Summary of risk management plan for TIVICAY (Dolutegravir)

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

TIVICAY 's SmPC and its package leaflet give essential information to healthcare professionals and patients on how TIVICAY should be used.

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

I. The medicine and what it is used for

TIVICAY is authorized for the treatment of HIV infected adults, adolescents and children, in combination with other anti-retroviral medicinal products (see SmPC for the full indication). It contains dolutegravir as the active substance and it is given by oral route.

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

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

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

II.A List of important risks and missing information

Important risks of TIVICAY 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 TIVICAY. 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);

List of important risks and missing information	
Important identified risks	Hypersensitivity reactions Hepatobiliary disorders Depression (including suicidal ideation and behaviours, particularly in patients with a pre-existing history of depression or psychiatric illness)
Important potential risks	Serious rash (DAIDS Grade 3 or 4) Neural tube defects
Missing information	Use in the elderly Use in pregnancy/ breastfeeding Long term safety data

II.B Summary of important risks

Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions have been reported with dolutegravir, characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Clinical study data from the development programme with dolutegravir plus data from post marketing sources provide the evidence for this risk.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.3, 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	A prospective Observational Cohort Study to Monitor and Compare the Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir (with or without ABC) or other Integrase Inhibitors

Important identified risk: Hepatobiliary disorders	
Evidence for linking the risk to the medicine	Clinical trials have shown that elevations of liver enzymes and hepatitis may occur with dolutegravir containing regimen; these events are uncommon. Post marketing experience has shown that, rarely, cases of more severe liver dysfunction may occur in patients with no pre-existing risk factors for such disease. Hepatobiliary disorders (Drug induced liver injury [DILI] and other clinically significant elevations in transaminases) are considered an identified risk for DTG. Clinical study data from the development programme with dolutegravir, plus data from post marketing sources provide the evidence for this risk.

Important identified risk: Hepatobiliary disorders	
Risk factors and risk groups	Other causes of liver injury in HIV-infected subjects such as antiretroviral toxicities, alcohol abuse, and non-alcoholism related fatty liver disease can also lead to significant hepatic impairment. Review of the data on patients co-infected with viral hepatitis does not suggest any increased safety concerns with the use of dolutegravir in these patients.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4 and 4.8 of the SmPC**.** **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	A prospective Observational Cohort Study to Monitor and Compare the Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir (with or without ABC) or other Integrase Inhibitors

Important identified risk: Depression (including suicidal ideation and behaviours, particularly in patients with a pre-existing history of depression or psychiatric illness)	
Evidence for linking the risk to the medicine	Depression and suicidal ideation and behaviours have been observed with dolutegravir. These events occur particularly in patients with a pre-existing history of depression or psychiatric illness. Clinical study data from the development programme with dolutegravir, plus data from post marketing sources provide the evidence for this risk.
Risk factors and risk groups	Patients with a history of psychiatric disease would be at increased risk.
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.8 of the SmPC **Additional risk minimisation measures:**

	None
Additional pharmacovigilance activities	None

Important potential risk: Serious rash (DAIDS Grade 3 or 4)	
Evidence for linking the risk to the medicine	Severe, potentially life-threatening, and fatal skin reactions are labelled for raltegravir so are considered a potential risk for dolutegravir
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.8 of the SmPC. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	A prospective Observational Cohort Study to Monitor and Compare the Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir (with or without Abacavir) or other Integrase Inhibitors.

Important potential risk: Neural tube disorders	
Evidence for linking the risk to the medicine	Preliminary findings from a birth outcomes surveillance study conducted in Botswana show a higher than expected number of neural tube defects (NTDs), among newborns whose mothers were exposed to dolutegravir -based antiretroviral therapy at conception. There are no relevant findings in pre-clinical studies. There is no evidence of a congenital abnormality signal related to the use of dolutegravir during pregnancy from any other source. The study is a large prospective study specifically designed to assess the incidence of NTDs.
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

Important potential risk: Neural tube disorders	
	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 minimisation measures	**Routine risk minimisation measures:** Section 4.6 of the SmPC. **Additional risk minimisation measures:** Direct health care professional communication
Additional pharmacovigilance activities	Antiretroviral pregnancy registry Study 208613 -DOLOMITE EPPICC Study Study 208759 -DOLOMITE NEAT ID Network Study

Missing Information: Use in the elderly	
Evidence for linking the risk to the medicine	There is limited information regarding the use of DTG in the elderly (>65 years old). The majority of subjects in the DTG clinical studies were <65 years of age.
Risk factors and risk groups	Not applicable

Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.2 and 5.2 of the SmPC. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Missing Information: Use in pregnancy	
Evidence for linking the risk to the medicine	At the time of the MAA. no studies had been conducted with dolutegravir in pregnant women and pregnant and breastfeeding women were excluded from the dolutegravir clinical studies. Subjects that became pregnant (intrauterine) were required to discontinue from the studies. Clinical experience of dolutegravir use during pregnancy is therefore limited.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.6 of the SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Antiviral Pregnancy Registry Study 200336- A Prospective, Interventional Pharmacokinetic and Safety Study of dolutegravir/abacavir/lamivudine in Pregnant Women[1] Study 208613 - DOLOMITE EPPICC Study Study 208759- DOLOMITE NEAT ID Network Study

1. This study is currently on hold

Missing Information: Long term safety data	
Evidence for linking the risk to the medicine	The initial dolutegravir marketing authorization application included long-term clinical safety data for approximately 1400 subjects receiving dolutegravir at the recommended dose or higher for 24 weeks or longer. Although some data are now available in subjects from two studies in children with HIV treated with DTG, further data from the ongoing paediatric study P1093 will be evaluated to provide additional information on the long term safety of DTG therapy in children. Long term safety data in adults and children are therefore considered to be missing information for DTG.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Ongoing paediatric Study P1093

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 TIVICAY.

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
Prospective Observational Cohort Study in Patients Receiving Dolutegravir (EuroSIDA Cohort)	To investigate the risk of hypersensitivity reaction, hepatotoxicity and serious rash (DAIDS category 3 or 4)	Hypersensitivity reaction Hepatotoxicity Serious rash (DAIDS category 3 or 4)	Ongoing	Final Report April 2020
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 cohort.	Use in pregnancy, neural tube defects	Ongoing	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the Antiretroviral Pregnancy Registry.
Study 200336 -A Prospective, Interventional Pharmacokinetic and Safety Study of DTG/ABC/3TC in Pregnant Women	To investigate the use of dolutegravir during pregnancy	Pregnant/breastfeeding women	On hold	End of study CSR anticipated 2020[1]
Study 208613 DOLOMITE EPPICC Study	Assess “real-world” maternal and foetal outcomes following dolutegravir use during pregnancy and to describe patterns of dolutegravir utilization	Use in pregnancy, neural tube defects	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	To assess the safety and effectiveness of dolutegravir in pregnancy in the NEAT-ID network of approximately 40 sites across Europe.	Use in pregnancy, neural tube defects	Planned	Final Report Expected October 2022	
Study ING112578 (P1093)	To assess the safety, tolerability and antiviral activity of DTG, in combination regimens in HIV-1 infected infants, children and adolescents	Long term safety data	Ongoing	Interim report	48 Week CSR expected Q4 2021.
				Final data	Expected 2025 (includes 3 year follow-up period).

1. This study is currently on hold, so this date is subject to change.