Module 1.8.2

European Union Risk Management Plan (EU-RMP) for TRIUMEQ (dolutegravir/abacavir/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	22.1
Data lock point for this RMP	15 May 2023
Date of final sign off	25 March 2024

Rationale for submitting an updated RMP
The RMP has been updated to reflect the extended paediatric indication (for use in children at least 3 months of age and weighing at least 6 kg).

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in the present EU-RMP**
Part I: Product(s) Overview		Updated to reflect the extension of the paediatric indication (for use in children at least 3 months of age and weighing at least 6 kg). In addition, the dispersible tablet dosing table was updated to reflect the weight bands 6 to less than 10 kg and 10 to less than 14 kg.
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	Addition of data from the Week 48 analysis of paediatric study IMPAACT 2019.
	Module SIV: Populations not studied in clinical trials.	Table 8 of Section SIV.3 was updated to reflect extension of the indication for DTG/ABC/3TC for use in children at least 3 months of age and weighing at least 6 kg, as supported by IMPAACT 2019 study data.
	Module SV: Post authorisation experience	Post-authorisation exposure included.

	Module SVI: Additional EU requirements for the safety specification	No change
	Module SVII: Identified and Potential Risks.	No change
	Module SVIII: Summary of Safety Concerns	No change
Part III: Pharmacovigilance Plan (including post authorisation safety studies).		Minor administrative change
Part IV: Plans for post-authorisation efficacy studies		Minor administrative change
Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities).		Minor administrative change
Part VI: Summary of RMP		Summary of important risks has been updated in line with the updated EU-RMP template.

Other RMP versions under evaluation		
RMP Version number	Submitted on	Procedure number
23.0	24 November 2023	EMEA/H/C/xxxx / WS / 2620

Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
21.0	EMEA/H/C/002754/x/0101/G	20 February 2023

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

ABC	Abacavir
ADR	Adverse drug reaction
AE	Adverse Event
APR	Antiretroviral pregnancy registry
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC	Area under the concentration curve
CART	Combined antiretroviral therapy
CHMP	Committee for Medicinal Products for Human Use
CLEE	Chronic liver enzyme elevations
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CVD	Cardiovascular disease
CVE	Cardiovascular event
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir
EMA	European Medicines Agency
ESLD	End stage liver disease
FDC	Fixed dose combination
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practice
HBV	Hepatitis B virus
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HSR	Hypersensitivity reaction
INSTI	Integrase inhibitor
IR	Incidence ratios
IRIS	Immune reconstitution inflammatory syndrome
KS	Kaposi’s sarcoma
LPV	Lopinavir
MAA	Marketing authorization application
MAH	Marketing authorization holder
MI	Myocardial infarction
NHL	Non-Hodgkin’s lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NTD	Neural tube defects
NVP	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitor
OCT	Organic cation transporter
PASS	Post-authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic

PRAC	Pharmacovigilance Risk Assessment Committee
PY	Patient or Person years
RAL	Raltegravir
RCT	Randomised clinical trial
RMP	Risk management plan
RPV	Rilpivirine
RR	Relative rate
SE	Single entity
SmPC	Summary of Product Characteristics
Srr	Summary relative risk
TB	Tuberculosis
TDF	Tenofovir
TFQ	Targeted follow up questionnaire
TP	Triphosphate
VH	ViiV Healthcare Ltd
ZDV	Zidovudine
3TC	Lamivudine

Trademark Information

Trademarks of VHL
TRIUMEQ
TIVICAY
KIVEXA
ZIAGEN
EPIVIR
EPZICOM
COMBIVIR
TRIZIVIR
DOVATO
JULUCA

Trademarks not owned by VHL
Atripla

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 Product Overview

Active substance(s) **(INN or common name)**	Dolutegravir/abacavir/lamivudine fixed dose combination
Pharmacotherapeutic group(s) (ATC Code)	J05AR13
Marketing Authorisation Holder/ Applicant	ViiV Healthcare Limited
Medicinal products to which this RMP refers	Dolutegravir/abacavir/lamivudine
Invented name(s) in the European Economic Area (EEA)	TRIUMEQ
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Dolutegravir/abacavir/lamivudine 50/600/300 mg fixed dose combination (DTG/ABC/3TC FDC) is a single film-coated tablet containing one integrase strand transfer inhibitor (DTG) and two nucleoside analogues (ABC and 3TC). DTG/ABC/3TC FDC is also available as a dispersible tablet formulation (DTG/ABC/3TC 5/60/30 mg). 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. ABC and 3TC are reverse transcriptase inhibitors (NRTIs) and are selective inhibitors of HIV-1 and HIV-2. Both ABC and 3TC are metabolised sequentially by intracellular kinases to the respective triphosphate (TP), which are the active moieties. Lamivudine-TP

	and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their 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. DTG in combination with ABC and 3TC exhibits synergistic anti-HIV activity against clinical isolates in cell culture.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).
Indication(s) in the EEA	Current: Film-coated tablets: Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing at least 25 kg. Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele. Dispersible tablets: Triumeq is indicated for the treatment of HIV infected children weighing at least 14 kg to less than 25 kg. Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele. Proposed indication: Film-coated tablets: Triumeq is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infected adults, adolescents and children weighing at least 25 kg. Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any

<table>
<tr>
<td></td>
<td>HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

Dispersible tablets:
Triumeq is indicated for the treatment of HIV-1 infected children of at least 3 months of age and weighing at least 6 kg to less than 25 kg.

Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.</td>
</tr>
<tr>
<td>Dosage in the EEA</td>
<td>Current:
Film-coated tablets:
Adults, adolescents and children (weighing at least 25 kg): The recommended dose of Triumeq in adults, adolescents and children is one tablet once daily.

Dispersible tablets:
Children (weighing at least 14 kg to less than 25 kg): The recommended dose of Triumeq dispersible tablets is determined according to weight (see Table 1).

Table 1: Dispersible tablet dose recommendations in children weighing at least 14 kg to less than 25 kg
<table>
<tr><th>Body Weight (kg)</th><th>Daily Dose</th><th>Number of Tablets</th></tr>
<tr><td>14 to less than 20</td><td>25 mg DTG, 300 mg ABC, 150 mg 3TC once daily</td><td>Five</td></tr>
<tr><td>20 to less than 25</td><td>30 mg DTG, 360 mg ABC, 180 mg 3TC once daily</td><td>Six</td></tr>
</table>
Proposed:
Film-coated tablets:
Adults, adolescents and children (weighing at least 25 kg): The recommended dose is one</td>
</tr>
</table>

tablet once daily.

Dispersible tablets:
Children (at least 3 months of age and weighing at least 6 kg to less than 25 kg): The recommended dose of Triumeq dispersible tablets is determined according to weight (see Table 1).

Table 1: Dispersible tablet dose recommendations in children at least 3 months of age and weighing at least 6 kg to less than 25 kg

Body Weight (kg)	Daily Dose	Number of Tablets
6 to less than 10	15 mg DTG, 180 mg ABC, 90 mg 3TC once daily	Three
10 to less than 14	20 mg DTG, 240 mg ABC, 120 mg 3TC once daily	Four
14 to less than 20	25 mg DTG, 300 mg ABC, 150 mg 3TC once daily	Five
20 to less than 25	30 mg DTG, 360 mg ABC, 180 mg 3TC once daily	Six

Pharmaceutical form(s) and strengths	Current: Film-coated tablet Purple, biconvex, film-coated oval tablets, approximately 22 x 11 mm, debossed with "572 Trı" on one side. Dispersible tablet Yellow, biconvex, capsule shaped, dispersible tablets, approximately 14 x 7 mm debossed with 'SV WTU' on one side.
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/ABC/3TC FDC is a fixed dose combination that does not contain a new active substance this module has not been populated as there is no new epidemiology information specific to the DTG/ABC/3TC FDC. Please refer to the latest approved RMPs for DTG, ABC and ABC/3TC 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/ABC/3TC FDC. Please refer to the latest approved DTG, ABC and ABC/3TC EU RMPs for the latest non-clinical information for the single entities.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The DTG/ABC/3TC 50/600/300 mg FDC (TRIUMEQ) has been developed as a complete regimen for the treatment of HIV infection in adults, adolescents and children weighing at least 25 kg who are antiretroviral treatment-naïve or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents in TRIUMEQ. A dispersible tablet formulation of DTG/ABC/3TC 5/60/30 mg FDC has been developed, and has been investigated for use in children weighing at least 6 kg.

DTG (TIVICAY) was initially approved as a once daily antiretroviral product for the treatment of HIV-1 infected adults and adolescents (≥12 years old) in combination with other antiretroviral medicinal products. DTG was first approved in Europe on 16 January 2014. DTG (TIVICAY) 5 mg dispersible tablets were subsequently approved in the EU on 11 January 2021 with an indication to treat adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

Abacavir and 3TC are both NRTIs that have been marketed as the single entity products ZIAGEN™ and EPIVIR™ since circa 1998/1999 and 1995/1996, respectively. Regulatory approvals for ABC and 3TC were originally given for twice daily dosing regimens, followed by approvals for once daily dosing. Tablet formulations of ABC and 3TC are approved for use in adults and paediatrics who weigh at least 14 kg while oral solution formulations can be administered to paediatric patients from 3 months of age. ABC and 3TC are also formulated into a fixed dose combination (ABC/3TC FDC) tablet, administered once daily, which has been marketed as EPZICOM™ in the USA and Japan and KIVEXA™ in all other markets since 2004. Abacavir, 3TC and the NRTI zidovudine (ZDV) have also been formulated in the FDC tablets 3TC/ZDV (COMBIVIR™) and ABC/3TC/ZDV (TRIZIVIR™), which have been marketed since 2004 and circa 2000, respectively, for twice daily administration in the treatment of HIV. A comprehensive programme of clinical trials with ABC, 3TC, the ABC/3TC FDC and the other ABC- and 3TC- containing products has previously been evaluated by the Committee for Medicinal Products for Human (CHMP) use throughout the lifecycle of these products.

The safety specification for the DTG/ABC/3TC FDC includes pooled safety analyses from studies involving subjects who were exposed to a once-daily regimen of DTG+ABC/3TC. As DTG is a newly authorised new chemical entity, exposure data for DTG has been presented in addition to data for DTG+ABC/3TC.

Adult Subjects

DTG/ABC/3TC

The safety specification for DTG/ABC/3TC at the time of the initial Marketing authorization application (MAA) included pooled safety analyses from studies involving

subjects who were exposed to a once-daily regimen of DTG+ABC/3TC. The studies in Antiretroviral therapy (ART)-naive subjects are: ING114467, ING113086, ING114915 and ING112276. The safety data from subjects receiving DTG+ABC/3TC were integrated for the initial MAA submission.

A bioequivalence study, ING114580, was conducted to establish a clinical bridge between DTG/ABC/3TC and the co-administration of DTG 50 mg (TIVICAY) plus ABC/3TC 600/300 mg (KIVEXA) in the Phase III studies (ING113086 and ING114467). The treatment phase of study ING114580was divided into two parts (Part A and Part B). Part A consisted of 2 single dose treatment sequences (AB, BA) in a randomized, two-period, crossover design with a ≥7-day washout between doses. Sixty-six subjects were enrolled in Part A. Twelve subjects who completed Part A participated in Part B and received a single dose of the combined formulated tablet administered with a high fat meal (Treatment C). Treatments were as follows:

- Treatment A DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet, fasted
- Treatment B DTG 50 mg tablet plus a single ABC/3TC FDC tablet, fasted
- Treatment C DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet with high fat meal

The results demonstrate that the DTG/ABC/3TC FDC tablet formulation was bioequivalent to the separate tablet formulations.

For ART-experienced (integrase inhibitor (INSTI)-naive) subjects, information on DTG from the Week 48 analysis of all subjects exposed to DTG in study ING111762 is included in the safety specification but safety data from this study is not integrated due to it being a different patient population. ING111762 is a Phase III randomized, double-blind study of the safety and efficacy of DTG 50 mg once daily versus raltegravir (RAL) 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The study design placed 2 limits on the choice of background drugs: the virus had to retain full susceptibility to the drug, and there could only be 1 or 2 active drugs total. As such, few subjects were placed on a DTG + ABC/3TC regimen (N = 9). However, the study provides support for the DTG/ABC/3TC FDC usage in this population, as it demonstrates safety and efficacy in subjects when DTG is combined with an active background regimen.

Limited safety information from study, ING116070 was also provided in the initial MAA since it included once daily use of DTG 50 mg in combination with ABC/3TC 600/300 mg.

The final data cut-off dates for individual studies included in the safety specification at the time of the initial MAA submission are listed in Table 1 below.

Table 1 Exposure to DTG+ABC/3TC in the pivotal and supporting Phase IIb/III/IIIb Studies with Adult Subjects

	Study	Study Time Point of Analysis[a]	Data Cut-off Date[b]	No. on DTG+ABC/3TC
DTG+ABC/3TC - Pivotal and Supportive Clinical Trials				
Studies in ART-Naïve Adults – Integrated analysis	ING114467	Week 96	04 May 2013	414
	ING113086	Week 96	23 January 2013	169
	ING114915	Week 48	22 April 2013	79
	ING112276	Post-Week 96	25 June 2012	17
	ING116070	Week 16	13 November 2012	13
DTG 50 mg component - Registrational and Supportive Clinical Trials				
Studies in ART-Experienced (INSTI-Naïve) Adults	ING111762	Week 48	25 February 2013	9

a. Study time point of analysis is when the last subject has reached the specified visit.
b. This data cut-off date is the date when the data used in the analysis was extracted, except for ING114915. This could either be Database Freeze (DBF) or Database Release (DBR), depending whether a new extraction was needed at DBF. For ING114915, the data cut-off date was Last Subject Last Visit date.

Additional analyses conducted since the initial application

Since the initial application the following further analyses have been completed:

- • Week 144 data from Phase III study ING114467 in ART-naïve subjects (data-cut 07 April 2014, N= 833; DTG+ABC/3TC 414, Atripla 419)
- • Week 96 data from Phase IIIb study ING114915 in ART-naïve subjects (data-cut 02 April 2014, N= 159; DTG+ABC/3TC 79, darunavir (DRV)/r 80)

Safety data from these two additional analyses have been included in the safety specification where relevant. These data have not been integrated and are provided in text format. Exposure data from ING114467 and ING114915 to 144 and 96 weeks respectively has been included in exposure tables below where possible (Table 2)

Randomised Blinded Trial Population

Exposure in ART Naïve Adult Subjects

Table 2 Exposure to DTG+ABC/3TC once daily in ART-Naïve Adult Subjects

	ING114467		ING113086		ING114915		ING112276	
	DTG 50 mg + ABC/3TC Once Daily N=414	EFV/TDF/FTC Once Daily N=419	DTG 50 mg + ABC/3TC Once Daily N=169	RAL 400 mg BID + ABC/3TC Once Daily N=164	DTG 50 mg + ABC/3TC Once Daily N=79	DRV 800 mg + RTV 100 mg BID + ABC/3TC Once Daily N=80	DTG 50 mg + ABC/3TC Once Daily N=17	EFV 600 mg + ABC/3TC Once Daily N=16
N	414	419	169	164	79	80	17	16
<12 weeks	15(4)	34(8)	4(2)	4(2)	2(3)	2(3)	1(6)	3(19)
12 to <24 weeks	7(2)	18(4)	5(3)	8(5)	1(1)	0	1(6)	0
24 to <48 weeks	25(6)	27(6)	11(7)	7(4)	2(3)	6(8)	0	0
48 to <96 weeks	22(5)	29(7)	45(27)	39(24)	22(28)	30(38)	4(24)	3(19)
>96 weeks	345 (83)[a]	311 (74) [a]	104(62)	106(65)	52(66)	42(53)	11(65)	10(63)
N	414	419	169	164	79	80	17	16
Mean	877.4	788.8	599.9	597.2	623.3	599.6	603.6	542.4
Sd	287.5	356.75	167.77	178.23	147.7	162.3	199.41	263.55
Median	1009.0	1007.0	672.0	672.0	673	672	672.0	672.0
Q1	998.0	608.0	668.0	667.0	668	650	670.0	587.0
Q3	1012.0	1009.0	673.0	673.0	676	673	674.0	675.0
Min.	1	3	13	8	31	1	1	5
Max.	1073	1046	685	700	691	693	685	700
Duration (Subject-years)	994.5	904.9	277.6	268.1	134.8	131.3	28.1	23.8

Table summarises exposure during the randomized phase

DTG= dolutegravir, ABC/3TC= abacavir/lamivudine, EFV/TDF/FTC = efavirenz/tenofovir/emtricitabine RAL= raltegravir,DRV= Darunavir ,RTV= Ritonavir

BID= twice daily

a. DTG+ABC/3TC 96 to <132 weeks 19 (5%), 132 to <144 weeks 86 (21%), >144 weeks 240 (58%), Atripla 96 to <132 weeks 28 (7%), 132 to <144 weeks 83 (20%), >144 weeks 200 (48%). Data Source ING114467, Week 144 CSR, Table 8.1

Data Source ISO Table 2.701, ING114467 Adhoc Table 1, ING114915 Adhoc Table 5

Table 3 Summary of Age, Gender and Ethnic Origin of Randomised Blinded Trial Population -ART Naïve Adult Subjects

	ING114467		ING113086		ING114915		ING112276		TOTAL DTG 50 mg + ABC/3TC Once Daily
	DTG 50 mg + ABC/3TC Once Daily	EFV/TDF/FTC Once Daily	DTG 50 mg + ABC/3TC Once Daily	RAL 400 mg BID + ABC/3TC Once Daily	DTG 50 mg + ABC/3TC Once Daily	DRV 800 mg + RTV 100 mg BID + ABC/3TC Once Daily	DTG 50 mg + ABC/3TC Once Daily	EFV 600 mg + ABC/3TC Once Daily	
	N=414	N=419	N=169	N=164	N=79	N=80	N=17	N=16	N=679
Age category, years, n (%)									
N	414	419	169	164	79	80	17	16	679
<50	361(87)	375(89)	159(90)	147(90)	70(89)	66(83)	17(100)	15(94)	607(89)
50-64	52(13)	38(9)	10(6)	15(9)	7(9)	14(18)	0	1(06)	69(10)
65-74	1(<1)	5(1)	0	1(<1)	2(3)	0	0	0	3(<1)
75-84	0	0	0	1(<1)	0	0	0	0	0
85+	0	1(<1)	0	0	0	0	0	0	0
Gender (n, %)									
N	414	419	169	164	79	80	17	16	679
Male	347(84)	124(73)	124(73)	129(79)	67(85)	64(80)	14(82)	16(100)	552(81)
Female	67(16)	63(15)	45(27)	35(21)	12(15)	16(20)	3(18)	0	127(19)
White									
Racial origin, n (%)									
N	414	419	169	164	79	80	17	16	679
Not specified	0	1(<1)	0	0	0	0	0	0	0
African American/ African heritage	98(24)	99(24)	26(15)	21(13)	21(27)	12(15)	2(12)	2(13)	147(22)
Asian	9(2)	9(2)	1(<1)	2(1)	1(1)	0	0	0	11(2)
White	284(69)	285(68)	140(83)	140(83)	55(70)	65(81)	12(71)	13(81)	491(72)
Other	23(6)	25(6)	2(1)	1(<1)	2(3)	3(4)	3(18)	1(6)	30(4)

DTG= dolutegravir, ABC/3TC= abacavir/lamivudine, EFV/TDF/FTC = efavirenz/tenofovir/emtricitabine RAL= raltegravir,DRV= Darunavir ,RTV= Ritonavir
BID= twice daily
Data Source ISO Table 1.716, 1.703, 2.704

Table 4 Exposure to DTG+ABC/3TC once daily in Special Populations in ART Naïve Adult Subjects

	ING114467		ING113086		ING114915		ING112276		TOTAL DTG 50 mg + ABC/3TC Once Daily
	DTG 50 mg + ABC/3TC Once Daily N=414	EFV/TDF/FTC Once Daily N=419	DTG 50 mg + ABC/3TC Once Daily N=169	RAL 400 mg BID + ABC/3TC Once Daily N=164	DTG 50 mg + ABC/3TC Once Daily N=79	DRV 800 mg + RTV 100 mg BID + ABC/3TC Once Daily N=80	DTG 50 mg + ABC/3TC Once Daily N=17	EFV 600 mg + ABC/3TC Once Daily N=16	N=679
HCV and/or HBV infected,	28(7)	30(7)	24(14)	22(13)	6(8)	6(8)	3(18)	0	61(9)
Renal impairment[1]									
N	36	22	10	14	8	7	3	1	57
Mild 60-<90 mL/min/1.73m2	34(8)	20(5)	10(6)	13(8)	8(10)	6(8)	3(18)	1(6)	55(8)
Moderate 30-<60 mL/min/1.73m2	2(<1)	2(<1)	0	1(<1)	0	1(1)	0	0	2(<1)
Severe <30 mL/min/1.73m2	0	0	0	0	0	0	0	0	0

Note: This table includes all subjects who received at least one dose of study medication.
Renal impairment categories based on Creatinine Clearance, estimated – Cockgroft-Gault formula at Baseline. Subjects with normal renal function are not presented in this summary,
Data source ISO Tables 2.764 and 2.767

DTG

The safety specification for DTG in adult subjects supporting the initial DTG MAA involved 41 completed and ongoing interventional clinical trials (30 Phase I, 4 Phase II, 4 Phase III, 3 Phase IIIb) and two compassionate use programmes.

Six Phase IIb and Phase III studies with DTG had complete, interim or final statistical analyses available to support the application. These comprised of four Phase III studies [Study ING113086 (SPRING-2), ING111762 (SAILING), ING112574 (VIKING-3) and ING114467 (SINGLE)] and two Phase IIb studies [Studies ING112276 (SPRING-1) and ING112961 (VIKING)] conducted with DTG in HIV-infected antiretroviral therapy naïve and experienced adults. The final data cut-off dates for individual studies are listed in Table 5 below:

Table 5 Data Cut-off Dates for Studies supporting the safety specification included in the initial application

	Study	Study Time Point of Analysis	Data Cut-off Date[a]
Pivotal and Supportive Clinical Trials			
Studies in ART-Naïve Adults	ING112276	Post Week 96[b]	25 June 2012
	ING113086	Post Week 48[b]	18 June 2012
	ING114467	Week 48[c]	04 June 2012
Studies in ART-Experienced (INSTI-Naïve) Adults	ING111762	Week 24[c]	04 September 2012[e]
Studies in ART-Experienced (INSTI-Resistant) Adults	ING112961	Post Week 96[b]	08 June 2012
	ING112574	Week 24[c, d]	18 June 2012 [e]

a. This data cut-off date is the date when the data used in the analysis was extracted. This could either be Database Freeze (DBF) or Database Release (DBR), depending whether a new extraction was needed at DBF.
b. The completed interim statistical analysis was more than six months prior to the planned submission date, so a new safety data cut was taken for reporting in this submission; thus, the data reported individually for these studies is not represented in a clinical study report.
c. Safety data for this submission are reported based on the latest Clinical Study Report available.
d. The interim analysis was planned to assess the first approximately 100 subjects that completed 24 weeks on study, and recruitment continued to allow enrolment of a further 50 to 100 subjects, as per protocol. All available safety data, as of the data cut, from all subjects enrolled contributed to the safety analysis. Thus, the planned interim analysis data cut was based on 114/183 subjects through Week 24.
e. Since the initial application further analyses have been conducted on these two studies (see below**)**

In the Safety Specification for DTG, the studies in ART-naïve subjects (ING112276, ING113086 and ING114467) were considered separately to studies in ART Experienced (INSTI-Naive) subjects (study ING111762) and ART Experienced (INSTI-resistant) subjects (studies ING112961 and ING112574) due to the different patient populations being studied and the different doses of DTG being administered (i.e., DTG 50 mg once daily versus DTG 50 mg twice daily).

Since the initial DTG application two further analyses have been completed for DTG

- Week 48 primary endpoint analysis for ING111762 (data-cut 25 February 2013, (N= 719; DTG 357, RAL 362)
- A second interim analyses through Week 24 for all subjects enrolled in study ING112574 (data-cut 17 December 2012, N=183)

The total number of subjects enrolled in ING111762 and ING112574 remains the same as reflected in Table 6.

Information on exposure to DTG in the pivotal and supporting Phase IIb/III Studies at the time of the initial application is presented in Table 6.

Table 6 Exposure to DTG in the pivotal and supporting Phase IIb/III Studies with Adult Subjects

Study Number	Phase	Patient type	Age range	No. on DTG	No. on comparator	Total
ING112276 (SPRING-1)	IIb	ART-naive	≥18 years	155	50	205
ING112961 (VIKING)	IIb	ART-experienced INI resistant	≥18 years	51	N/A	51
ING113086 (SPRING-2)	III	ART-naive	≥18 years	411	411	822
ING114467 (SINGLE)	III	ART-naive	≥18 years	414	419	833
ING111762 (SAILING)	III	ART-experienced, INI-naive	≥18 years	357	362	719
ING112574 (VIKING-3)	III	ART-experienced INI resistant	≥18 years	183	N/A	183

Data source ISO Table 2.501

Paediatric Subjects

DTG/ABC/3TC

IMPAACT 2019 (205860) was a Phase I/II study of the pharmacokinetic, safety and tolerability of DTG/ABC/3TC tablets and dispersible tablets (DT) in children living with HIV-1 infection less than 12 years of age. As of 12 July 2021, 57 participants have been accrued across 5 weight bands.

A total of 57 participants were enrolled across the weight bands. The study population was comprised mainly of Black/African American and Asian participants, and most participants were ART-experienced and virologically suppressed prior to enrollment. Week 48 analysis of the pharmacokinetics, safety and efficacy data of the DTG/ABC/3TC DT and tablets supported the extension of indication in children down to 6 kg. Table 7 provides a summary of the exposure to study drug through end of study by enrollment weight band.

Table 7 Summary of Exposure to Study Drug through End of Study, by Enrollment Weight Band (All Treated Population)

	≥6 to <10 kg N=9	≥10 to <14 kg N=12	≥14 to <20 kg N=15	≥20 to <25 kg N=10	≥25 kg N=11	Total N=57
Status, n (%)						
Completed Week 24	8 (88.9)	11 (91.7)	15 (100.0)	10 (100.0)	11 (100.0)	55 (96.5)
Completed Week 48	8 (88.9)	11 (91.7)	15 (100.0)	10 (100.0)	11 (100.0)	55 (96.5)
Complete Week 60[a]	0	0	4 (26.7)	3 (30.0)	3 (27.3)	10 (17.5)
Exposure, weeks						
Mean (SD)	42.03 (15.515)	43.99 (13.540)	50.99 (5.551)	50.04 (7.217)	50.60 (4.556)	47.86 (10.188)
Median	47.00	48.00	48.14	47.79	48.14	48.14
(Q1, Q3)	(46.29, 48.00)	(46.93, 48.57)	(47.14, 58.14)	(46.86, 58.14)	(48.00, 55.14)	(46.86, 49.14)
(Min, Max)	(0.7, 48.3)	(1.1, 49.7)	(45.9, 62.0)	(37.0, 61.1)	(46.6, 59.0)	(0.7, 62.0)
Sex at birth n (%)						
Male	5 (55.6)	7 (58.3)	5 (33.3)	3 (30.0)	6 (54.5)	26 (45.6)
Female	4 (44.4)	5 (41.7)	10 (66.7)	7 (70.0)	5 (45.5)	31 (54.4)
Age (years)	1.350	3.555	6.440	8.405	9.740	6.380
Median (range)	(0.98, 2.02)	(1.51, 4.51)	(3.88, 9.58)	(6.38, 8.91)	(8.68, 11.28)	(0.98, 11.28)
Race n (%)						
Asian	3 (33.3)	1 (8.3)	7 (46.7)	4 (40.0)	3 (27.3)	18 (31.6)
Black or African American	6 (66.7)	10 (83.3)	7 (46.7)	6 (60.0)	8 (72.7)	37 (64.9)
Unknown	0	0	1 (6.7)	0	0	1 (1.8)
White	0	1 (8.3)	0	0	0	1 (1.8)

Source: IMPAACT 2019 CSR [2022N501029_00] Table 1.7, 1.8, 1.9.

Note: N = Number of participants in each weight band.

Note: Duration is calculated starting at treatment start until treatment end. Any time off treatment but on study is not counted in treatment duration

a. Participants remained on-study after the Week 48 visit until they could access the drug through a non-study source.

DTG

Study ING112578 (P1093) is an ongoing Phase I/II multicenter, open-label, non-comparative study to evaluate the pharmacokinetic parameters, safety, tolerability and antiviral activity of DTG once daily in combination regimens in HIV-1 infected infants, children and adolescents aged ≥4 weeks to <18 years.

Week 24 data (Pharmacokinetic (PK), safety and efficacy) from Cohort I, Stages I and II, comprising 23 subjects, were available at the time of the TRIUMEQ MAA (study cut off 17 December 2012) and supported the use of DTG/ABC/3TC in adolescents (≥ 12 to <18 years of age). For updated exposure from study ING112578 (P1093) refer to the latest approved DTG EU-RMP.

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

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

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 recognized risk for ART containing DTG and ABC Hypersensitivity is a rare but recognized risk for ART containing DTG, regardless of dose and is contraindicated in patients receiving DTG.	No	DTG/ABC/3TC is contraindicated in anyone with hypersensitivity to DTG, ABC, 3TC or to any of the excipients and a warning around Hypersensitivity reactions is included in module 4.4 of the Summary of Product Characteristics (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 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	Patients with HIV infection receiving DTG/ABC/3TC may have a HCV co-infection. Safety data across all patient populations supports the administration of DTG/ABC/3TC in HIV infected patients co-infected with HCV Treatment with DTG/ABC/3TC will be guided by established guidance and medical practice.
Subjects positive for hepatitis B virus (HBV) at screening (+HbsAg)	Hepatitis B surface antigen positivity was an exclusion criterion for ING114467 due to the blinded use of ABC/3TC in the DTG arm, whereas	No	Patients with HIV infection receiving DTG/ABC/3TC may have a HBV co-infection. Safety data across all patient populations supports the administration of

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	treatment guidelines (e.g., EACS guidelines) recommend ART initiation with tenofovir (TDF)-based therapy for HBV-co-infected patients in need of anti-HBV therapy and/or with CD4+ cell counts <500. This exclusion only applied to study ING114467 and not the other studies supporting the DTG/ABC/3TC MAA submission.		DTG/ABC/3TC in HIV infected patients co-infected with HBV. Treatment with DTG/ABC/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/ABC/3TC in hepatitis B co-infected patients.
Moderate to severe hepatic impairment as determined by Child-Pugh	Hepatic metabolism is the main route of elimination of ABC. Consistent with this, a previous study has shown that plasma concentrations of ABC were elevated and more variable in subjects with hepatic impairment [ZIAGEN SmPC]. Based on data obtained for ABC, DTG/ABC/3TC is not recommended in patients with moderate and severe hepatic impairment	No	In relation to the use of ABC in hepatic impairment, an increase in significant safety findings has not been observed following increased exposure. The finding of increased ABC exposure (1.89 AUC) from the study CNAB1006 did not indicate an associated increased safety risk, while during study CNAA2001 subjects were exposed to ABC doses of 1200mg or 1800mg daily, for up to 12 weeks (either with zidovudine, or with placebo), an increased ABC exposure was associated with an increased risk of nausea and rash, but not vomiting, dizziness or headache. Pharmacovigilance activities have also not identified a greater prevalence of safety findings in patients with increased ABC exposure.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			As part of routine risk minimization the SmPC states that DTG/ABC/3TC is not recommended for use in patients with moderate or severe hepatic impairment
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+ABC/3TC studies.	No	Based on 3TC data, DTG/ABC/3TC was not recommended for patients with creatinine clearance of <50 ml/min. This has subsequently been updated in the SmPC as dose adjustment is now only required with a creatinine clearance of <30 ml/min (for patients weighing ≥25 kg). Treatment with DTG/ABC/3TC will be guided by established guidance and medical practice.
History of malignancy within the past 6 months (ING113086) or 5 years	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/ABC/3TC may have a history of 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/ABC/3TC will be guided by established guidance and medical practice.
Recent history (≤3 months) of any upper or lower gastrointestinal (GI) bleed, with the exception of anal or rectal bleeding	Gastrointestinal intolerance (severe diarrhoea and gastric erosion) was observed in the 6- and 9-month long-term animal (rat and monkey, respectively) toxicity studies conducted for DTG.	No	As the early signal observed during animal studies has not translated into significant findings and only mild to moderate events of general GI intolerance, similar to other antiretrovirals, have been observed during the clinical development programme, the likelihood of serious adverse GI effects occurring post

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	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		marketing is considered to be very low. Additionally, only 4 subjects were excluded from the Phase III studies for this reason, and subjects with pre-existing GI history that either included bleeding (more than 3 months prior to enrolment) or would increase the risk of GI bleeding were enrolled without significant incidence of GI ulcers or erosions. There is therefore no reason to contraindicate the use of DTG in these patients and this exclusion criterion has been removed from protocols for planned studies. Treatment with DTG/ABC/3TC will be guided by established guidance and medical practice.
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/ABC/3TC should be contraindicated in these patients. Treatment with DTG/ABC/3TC will be guided by established guidance and medical practice.

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

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	At the data-cut for the initial submission, DTG+ABC/3TC had been used in approximately 700 patients with HIV infection for periods up to 96 weeks (or longer).	Adverse drug reactions (ADRs) with a frequency greater than 1 in 233 could be detected if there were no background incidence (i.e. uncommon ADRs as per CIOMS criteria).
Due to prolonged exposure	With antiretroviral therapies, some toxicities have taken considerable time/ years to manifest. The MAA for the DTG/ABC/3TC FDC submission included clinical safety data for approximately 700 subjects receiving DTG+ABC/3TC for periods of up to 96 weeks (or longer). The programme is also informed by the accumulated clinical experience with the first in class INSTI RAL, which has been approved for use since 2007, and ABC and 3TC which have been approved since 1998 (ABC) 1995(3TC) and 2004 (ABC/3TC).	Although information on long-term safety of DTG+ABC/3TC is limited, no long-term adverse effect of DTG+ABC/3TC is apparent from clinical studies to date. In addition, no long-term toxicities have been noted for RAL or confirmed for ABC/3TC. Longer term data from study ING114467 demonstrated that the DTG+ABC/3TC had long term durability with a low rate of discontinuation due to virologic failure; as well as a safety and tolerability profile that was generally favourable to that of comparator (Atripla) through Week 144. The long-term safety of DTG/ABC/3TC will be monitored through routine pharmacovigilance.
Due to cumulative effects	With antiretroviral therapies, some toxicities have taken considerable time/ years to manifest. The MAA for the DTG/ABC/3TC FDC submission included clinical safety data for approximately 700 subjects receiving DTG+ABC/3TC for periods of up to 96 weeks (or longer). The programme is also informed by the accumulated clinical experience with RAL and ABC/3TC.	There were no new safety signals identified during longer term treatment with DTG+ABC/3TC that might have been due to cumulative effects. No specific organ toxicity was detected. In addition, no long-term toxicities have been noted for RAL or confirmed for ABC/3TC. The long-term safety of DTG/ABC/3TC will be monitored through routine pharmacovigilance
Which have a long latency	The assessment of longer-term toxicities seen with CART, such as	Although information on long-term safety is limited, no long-term adverse effect of

	bone disorders and lipodystrophy require a considerably extended follow up period. The MAA for the DTG/ABC/3TC FDC submission includes clinical safety data for approximately 700 subjects receiving DTG+ABC/3TC for periods of up to 96 weeks (or longer). The programme is also informed by the accumulated clinical experience with RAL and ABC/3TC.	DTG+ABC/3TC is apparent from clinical studies to date. In addition, no long-term toxicities, have been noted for the first in class INSTI RAL, or confirmed for ABC or 3TC. The long-term safety of DTG/ABC/3TC will be monitored through routine pharmacovigilance

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

Table 8 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/ABC/3TC clinical studies. Subjects that became pregnant (intrauterine) were required to discontinue from the studies. Clinical experience of DTG/ABC/3TC use during pregnancy is therefore limited (See Section 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 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 (<60 mL/min) and severe (<30 mL/min) renal impairment, were excluded from the DTG+ABC/3TC clinical studies
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical programme covered the full spectrum of HIV disease (i.e., no CD4+ cell count restrictions and no upper limit on viral load) and therapy experience.

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.
Subpopulations carrying relevant genetic polymorphisms	Subjects with genetic polymorphisms were not excluded from the clinical studies.
Paediatrics	An MAA has been approved for DTG in the EU with an indication in children at least 4 weeks of age and weighing at least 3 kg, supported by data from study ING112578 (Paediatric Study P1093) and ODYSSEY weight band pharmacokinetic sub-studies (PENTA 20). ABC and 3TC are also approved for use in children from 3 months of age. Use of DTG/ABC/3TC in paediatrics at least 3 months of age and weighing at least 6 kg is supported by data from study IMPAACT 2019, in which a paediatric formulation of DTG/ABC/3TC was used, as agreed in the Paediatric Investigation Plan (PIP).

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/ABC/3TC.

Total cumulative post-approval exposure to DTG/ABC/3TC is estimated at 1,417,383 patient years from licensure (22 August 2014) up to 31 March 2023.

In the EU/European Economic Area (EEA)* total cumulative exposure to 31 March 2023 is 587,542 patient years.

*The EU/EEA includes data from the following countries (as at 31 March 2023): Spain, Italy, France, Germany, Portugal, Netherlands, Belgium, Sweden, Austria, Denmark, Romania, Bulgaria, Hungary, Slovakia, Poland, Ireland, Norway, Latvia, Finland, Czech Republic, Croatia, Slovenia and Luxembourg. Belarus, United Kingdom, Switzerland and Serbia are also included in this region.

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

Potential for misuse for illegal purposes

The MAH does not consider that there is a potential for misuse for illegal purposes with DTG/ABC/3TC.

The INSTI and NRTI classes of compounds have no known drug abuse potential. The mechanisms of action for DTG, ABC and 3TC do not involve receptors or neurotransmitters known to be involved in drug dependence. In secondary pharmacology evaluations, DTG and ABC did not significantly bind to any receptors or ion channels that would be considered relevant to abuse liability (including monoamine oxidase A and B, cannabinoid CB1 or CB2, nicotinic cholinergic, dopamine D1 or D2, dopamine transporter, GABA A or GABA B, glutamate NMDA, opiate, serotonin 5-HT1, 5-HT2, or 5-HT3).

No effects related to DTG, ACB or 3TC administration on central and peripheral nervous system or body temperature were noted in preclinical studies, even following dosing withdrawal in different preclinical species including nonhuman primates. The results from a quantitative whole-body autoradiography studies in rats indicated that the ability of DTG, ABC and 3TC or metabolites to cross the blood brain barrier in rats was limited.

Considering that: a) DTG, ABC and 3TC are not centrally active, b) there is clear evidence that those compounds have very low blood brain barrier penetration, c) mechanistically they do not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, d) preclinical and extensive clinical data generated are not indicative of an abuse liability, the likelihood of abuse liability for the combination of DTG, ABC and 3TC is considered extremely low and further studies are not necessary.

No instances of the abuse of study medications were reported in the clinical studies in the original adult clinical programmes for ABC and 3TC and no signal has been identified from post marketing data.

In summary, there are no data suggesting that TRIUMEQ has the potential to imply illicit use, abuse, or dependency.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

This section is not applicable.

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

There are no proposals to add new safety concerns or reclassify safety concerns at this time.

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 ABC and 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 removed from this RMP. Please refer to the RMPs for the single entities (DTG, ABC, ABC/3TC) for this information.

SVII.3.2 Presentation of the missing information

Pregnant or Breast-Feeding Women

Evidence Source:

Use in Pregnancy

At the time of the initial MAA, no studies had been conducted with DTG+ABC/3TC in pregnant women, and pregnant women were excluded from the studies. Subjects who became pregnant (intrauterine) were required to discontinue from the clinical studies. Clinical experience of DTG/ABC/3TC use during pregnancy is therefore limited and use in pregnancy and breast feeding has been considered missing information for in the RMP since the initial MAA approval.

The MAH initiated an open-label interventional study for women who become pregnant whilst receiving DTG/ABC/3TC (Study ING200336. 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 in total 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). The 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.

TRIUMEQ was added to the list of the ARVs monitored by the Antiretroviral Pregnancy Registry (APR) on 11 November 2014. 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. Exposures in the APR are reported and recorded against individual drugs (e.g. DTG, ABC and 3TC) rather than FDC products such as TRIUMEQ Data and analysis from the APR are submitted within the PBRER for DTG/ABC/3TC.

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

Use in pregnancy is also 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 DTG/ABC/3TC are provided in the PBRER.

Use in Breastfeeding

Dolutegravir is excreted in human milk in small amounts. There is insufficient information on the effects of dolutegravir in neonates/infants. Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of

mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of abacavir and lamivudine when administered to babies less than three months old. European and U.S. guidelines recommend that HIV infected women do not breast feed their infants in order to avoid transmission of HIV. However, the WHO guideline for infant feeding states that in geographic regions where formula feeding is not feasible women can breastfeed while receiving appropriate antiretroviral therapy during breastfeeding to reduce the risk of HIV transmission [WHO, 2010].

Population in need of further characterisation:

As clinical experience of the use of DTG/ABC/3TC 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 DTG/ABC/3TC.

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). Data and analysis from these studies will be submitted in the RMP and PBRER for the DTG products as they become available (unless a more urgent escalation of information is warranted).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Summary of safety concerns The safety profile of DTG taken in combination with ABC and 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.	
Important identified risks	**ABC** • Hypersensitivity reactions
Important potential risks	**DTG** • Neural tube defects
Missing information	• 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:

Specific adverse reaction follow-up questionnaires for

- Neural tube defects are a potential risk in babies exposed to DTG in utero. 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 for

- 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

A summary of the studies that are planned/ongoing for DTG/ABC/3TC to address specific safety concerns, is presented below.Copies of relevant protocols is provided in ANNEX 3.

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 MAH sponsored study involving the collaborative effort of multiple companies [Antiretroviral Pregnancy Registry, 2018].

Data from the APR is used to monitor use of the DTG 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) [Texas Birth Defect Surveillance System, 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 1300-1700 pregnant women exposed to antiretroviral drugs for the treatment of HIV and HBV infection and prevention of HIV infection. This number includes approximately 1300 or 15% of the 8,700 HIV infected women who give birth to live infants annually in the US and approximately 350 pregnant women from other countries [Antiretroviral Pregnancy Registry, 2018]

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.

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 three partners, NEAT-ID Network, PANNA Network and European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) to design and conduct three studies of DTG in pregnancy; the following two studies have the ability to capture pregnancies exposed to DTG at conception:

Study short name and title:

DOLOMITE EPPICC Study (208613)

Pregnancy and Neonatal Outcomes following Prenatal Exposure to Dolutegravir: Data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Rationale and study objectives:

The study will assess "real-world" maternal and foetal outcomes following DTG use during pregnancy and to describe patterns of DTG utilization using data from the EPPICC in order to increase knowledge of the safety profile of DTG in pregnancy. 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:

Observational study

Study population:

EPPICC is a collaboration of observational studies (cohorts and surveillance) conducting epidemiological research on HIV-positive pregnant women, children and children exposed to HIV in utero. The goal of the collaboration is to address key, contemporary questions regarding HIV infection in pregnancy and PMTCT, alongside management, treatment and long-term outcomes of HIV-infected children and adolescents. The collaboration was established in 2009. EPPICC currently includes 10 cohorts/studies across 11 European countries (Belgium, Ireland, Italy, Netherlands, Portugal, Romania, Russia, Spain, Switzerland, UK and Ukraine) that collect prospective data on pregnant women living with HIV and their newborns, whereby antiretroviral exposure data is collected before the pregnancy outcome is known.

Milestones:

Protocol effective date: 14 February 2018

Study start: 08 March 2018

Final report: June 2023

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:

Protocol effective date: 13 November 2018

Expected Study start: 1 March 2019 or after Ethics' committee approval

Expected Final report: October 2023

III.3 Summary Table of additional Pharmacovigilance activities

There are no category 1 or 2 studies for DTG

Table 9 Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry 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 NTDs	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR is presented in the PBRER.	-
Study 208613 DOLOMITE EPPICC Ongoing	Assess "real-world" maternal and foetal outcomes following DTG use during pregnancy and to describe patterns of DTG utilization using data from the EPPICC in order to increase knowledge of the safety profile of DTG in	Use in pregnancy, NTDs: 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.	Protocol effective date	14 February 2018
			Study start	08 March 2018

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	pregnancy. 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.		Final Report	June 2023
Study 208759 DOLOMITE NEAT ID Network 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, NTDs 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.	Protocol effective date	13 November 2018
			Study start Expected Final Report	01 March 2019 or after EC approval October 2023

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

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

V.1 Routine Risk Minimization Measures

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

Safety concern (risk/ missing information)	**Routine risk minimization activities**
Hypersensitivity reactions (Important identified risk for ABC)	**Routine risk communication:** Information is included in module 4.3, 4.4 and 4.8 of the SmPC A contraindication for patients with hypersensitivity to ABC is included in section 4.3 of the SmPC. A boxed warning around hypersensitivity is also included in section 4.4 and hypersensitivity is included as an ADR in section 4.8 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** DTG/ABC/3TC is contraindicated in patients with hypersensitivity to DTG, ABC or 3TC or excipients in SmPC section 4. Recommendations regarding not initiating DTG/ABC/3TC in patients with a positive *HLA-B*5701 status,* and immediately stopping and avoiding restarting DTG/ABC/3TC in patients that experience ABC HSR is in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV

Safety concern (risk/ missing information)	**Routine risk minimization activities**
Neural tube defects (Important 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. Women of childbearing potential (WOCBP) should be counselled about the potential risk of neural tube defects with dolutegravir (a component of dolutegravir/abacavir/lamivudine, see below), including consideration of effective contraceptive measures. If a woman plans pregnancy, the benefits and the risks of continuing treatment with dolutegravir/abacavir/lamivudine should be discussed with the patient. **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/ABC/3TC 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.

The safety information in the product information for the DTG/ABC/3TC FDC is aligned to the reference medicinal products (DTG ABC and 3TC).

V.2 Additional Risk Minimization Measures

ABC Hypersensitivity

Each pack of TRIUMEQ medication contains an Alert Card for patients and information on the risk of HSR with ABC in the Patient Information Leaflet.

Neural tube defects

In Version 15 of the RMP, NTDs were added to the RMP as a potential risk for DTG based on preliminary data from an unplanned review of a birth outcomes surveillance study conducted in Botswana (see Part SVII.2 and the DTG RMP for further information on this potential risk). On the basis of this data, which showed a higher than expected number of NTDs, among newborns whose mothers were exposed to DTG-based ART at conception, ViiV Healthcare distributed a Direct Health Care Professional communication (DHPC) making specific recommendations for the use of DTG in women of child-bearing potential. A communication was also sent to study investigators to ensure awareness of this issue with emphasis on pregnancy avoidance measures as per the protocol. This additional risk minimization measure is now considered to be complete but the details are included here for completeness.

Objectives:

The objectives of the DHPC was to inform health care professionals and investigators about the potential increased risk of neural tube defects in newborns exposed to DTG-based ART at conception and to minimize any risk in women of child bearing potential taking DTG who are actively trying to become pregnant.

The DHPC made specific recommendations for the use of DTG in women of child-bearing potential based on the data currently available and World Health Organisation (WHO) current guidance. The key messages from the DHPC letter are provided in ANNEX 6 for completeness.

Rationale for the additional risk minimization activity:

A DHPC was considered to be appropriate to inform health care professionals and investigators about the potential increased risk of neural tube defects in newborns exposed to DTG-based ART at conception, and to minimize any risk in women of child bearing potential taking DTG who are actively trying to become pregnant

Target audience and planned distribution path:

On 23 May 2018, following PRAC and CHMP approval ViiV Healthcare distributed the DHPC to Local Operating Companies for local Agency approval (if required) followed by onward distribution to appropriate Healthcare Professionals

The DHPC was distributed to Healthcare Professionals who are principal caregivers for people living with Human Immunodeficiency Virus.

In most countries the following specialties were included as agreed locally with the Regulatory Agency:

- Infectious Diseases specialists

- Genito-urinary medicine physicians

- Clinical Virologists

- Obstetrics & Gynaecology and/or Paediatricians where appropriate

- Sexual Health and HIV medicine specialists

- HIV nurses, pharmacists, General Practitioners

National Organisations, Guidelines Committees, Patient Advocacy Groups and ViiV Healthcare Partners were also included in the distribution.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the risk minimiztion measures will be measured by routine pharmacovigilance which includes monitoring of post marketing reports and literature for any cases of NTD. The MAH will continue to monitor reports of DTG use in pregnancy, including where used in the first trimester. Findings from this assessment will be provided in the PBRER, unless they warrant more urgent action such as an update to the RMP or SmPC.

The DHPC was distributed in 2018 to initially inform health care professionals and investigators about the potential increased risk of NTDs following exposure to DTG-based ART at the time of conception and to minimize the risk in women of childbearing potential and during pregnancy. The possible risk of NTDs is now widely known and has been effectively communicated through the DHPC and updates to the EU SmPCs. This risk is being effectively managed through routine risk minimization and no further additional risk minimization measures are considered necessary.

V.3 Summary of risk minimization measures

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

Safety concern (risk/ missing information)	Risk minimization measures	Pharmacovigilance activities
Hypersensitivity reactions (Important identified risk for ABC)	**Routine risk minimization measures:** Sections 4.3, 4.4 and 4.8 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** Each pack of TRIUMEQ medication contains an Alert Card for patients and information on the risk of HSR with ABC in the Patient Information Leaflet.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Neural tube defects (Important potential risk for DTG)	**Routine risk minimization measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** Direct health care professional communication completed in 2018	**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 208613 -DOLOMITE EPPICC Study 208759- DOLOMITE NEAT ID Network Study

Safety concern (risk/ missing information)	Risk minimization measures	Pharmacovigilance activities
Pregnant/ breastfeeding women (missing information)	**Routine risk minimization measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Review of the APR Study 208613 -DOLOMITE EPPICC Study 208759- DOLOMITE NEAT ID Network Study

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for TRIUMEQ

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

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

This summary of the RMP for TRIUMEQ 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 TRIUMEQ RMP.

I. The medicine and what it is used for

TRIUMEQ is authorized for the treatment of HIV infected adults, adolescents and children (see SmPC for the full indication). It contains DTG, ABC and 3TC as the active substance and it is given by oral route.

Further information about the evaluation of the benefits of TRIUMEQ can be found in the TRIUMEQ 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/triumeq

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The 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 minimize its risks.

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

In the case of TRIUMEQ these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of TRIUMEQ are risks that need special risk management activities to further investigate or minimize 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 TRIUMEQ. 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).

TRIUMEQ is a medicine that does not contain a new active substance. The identified and potential risks for TRIUMEQ have been taken from the approved TIVICAY (dolutegravir (DTG)) and Ziagen (ABC) or Kivexa (ABC/3TC) RMPs. No new risks have been identified for TRIUMEQ.

Summary of safety concerns The safety profile of DTG taken in combination with ABC and 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.	
Important identified risks	**ABC** • Hypersensitivity reactions
Important potential risks	**DTG** • Neural tube defects
Missing information	• Use in pregnancy/ breastfeeding

II.B Summary of important risks

TRIUMEQ is a medicine that does not contain a new active substance. The identified and potential risks for TRIUMEQ have been taken from the approved TIVICAY (dolutegravir) and ZIAGEN (ABC) or KIVEXA (ABC/3TC) RMPs. No new risks have been identified for TRIUMEQ.

The safety information in the Product Information for TRIUMEQ is aligned to the reference medicinal products (TIVICAY and ZIAGEN or KIVEXA).

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

Important identified risk (ABC): Hypersensitivity	
Evidence for linking the risk to the medicine	Hypersensitivity reactions have been reported with ABC containing products, generally characterized by rash and constitutional syndromes. More rarely, hypersensitivity reaction leads to organ dysfunction, including severe liver reactions. Clinical study data from the development programme with the ABC containing products and data from post-marketing sources provide evidence for this risk.
Risk factors and risk groups	Higher risk has been identified in patients with a positive *HLA-B*5701 status.*
Risk minimization measures	**Routine risk minimization activities:** DTG/ABC/3TC is contraindicated in patients with hypersensitivity to ABC in SmPC section 4.3. Recommendations regarding not initiating DTG/ABC/3TC in patients with a positive HLA-B*5701 status; and immediately stopping and avoiding restarting DTG/ABC/3TC in patients that experience ABC hypersensitivity is in SmPC section 4.4. Other routine risk minimization measures beyond the Product Information:

	This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** Each pack of TRIUMEQ medication contains an Alert Card for patients and information on the risk of hypersensitivity with ABC in the Patient Information Leaflet.
Additional pharmacovigilance activities	No additional pharmacovigilance activities

Important potential risk (DTG): Neural tube defects	
Evidence for linking the risk to the medicine	Preliminary findings from a birth outcomes surveillance 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.
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:** Direct health care professional communication completed

	in 2018
Additional pharmacovigilance activities	Antiretroviral Pregnancy Registry Study 208613 -DOLOMITE EPPICC Study Study 208759 -DOLOMITE NEAT ID Network Study

Missing Information: Use in pregnancy/breastfeeding	
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 208613 -DOLOMITE EPPICC Study Study 208759 -DOLOMITE NEAT ID Network Study

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 TRIUMEQ.

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	Monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration	Use in pregnancy	Ongoing	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the PBRER.
Study 208613 DOLOMITE EPPICC Study	Assess “real-world” maternal and foetal outcomes following DTG use during pregnancy and to describe patterns of DTG utilization	Use in pregnancy, NTDs 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.	Ongoing	Final Report June 2023

Study/Activity (including study number)	**Objectives**	**Safety concerns/efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final study results**
Study 208759 DOLOMITE NEAT ID Network Study	To assess the safety and effectiveness of DTG in pregnancy in the NEAT-ID network of approximately 40 sites across Europe.	Use in pregnancy, NTDs 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.	Ongoing	Final Report October 2023

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 ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Abacavir Hypersensitivity

An ‘Alert’ card is included in every pack of an ABC containing product, which the patient should carry with them at all times. This describes the symptoms of the allergic reaction and warns patient’s that these reactions can be life-threatening if treatment with an ABC containing product is continued. The alert card also warns patients that if treatment with an ABC containing product is discontinued to this type of reactions then the patient must never take an ABC containing product or any other medicine containing ABC ever again as it could result in a life-threatening lowering of blood pressure or death.

A direct healthcare provider communication regarding NTDs with DTG was completed in 2018 and included here for completeness.

CONFIDENTIAL

Direct Healthcare Professional Communication

Date: 22 May 2018

Tivicay{dolutegravir},Triumeq {dolutegravir,abacavir,lamivudine}, Juluca {dolutegravir,rilpivirine}: neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception

Dear Healthcare Professional

ViiV Healthcare, in agreement with the European Medicines Agency, would like to inform you of the following:

Summary

- In an ongoing birth outcome surveillance study, conducted in Botswana, the Tsepamo study, 4 cases of neural tube defects (NTD) have been reported in 426 infants born to women who took dolutegravir as part of combined antiretroviral therapy at the time of conception. This represents an incidence of about 0.9% compared with an expected background rate of about 0.1% in infants born to women taking other antiretroviral medicines at the time of conception.
- While this safety signal is being evaluated, the following measures are recommended:
    - **In women of child bearing potential (WOCBP) pregnancy testing should be performed and pregnancy should be excluded before initiation of treatment.**
    - **WOCBP who are taking dolutegravir should use effective contraception throughout treatment.**
    - **In WOCBP who are actively seeking to become pregnant, it is recommended to avoid dolutegravir.**
    - **In case a woman becomes pregnant while taking dolutegravir and the pregnancy is confirmed in the first trimester, it is recommended switch to an alternative treatment unless there is no suitable alternative.**

Background information

The issue has been identified from a preliminary unscheduled analysis of the ongoing Tsepamo study in Botswana. Further data from this study will be captured during the ongoing surveillance. This information will help to further inform about the safety of dolutegravir during pregnancy.

Although there is limited experience with the use of dolutegravir in pregnancy, the cur r ently available data from other sources including Antiretroviral Pregnancy Registry, clinical trials and post-marketing use has not indicated a similar safety issue. There is only one other report of NTD reported spontaneously from Namibia in which dolutegravir was used a few months prior to conception and during pregnancy.

There are currently no congenital abnormality signals (including NTD) associated with the use of dolutegravir during pregnancy from other data sources. Dolutegravir was tested in a complete package of reproductive toxicology studies, including embryofetal development studies, and no relevant findings were identified.

Neural tube defects occur when the neural tube fails to completely form (between 0 and 28 days after conception), and the spinal cord, brain and related structures do not form properly.

This new finding is being considered in the context of other available data and the product information of TIVICAY/TRIUMEQ will be updated accordingly and further information will be communicated as appropriate.

PPD

Chief Scientific and Medical Officer

ViiV Healthcare