Module 1.8.2

European Union Risk Management Plan (EU-RMP) for JULUCA (dolutegravir/rilpivirine)

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	9.0
Data lock point for this RMP	28 February 2025
Date of final sign off	15 May 2025

Rationale for submitting an updated RMP
The RMP has been updated to include the 2024 Antiretroviral Pregnancy Registry data. Update to the submission date for the final CSR for category 3 PASS study DOLOMITE-NEAT ID (208759) to September 2026. Post-authorisation exposure data updated to latest available data. Aligned with other DTG-containing products to include overall exposure and EU exposure.

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in EU-RMP version 9.0**
PART I: Product(s) Overview		No change
PART II: Safety Specification	Module SI: Epidemiology of the Indication(s) and target population(s).	No change.
	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	Post-authorisation exposure data updated. Aligned with other DTG-containing products to include overall exposure and EU exposure.

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in EU-RMP version 9.0**
	Module SVI: Additional EU requirements for the safety specification	No change.
	Module SVII: Identified and Potential Risks.	Updated to add 2024 Antiretroviral Pregnancy Registry data.
	Module SVIII: Summary of Safety Concerns	No change.
PART III: Pharmacovigilance Plan (including post authorisation safety studies).		Update to DOLOMITE NEAT ID (208759) Category 3 PASS study CSR submission date. Updated 2024 Antiretroviral Pregnancy Registry 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		Update to DOLOMITE NEAT ID (208759) Category 3 PASS study CSR submission date.
Part VII: Annexes		No change.

Other RMP versions under evaluation		
RMP Version number	Submitted on	Procedure number
Not applicable		

Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
8.0	EMEA/H/C/WS2620	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
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
EU	European Union
EU-RMP	European Union-Risk Management Plan
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
HIV-1	Human immunodeficiency virus type 1
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
PI	Protease inhibitor
PIP	Paediatric investigation plan
PK	Pharmacokinetics
RAL	Raltegravir
aRMM	Additional 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
TDF	Tenofovir disoproxil fumarate
TdP	Torsades de Pointes
TFQ	Targeted follow up questionnaire
UGT	Uridine diphosphate glucuronosyl transferase
VH	ViiV Healthcare UK Limited
3TC	Lamivudine

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 Product Overview

Active substance(s) (INN or common name)	Dolutegravir and rilpivirine
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Antiviral for systemic use, Antivirals for treatment of HIV infections, combinations ATC Code: J05AR21
Marketing Authorisation Holder	ViiV Healthcare Limited (VH)
Medicinal products to which this RMP refers	Dolutegravir/rilpivirine fixed dose combination
Invented name(s) in the European Economic Area (EEA)	JULUCA
Marketing authorisation procedure	Centralised
Brief description of the product	Dolutegravir/rilpivirine 50 mg/25 mg fixed dose combination (DTG/RPV FDC) is a single tablet containing one integrase strand transfer inhibitor (INSTI) (DTG) and one diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (RPV). 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. RPV is mediated by non-competitive inhibition of HIV type 1 (HIV-1) reverse transcriptase. RPV does not inhibit the human cellular DNA
Reference to the Product Information	Please refer to product information (section 1.3.1 of the eCTD).

Indication(s) in the EEA	Current: JULUCA is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose of Juluca is one tablet once daily. Juluca must be taken with a meal. Separate preparations of dolutegravir or rilpivirine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases, the physician should refer to the Summary of Product Characteristics for these
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablet (tablet) Pink, oval, biconvex tablets, approximately 14 x 7 mm, debossed with 'SV J3T' on one side Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir and rilpivirine hydrochloride equivalent to 25 mg rilpivirine.
	Proposed: Not applicable
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 the DTG/RPV FDC is a fixed dose combination that does not contain a new active substance, and as RMPs are available for each of the components of this FDC for the same disease, this module has not been populated as there is no new epidemiology information specific to the DTG/RPV FDC. Please refer to the latest approved DTG and RPV EU RMPs 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/RPV FDC. Please refer to the latest approved DTG and RPV EU RMPs for the latest non-clinical information for the single entities.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The safety specification for the DTG/RPV FDC in adult subjects supporting the initial application involved 2 ongoing Phase III clinical trials using DTG 50 mg + RPV 25 mg together as individual tablets.

The MAH has also undertaken a bioequivalence study (201676) to confirm that the DTG/RPV FDC tablet is equivalent to DTG and RPV given as two separate tablets together, and a relative bioavailability study (201674), both studies were in healthy adult volunteers.

The Phase I open-label randomised two-way crossover study (201676) evaluated the bioequivalence between the DTG/RPV FDC 50 mg/25 mg tablet formulation compared to co-administration of the separate tablet formulations of DTG 50 mg and RPV 25 mg in healthy adult volunteers in the fed state.

Bioequivalence was confirmed in terms of both DTG and RPV for the FDC tablet formulation of DTG/RPV 50 mg/25 mg compared to separate tablet formulations of DTG 50 mg plus RPV 25 mg, when administered after a moderate fat meal. The safety results showed that dosing with the DTG/RPV FDC tablet and separate DTG and RPV tablets did not lead to any noted differences in reported adverse events (AEs) or laboratory changes, and both treatments were well tolerated.

A Phase I drug interaction study (LAI116181) has also evaluated the pharmacokinetics and safety of DTG and RPV in healthy adult subjects. This study has shown that there are no significant interactions between DTG and RPV.

In the Phase I studies, 189 healthy volunteers were exposed to co-administered DTG and RPV as follows:

- In 201676 (Phase I bioequivalence study), 113 subjects received a single dose of study drug in each of two treatment periods (DTG/RPV FDC in one period, and DTG + RPV single tablets taken together in the other period)
- In 201674 (Phase I bioavailability study), 60 subjects received single doses of the study drug in each of 3 treatment periods (DTG + RPV in one period and the DTG/RPV FDC in two periods)
- In LAI116181 (Phase I drug interaction study), 16 subjects received DTG + RPV once daily for 5 days (all subjects completed 5 days of treatment).

Two identical Phase III clinical trials (201636 (SWORD-1) and 201637 (SWORD-2)) investigating a switch to DTG 50 mg + RPV 25 mg administered as separate tablets compared to continuation of current antiretroviral regimen (CAR) are now complete. Subjects who were enrolled were on a stable suppressive CAR containing 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either an integrase inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI). Eligible subjects were randomised 1:1 to continue their CAR or be switched to the 2-drug regimen DTG + RPV administered daily. At Week 52 subjects randomised to continue their CAR in the Early Switch Phase and who remained virologically suppressed and in the clinical

trial were switched to DTG + RPV. Data up to Week 148 and data from Week 148 through the end of study during the Continuation Phase have now been analysed from these studies.

- In 201636 (SWORD 1), 508 participants received at least 1 dose of study medication: 252 participants on DTG+RPV and 256 participants on CAR. Of the 256 participants randomized at Day 1 to remain on CAR, 238 participants switched to DTG + RPV at Week 52 for the Late Switch Phase and 183 participants entered the Continuation Phase (after Week 148). Of the 252 participants randomised at Day 1 to start treatment with DTG + RPV, 239 continued treatment during the Late Switch Phase (Weeks 52 to 148) and 186 participants entered the Continuation Phase (after Week 148).
- In 201637 (SWORD 2), 516 participants received at least 1 dose of study medication: 261 participants on DTG+RPV and 255 participants on CAR. Of the 255 participants randomized at Day 1 to remain on CAR, 239 participants switched to DTG + RPV at Week 52 for the Late Switch Phase and 204 participants entered the Continuation Phase (after Week 148). Of the 261 participants randomised at Day 1 to start treatment with DTG + RPV, 245 continued treatment during the Late Switch Phase (Weeks 52 to 148) and 208 participants entered the Continuation Phase (after Week 148).

A sub-study (202094) which enrolled subjects from these two-Phase III clinical trials is now complete. This study evaluated the change in bone mineral density of those subjects who have switched from a tenofovir (TDF) containing regimen to DTG + RPV compared to those who remained on a TDF containing current regimen. No additional investigational product was administered as part of this sub-study. Subjects enrolled in the sub-study received their investigational product in the parent studies (201636 and 201637).

A Phase I/II paediatric study (205868) of switching to DTG/RPV FDC among virologically suppressed children, 6 to less than 12 years of age, living with HIV-1 is ongoing.

The pooled cumulative subject exposure to DTG+RPV single entity shown in Table 1 below includes data from completed studies 201636 and 201637 (SWORD 1 and 2) only.

Table 1 Cumulative Number of Subject Exposure to Dolutegravir + Rilpivirine Given as the Single Entity from SWORD Studies 201636 and 201637 by Age, Sex and Racial Group[a]

	SWORD-1 and SWORD-2[b]
Total	990
Age (yrs)	
<18	0
18 – 64	959
65 – 74	25
>=75	6
Sex	
Male	774
Female	216
Racial Group	
African American/African Heritage	80
American Indian or Alaskan Native	25
Asian - Central/South Asian Heritage	0
Asian - East Asian Heritage	0
Asian - Japanese Heritage	87
Asian - South East Asian Heritage	0
Native Hawaiian or Other Pacific Islander	2
White - Arabic/North African Heritage	0
White - White/Caucasian/European Heritage	793
White – Mixed race	0
Missing	0
Mixed race	3

a. Data as of 17 October 2023.
b. The table includes 238 subjects who switched from current antiretroviral regimen (CAR) to DTG in study 201636 and 239 subjects who switched from CAR to DTG in study 201637 at week 52 for the Late Switch Phase.

The tables below show cumulative subject exposure to DTG/RPV FDC from phase 1-3 studies.

Table 2 Cumulative Number of Dolutegravir/rilpivirine FDC Subjects from Ongoing and Completed VH-Sponsored Interventional Studies[a]

Phase / Study / Treatment	Number of Subjects Exposed		
	Ongoing Studies	Completed Studies	Total
Phase 1 and 2a - Total (including comparator and placebo)	1	194[b,c]	195[b,c]
201674			
Dolutegravir/rilpivirine FDC	0	63[b]	63
201676			
Dolutegravir/rilpivirine FDC	0	115[c]	115
212312			
Dolutegravir/rilpivirine FDC	0	16	16
205868[f]			
Dolutegravir/rilpivirine FDC	1	0	1
Phase 2b/3/3b/4 - Total (including placebo/comparator)	0	149[d,e]	149[d,e]
209035			
Dolutegravir/rilpivirine FDC	0	7	7
Long acting cabotegravir/rilpivirine	0	091	91
201636			
Dolutegravir/rilpivirine FDC	0	26[d]	26
201637			
Dolutegravir/rilpivirine FDC	0	25[e]	25
TOTAL Dolutegravir/ rilpivirine FDC	1	252[b,c,d,e]	253[b,c,d,e]

Abbreviations: DTG – dolutegravir, RPV – rilpivirine, FDC – fixed dose combination

a. Data as of 17 October 2023. Note: Table only includes studies using the DTG/RPV FDC. Data from studies 201636 and 201637 (SWORD 1 and 2) which supported the marketing authorisation application of DTG/RPV FDC (JULUCA), and which used DTG and RPV as the single entities (SE), are included in Table 1

b. Subjects also received DTG+RPV SE (see Table 1).

c. This was a cross-over study where a total of 118 subjects participated, of which 113 completed both periods. A total of 115 subjects completed Treatment A (DTG/RPV FDC) and 116 completed Treatment B (DTG+RPV SE).

d. A total of 26 subjects from DTG+RPV SE switched to DTG/RPV FDC

e. A total of 25 subjects from DTG+RPV SE switched to DTG/RPV FDC

f. This is a Phase 1/2 study of switching to DTG/RPV FDC among virologically supressed children, 6 to less than 12 years of age living with HIV-1.

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

	Number of Subjects
Total	252
Age (yrs)	
<18	0
18 – 64	252
65 – 74	0
>=75	0
Sex	
Male	171
Female	81
Racial Group	
African American/African Heritage	55
American Indian or Alaskan Native	1
Native Hawaiian or Other Pacific Islander	2
Asian – Japanese Heritage	16
White - White/Caucasian/European Heritage	174
Mixed race	4

a. Data as of 17 October 2023.
b. The completed VH sponsored interventional studies included in this table are 209035, 201674, 201676, 201636, 201637 and 212312.

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

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

Important exclusion criteria in the Phase III DTG + RPV 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 to the study drugs or their components or drugs of their class	Hypersensitivity (HSR) is a rare but recognized risk for antiretroviral therapy (ART) containing DTG, regardless of dose.	NO	Overall the risk of HSR with the DTG/RPV FDC was low in the clinical development programme and it is anticipated to remain low post marketing, particularly the risk of serious HSR. As part of routine risk minimisation the DTG/RPV FDC is contraindicated in anyone with hypersensitivity to DTG, RPV or to any of the excipients and a warning around HSR is included in section 4.4 of the Summary of Product Characteristics (SmPC).

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Use of dofetilide and pilsicainide (pilsicainide is not available in the EU)	DTG may inhibit renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity. Included as a contraindication in the SmPC	NO	As concomitant use of the DTG/RPV FDC and dofetilide is contraindicated, events resulting from this drug interaction are anticipated to be very rare. Additionally, dofetilide is used infrequently due to risk for ventricular tachyarrhythmias. Use of dofetilide in HIV patients is thought to be low as this population is not at a particularly increased risk for [persistent] atrial fibrillation and flutter [after cardioversion], which is the indication for this drug.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Use of the following prohibited medicines: • the anticonvulsants carbamazepine, oxcarbamazepine, phenobarbital and phenytoin • the antimycobacterials rifampicin and rifapentine • proton pump inhibitors such as omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole • St. John's wort (Hypericum perforatum). • Systemic dexamethasone	Co-administration may significantly decrease DTG or RPV plasma concentrations. Included as a contraindication in the SmPC	NO	Contraindication in the SmPC

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Subjects in the clinical trials had to be suppressed on their current ART regimen with a viral load <50 c/mL. Subjects needed to have documented evidence of at least two plasma HIV-1 RNA measurements <50 c/ml in 12 months prior to screening; one within the 6 to 12 month window and one within 6 months of screening. Subjects must have been on uninterrupted current regimen (either initial or second cART regimen) for at least 6 months prior to screening.	This study entry criterion ensured that subjects who enrolled into the study and onto both arms were balanced and similar.	NO	There are no plans currently to study the excluded population which is why it is not considered missing information for the DTG/RPV FDC. This exclusion criteria aligns with the indication (see Part I).

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
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 are limited data from the use of DTG and RPV in pregnant women (see SVII.3.2) There is an increasing amount of data from the use of DTG in pregnant women. (see SVII.1.2). RPV in combination with a background regimen has been evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. RPV was well tolerated during pregnancy and postpartum. Virological response was preserved throughout the trial and no mother to child transmission occurred.
Evidence of an active Centers for Disease Control and Prevention (CDC) Category C disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm^3 Evidence of ongoing malignancy.	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	There are no plans currently to study this population which is why it is not considered missing information for the DTG/RPV FDC.

Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh Classification	Pharmacokinetic (PK) studies investigating the use of DTG and RPV have only been performed in subjects with mild and moderate hepatic impairment (class A and B).	NO	There was no change in DTG PK in patients with moderate hepatic impairment in a single dose PK study, and therefore no expected change in subjects with mild hepatic impairment. Multiple dose exposure (area under the concentration curve (AUC)24h) of RPV was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of DTG has not been studied; however, uridine diphosphate glucuronosyl transferase (UGT)1A1 is generally less affected by hepatic impairment compared to CYP3A4. Thus, exposure in subjects with severe hepatic impairment is not expected to be significantly different than those with moderate impairment. There are no plans currently to study this population which is why it is not considered missing information for the DTG/RPV FDC.
Subjects positive for hepatitis B virus (HBV) at screening	HBV co-infected subjects were excluded from the Phase III clinical trials due to the	NO	There are no plans currently to study this population which is why it is not considered missing

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	current treatment guidelines which recommend the use of TDF with either emtricitabine (FTC) or lamivudine (3TC) to effectively treat both HBV and HIV. Use of these medications would mean that subjects were no longer on a dual-regimen to treat their HIV.		information for the DTG/RPV FDC. It is considered unlikely that treating physicians would switch HBV co-infected patients stable on TDF/FTC or TDF + 3TC containing ART to the DTG/RPV FDC. Theoretically, HBV co-infection could still be effectively maintained by adding TDF to the DTG/RPV FDC. Patients becoming newly HBV infected on the DTG/RPV FDC may have to switch to a TDF/FTC or TDF + 3TC containing regimen.
Anticipated need for hepatitis C virus (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	There are no plans currently to study this population which is why it is not considered missing information for the DTG/RPV FDC.
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	Depression, including suicidal ideation and behaviour particularly in patients with a pre-existing history of depression or psychiatric illness is an identified risk for the DTG/RPV FDC.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Use of medications associated with Torsades de Pointes (TdP) or subjects with corrected QT interval (QTc (Bazett)) >450 msec or QTc (Bazett) >480 msec for subjects with bundle branch block	Due to a risk of QT prolongation with supratherapeutic doses of RPV (75 mg and 300 mg once daily), subjects with a prolonged QT at screening were excluded from the studies at the request of the Food and Drug Administration (FDA).	NO	QT interval prolongation is a potential risk for the DTG/RPV FDC that is not categorized as important. The DTG/RPV FDC SmPC includes a warning that it should be used with caution when co-administered with medicinal products with a known risk of TdP.

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

The 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.

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

Table 4 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant and breast feeding women	No studies have been conducted with the DTG/RPV FDC in pregnant women and pregnant and breastfeeding women were excluded from the Phase III DTG + RPV clinical trials. Subjects that became pregnant (intrauterine) regardless of termination status of the pregnancy were required to discontinue from the trials. At the time of the marketing authorization application (MAA) (up to 16 January 2017), four pregnancies had occurred in patients receiving

Type of special population	Exposure
	DTG + RPV in the two Phase III clinical trials. See SVII.3.2 for further information on exposures during pregnancy.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with severe hepatic impairment (Child Pugh score C) were excluded from the two Phase III DTG + RPV clinical trials.
Patients with renal impairment	Subjects with mild renal impairment (estimated glomerular filtration rate (eGFR) 60 - <90 ml/min/1.73m^2, DTG + RPV 138, 27%, CAR 131, 26%) or moderate renal impairment (eGFR 30 - <60 ml/min/1.73m^2, DTG + RPV 6, 1%, CAR 4, <1%) were enrolled into the Phase III DTG + RPV clinical trials. No subjects with severe renal impairment (eGFR <30ml/min/1.73m^2) were enrolled (Data Source: ISO Table 1.803).
Patients with a disease severity different from inclusion criteria in clinical trials	The majority of subjects who enrolled into the Phase III DTG + RPV clinical trials were CDC Category A, but there were a number of subjects who were CDC category B and C at baseline (approximately 10% in each category in each arm) (Table 4).
Population with relevant different ethnic origin	The Phase III DTG + RPV clinical trials were conducted internationally. Although the majority of subjects in the clinical trials were white, no ethnicities were excluded (Table 3).
Subpopulations carrying relevant genetic polymorphisms	Subjects with genetic polymorphisms were not excluded from the Phase III DTG + RPV clinical trials.

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/RPV.

SV.1.1 Method used to calculate exposure

Post-marketing exposure was based on IQVIA sales volume data (IQVIA data can be up to 6 months in arrears from the cut-off date). The algorithm used to derive post-approval exposure data from IQVIA assumes a standard dose of DTG/RPV FDC of 50 mg/25 mg once daily.

SV.1.2 Exposure

Cumulative post-marketing exposure to DTG/RPV to 31 December 2024 is estimated to be 246,206 patient years.

In the EU/EEA* total cumulative exposure to 31 December 2024 is 113,479 patient-years.

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

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

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

As the DTG/RPV FDC is a fixed dose combination that does not contain a new active substance, and as RMPs are available for each of the components of this FDC, this module has not been populated as there is no new information specific to the DTG/RPV FDC. Please refer to the latest approved DTG and RPV 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/RPV FDC is a fixed dose combination that does not contain a new active substance. The following identified and potential risks for DTG and RPV are applicable to the DTG/RPV FDC and have been taken from the approved DTG and RPV EU RMPs. Data for the DTG/RPV FDC for each of these risks is included in m.2.7.4 (Summary of Clinical Safety) supporting the original MAA submission on 23 May 2017 for the DTG/RPV FDC. No new risks have been identified specifically for the DTG/RPV FDC.

As the risk of drug resistance for the DTG/RPV FDC is not identical to the risks identified with the single entities, given the differences in the indications, further details on this risk are provided within this EU RMP (see SVII.1.2)

For further information on the other risks please refer to the latest approved DTG and RPV EU RMPs.

Important identified risks	**DTG, RPV** • Depression (including suicidal ideation and behaviours particularly in patients with a pre-existing history of depression or psychiatric illness) • Drug resistance **Identified risk for DTG, potential risk for RPV** • Hepatotoxicity **DTG** • Hypersensitivity • Interaction with dofetilide or pilsicainide
Important potential risks	**DTG, RPV** • Severe or serious rash (Division of AIDS (DAIDS) Grade 3/4) **DTG** • Renal disorders • Rhabdomyolysis • Pancreatitis **RPV** • QT interval prolongation • Blood cortisol decreased

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the Initial RMP for the DTG/RPV FDC

Not all adverse drug reactions (ADRs) of the DTG/RPV FDC are considered important risks in the EU RMP. There are no new ADRs in the SmPC for the DTG/RPV FDC which do not already appear in the SmPCs for the already approved single entities (DTG and RPV). A justification for the non-inclusion of all the ADRs as risks for the DTG/RPV FDC has not been included in this module as this information is already approved for the single entities.

A number of risks currently in the approved EU RMPs for DTG and RPV have not been added as risks for the DTG/RPV FDC. Further information on which risks these are and the reason they are not considered risks for the DTG/RPV FDC is provided below:

GASTROINTESTINAL (GI) DISORDERS AND EROSIONS

- The important potential risk of GI disorders and erosions for DTG has not been added as a potential risk for the DTG/RPV FDC. The risk of GI intolerance and erosions was identified for DTG based on non-clinical findings, but these have not translated into significant clinical findings. As presented in the DTG PBRER, clinical trial data and post-marketing experience to date with DTG do not suggest an increased risk of GI ulceration or intolerance compared to other antiretroviral regimens. Subsequently, the MAH does not consider this a risk for the DTG/RPV FDC and is additionally proposing to remove the risk of GI intolerance and erosions from the DTG EU RMP at the time of the five-year EU renewal.

INCREASED OCCURRENCE OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

- There is no risk of IRIS in the RPV EU RMP. The important potential risk of increased occurrence of IRIS for DTG has not been added as a potential risk as it does not apply to the DTG/RPV FDC. The risk in the DTG EU RMP states '*While rapid HIV-1 RNA decline and early recovery of CD4+ cell counts have been observed with the integrase class and may be advantageous for subjects with profound immune suppression, it could also theoretically lead to increased cases of IRIS.*' Clearly this risk cannot apply to the DTG/RPV FDC since patients' viral loads will already be fully suppressed and their CD4+ cell counts will have been restored before commencement of DTG/RPV FDC therapy. Since prescribers may identify late manifestations of IRIS with any ART regimen, the MAH agrees to include IRIS in the Warnings and Precautions section and also in the Adverse Reactions section of the SmPC. In summary, IRIS is not a particular risk for the DTG/RPV FDC and the risk that applies to all ART is described in the SmPC. Therefore, the MAH considers there is no need to include IRIS as a risk in the RMP for the DTG/RPV FDC.

OVERDOSE

- The important potential risk of overdose for RPV has not been added as a potential risk for the DTG/RPV FDC. Intake of supratherapeutic doses of RPV could occur as a result of an intentional overdose of large quantities of RPV tablets and/or fixed

dose combination tablets containing RPV. There is a potential for an intentional overdose to lead to a clinically significant prolongation of the QT interval. This risk would be captured under the important potential risk of QT interval prolongation. Intentional overdose resulting from a suicidal attempt would be captured under the important identified risk of Depression (including suicidal ideation and behaviours particularly in patients with a pre-existing history of depression or psychiatric illness).

OFF-LABEL USE

- The important potential risk of off-label use for RPV has not been added as a potential risk for the DTG/RPV FDC. Off label use may also occur with the DTG/RPV FDC outside the agreed indication. However, the adverse consequences of off label use would be development of resistance which is already captured under the important identified risk of drug resistance.

BLEEDING DISORDERS

- The important potential risk of bleeding disorders for RPV has not been added as a potential risk for the DTG/RPV FDC. Bleeding disorders are an important potential risk in the Edurant EU RMP and it was included in the RPV EU RMP at the request of the Committee for Medicinal Products for Human Use (CHMP). Decreases in platelet counts were observed in the clinical studies, however, these decreases were also observed in the control groups and were not considered clinically relevant. While earlier RPV clinical studies did not indicate an increase in bleeding disorders for RPV compared to control, and no pattern of abnormalities was observed with coagulation parameters, assessments of coagulation parameters were not performed in the Phase III studies with RPV and therefore, bleeding disorders have been followed as a potential risk in the EU RMP.
- The MAH for RPV does not consider this an important potential risk in the core RMP as clinical trial data and post-marketing experience to date with RPV do not suggest an increased risk of bleeding disorders with RPV use. Since initial Edurant marketing authorization in 2011, there has been no signal for bleeding disorder or haemorrhage in subsequent clinical trials, other studies or postmarketing experience. As reported in the most recent RPV PBRER (with data lock point (DLP) 19 May 2017) there were cumulatively three spontaneous cases identified in the Janssen Global Safety database within the Haemorrhages Standardised Medical Dictionary for regulatory activities (MedDRA) Query (SMQ) (Broad), and none of the cases provided evidence of a causal relationship between RPV and bleeding. Please refer to the RPV PBRER for further information.
- The MAH considers that based on currently available evidence from clinical trials and postmarketing pharmacovigilance activities, there has been no evidence that there is any increased risk of bleeding disorders or haemorrhage in patients taking RPV. The Edurant MAH is planning to propose to remove Bleeding disorders as an important potential risk from the RPV EU-RMP at the next update. The MAH therefore proposes not to include bleeding disorders as a potential risk for the DTG/RPV FDC.

Some pieces of missing information currently in the approved EU RMPs for DTG and RPV have not been added to the EU RMP for the DTG/RPV FDC. Further information on which pieces of missing information this refers to and the reason it is not considered missing information for the DTG/RPV FDC is provided below:

USE IN PATIENTS WITH SEVERE HEPATIC IMPAIRMENT

- Use in patients with severe hepatic impairment has not been added as missing information for the DTG/RPV FDC, although it is considered missing information in both the DTG and RPV EU RMPs. Phase I studies in subjects with mild and moderate hepatic impairment have been conducted for both DTG and RPV. Both studies showed an increase in the exposure, however this was not considered clinically relevant. No dose adjustment of DTG or RPV is necessary in subjects with mild or moderate hepatic impairment. Per EU SmPC RPV is not recommended in patients with severe hepatic impairment and in the DTG EU SmPC it is advised that it is used with caution in patients with severe hepatic impairment. Since there are no data in subjects with severe hepatic impairment and it is difficult to study this population, the DTG/RPV FDC product information advises that Juluca is not recommended in these patients.
- The effect of severe hepatic impairment on the pharmacokinetics of DTG has not been studied; however UGT1A1 is a high capacity enzyme which is less affected by hepatic impairment compared to CYP3A4. Thus, exposure in subjects with severe hepatic impairment is not expected to be significantly different than those with moderate impairment. Although RPV concentrations are increased in patients with mild and moderate hepatic impairment, the increased exposure is not thought to be clinically relevant.
- The new guidance around the removal or reclassification of safety concerns in Good Pharmacovigilance Practice (GVP) Module V states that safety concerns may be removed *'...when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the areas of missing information'*. Therefore, and because the DTG/RPV FDC is not recommended in patients with severe hepatic impairment as per the SmPC, and it is difficult to study this population, the MAH does not consider use in patients with severe hepatic impairment to be missing information for the DTG/RPV FDC. No additional pharmacovigilance activities are proposed to address the use of the DTG/RPV FDC in this population. The MAH will however monitor the use in patients with severe hepatic impairment through routine safety surveillance and pharmacovigilance measures.

USE IN PATIENTS WITH SEVERE RENAL IMPAIRMENT

- Use in patients with severe renal impairment has not been added as missing information for the DTG/RPV FDC, although it is considered missing information in the RPV EU RMP. No Phase I studies have been conducted for RPV in subjects with renal impairment, however a mass-balance study showed that most of the administered 14C-RPV related radioactivity was excreted in faeces with only trace amounts of unchanged RPV detected in the urine. A Phase I study in subjects with

severe renal impairment has been conducted for DTG, which noted a moderate reduction in exposure which was not considered clinically significant. No dose adjustment of DTG or RPV is necessary in subjects with mild or moderate renal impairment. As there are no data available with RPV and co-administration of RPV and medicinal products that inhibit CYP3A has been observed to increase the plasma concentrations of RPV, the DTG/RPV FDC product information advises that: '*In patients with severe renal impairment or end stage renal disease, the combination of Juluca with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk.*'

- Given the new guidance around missing information in GVP Module V, as there are no additional pharmacovigilance activities proposed to address the use of RPV or the DTG/RPV FDC in this population and the product information provides guidance on use in this population, the MAH does not consider use in patients with severe renal impairment to be missing information for the DTG/RPV FDC. No additional pharmacovigilance activities are proposed to address the use of the DTG/RPV FDC in this population. The MAH will however monitor the use in patients with severe renal impairment through routine safety surveillance and pharmacovigilance measures.

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

The DTG/RPV FDC is a fixed dose combination that does not contain a new active substance. The identified and potential risks for the DTG/RPV FDC have been taken from the approved DTG and RPV EU RMPs. No new risks have been identified for the DTG/RPV FDC (see SVII.1).

As the risk of drug resistance for the DTG/RPV FDC is not identical to the risks identified with the single entities, given the differences in the indications, further details on this risk are provided below. For further information on the other risks please refer to the latest approved DTG and RPV EU RMPs.

IMPORTANT IDENTIFIED RISK: DRUG RESISTANCE

All antivirals are prone to the development of resistance in the setting of inadequate combination therapy and/or incomplete adherence to therapy. Protocol-defined confirmed virological withdrawal (CVW) through Week 48 was low in each treatment group, with 2 subjects in each treatment group meeting CVW criteria at any time during the early switch phase. Of these 4 subjects, NNRTI-associated genotypic resistance was observed for 1 subject with adherence issues in the DTG + RPV treatment group, but resistance was not observed for the other 3 subjects. After Week 48 and through Week 100, one subject randomised to the DTG + RPV treatment group met CVW, this subject had baseline NNRTI mutations and had an additional M230M/L mutation at CVW. IN genotype showed no resistance mutations.

Risk-benefit impact:

Drug resistance reduces the therapeutic options for patients.

MISSING INFORMATION 1: USE IN THE ELDERLY (>65 YEARS)

There is limited information regarding the use of the DTG/RPV FDC in the elderly (>65 years old). The majority of subjects in the two Phase III DTG + RPV clinical trials were <65 years of age. Only 18 subjects (4%) on DTG + RPV were 65 years of age or older; 15 subjects were aged 65-74 and 3 subjects were aged 75-84. Population PK analysis conducted with DTG and RPV did not show an effect of age.

Risk-benefit impact:

The PK of the DTG/RPV FDC have not been formally evaluated in the elderly population, however, there is no evidence to suggest that the DTG/RPV FDC would have a different safety profile in elderly patients or that elderly patients require a different dose than younger patients. It is not anticipated that there will be an adverse impact on the risk-benefit profile in these patients.

MISSING INFORMATION 2: USE IN PREGNANCY AND BREAST FEEDING

No studies have been conducted with the DTG/RPV FDC in pregnant women and pregnant and breastfeeding women were excluded from the Phase III DTG + RPV 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/RPV FDC use during pregnancy is therefore limited. Reproductive toxicity is not considered to be a risk for the DTG/RPV FDC based on nonclinical and clinical findings, and Post-marketing experience to date with DTG and RPV.

Risk-benefit impact:

As clinical experience with the use of the DTG/RPV FDC during pregnancy is limited it is not possible to define the risk in this patient population.

MISSING INFORMATION 3: USE IN CHILDREN AND ADOLESCENTS (<18 YEARS)

The safety and efficacy of the DTG/RPV FDC has not been evaluated in children or adolescents.

Risk-benefit impact:

Paediatric studies conducted to date with DTG and RPV have not identified any differences in the paediatric safety profile in children (≥6 to <18 years with DTG and ≥ 12 to <18 years with RPV) compared to adults. The sponsor is planning to conduct a study to evaluate the efficacy and safety of DTG + RPV in children aged ≥6 to >18.

MISSING INFORMATION 4: LONG TERM SAFETY

Experience with long term use of the DTG/RPV FDC is limited. To date no long-term toxicities have been noted in clinical trials or post-marketing for DTG or RPV which have been approved since 2013 and 2011 respectively.

Risk-benefit impact:

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

Data for the DTG/RPV FDC for each of the identified and potential risks are taken from the EU RMPs for the single entities. No new risks have been identified specifically for the DTG/RPV FDC.

SVII.3.2 Presentation of the missing information

USE IN PREGNANCY AND BREAST FEEDING:

Evidence Source:

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

Use in pregnancy and breast feeding is also considered missing information for the DTG and RPV single entities. Further information is provided in the RMPs and the PBRERs for each of the single entities.

The MAH initiated an open-label interventional study for women who become pregnant whilst receiving the DTG/ABC/3TC FDC (Study 200336). The study is an MAH-sponsored, prospective, interventional pharmacokinetic and safety study of DTG/ABC/3TC in Pregnant Women in which DTG/ABC/3TC is being made available to women who inadvertently become pregnant while participating in study ING117172 [open-label, active-controlled, non-inferiority study of DTG in a single tablet regimen as DTG/ABC/3TC compared to atazanavir plus ritonavir and tenofovir disoproxil fumarate/ emtricitabine (fixed dose combination) in women] in order that they may continue to maintain virologic suppression. The study was initiated on 17 December 2014. Only four

women enrolled into the study; all had live births and infant outcomes were normal. Enrollment was placed on hold on 23 May 2018 due to a potential safety issue related to neural tube defects in infants born to women with exposure to DTG at the time of conception. In June 2020, the MAH took the decision to terminate the study as it was unclear if or when the enrolment hold might be lifted, and it was deemed unlikely that there would be further participants eligible for enrolment from study ING117172. Other larger studies were ongoing addressing Use in pregnancy as missing information (see Part III). A final study report was completed on 25 February 2022. The maternal and infant outcome data did not show any risk in the use of DTG/ABC/3TC in pregnancy or to the developing fetus. This study has not resulted in any new or updated safety concerns or missing information.

The DTG/RPV FDC has been added to the list of antiretrovirals (ARVs) monitored by the Antiretroviral Pregnancy registry (APR). The APR was initially established in January 1989 and is an ongoing, collaborative effort of multiple companies [Antiretroviral Pregnancy Registry, 2018]. The objective of the APR is to detect an early signal of any major teratogenic effect of antiretroviral drugs included in the programme. The registry is a passive surveillance system designed to address the effect of ART in neonates exposed to ART in utero. This programme collects voluntary reports of ART exposure during pregnancy, which includes background and risk information and birth outcome associated with antiretroviral drugs, including ViiV Healthcare's marketed antiretroviral products. Registration is voluntary. Healthcare professionals are strongly encouraged to enroll their ART- exposed pregnant patients into the Registry as early in the pregnancy as possible, preferably before prenatal testing is done. Patients are followed through health care providers who provide information on maternal risk factors, pregnancy outcome, and neonatal health. In the month of expected delivery, a short follow-up form is sent to the health care provider to ascertain the pregnancy outcome and completion of the antiviral therapy information. Additional follow-up is not sought from health care providers. Data are reviewed periodically by an advisory board. Data and analysis from the APR relating to DTG and RPV are submitted within the PBRERs for DTG and RPV.

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 were therefore added as a potential risk to the RMPs for the DTG containing products (see Section SVII.2 and the DTG RMP for further information on this risk).

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 also 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. 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 NTDs 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 and ongoing DOLOMITE NEAT ID PASS studies 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.

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 990 exposures to rilpivirine during pregnancy resulting in live births. These consist of 770 exposures during the first trimester, 220 exposures during the second/third trimester and included 15 and 2 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to rilpivirine in the first trimester was 1.9% (1.1%, 3.2%) and in the second/third trimester, 0.9% (0.1%, 3.2%).

Other studies including literature and VH safety 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). Data and analysis from these sources are submitted in the PBRER for DTG/RPV FDC as it becomes available.

Information on the use of the DTG/RPV FDC in pregnant and breastfeeding women is provided in the SmPC.

Population in need of further characterisation:

As clinical experience of the use of the DTG/RPV FDC during pregnancy is limited it is not possible to define the risk in this patient population. Further information is required to understand the safety profile (e.g. pregnancy outcomes and risk of birth defects) in pregnant women taking the DTG/RPV FDC.

Further studies are currently ongoing to collect additional information on the use of the DTG containing products during pregnancy (see Part III for further information).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 6 Summary of safety concerns

Summary of safety concerns The safety profile of DTG taken in combination with RPV is consistent with the safety profile of the single entities, and no additional risks or safety issues due to combination therapy have been identified.	
Important identified risks	None
Important potential risks	**DTG** • Neural tube defects
Missing information	• Use in pregnancy and breast feeding

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:

Specific adverse reaction follow-up questionnaires for NTDs

- 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 **Error! Reference source not found.**.

Other forms of routine pharmacovigilance activities

- Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy will be reviewed as part of routine pharmacovigilance. Results will be provided to regulatory agencies as appropriate as they become available.

III.2 Additional pharmacovigilance activities

The following ongoing category 3 studies in the DTG EU RMP are applicable for the DTG/RPV FDC. Copies of the protocols are provided in ANNEX 3, where available:

ANTIRETROVIRAL PREGNANCY REGISTRY (APR)

Study short name and title:

Antiretroviral Pregnancy Registry

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, 2023].

Data from the APR will be used to monitor use of the DTG/RPV FDC or combination of single entities (DTG and RPV) 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 enrollments 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 summarizing 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 990 exposures to RPV during pregnancy resulting in live births. These consist of 770 exposures during the first trimester, 220 exposures during the second/third trimester and included 15 and 2 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to RPV in the first trimester was 1.9% (1.1%, 3.2%) and in the second/third trimester, 0.9% (0.1%, 3.2%).

DOLOMITE

DOLOMITE, the DTG in pregnancy program is set up to provide comprehensive data on pharmacokinetics, usage, safety and effectiveness of DTG in pregnancy in real world settings in Europe. With PENTA Foundation functioning as the coordinating centre, the MAH is working with two partners, NEAT-ID Network and PANNA Network to design and conduct two studies of DTG in pregnancy; the DOLOMITE NEAT ID Network Study (208759) has the ability to capture pregnancies exposed to DTG at conception. The DOLOMITE EPPICC study which was a Category 3 post-authorisation safety study (PASS) addressing Important Potential Information on 'Neural Tube Defects' has now been completed. This study has not resulted in any new safety concerns or missing information.

Study short name and title:

DOLOMITE NEAT ID Network Study (208759)

A non-interventional, multi-site observational study to define the safety and effectiveness of Dolutegravir use in HIV positive pregnant women

Rationale and study objectives:

The study aims to assess the safety and effectiveness of DTG in pregnancy in a network of approximately 40 sites across Europe and Canada. DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Study design:

Multi-site observational study

Study population:

Data on all consenting, DTG exposed pregnant women since its approval and availability in, from participating clinical sites across Europe and Canada will be included in the study.

Milestones:

Expected Final report: 30 September 2026

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, NTD	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the PBRER.	
DOLOMITE NEAT ID Network Study (208759) Ongoing	To assess the safety and effectiveness of DTG in pregnancy in the NEAT-ID network of approximately 40 sites across Europe.	Use in pregnancy, NTD DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.	Expected Final Report	30 September 2026

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

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern (risk/ missing information)	Routine risk minimisation activities
Neural tube defects (Potential risk for DTG)	**Routine risk communication:** Information on NTDs 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
Use in pregnancy and breast feeding (Missing information)	**Routine risk communication:** Information on the use of DTG/RPV FDC 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/RPV FDC 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.

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 for DTG)	**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 Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy **Additional pharmacovigilance activities:** Review of the APR Study 208759- DOLOMITE NEAT ID Network Study
Use in pregnancy and breast feeding (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:** Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy **Additional pharmacovigilance activities:** Review of the APR Study 208759- DOLOMITE NEAT ID Network Study

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan (RMP) for JULUCA (dolutegravir/rilpivirine)

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

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

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

I. The medicine and what it is used for

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

Further information about the evaluation of JULUCA's benefits can be found in JULUCA'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/juluca

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

Important risks of JULUCA, together with measures to minimise such risks and the proposed studies for learning more about JULUCA'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 JULUCA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of JULUCA 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 JULUCA. 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);

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	**DTG** • Neural tube defects
Missing information	• Use in pregnancy and breast feeding

II.B Summary of important risks

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

The safety information in the Product Information for JULUCA is aligned to the reference medicinal products (TIVICAY and EDURANT).

Additional pharmacovigilance and additional risk minimisation activities (where applicable) for JULUCA 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 new-borns whose mothers were exposed to DTG-based ART 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 minimization measures: Section 4.6 of the SmPC. Additional Risk minimization measures: None
Additional pharmacovigilance activities	Antiretroviral Pregnancy Registry Study 208759 -DOLOMITE NEAT ID Network Study See section II.C of this summary for an overview of the post-authorization development plan

Missing information: Use in pregnancy and breast feeding	
Risk minimization measures	Routine risk minimization measures: Section 4.6 of the SmPC. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry Study 208759 -DOLOMITE NEAT ID Network Study See section II.C of this summary for an overview of the post-authorization development plan

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 JULUCA

II.C.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).
DOLOMITE NEAT ID Network Study (208759)	To assess the safety and effectiveness of DTG in pregnancy in the NEAT-ID network of approximately 40 sites across Europe.	Use in pregnancy Neural tube defects	Ongoing	Final report expected 30 September 2026

PART VII: ANNEXES

LIST OF 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.