MODULE 2.6.1. INTRODUCTION

1. INTRODUCTION

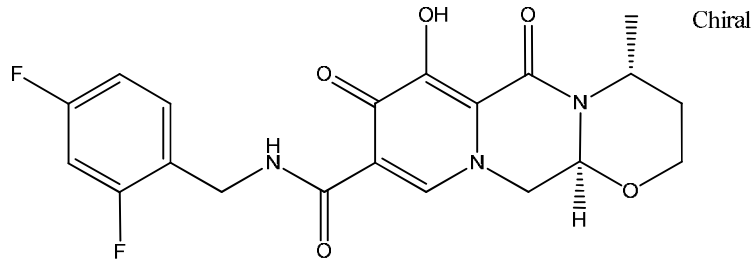
Dolutegravir (DTG; GSK1349572) is an HIV integrase inhibitor (INI) approved for use in antiretroviral treatment-naïve and treatment-experienced HIV-infected adults and adolescents at a dose of 50 mg once daily (TIVICAY®). Rilpivirine (RPV; TMC278, GSK1329758) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for use in antiretroviral treatment-naïve HIV-1-infected adults with a viral load ≤100,000 HIV-1 RNA copies/mL, at a dose of 25 mg once daily taken with meal (EDURANT®) (see Table 1.1). The structure of each compound is shown in Figure 1.1.

DTG/RPV FDC is a two-drug, NRTI sparing regimen, differing from the current standard of care, which typically includes 2 NRTIs plus a third agent from the PI, NNRTI or INI class. The proposed new combination treatment regimen of DTG and RPV targets HIV replication at the early and late stage of the virus life cycle, respectively, resulting in suppression of HIV-1 replication in a substantial proportion of infected cells. Based on the established tolerability and combined resistance profiles of DTG and RPV, this simplified two-drug regimen offers favorable tolerability and suppression of resistance similar to other DTG based HIV-1 treatment regimens.

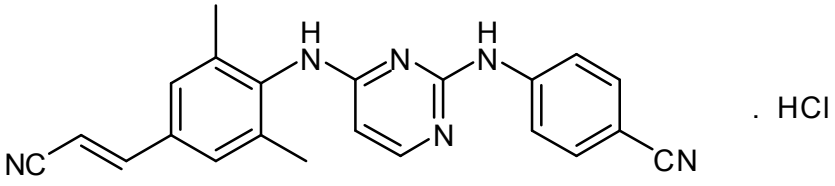
Table 1.1 US Approvals of Dolutegravir and Rilpivirine

Product	NDA Number	US Approval Date
TIVICAY Tablets (Dolutegravir 50 mg)	NDA 204790	12 August 2012
EDURANT Tablets (Rilpivirine 25 mg)	NDA 202022	20 May 2011

Figure 1.1 Structure of DTG and RPV



Dolutegravir (DTG)



Rilpivirine (RPV)

Where dolutegravir and rilpivirine have been approved as monotherapies or in combination in the treatment of HIV-1, comprehensive packages of nonclinical pharmacodynamic, pharmacokinetic and toxicological evaluations have been submitted along with nonclinical study reports (see Table 1.1 for NDA numbers).

In agreement with ICH Guidance M3 (R2), nonclinical combination studies have not been conducted with DTG/RPV, with the exception that combination pharmacokinetics studies in dogs were performed with DTG and RPV together to determine any potential effects of co-administration on the pharmacokinetics and using various formulations.

Studies described in m2.6 were performed using either the sodium salt form of dolutegravir or the hydrochloride salt form of rilpivirine. All dosages and concentrations quoted in this summary are expressed in terms of the parent compounds (referred to simply as dolutegravir and rilpivirine).

In dolutegravir study reports with, the parent form of dolutegravir was designated as ERC-349572A, ERC-349572 free acid or GSK1349572B, and the sodium salt was designated as ERC-349572B, ERC-349572 sodium or GSK1349572A.

In rilpivirine study reports, rilpivirine was referred to as TMC278 and R278474 (base form) (early in development) and R314585 (HCl salt) (later in development). In the m2.6 summaries, rilpivirine base is referred to when the base was administered and rilpivirine is referred to when the hydrochloride (HCl) salt was administered.

The new pharmacokinetic studies summaries are provided in m2.6.4 and m2.6.5 and the corresponding company reports are located in m4.2, Study Reports.

Filing Strategy

The nonclinical pharmacokinetic study summaries presented in m2.6.4 and m2.6.5 support either the FDC or are new monotherapy nonclinical studies which have not been previously submitted.