Swiss Summary of the Risk Management Plan (RMP) for Tivicay (Dolutegravir)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Tivicay is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Tivicay in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. ViiV Healthcare GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tivicay.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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:
https://www.ema.europa.eu/en/medicines/human/EPAR/tivicay

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	None
Important potential risks	Neural tube defects
Missing information	Use in pregnancy/ breastfeeding Long term safety data

II.B Summary of important risks

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 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 minimisation measures	**Routine risk minimisation measures:** Section 4.6 of the SmPC. **Additional risk minimisation 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	
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	Antiretroviral Pregnancy Registry Study 208613 - DOLOMITE EPPICC Study Study 208759- DOLOMITE NEAT ID Network Study

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	
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 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 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	Ongoing	Final Report Expected October 2023	
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 completed 16 December 2021.
				Final data	Expected 2025 (includes 3- year follow-up period).