marketing experience, assuming all patients take a single tablet of DTG/3TC, from licensure (08 April 2019) to 31 December 2024 is estimated to be 762,748 patient years.

In the EU/EEA* total cumulative exposure to 31 December 2024 is 410,178 patient-years.

*The EU/EEA includes the following countries for purpose of exposure data (as at 31 December 2024): Spain, Italy, France, United Kingdom, Germany, Portugal, Netherlands, Belgium, Switzerland, Sweden, Austria, Denmark, Romania, Bulgaria, Serbia, Denmark, Hungary, Slovakia, Belarus, Poland, Ireland, Norway, Latvia, Finland, Czech Republic, Hungary, Croatia, Slovenia, and Luxembourg.

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

As the DTG/3TC FDC does not contain a new active substance, this module has not been populated as there is no new information specific to the DTG/3TC FDC. Please refer to the latest approved DTG and ABC/3TC EU RMPs for the latest information.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

The DTG/3TC FDC does not contain a new active substance. The following identified and potential risks for DTG are applicable to the DTG/3TC FDC and have been taken from the approved DTG EU RMP. There are no important risks for the 3TC component of the FDC for inclusion in this RMP. Data for the DTG/3TC FDC for each of these risks is included in m.2.7.4 (Summary of Clinical Safety) supporting the original MAA submission for the DTG/3TC FDC. No new risks have been identified specifically for the DTG/3TC FDC.

Important identified risks	**DTG*** • Hypersensitivity reaction • Hepatobiliary disorders
Important potential risks	**DTG** • Serious rash (Division of AIDS (DAIDS) Grade 3/4) • Neural Tube Defect (NTD)

*Depression and suicidal ideation/behaviours is an important identified risk in the DTG EU-RMP. However, it is not included as an important identified risk for DTG/3TC FDC EU-RMP at the request of the EMA since there are no additional PV or risk minimisation activities ongoing to characterize or mitigate this risk (see Section SVII.1.1).

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Depression (including suicidal ideation and behaviours particularly in patients with a pre-existing history of depression or psychiatric illness)

- The risk of depression (including suicidal ideation and behaviours) has been present in the DTG RMP since marketing authorization and was re-classified from a potential to an identified risk. With the adoption of the new EU-RMP template, and additional guidance received from EMA, this has not been captured as an important risk for DTG/3TC FDC since no additional PV or risk minimisation activities are being conducted to further characterize or mitigate this risk.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The DTG/3TC FDC does not contain a new active substance. The identified and potential risks for the DTG/3TC FDC have been taken from the approved DTG EU-RMP except for the risk of depression (including suicidal ideation and behaviours) (see SVII.1.1). There are no important identified or potential risks for the 3TC component in adolescents and adults. For further information on the risks (described in SVII.1 ; hypersensitivity reactions, hepatobiliary disorders, serious rash and neural tube defects) please refer to the latest approved DTG EU-RMP.

MISSING INFORMATION 1: USE IN PREGNANCY AND BREAST FEEDING

No studies have been conducted with the DTG/3TC FDC in pregnant women and pregnant and breastfeeding women were excluded from the Phase III DTG + 3TC clinical trials. Subjects that became pregnant (intrauterine) regardless of termination status of pregnancy were required to discontinue from the trials. Clinical experience of the DTG/3TC FDC use during pregnancy is therefore limited.

Risk-benefit impact:

As clinical experience with the use of the DTG/3TC FDC during pregnancy is limited it is not possible to fully define the benefit-risk impact in this patient population. The potential risk of NTD with the DTG component is also relevant to this FDC, however this potential risk is considered manageable through the information included in the product formation and communication to prescribers.

The antiretroviral pregnancy registry (APR) will collect data on pregnancy with DTG/3TC FDC. Further studies are currently ongoing to collect additional information on the use of DTG during pregnancy, these are described in the approved DTG RMP

MISSING INFORMATION 2: LONG TERM SAFETY

Experience with long term use of the DTG/3TC FDC is limited. To date no long-term toxicities have been noted in clinical trials or post-marketing for DTG or 3TC which have been approved since 2013 and 1996 respectively in the EU.

Risk-benefit impact:

There is no evidence from experience with DTG and 3TC single entities to suggest that the long-term safety profile of the DTG/3TC FDC would be any different. The long-term safety of the DTG/3TC FDC will be monitored through routine and additional pharmacovigilance activities, which includes review of data from the ongoing Phase III DTG + 3TC clinical trials.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no important identified or potential risk or missing information proposed to be added, removed or reclassified as part of this RMP update.

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

As the safety profile of DTG taken in combination with 3TC is consistent with the safety profiles of the single agents, and no additional risks or safety issues due to combination therapy have been identified, in line with guidance provided in GVP Module V (Rev.2 on 30 March 2017) relating to FDCs with no new active substance, detailed risk information has been omitted from this RMP. Please refer to the DTG RMP for this information.

SVII.3.2 Presentation of the missing information

MISSING INFORMATION 1: USE IN PREGNANCY AND BREAST FEEDING

No studies have been conducted with the DTG/3TC FDC in pregnant women. Pregnant and breastfeeding women were excluded from the Phase III DTG+3TC clinical trials. Subjects that became pregnant (intrauterine) regardless of termination status of pregnancy were required to discontinue from the trials. Clinical experience of the DTG/3TC FDC use during pregnancy is therefore limited.

At the time of the initial MAA submission, three patients had become pregnant in study 204861 (DTG+3TC: n=1; DTG+TDF/FTC: n=2). One pregnancy in each treatment group ended in spontaneous abortion with no apparent anomaly (reported as occurring at 7 weeks for the subject on DTG+3TC and at 4-5 weeks gestation. The other pregnancy (DTG + TDF/FTC group) was electively terminated, with no medical reasons for the termination.

In study 205543 one subject became pregnant while taking DTG+3TC. The pregnancy was electively terminated with no apparent congenital anomaly present.

Use in pregnancy and breast feeding is also considered missing information for the DTG single entity. Information is provided in the DTG EU-RMP and the PBRER.

In May 2018, preliminary findings from a birth outcomes surveillance study conducted in Botswana showed a higher than expected number of NTDs, among new-borns whose mothers were exposed to DTG-based ART at conception (Tsepamo study). Neural tube defects are included as a potential risk to the RMPs for the DTG EU-RMP (see Section Module SVII). Further studies are currently ongoing to collect additional information on the use of DTG during pregnancy.

The MAH conducted a review in 2018 of available data relating to the use of DTG in pregnancy, from the time of conception through all trimesters of pregnancy. The early signal has been refuted by subsequent data from two large birth surveillance studies. The

MAH has reviewed data from two key studies, the APR, as well as a number of other data sources including the DOLOMITE studies which are considered additional Pharmacovigilance Activities for DTG. The most recent data from the Tsepamo study in Botswana (over 9000 pregnancies with DTG peri-conception exposure as of March 2022), show no evidence of a statistically significant difference in NTD prevalence between infants exposed to DTG and non-DTG ART nor with any other exposure groups. The Eswatini birth outcome surveillance study including over 4800 exposures to DTG at conception through to September 2022 reported no difference in NTD prevalence when mothers take DTG at conception compared to women without HIV. Taken together these 2 large birth surveillance studies, undertaken in countries without folate food fortification, include a total of over 14 000 women taking DTG at conception through to September 2022, and provide evidence that there is no increased risk of NTDs following peri-conception DTG exposure. The exposure threshold of over 2000 needed to confirm or rule out a three-fold or higher increased risk of NTDs with DTG is therefore reached. Based on the latest data from these studies, the prevalence of NTD in infants born to women taking DTG at conception did not differ significantly from the background rate in women without HIV, or other exposure groups.

The DOLOMITE EPPICC study was an additional pharmacovigilance activity for this risk (for DTG) and it is now completed. After 833 pregnancy exposures, the results showed no increased risk of birth defects following DTG pregnancy exposure compared to background rates. Although the DOLOMITE-EPPICC or ongoing DOLOMITE-NEAT ID PASS studies (for single active DTG) are not powered with sufficient DTG exposures to detect rare events (>500 and <190 respectively), there have been no NTDs reported.

The APR has received reports of over 1800 exposures to DTG in pregnancy resulting in live births. Data from the APR through 31 July 2024 do not demonstrate an increased risk of overall birth defects with DTG use above population expected rates of birth defects. [APR 2024].

Birth defects were reported in 38/1160 live births with first trimester DTG exposure. The first trimester prevalence rate was 3.3% (95% CI: 2.3, 4.5). Birth defects were reported in 31/642 second/third trimester DTG exposures with a prevalence rate of 4.8% (95% CI: 3.3, 6.8). Overall, 69/1802 (3.8%) birth defects were reported with any DTG exposure, compared with population expected rates from birth defects registries of 2.7% (MACDP, Atlanta) and 4.2% (TBDR, Texas). Therefore APR data have not demonstrated an increased risk of overall birth defects, or by trimester of exposure, with DTG use compared with population-based surveillance systems [APR 2024].

The APR has received reports of over 13,200 exposures to lamivudine during pregnancy resulting in live births. These consist of over 5700 exposures during the first trimester, over 7550 exposures during the second/third trimester and included 174 and 219 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to lamivudine in the first trimester was 3.0% (2.6%, 3.5%) and in the second/third trimester, 2.9% (2.5%, 3.3%). [APR 2024]

Other studies including literature and VH database information reviewed, did not show any evidence of NTDs that would contradict the primary data from the birth outcome driven African studies mentioned above. Further studies are currently ongoing to collect

additional information on the use of DTG during pregnancy (see Part III for further information). Use in pregnancy is considered Missing Information for the DTG single entity. Information on the use of DTG in pregnancy is provided in the TIVICAY RMP and information on pregnancy exposures with both DTG and 3TC are provided in the PBRER.

Information on the use of the DTG/3TC FDC in pregnant and breastfeeding women is provided in the SmPC (see Section 4.6; Module 1.3.1).

Population in need of further characterisation:

As clinical experience of the use of the DTG/3TC FDC during pregnancy is limited it is not possible to fully define the benefit/risk in this patient population, although there is information on the use of single entities in pregnancy. Further information is required to understand the safety profile (e.g. pregnancy outcomes and risk of birth defects) in pregnant women taking the DTG/3TC FDC.

The MAH is supporting a number of studies that will provide additional data regarding the use of DTG-containing products in pregnancy (described in the DTG RMP).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	DTG ➢ Neural tube defects
Missing information	DTG/3TC ➢ Use in pregnancy/breastfeeding

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are required for the following:

Specific adverse reaction follow-up questionnaires for neural tube defects

- Neural tube defects are a potential risk in infants whose mothers were exposed to DTG-based ART at the time of conception. A Targeted follow-up questionnaire (TFQ) for cases reporting NTDs has been created for all DTG containing products to ensure the collection of consistent detailed information on these events and the pregnancy exposure. A copy of the TFQ is provided in ANNEX 4

Other forms of routine pharmacovigilance activities

- Review of data from ongoing/planned external and MAH supported studies investigating the use of the DTG component during pregnancy (as described in the DTG RMP) will be reviewed as part of routine pharmacovigilance for all DTG-containing products. Results will be provided to regulatory agencies as appropriate as they become available.

III.2 Additional pharmacovigilance activities

The following ongoing category 3 study is applicable for the DTG/3TC FDC. In addition, the risk of NTD has ongoing additional pharmacovigilance activities collecting data on the DTG component of the DTG/3TC FDC; these studies are described in the DTG RMP.

ANTIRETROVIRAL PREGNANCY REGISTRY (APR)

Study short name and title:

Antiretroviral Pregnancy Registry (APR)

Rationale and study objectives:

The APR is an international registry that monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a MAH sponsored study involving the collaborative effort of multiple companies [Antiretroviral Pregnancy Registry, APR is a MAH sponsored study involving the collaborative effort of multiple companies [Antiretroviral Pregnancy Registry, 2024].

Data from the APR will be used to monitor use of the DTG/3TC FDC or combination of single entities (DTG and 3TC) in pregnancy.

Study design:

Clinicians register pregnant women with prenatal exposures to any ARV before the outcome of pregnancy is known, report data on exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential. Defects are reviewed by a teratologist, and all data are reviewed semiannually by an independent Advisory Committee. Exposure is classified and analysed by the earliest trimester of exposure to each individual ARV medication. Birth defect prevalence (any pregnancy outcome > 20 weeks of gestation with a defect/live births) is compared to both internal and external comparator groups. The external comparators used are two population-based surveillance systems – Metropolitan Atlanta Congenital Defects Program (MACDP) [Correa, 2008; Correa-Villasenor, 2003] by the CDC and the Texas Birth Defects Registry (TBDR) [TBDR, 2013]. Internal comparators include exposures to other drugs and exposures in the 2nd or 3rd trimester of pregnancy relative to 1st trimester exposures when organogenesis occurs.

Study population:

Annually, the Registry enrolls approximately 1000 pregnant women exposed to antiretroviral drugs for the treatment of HIV and HBV infection and prevention of HIV infection. During the last 6 month report period, 471 new prospective enrolments were received bringing the total number of enrolled people to 27,338. [Antiretroviral Pregnancy Registry, 2024]

Milestones:
The registry reviews data every six months and publishes interim reports semi-annually summarising the data. These updated data from the APR are presented in the DTG PBRER. The semiannual interim report doesn't differentiate ARV exposures at conception from post conception-first trimester exposures. The MAH will work with the APR to conduct additional analyses to provide data on DTG exposure at conception among prospectively reported pregnancies.

Data Summary:

As of 31 July 2024, birth defects were reported in 38 out of 1160 live births with first trimester DTG exposure with a first trimester prevalence rate of 3.3% (95% CI: 2.3, 4.5). Birth defects were reported in 31 out of 642 second/third trimester DTG exposures with a prevalence rate 4.8% (95% CI: 3.3, 6.8). Overall, 69/1802 (3.8%) birth defects were reported with any DTG exposure, compared with population expected rates from birth defects registries of 2.7% (MACDP, Atlanta) and 4.2% (TBDR, Texas). The number of pregnancies enrolled in the APR with DTG peri-conception exposure are currently insufficient for definitive conclusions of any potential association of DTG with NTDs. APR data have not demonstrated an increased risk of overall birth defects, or association by trimester of exposure, with DTG use compared with population-based surveillance systems. The APR has received reports of over 13,200 exposures to 3TC during pregnancy resulting in live births. These consist of over 5,700 exposures during the first trimester, over 7,550 exposures during the second/third trimester and included 174 and 219 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to lamivudine in the first trimester was 3.0% (2.6%, 3.5%) and in the second/third trimester, 2.9% (2.5%, 3.3%).

III.3 Summary Table of additional Pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities*				
Antiretroviral Pregnancy Registry (APR) Ongoing	Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnancy, Neural tube defects	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the PBRER.	-

*The NTD risk has ongoing additional pharmacovigilance activities collecting data on the DTG component of the DTG/3TC FDC; these studies are described in the DTG RMP

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorization efficacy study required for this product.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Safety concern (risk/ missing information)	**Routine risk minimisation activities**
Neural tube defects (Potential Risk)	**Routine risk communication:** Information on NTDs are included in section 4.6 of the SmPC and is aligned with the TIVICAY SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for use of DTG containing products in women of childbearing age is included in section 4.6 of the SmPC. **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV.
Pregnant/ breastfeeding women (Missing Information)	**Routine risk communication:** Information on the use of DTG in pregnant/breastfeeding women is included in section 4.6 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for use of DTG containing products in women of childbearing age is included in section 4.6 of the SmPC. **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV.

V.2. Additional Risk Minimisation Measures

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

Removal of additional risk minimization activities

The DHPC was completed in 2018 and therefore has been removed from the EU RMP as this is no longer considered a current additional risk minimization activity for the potential risk of NTD. In addition, the NTD signal has been refuted by the latest data from the Tsepamo and Eswatini Studies, and is supported by the data from the APR and other sources.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern (risk/ missing information)	Risk minimisation measures	Pharmacovigilance activities
Neural tube defects (potential risk)	**Routine risk minimisation measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Target Follow-up questionnaire **Additional pharmacovigilance activities:** Antiretroviral pregnancy registry (APR)*
Pregnant/ breastfeeding women(missing information)	**Routine risk minimisation measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:**None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Antiretroviral pregnancy registry (APR)

* The NTD risk has ongoing additional pharmacovigilance activities collecting data on the DTG component of the DTG/3TC FDC; these studies are described in the DTG RMP

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for DOVATO (dolutegravir/lamivudine)

This is a summary of the risk management plan (RMP) for DOVATO. The RMP details important risks of DOVATO, how these risks can be minimised, and how more information will be obtained about DOVATO's risks and uncertainties (missing information).
DOVATO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how DOVATO should be used.
This summary of the RMP for DOVATO 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 DOVATO's RMP.

I. The medicine and what it is used for

DOVATO is authorised for the treatment of HIV infection (see SmPC for the full indication). It contains dolutegravir and lamivudine as the active substances and it is given as a tablet by mouth.

Further information about the evaluation of DOVATO's benefits can be found in DOVATO'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/dovato

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

Important risks of DOVATO, together with measures to minimise such risks and the proposed studies for learning more about DOVATO'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 healthcare 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 (e.g. with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 DOVATO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of DOVATO 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 DOVATO. 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);

DOVATO is a new medicine that does not contain a new active substance. The identified and potential risks for DOVATO have been taken from the approved TIVICAY (dolutegravir (DTG)) RMP. No new risks have been identified for DOVATO.

List of important risks and missing information	
Important identified risks	None
Important potential risks	<>Dolutegravir ➢ Neural tube defects
Missing information	<>Dolutegravir/lamivudine ➢ Use in pregnancy/ breastfeeding

II.B Summary of important risks

DOVATO is a new medicine that does not contain a new active substance. The identified and potential risks for DOVATO have been taken from the approved TIVICAY (dolutegravir) EU-RMP. No new risks have been identified for DOVATO.

The safety information in the proposed Product Information for DOVATO is aligned to the reference medicinal product (TIVICAY).

Additional pharmacovigilance and additional risk minimisation activities (where applicable) for DOVATO are provided in the table below:

Important potential risk: Neural tube defects	
Evidence for linking the risk to the medicine	Preliminary findings from a birth outcomes surveillance study (the Tsepamo Study) conducted in Botswana showed a higher than expected number of neural tube defects (NTDs), among newborns whose mothers were exposed to dolutegravir -based antiretroviral therapy at conception. Review of further data from large observational studies (Eswatini and Tsepamo) also with other sources such as APR, literature and MAH database as well as the completed DOLOMITE EPPICC study, have refuted this signal.
Risk factors and risk groups	Although the exact timing of types of defect may not be known, it is thought they occur early in pregnancy and therefore the potential risk would concern women exposed to dolutegravir at the time of conception and first trimester of pregnancy. The exact causes of NTDs are not known but environmental and genetic factors are known to play a part. Risk factors include: folate and Vitamin B12 deficiency, obesity, diabetes, certain medicines such as some anti-epileptic medications (e,g, sodium valproate, carbamazepine), maternal age and hyperthermia/febrile illness. There is no evidence that NTDs occur more commonly in women living with HIV. Taking folic acid, before and during pregnancy is known to substantially reduce the occurrence of neural tube defects, by up to 70%.

Risk minimization measures	Routine risk minimisation measures. Section 4.6 of the SmPC Additional risk minimization measures: No additional risk minimization measures
Additional pharmacovigilance activities*	Antiretroviral pregnancy registry (APR) See section II.C of this summary for an overview of the post-authorization development plan

* The risk of NTD has additional pharmacovigilance activities collecting data on the dolutegravir component of the DTG/3TC FDC; these studies are described in the Dolutegravir RMP

Missing Information: Use in Pregnancy and Breastfeeding	
Risk minimization measures	Routine risk minimisation measures Section 4.6 of the SmPC Additional risk minimization measures: None
Additional pharmacovigilance activities	Antiretroviral pregnancy registry (APR) See section II.C of this summary for an overview of the post-authorization development plan

II.A Post-authorisation development plan

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

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

II.B Post-authorisation development plan

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

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

II.B.2 Other studies in post-authorisation development plan*

Study/Activity (including study number)	Objectives	Safety concerns/efficacy issue addressed	Status	Planned date for submission of (interim and) final study results
Antiretroviral Pregnancy Registry (APR)	Monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnancy, Neural tube defects	Ongoing	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the Periodic Benefit Risk Evaluation Report (PBRER).

*The NTD risk has ongoing additional pharmacovigilance activities collecting data on the dolutegravir component of the DTG/3TC FDC; these studies are described in the Dolutegravir RMP

PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific adverse reaction follow-up questionnaire for:

- Neural tube defects

Targeted Follow Up Questionnaire

Dolutegravir; Dolutegravir/abacavir/lamivudine; Dolutegravir/rilpivirine; Dolutegravir/lamivudine and Neural Tube Defects

Patient/subject ID: **DOB/initials:**	**Sex/weight/(is patient obese if weight unknown)** **/Body Mass Index (if known):**	**GSK CASE No:**

Description of the Event:

	Yes	**No**
Was there a neural tube defect? If yes, please describe type, nature and outcome	☐	☐
Did the pregnancy go to full term? If the pregnancy resulted in a spontaneous abortion/miscarriage, please provide week of gestation this occurred.	☐	☐
Were there any other adverse events? If yes, please specify	☐	☐
Please provide information on antiretroviral drug exposure at time of conception and during pregnancy? Specify all drugs and start and stop dates relevant to pregnancy		
If the suspect drug was discontinued, was it subsequently restarted? If *yes*, please specify date and outcome:	☐	☐

Diagnostic Tests:

Please provide a summary of main results of abnormal laboratory values / investigations (or provide copies of relevant results):

	Yes	**No**
Was an ultrasound performed? If yes, please indicate date and results:		

Was the triple or combined screening test performed? If yes, please indicate date and results:	☐	☐
Were any other relevant laboratory investigations such as genetic tests, free fetal DNA performed? If yes, please indicate date and results:	☐	☐
Please provide relevant information regarding the diagnosis method for the neural tube defect		

History:

Social:

Is there a history or current use of (please include details, frequency and amount):	**Yes**	**No**
Smoking	☐	☐
Alcohol	☐	☐
Recreational drugs	☐	☐
Occupation: Please provide details		

Medical history

Is there a family history of birth defects? If yes, please provide details	☐	☐
Is there a history of: (If yes, please provide details)	**Yes**	**No**
Diabetes	☐	☐
Epilepsy	☐	☐
Other relevant history: Please provide details	☐	☐

HIV specific medical history (please provide details)		
Date of initial diagnosis of HIV		
Viral load, CD4 count, CD4 nadir		
Toxoplasma/CMV		
Tuberculosis and Tuberculosis therapy		
Concurrent medications (Please provide drug and duration of use relative to pregnancy)		
Sodium valproate		
Opioids		
Obstetric history		
Serology: Rubella/CMV/toxo/HSV/HCV and HBV Please provide details		
Antenatal screening. Please provide details		
Combined test (age, nuchal, PAPP-A, BHCG		
Triple test: AFP, BHCG, UE3		
Anomaly scan		
Please provide detail of folate use.		
Number of live births (Please provide GP+2 [G is gravida (amount of times pregnant), P is number of live births, with +2 relating to any other pregnancy e.g. medical termination or miscarriage). For live births please provide gestational age.		
Number of spontaneous abortions		
Number of elective terminations		
Previous birth defects including neural tube defects		
Was there exposure to any antiretroviral before or during the previous pregnancies? If yes, please confirm antiretroviral and outcome.		

Travel history to area where Zika prevalent		
	Yes	**No**
Is there history of travel to an area where Zika is prevalent? If yes, please provide Zika Serology	☐	☐

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.