PRODUCT INFORMATION

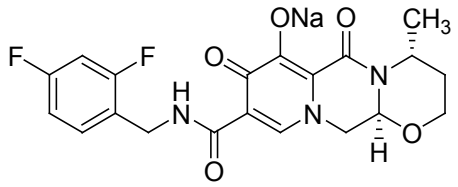
TIVICAY[â] (dolutegravir) Tablets

NAME OF THE MEDICINE

TIVICAY[â] film-coated tablets contain dolutegravir (as dolutegravir sodium) which is an integrase inhibitor active against Human Immunodeficiency Virus (HIV).

The chemical (IUPAC) name for dolutegravir sodium is Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate.

The structural formula is:



Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

Molecular weight of 441.36 g/mol.

CAS Registry Number: 1051375-19-9

DESCRIPTION

Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water. The partition coefficient (log P) for dolutegravir sodium is 2.2 and the pKa is 8.2.

TIVICAY is supplied as film-coated tablets each containing 52.6 mg of dolutegravir sodium, equivalent to 50 mg of dolutegravir free acid. TIVICAY tablets also contain: mannitol, microcrystalline cellulose, povidone, sodium starch glycolate Type A, sodium stearylfumarate, polyvinyl alcohol – part hydrolyzed, titanium dioxide, macrogol 3350, talc, and iron oxide yellow.

PHARMACOLOGY

Mechanism of Action

Dolutegravir 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. In vitro, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t ½ 71 hours). Two in vitro strand transfer biochemical assay formats using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC50s of 2.7 nM and 12.6 nM.

Pharmacodynamic Effects

In a randomized, dose-ranging trial, HIV 1–infected patients treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean declines from baseline to day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 log10 for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild type HIV-1 in peripheral blood mononuclear cells (PBMC) and MT4 cells with mean IC_{50}s of 0.5 nM to 2.1 nM.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to laboratory strains, with a mean IC_{50} of 0.52 nM. When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clade A, B, C, D, E, F and G) and group O] and 3 HIV-2 clinical isolates, the geometric mean IC_{50} was 0.20 nM and IC_{50} values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean IC_{50} was 0.18 nM and IC_{50} values ranged from 0.09 to 0.61 nM for HIV-2 isolates.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of dolutegravir in vitro was not antagonistic with the integrase inhibitor (INI) raltegravir; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir or stavudine; the protease inhibitors (PIs) amprenavir or lopinavir; the CCR5 co-receptor antagonist maraviroc; or the fusion inhibitor enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor adefovir, or inhibited by the antiviral ribavirin.

Resistance In Vitro

Dolutegravir-resistant viruses were selected in studies of potential resistance using different wild type strains and clades of HIV-1. Amino acid substitutions that emerged during passaging included E92Q, G193E, G118R, S153F or Y, and R263K, and were associated with decreased susceptibility to dolutegravir of up to 11-fold.

In resistance development studies starting with the single raltegravir resistance mutants Q148H, Q148K or Q148R, additional mutations detected during passage with dolutegravir included E138K/Q148K, E138K/Q148R, Q140S/Q148R and G140S/Q148R, which all exhibited greater than ten-fold reductions in sensitivity to dolutegravir.

Anti-HIV Activity Against Resistant Strains: Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant, and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wildtype strain.

Cross Resistance: Integrase Inhibitor-Resistant HIV-1 Strains: Sixty integrase inhibitor-resistant mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) were produced from wild-type virus NL-432 using site-directed mutagenesis. Dolutegravir showed anti-HIV activity (susceptibility) with FC <5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H. A G118R substitution conferred a 10 fold reduction in dolutegravir susceptibility but has not been observed during DTG clinical studies. The single INSTI resistance substitutions T66K, I151L, and S153Y conferred a >2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at

E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Cross Resistance: Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on patients infected with HIV-2 and treated with raltegravir who showed virologic failure. HIV-2 mutants with combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D were associated with four-fold reductions in dolutegravir susceptibility, while susceptibility of viruses with E92Q/N155H and G140S/Q148R substitutions were decreased 8.5 and 17 fold, respectively.

Clinical Isolates From Raltegravir Treatment Virologic Failure Patients: Thirty clinical isolate samples with genotypic and phenotypic resistance to raltegravir (median FC >81) were examined for susceptibility to dolutegravir (median FC 1.5). The median FC to dolutegravir for isolates containing changes at G140S + Q148H was 3.75; G140S + Q148R was 13.3; T97A + Y143R was 1.05 and N155H was 1.37.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analysed for susceptibility to dolutegravir. Dolutegravir has a <10 FC against 93.9% of the 705 clinical isolates. Dolutegravir has a ≤10 FC against 67 (73%) of the 92 clinical isolates with Q148 + ≥ 2 INSTI-resistance substitutions and 168 (91%) of the 184 isolates with Q148 + 1 INSTI resistance substitutions.

Resistance In Vivo: Integrase Inhibitor Naïve Patients

No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment–naive studies (SPRING-1, SPRING-2 and SINGLE studies). In the SAILING study for treatment experienced (and integrase naïve) patients (n=354 in the dolutegravir arm), treatment emergent integrase resistance was observed in 2 of 9 patients with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum FC of 1.93 (*see Clinical Trials*).

Resistance In Vivo: Integrase Inhibitor Resistant Patients

The VIKING-3 study examined dolutegravir (plus optimized background therapy) in patients with pre-existing INI resistance. Twenty six patients (26/114) experienced protocol defined virologic failure through to Week 24. Of these, 25 had paired baseline and PDVF resistance data for analysis and 13/25 (52%) had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were E92Q (n=2), T97A (n=6), E138K/A (n=4), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=3), and N155H (n=1). Eleven of the 13 patients with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically.

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy patients received single dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. Dolutegravir did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec).

Effects on Renal Function

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3 arm, parallel, placebo-controlled study in 37 healthy patients, who were administered dolutegravir 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily

(n=12) for 14 days. A modest decrease in CrCl was observed with dolutegravir within the first week of treatment, consistent with that seen in clinical studies. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support in vitro studies which suggest that the small increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Pharmacokinetics:

Dolutegravir pharmacokinetics is similar between healthy and HIV-infected patients. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy patients, between-patient CVb% for AUC and Cmax ranged from ~20 to 40% and Ct from 30 to 65% across studies. The between-patient PK variability of DTG was higher in HIV-infected patients than healthy patients and CVb% was estimated to be 30-50% for AUC and Cmax, and at 55-140% for Ct. Within-patient variability (CVw%) is lower than between-patient variability.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-¥)}$ by 34%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99.3%) to human plasma proteins based on in vitro data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12.5 L. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components Free fraction of dolutegravir in plasma is estimated at approximately 0.2 to 1.1% in healthy patients, approximately 0.4 to 0.5% in patients with moderate hepatic impairment, and 0.8 to 1.0% in patients with severe renal impairment and 0.5% in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve patients on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged at 18 ng/mL (comparable to unbound plasma concentration, and above the IC50) and CSF:plasma concentration ratio of dolutegravir ranged from 0.11 to 0.66%. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2.1 log after 2 weeks of therapy (*see Pharmacodynamics*).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6 to 10% of that in corresponding plasma at steady-state. AUC was 7% in semen and 17% in rectal tissue, of those in corresponding plasma at steady-state.

Metabolism

Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (<1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Excretion

Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0.56 L/hr.

Special Patient Populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected children and adolescents 12 to <18 years of age showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure in paediatric patients comparable to that observed in adults who received dolutegravir 50 mg once daily.

Table 1 Paediatric pharmacokinetic parameters

Age/weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
		$AUC_{(0-24)}$ mg.hr/mL	C_{max} mg/mL	C_{24} mg/mL
12 to 18 years ³ 40 kg [a]	50 mg once daily [a]	46 (43)	3.49 (38)	0.90 (59)

[a] One patient weighing 37 kg received 35 mg once daily.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in patients of >65 years old are limited.

Renal Impairment

Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in patients with severe renal impairment (CLcr <30 mL/min). No clinically important pharmacokinetic differences between patients with severe renal impairment (CLcr <30 mL/min) and matching healthy patients were observed. No dosage adjustment is necessary for patients with renal impairment. Caution is warranted for INI-experienced patients (with certain INI-associated resistance substitutions or clinically suspected INI resistance) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic Impairment

Dolutegravir is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in Drug Metabolising Enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomic samples collected in clinical studies in healthy patients, patients with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with patients with genotypes associated with normal metabolism via UGT1A1 (n=41). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Gender

The dolutegravir exposure in healthy patients appear to be slightly higher (~20%) in women than men based on data obtained in a healthy patient study (males n=17, females n=24). Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race

Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese patients appear similar to observed parameters in Western (US) patients.

Co-infection with Hepatitis B or C

Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on patients with hepatitis B co-infection.

CLINICAL TRIALS

Antiretroviral Naïve Patients

The efficacy of TIVICAY in HIV-infected, therapy naive patients is based on the analyses of 48-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING-2, 822 adults were randomized and received at least one dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC). At baseline, median patient age was 36 years, 14% were female, 15% non-white, and 12% had hepatitis B and/or C co-infection and 2% were CDC Class C; these characteristics were similar between treatment groups.

In SINGLE, 833 patients were randomized and received at least one dose of either TIVICAY 50 mg once daily with fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). At baseline, median patient

age was 35 years, 16% were female, 32% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.

Week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 2.

Table 2 Virologic Outcomes of Randomized Treatment of SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm)

	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTI N=411	RAL 400 mg Twice Daily + 2 NRTI N=411	TIVICAY 50 mg + ABC/3TC Once Daily N=414	EFV/TDF/FTC Once Daily N=419
HIV-1 RNA <50 copies/mL	88%	85%	88%	81%
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%) P=0.003	
Virologic failure†	5%	8%	5%	6%
No virologic data at Week 48 window	7%	7%	7%	13%
Reasons				
Discontinued study/study drug due to adverse event or death‡	2%	1%	2%	10%
Discontinued study/study drug for other reasons§	5%	6%	5%	3%
Missing data during window but on study	0%	0	0	<1%
HIV-1 RNA <50 copies/mL by Baseline Plasma Viral Load (copies/mL)	n / N (%)	n / N (%)	n / N (%)	n / N (%)
£100,000	267 / 297 (90%)	264 / 295 (89%)	253 / 280 (90%)	238 / 288 (83%)
>100,000	94 / 114 (82%)	87 / 116 (75%)	111 / 134 (83%)	100 / 131 (76%)
HIV-1 RNA <50 copies/mL by Baseline CD4+ (cells/ mm^3)				
<200	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)
200 to <350	128 / 144 (89%)	118 / 139 (85%)	143 / 163 (88%)	126 / 159 (79%)
³ 350	190 / 212 (90%)	199 / 222 (90%)	176 / 194 (91%)	164 / 198 (83%)
HIV RNA <50 copies/mL by NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Gender				
Male	308 / 348 (89%)	305 / 355 (86%)	307 / 347 (88%)	291 / 356 (82%)

	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTI N=411	RAL 400 mg Twice Daily + 2 NRTI N=411	TIVICAY 50 mg + ABC/3TC Once Daily N=414	EFV/TDF/FTC Once Daily N=419
Female	53 / 63 (84%)	46 / 56 (82%)	57 / 67 (85%)	47 / 63 (75%)
Race				
White	306 / 346 (88%)	301 / 352 (86%)	255 / 284 (90%)	238 /285 (84%)
Non white	55 / 65 (85%)	50 / 59 (85%)	109 / 130 (84%)	99 / 133 (74%)
Age (years)				
<50	324 / 370 (88%)	312 / 365 (85%)	319 / 361 (88%)	302 / 375 (81%)
³ 50	37 / 41 (90%)	39 / 46 (85%)	45 / 53 (85%)	36 / 44 (82%)

* Adjusted for baseline stratification factors.
† Includes patients who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), patients who discontinued prior to Week 48 for lack or loss of efficacy and patients who are ³ 50 copies in the 48 week window.
‡ Includes patients who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window.
§ Includes reasons such as withdrew consent, loss to follow-up, moved, protocol deviation.
Notes: ABC/3TC = abacavir 600 mg, lamivudine 300 mg in the form of Kivexa fixed dose combination (FDC)
EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg FDC.
N = Number of patients in each treatment group

In the SPRING-2 study, virologic suppression (HIV-1 RNA <50 copies/mL) in the TIVICAY group (88%) was non-inferior to the raltegravir group (85%). The median change in CD4+ T cell count from baseline were +230 cells/mm^3 in the group receiving TIVICAY and the raltegravir group at 48 weeks.

In the SINGLE study, virologic suppression (HIV-1 RNA <50 copies/mL) in the TIVICAY + ABC/3TC arm was 88%, which was superior to the EFV/TDF/FTC arm (81%), based on the primary analysis (p=0.003). The adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm^3 in the group receiving TIVICAY + ABC/3TC and 208 cells/mm^3 for the EFV/TDF/FTC arm in SINGLE at 48 weeks. The adjusted difference and 95% CI was 58.9 (33.4, 84.4), p<0.001 (repeated measure model adjusting for the baseline stratification factors: baseline HIV-1 RNA and baseline CD4+ T cell count, among other factors). This analysis was pre-specified and adjusted for multiplicity. The median time to viral suppression was 28 days in the group receiving TIVICAY + ABC/3TC and 84 days in the EFV/TDF/FTC arm in SINGLE at 48 weeks (p<0.0001). This analysis was pre-specified and adjusted for multiplicity.

In both SPRING-2 and SINGLE studies virologic suppression (HIV-1 RNA <50 copies/mL), treatment differences were comparable across baseline characteristics (gender, race and age).

Through 48 weeks in SPRING-2 and SINGLE, no INI-resistant mutations or treatment emergent resistance in background therapy were isolated on the TIVICAY-containing arms. In SPRING-2, four patients on the raltegravir arm failed with major NRTI mutations and one patients developed raltegravir resistance; in SINGLE, four patients on the EFV/TDF/FTC arm failed with mutations associated with NNRTI resistance and one developed a major NRTI mutation.

Sustained virological response was demonstrated in the SPRING-1 study (ING112276), in which 88% of patients receiving TIVICAY 50 mg (n=51) once daily) had HIV-1 RNA <50 copies/mL, compared to 72% of patients in the efavirenz group (n=50) at 96 weeks. No INI-resistant mutations or treatment emergent resistance in background therapy were isolated with TIVICAY 50 mg once daily through 96 weeks.

Antiretroviral Experienced (and Integrase Inhibitor Naïve) Patients

In the international, multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, ART-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator selected background regimen (BR) consisting of up to 2 agents (including at least one fully active agent). At baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection, and 46% were CDC Class C. All patients had at least two class ART resistance, and 49% of patients had at least 3-class ART resistance at baseline.

Week 24 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 3.

Table 3 Virologic Outcomes of Randomized Treatment of SAILING at 24 Weeks Interim Analysis (Snapshot algorithm)

	SAILING	
	TIVICAY 50 mg Once Daily + BR N=354§	RAL 400 mg Twice Daily + BR N=361§
HIV-1 RNA <50 copies/mL	79%	70%
Adjusted Treatment Difference‡	9.7% (95% CI: 3.4%, 15.9%) P=0.003	
Virologic failure	15%	24%
No virologic data at Week 24 window	6%	6%
Reasons		
Discontinued study/study drug due to adverse event or death‡	2%	2%
Discontinued study/study drug for other§	3%	3%
Missing data during window but on study	<1%	<1%
HIV-1 RNA <50 copies/mL by Baseline Plasma Viral Load (copies/mL)	n / N (%)	n / N (%)
£50,000 copies/mL	207 / 249 (83%)	195 / 254 (77%)
>50,000 copies/mL	74 / 105 (70%)	57 / 107 (53%)
HIV-1 RNA <50 copies/mL by Baseline CD4+ (cells/ mm^3)		
<50	41 / 62 (66%)	31 / 59 (53%)
50 to <200	87 / 111 (78%)	84 / 125 (67%)
200 to <350	68 / 82 (83%)	58 / 79 (73%)
^{3} 350	85 / 99 (86%)	79 / 98 (81%)
HIV-1 RNA <50 copies/mL by Background Regimen		
Phenotypic Susceptibility Score* <2	83 / 105 (79%)	67 / 94 (71%)
Phenotypic Susceptibility Score* =2	198 / 249 (80%)	185 / 267 (69%)
Genotypic Susceptibility Score* <2	171 / 216 (79%)	134 / 196 (68%)
Genotypic Susceptibility Score* =2	110 / 138 (80%)	118 / 165 (72%)
Use of DRV without PI mutations		
Yes	57 / 71 (80%)	63 / 78 (81%)
No	224 / 283 (79%)	189 / 283 (67%)
HIV-1 RNA <50 copies/mL by Gender		
Male	192 / 247 (78%)	167 / 238 (70%)
Female	89 / 107 (83%)	85 / 123 (69%)
HIV-1 RNA <50 copies/mL by Race		

	SAILING	
	TIVICAY 50 mg Once Daily + BR N=354§	RAL 400 mg Twice Daily + BR N=361§
White Non white	140 / 178 (79%) 140 / 175 (80%)	121 / 175 (69%) 131 / 185 (71%)
HIV-1 RNA <50 copies/mL by Age (years)		
<50 ³ 50	215 / 269 (80%) 66 / 85 (78%)	185 / 277 (67%) 67 / 84 (80%)
HIV-1 RNA <50 copies/mL by HIV sub type		
Clade B Clade C Other†	192 / 241 (80%) 42 / 55 (76%) 46 / 57 (81%)	176 / 245 (72%) 30 / 48 (63%) 46 / 68 (68%)

‡ Adjusted for baseline stratification factors
§ 4 patients were excluded from the efficacy analysis due to data integrity at one study site
*The Phenotypic Susceptibility Score (PSS) and the Genotypic Susceptibility Score (GSS) were defined as the total number of ARTs in BR to which a patient's viral isolate showed susceptibility at baseline based upon phenotypic or genotypic resistance tests. Background regimen was restricted to £ 2 ART with at least one fully active agent, however, n=11 PSS 0, n=2 PSS 3.
†Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.
Notes: BR = background regimen, RAL = raltegravir; N = Number of patients in each treatment group

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir arm (79%) was statistically superior to the raltegravir arm (70%), based on the Week 24 prespecified analysis (p=0.003). Virologic suppression (HIV-1 RNA <50 copies/mL) treatment differences were comparable across the baseline characteristics of gender, race, and HIV sub type. The mean changes in CD4+ T cell count from baseline were 113.9 cells/mm^3 in the group receiving TIVICAY and 105.8 cells/mm^3 for the raltegravir group.

Statistically fewer patients failed therapy with treatment-emergent resistance in the IN gene on TIVICAY (2/354, 0.6%) than on raltegravir (10/361, 2.8%) (p=0.016).

Integrase Inhibitor Resistant Patients

In the Phase IIb, international multicentre, open-label, single arm, non-comparative sequential cohort VIKING pilot study (ING112961), two sequential cohorts of patients with multiclass resistance including resistance to HIV integrase inhibitors were enrolled to examine the antiviral activity of TIVICAY 50 mg once daily (n=27) vs. 50 mg twice daily (n=24) after 10 days of functional monotherapy. Responses were greater with twice daily (1.8 log10 change from baseline in HIV RNA) than with once daily dosing (1.5 log10 change from baseline, adjusted difference 0.3 log10, p=0.017). Higher response rates with twice daily dosing were maintained with continued TIVICAY dosing and optimization of the background regimen through 48 weeks of therapy (33% vs. 71% <50 c/mL, ITT-E TLOVR analysis). A comparable safety profile was observed across doses. Subsequently, VIKING-3 examined the effect of TIVICAY 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy and continued TIVICAY twice daily treatment.

In the multicentre, open-label, single arm, non-comparative VIKING-3 study (ING112574), HIV-1 infected, ART-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days but with optimised background ART from Day 8. One hundred and eighty-three patients enrolled, 124 with INI-resistance at Screening and 59 with historical (but no Screening) resistance. At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4 was 140 cells/mm^3, median duration of prior ART was 13 years, and 56% were CDC Class C. Patients showed multiple class ART

resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was 1.4log10 (95% CI 1.3 – 1.5log10, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 4.

Table 4 Virologic Response (Plasma HIV-1 RNA) at Day 8 by Derived baseline IN Resistance Mutation Group [Day 8 Virologic Outcome (VO) Population]

Derived IN Mutation Group	Number of patients (VO population)	Mean CFB (SD) at Day 8	%>1log10 decline at Day 8*
No Q148H/K/R mutations#	122	-1.59 (0.51)	92%
Q148 + 1 secondary mutation^	35	-1.18 (0.52)	71%
Q148 + ³ 2 secondary mutations^	20	-0.92 (0.81)	45%
# Includes primary INI resistance mutations N155H, Y143C/H/R, T66A, E92Q, or historical evidence of INI resistance only * Includes patients with HIV RNA <50 copies/mL at Day 8 ^ G140A/C/S, E138A/K/T, L74I			

After the monotherapy phase, patients had the opportunity to re-optimize their background regimen when possible.

Of the 114 patients who completed 24 weeks on study or discontinued before data cut-off, 72 (63%) had <50 copies/mL RNA at Week 24 (Snaphot algorithm). Patients harbouring virus with Q148 with additional Q148-associated secondary mutations has lower response at Week 24. Background overall susceptibility score (OSS) was not associated with Week 24 response.

Table 5 Week 24 Virologic Response by Derived baseline IN Resistance Mutation Group and OSS of OBR (HIV-1 RNA <50 c/mL, Snapshot algorithm), Week 24 VO Population

Derived IN Mutation Group	OSS=0	OSS=1	OSS=2	OSS>2	Total
No Q148H/K/R mutations[1]	2/2 (100%)	24/29 (83%)	21/28 (75%)	10/13 (77%)	57/72 (79%)
Q148 + 1 secondary mutation[2]	2/2 (100%)	3/7 (43%)	4/11 (36%)	-	9/20 (45%)
Q148 +≥2 secondary mutations[2]	1/2 (50%)	0/7	-	-	1/9 (11%)
[1] N155H, Y143C/H/R, T66A, E92Q, or historical evidence of INI resistance only. [2] G140A/C/S, E138A/K/T, L74I OSS: Overall susceptibility score [combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment)]					

Virologic suppression (HIV-1 RNA <50 copies/mL) was comparable across baseline characteristics (gender, race and age). At Week 24 the median change in CD4+ T cell count from baseline was 65 cells/mm^3 for VIKING-3 based on observed data.

Children

In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of TIVICAY was evaluated in combination regimens in HIV-1 infected infants, children and adolescents.

At 24 weeks, seven of ten (70%) adolescents (12 to less than 18 years of age) treated with TIVICAY once daily (35 mg n=1, 50 mg n=9) plus OBR achieved viral load less than 50 copies/mL.

INDICATIONS

TIVICAY is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age and weighing 40kg or more.

CONTRAINDICATIONS

TIVICAY is contraindicated in combination with dofetilide.

TIVICAY is contraindicated in patients with known hypersensitivity to TIVICAY or to any of the excipients.

PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including TIVICAY, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jiroveci (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of TIVICAY therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective

hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (*see Adverse Effects*).

Opportunistic Infections

Patients receiving TIVICAY or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection

Patients should be advised that current antiretroviral therapy, including TIVICAY, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Drug Interactions

Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of TIVICAY or medications that may have their exposure changed by TIVICAY (*see Contraindications and Interactions with Other Medicines*).

The co-administration of TIVICAY with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir+ritonavir (ATV+RTV), lopinavir+ritonavir (LPV+RTV) or darunavir + ritonavir (DRV+RTV) (*see Interactions with Other Medicines*).

The recommended dose of TIVICAY is 50 mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (*see Interactions with Other Medicines*).

TIVICAY should not be co-administered with polyvalent cation-containing antacids. TIVICAY is recommended to be administered two hours before or six hours after these agents (*see Interactions with Other Medicines*).

Metformin concentrations may be increased by TIVICAY. Patients should be monitored during therapy and a dose adjustment of metformin may be required (*see Interactions with Other Medicines*).

Effects on Fertility:

There are no data on the effects of TIVICAY on human male or female fertility. TIVICAY did not affect male or female mating or fertility in rats at doses up to 1000 mg/kg/day associated with an exposure level 24 times the clinical exposure based on AUC at the maximum recommended dose of 50 mg BID.

Use in Pregnancy (Category B1):

There are no adequate and well-controlled studies of TIVICAY in pregnant women. The effect of TIVICAY on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. TIVICAY should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (27 times the 50 mg human clinical exposure based on AUC at the maximum recommended dose of 50 mg BID).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation was associated with marked maternal toxicity, but did not elicit developmental toxicity or teratogenicity in the offspring (0.4 times the clinical exposure based on AUC).

Use in Lactation:

Health experts recommend that where possible HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV. It is expected that dolutegravir will be secreted into human milk based on studies in lactating rats and their offspring, although this has not been confirmed in humans. It is recommended that mothers taking TIVICAY do not breast feed.

Paediatric Use:

The safety and efficacy of TIVICAY has not yet been established in children (< 12 years or weighing less than 40 kg.).

Use in the Elderly:

There are limited data available on the use of TIVICAY in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (*see Pharmacokinetics – Special Patient Populations*).

Genotoxicity:

Dolutegravir was not mutagenic or clastogenic using in vitro tests in bacteria and cultured mammalian cells, and an in vivo rodent micronucleus assay.

Carcinogenicity:

In long-term oral carcinogenicity studies conducted with dolutegravir no drug-related increases in tumour incidence were found in mice at doses up to 500 mg/kg/day (14 times the human systemic exposure based on AUC at the maximum recommended dose of 50 mg BID) or in rats at doses up to 50 mg/kg/day (12 times the human systemic exposure based on AUC at the maximum recommended dose).

Effects on ability to drive and use machines:

There have been no studies to investigate the effect of TIVICAY on driving performance or the ability to operate machinery.

The clinical status of the patient and the adverse event profile of TIVICAY should be borne in mind when considering the patient's ability to drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES

Effect of TIVICAY on the Pharmacokinetics of Other Agents

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In vitro, dolutegravir inhibited the renal organic cation transporter, OCT2 (IC50 = 1.93 µM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 (dofetilide and metformin) (see Table 6).

In vitro, dolutegravir did not inhibit (IC50 >50 µM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

Effect of Other Agents on the Pharmacokinetics of TIVICAY

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those

enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Selected drug interactions are presented in Table 6. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 6 Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ¯ AUC ¯ 71% C_{max} ¯ 52% Ct ¯ 88% ETR «	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ¯ AUC ¯ 57% C_{max} ¯ 39% Ct ¯ 75% EFV «	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ¯	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir - AUC - 91% C_{max} - 49% Ct - 180% ATV «	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV/RTV)	Dolutegravir - AUC - 62% C_{max} - 33% Ct - 121% ATV « RTV «	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV/RTV)	Dolutegravir ¯ AUC ¯ 59% C_{max} ¯ 47% Ct ¯ 76% TPV « RTV «	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir or Concomitant Drug	Clinical Comment
Protease Inhibitor: Fosamprenavir/ritonavir (FPV/RTV)	Dolutegravir ¯ AUC ¯ 35% C_{max} ¯ 24% Ct ¯ 49% FPV « RTV «	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Nelfinavir	Dolutegravir «	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir	Dolutegravir ¯ AUC ¯ 32% C_{max} ¯ 11% Ct ¯ 38%	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir	Dolutegravir «	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine	Dolutegravir « AUC - 10% Cmax - 7% Ct - 28% LPV « RTV «	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine	Dolutegravir ¯ AUC ¯ 25% Cmax ¯ 12% Ct ¯ 36% DRV « RTV «	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Agents		
Dofetilide	Dofetilide -	Co-administration of dolutegravir has the potential to increase dofetilide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration.
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort	Dolutegravir¯	Co-administration with these metabolic inducers may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ¯ AUC ¯ 74% C_{max} ¯ 72%	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. Dolutegravir is recommended to be administered 2 hours before or 6 hours after

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir or Concomitant Drug	Clinical Comment
	C24 ¯ 74%	taking antacid products containing divalent cations.
Metformin	Metformin -	Co-administration of dolutegravir has the potential to increase metformin plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Careful patient monitoring is advised particularly when starting or ending concomitant treatment.
Rifampicin	Dolutegravir ¯ AUC ¯ 54% C_{max} ¯ 43% Ct ¯ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN))	Effect of Dolutegravir: EE « AUC - 3% C_{max} ¯ 1% Ct - 2% Effect of Dolutegravir: NGMN « AUC ¯ 2% C_{max} ¯ 11% Ct ¯ 7%	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Methadone	Effect of Dolutegravir: Methadone « AUC ¯ 2% C_{max} « 0% Ct ¯ 1%	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with dolutegravir.

Abbreviations: - = Increase; ¯ =decrease; « = no significant change; AUC=area under the concentration versus time curve; C_{max}=maximum observed concentration, Ct =concentration at the end of dosing interval

ADVERSE EFFECTS

Clinical trial data

Antiretroviral Naïve Patients

The safety assessment of TIVICAY in HIV-1–infected treatment-naïve patients is based on the analyses of 48-week data from 2 ongoing, international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING 2, 822 patients were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate/lamivudine or emtricitabine/tenofovir). The rates of discontinuation due to adverse events were 2% in patients receiving TIVICAY 50 mg once daily + either abacavir sulfate/lamivudine or emtricitabine/tenofovir and 1% in patients receiving raltegravir 400 mg twice daily + either abacavir sulfate/lamivudine or emtricitabine/tenofovir.

In SINGLE, 833 patients were randomized and received at least 1 dose of either TIVICAY 50 mg with fixed-dose abacavir sulfate/lamivudine once daily or fixed-dose efavirenz/emtricitabine/tenofovir once daily. The rates of discontinuation due to adverse events were 2% in patients receiving TIVICAY 50 mg once daily + abacavir sulfate/lamivudine and 10% in patients receiving efavirenz/emtricitabine/tenofovir once daily.

Treatment-emergent adverse reactions (adverse events assessed as causally related by the investigator) of moderate to severe intensity with a ³2% frequency in either treatment are provided in Table 7. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 7 Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and ³2% Frequency in Treatment-Naive Patients in SPRING-2 and SINGLE Trials (Week 48 Analysis)

	SPRING-2		SINGLE	
Body System/ Preferred Term	TIVICAY 50 mg Once Daily+ 2 NRTIs (N = 411)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
Psychiatric				
Insomnia	1 (<1%)	1 (<1%)	13 (3%)	9 (2%)
Abnormal dreams	1 (<1%)	1 (<1%)	2 (<1%)	8 (2%)
Nervous System				
Dizziness	1 (<1%)	1 (<1%)	2 (<1%)	19 (5%)
Headache	3 (<1%)	4 (<1%)	7 (2%)	9 (2%)
Gastrointestinal				
Nausea	6 (1%)	5 (1%)	3 (<1%)	12 (3%)
Diarrhea	2 (<1%)	2 (<1%)	4 (<1%)	7 (2%)
Skin and Subcutaneous Tissue				
Rash	0	2 (<1%)	1 (<1%)	14 (3%)
Ear and Labyrinth				
Vertigo	0	1 (<1%)	0	7 (2%)

Laboratory abnormalities with a worsening grade from baseline in ³2% (for Grades 3 to 4 combined) of patients are presented in Table 8. The mean change from baseline observed for selected lipid values is presented in Table 9. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 8 Laboratory Abnormalities (³ 2% for Grades 3 to 4 Combined) in Treatment-Naive Patients in SPRING-2 and SINGLE Trials (Week 48 Analysis)

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term (Unit)	TIVICAY 50 mg Once Daily+ 2 NRTIs (N = 411)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
ALT (IU/L)				
Grade 3 (5.1-10.0 x ULN)	4 (<1%)	5 (1%)	0	1 (<1%)
Grade 4 (>10.0 x ULN)	5 (1%)	2 (<1%)	1 (<1%)	1 (<1%)
AST (IU/L)				
Grade 3 (5.1-10.0 x ULN)	7 (2%)	8 (2%)	0	8 (2%)
Grade 4 (>10.0 x ULN)	4 (<1%)	1 (<1%)	0	2 (<1%)
Creatine kinase (IU/L)				
Grade 3 (10.0-19.9 x ULN)	7 (2%)	7 (2%)	6 (1%)	7 (2%)
Grade 4 (³ 20.0 x ULN)	13 (3%)	7 (2%)	5 (1%)	12 (3%)
Lipase (U/L)				
Grade 3 (3.1-5.0 x ULN)	5 (1%)	8 (2%)	7 (2%)	7 (2%)
Grade 4 (>5.0 x ULN)	2 (<1%)	6 (1%)	4 (<1%)	1 (<1%)
Total neutrophils (10^3/mL)				
Grade 3 (0.50-0.749 x 10^9)	5 (1%)	3 (<1%)	5 (1%)	7 (2%)
Grade 4 (<0.50 x 10^9)	3 (<1%)	4 (<1%)	2 (<1%)	5 (1%)

ULN = Upper limit of normal.

Table 9 Mean Change From Baseline in Lipid Values in Treatment-Naive Patients in SPRING-2 and SINGLE Trials (Week 48 Analysis)

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 411)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
Cholesterol (mg/dL)	7.0	8.9	17.1	24.0
HDL cholesterol (mg/dL)	2.7	2.7	5.2	7.9
LDL cholesterol (mg/dL)	3.0	3.4	8.5	13.1
Triglycerides (mg/dL)	9.0	8.7	17.7	18.6

Antiretroviral Experienced (and Integrase Inhibitor Naïve) Patients

In an international, multicenter, double-blind trial SAILING (ING111762), 719 HIV-1–infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent.

At 24 weeks, the rates of discontinuation due to adverse events were <1% (3/354) in patients receiving TIVICAY 50 mg once daily + background regimen and 3% (12/361) in patients receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent adverse reaction (adverse event assessed as causally related by the investigators) of moderate to severe intensity with a ³ 2% frequency in either treatment group was diarrhea, 1% (5/357) in patients receiving TIVICAY 50 mg once daily + background regimen and 2% (6/362) in patients receiving raltegravir 400 mg twice daily + background regimen.

Laboratory abnormalities with a worsening grade from baseline in ³ 2% (for the combined Grades 3 to 4) of patients are presented in Table 10. The mean change from baseline observed for lipid values was similar across both treatment groups at Week 24.

Table 10 Laboratory Abnormalities (³ 2% for Grades 3 to 4 Combined) in Antiretroviral Treatment-Experienced and Integrase Inhibitor-Naïve Patients in the SAILING Trial (Week 24 Analysis)

Laboratory Parameter Preferred Term (Unit)	TIVICAY 50 mg Once Daily + BR[a] (N = 357)	Raltegravir 400 mg Twice Daily + BR[a] (N = 362)
ALT (IU/L)		
Grade 3 (5.1-10.0 x ULN)	5 (1%)	5 (1%)
Grade 4 (>10.0 x ULN)	4 (1%)	1 (<1%)
AST (IU/L)		
Grade 3 (5.1-10.0 x ULN)	6 (2%)	2 (<1%)
Grade 4 (>10.0 x ULN)	6 (2%)	3 (<1%)
Bilirubin (mMol/L)		
Grade 3 (2.6 to 5.0 x ULN)	16 (4%)[b]	10 (3%)[b]
Grade 4 (>5.0 x ULN)	3 (<1%)[b]	2 (<1%)[b]
Creatine kinase (IU/L)		
Grade 3 (10.0-19.9 x ULN)	5 (1%)	2 (<1%)
Grade 4 (³ 20.0 x ULN)	2 (<1%)	2 (<1%)
Lipase (U/L)		
Grade 3 (3.1-5.0 x ULN)	3 (<1%)	4 (1%)
Grade 4 (>5.0 x ULN)	1 (<1%)	3 (<1%)
Total neutrophils (10^3/mL)		
Grade 3 (0.50-0.749 x 10^9)	8 (2%)	6 (2%)
Grade 4 (<0.50 x 10^9)	4 (1%)	3 (<1%)

[a] BR = Background regimen.

[b] Only 1 patient in each treatment group and grade was not receiving atazanavir.

ULN = Upper limit of normal.

Integrase Inhibitor Resistant Patients

In a multicenter, open-label, single-arm trial VIKING-3 (ING112574), 183 HIV-1–infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of discontinuation due to adverse events was 4% of patients at Week 24.

Treatment-emergent adverse reactions (adverse events assessed as causally related by the investigator) of moderate to severe intensity with a ³ 2% frequency are listed in Table 11.

Table 11 Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and ³ 2% Frequency in Integrase Inhibitor-Resistant Patients in the VIKING-3 Trial

Body System/ Preferred Term	TIVICAY 50 mg Twice Daily + Optimized Background Therapy (N = 183)
Gastrointestinal	
Diarrhea	4 (2%)
Nervous System	
Headache	3 (2%)

Treatment-emergent changes in clinical chemistry to Grade 3 events occurred in 16% (29/183) of patients and 3% (6/183) had a Grade 4 event. The most common laboratory abnormality was Grade 3 to 4 elevated creatine kinase (4%, 7/183). Two percent (3/183) of patients had a Grade 3 to 4, treatment-emergent hematology laboratory abnormality, with neutropenia (1%, 2/183) being the most frequently reported.

Changes in Clinical Laboratory Values

Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 24 to 48 weeks. In treatment-naïve patients, a mean change from baseline of 0.11 mg/dL (range: -0.60 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced patients. These changes in serum creatinine are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (GFR) (*see Pharmacology – Effects on Renal Function*).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the clinical trials. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway, uridine diphosphate glucuronosyltransferase (UGT1A1).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials

The following adverse reactions occurred in <2% of treatment-naïve or treatment-experienced patients in any one trial receiving TIVICAY in a combination regimen. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

General Disorders: Fatigue.

Hepatobiliary Disorders: Hepatitis.

Immune System Disorders: Hypersensitivity, immune reconstitution syndrome.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Paediatric population

Based on limited available data in children and adolescents (12 to less than 18 years of age and weighing at least 40 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

Co-infection with Hepatitis B or C

In Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some patients with hepatitis B and/or C co-infection at the start of TIVICAY therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (*see Precautions*).

Post marketing data

At the time of registration there is limited data regarding long-term exposure with dolutegravir.

DOSAGE AND ADMINISTRATION

TIVICAY therapy should be initiated by a physician experienced in the management of HIV infection.

TIVICAY can be taken with or without food.

Adults

Patients infected with HIV-1 without resistance to the integrase class

The recommended dose of TIVICAY is 50 mg once daily.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)

The recommended dose of TIVICAY is 50 mg twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (*see Clinical Trials*).

The following should be considered prior to initiating treatment with TIVICAY 50 mg twice daily:

- Reduced virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an INI-resistance Q148H/K/R mutation plus 2 or more additional INI-resistance mutations including, but not limited to G140A/C/S, E138A/K/T, or L74I *(see Pharmacology)*.

Adolescents

In patients who have not previously been treated with an integrase inhibitor, (12 to less than 18 years of age and weighing greater than or equal to 40 kg) the recommended dose of TIVICAY is 50 mg once daily.

There are insufficient data to recommend a dose for TIVICAY in integrase inhibitor resistant children and adolescents under 18 years of age.

Children

There are insufficient safety and efficacy data available to recommend a dose for TIVICAY in children below age 12 or weighing less than 40 kg.

Populations

Elderly

There are limited data available on the use of TIVICAY in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (*see Pharmacokinetics – Special Patient Populations*).

Renal Impairment

No dosage adjustment is required in patients with mild, moderate or severe (CrCl<30 mL /min, not on dialysis) renal impairment. No data are available in patients receiving dialysis, although differences in pharmacokinetics are not expected in this population (*see Pharmacokinetics — Special Patient Populations*).

Treatment with TIVICAY resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant (*see Adverse Effects*).

TIVICAY has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when TIVICAY is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance.

Hepatic Impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C) (*see Pharmacokinetics – Special Patient Populations*).

OVERDOSAGE

Symptoms and Signs

There is currently limited experience with overdosage in TIVICAY.

Limited experience of single higher doses (up to 250 mg in healthy patients) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of TIVICAY. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As TIVICAY is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Yellow, film-coated, round, biconvex tablets, debossed with 'SV 572' on one side and '50' on the other side. Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium).

TIVICAY tablets are supplied in HDPE (high density polyethylene) bottles containing 30 tablets.

Storage Conditions

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

ViiV Healthcare Pty Ltd,

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 17 January 2014

Date of most recent amendment: 17 January 2014

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