Tivicay (dolutegravir) 50 mg tablets

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

VIKING STUDIES

Efficacy and safety of dolutegravir in treatment-experienced subjects

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DTG TRIALS IN TREATMENT-EXPERIENCED ADULT SUBJECTS WITH HIV

SAILING[1] **INI-naïve**	N=715	Phase III, randomised, double-blind, active-controlled, parallel group, non-inferiority, multicentre study of: • DTG (50 mg QD) + ART • RAL (400 mg BID) + ART
VIKING[2] **(Cohort I)** **INI-resistant**	N=27	Phase IIb open-label, single-arm multicentre study (Cohort I) of: • DTG 50 mg QD + OBR (not incl. RAL)
VIKING[2] **(Cohort II)** **INI-resistant**	N=24	Phase IIb open-label, single arm multicentre study (Cohort II) of: • DTG (50 mg BID) + OBR (not incl. RAL) • subjects required to have ≥1 fully active ARV for Day 11 optimisation (not required for Cohort I)
VIKING-3[3] **INI-resistant**	N=183	Phase III, open-label, single-arm, multicentre study of: • DTG (50 mg BID) + OBR (not incl. RAL)

BID, twice daily; QD, once daily; OBR, optimised background regimen

1. Cahn P, et al. Lancet 2013;382(9893):700-708
2. Eron JJ, et al. *J Infect Dis* 2013;207:740–8
3. Nichols G, et al. IAS 2013. Poster TULBPE19

VIKING-3: KEY OBJECTIVES

Primary objective: antiviral efficacy at Day 8 and Week 24

Primary endpoints

Change from baseline in HIV-1 RNA with DTG 50 mg BID at Day 8

Proportion of subjects with HIV-1 RNA <50 c/mL at Week 24

Secondary endpoints incl.

Predictors of response (e.g. baseline INI resistance)

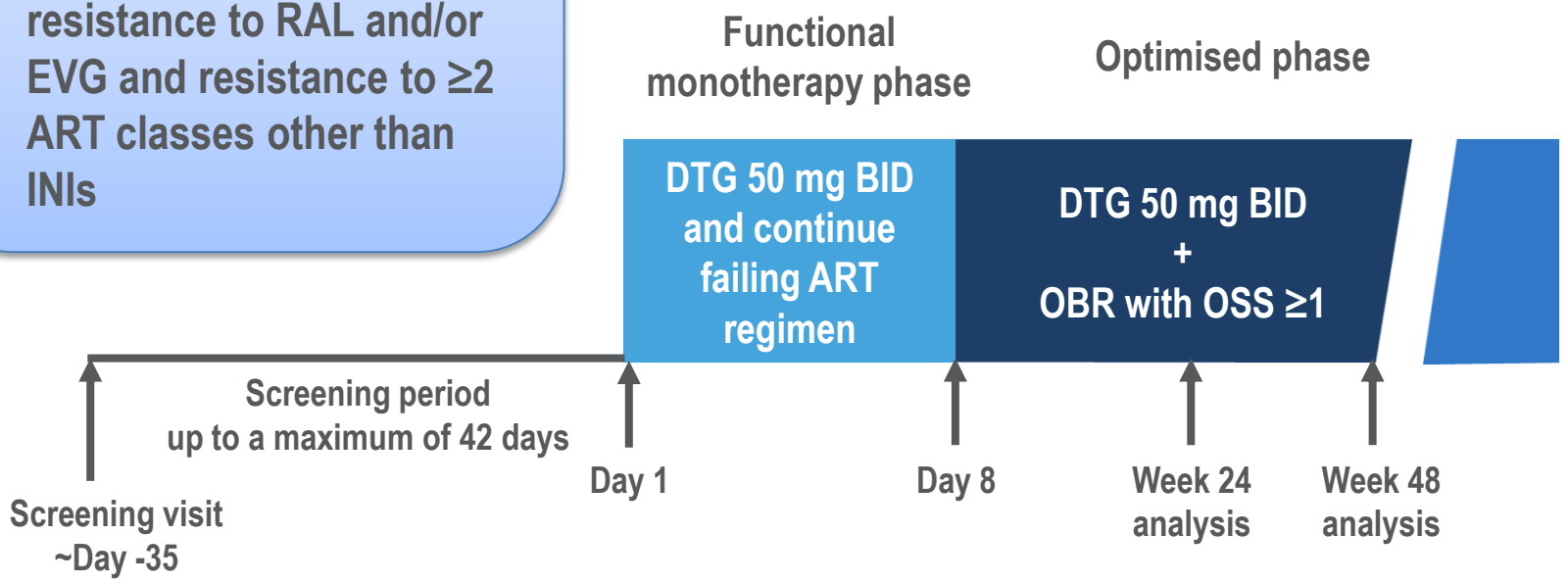
Safety and tolerability

Nichols G, et al. HIV11 2012. Abstract O232

VIKING-3: STUDY DESIGN (N=183)

Main eligibility criteria:

- HIV-1 RNA ≥500 c/mL
- Screening or documented historic evidence of resistance to RAL and/or EVG and resistance to ≥2 ART classes other than INIs



OSS, overall susceptibility score, determined by Monogram Biosciences net assessment

. Nichols G, et al. IAS 2013. Poster TULBPE19

BASELINE CHARACTERISTICS[1,2]

Characteristic, n (%)*	DTG 50 mg BID (N=183)
Male gender	141 (77)
African American/African heritage	49 (27)
CD4+ cells/mm^3, median (IQR)	140 (19–1110)
CDC class C, n (%)	102 (56)
Hepatitis B and/or hepatitis C positive, n (%)	38 (21)

VIKING-3 is being conducted in a diverse population of patients with advanced disease[1]

1. Adapted from Nichols G, et al. HIV11 2012. Abstract O232
2. Adapted from Nichols G, et al. IAS 2013. Poster TULBPE19

PATIENTS HAD EXTENSIVE PRIOR USE OF MULTIPLE ARVS AND EXTENSIVE ARV RESISTANCE

Characteristic	DTG 50 mg BID (N=183)
Prior ART	
Duration in years, median (range)	13 (0.3–25)
Number of ARVs, median (range)	14 (3–23)
DRV/r, n (%)	134 (73)
ETR, n (%)	102 (56)
ENF, n (%)	90 (49)
MVC, n (%)	59 (32)
Resistance, n (%)	
INI (RAL and/or EVG)*	183 (100)
≥2 NRTI resistance-associated mutation	137 (75)
≥1 NNRTI resistance-associated mutation	128 (70)
≥2 PI resistance-associated mutation	113 (62)

*INI resistance = presence of T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, N155H or a RAL FC >1.5 or EVG FC >2.5; 68% at screening, 32% with documented resistance from prior INI failure
NRTI, nucleoside reverse transcriptase inhibitor
NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor

Adapted from. Nichols G, et al. IAS 2013. Poster TULBPE19
Nichols G, et al. HIV11 2012. Abstract O232

PATIENTS HAD A BROAD RANGE OF GENOTYPIC AND PHENOTYPIC INI RESISTANCE AT BASELINE

- Median DTG FC = 1.29 (0.45−37) and median RAL FC = 47.5 (0.49→Max)

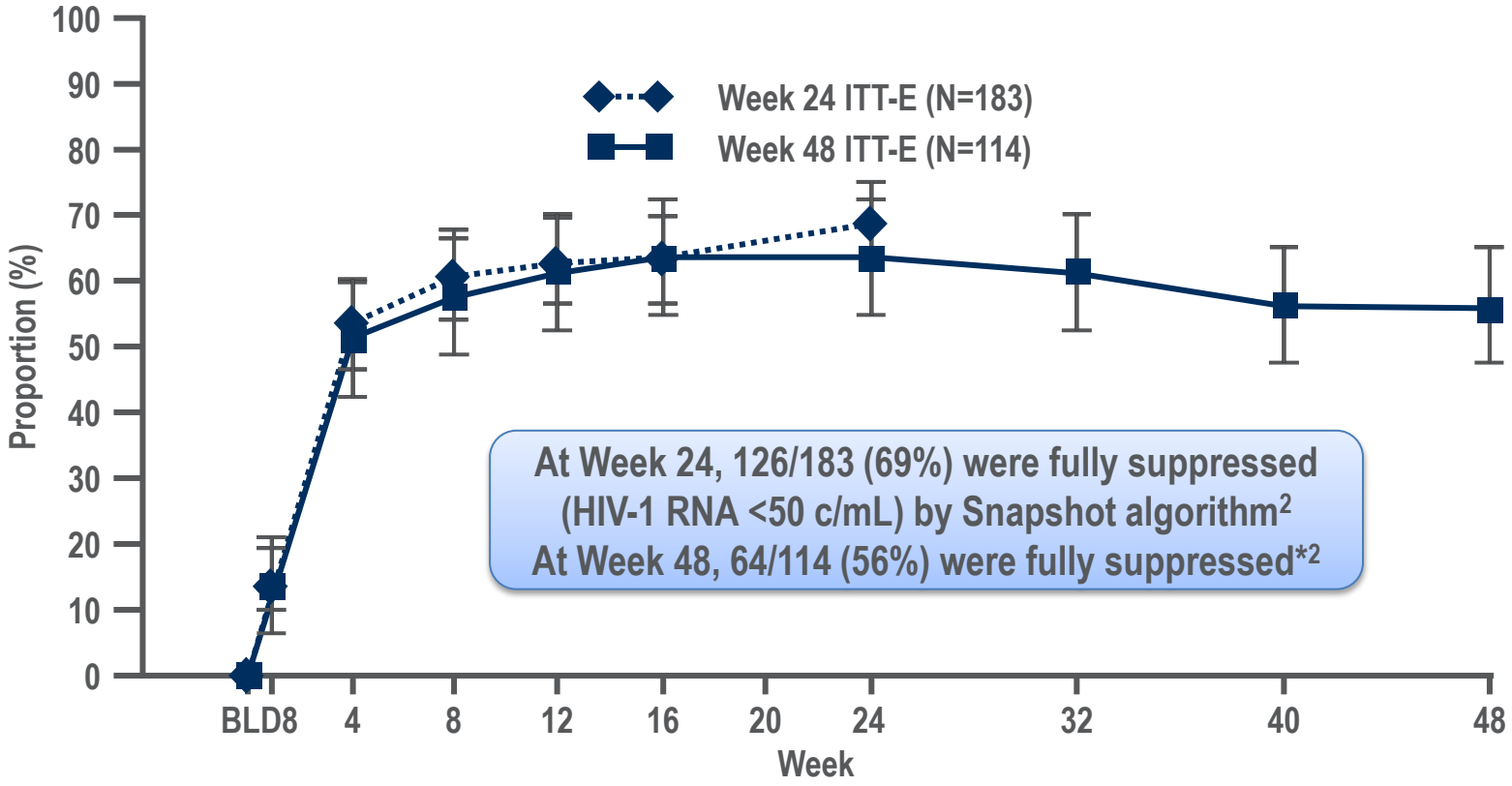
	Q148 + ≥2	Q148 + 1	N155	Y143	≥2 Primary*	Primary not detected
n (%)	21 (11)	31 (17)	30 (18)	28 (15)	7 (4)	59 (32)
Median DTG FC	**10.00**	**4.60**	**1.49**	**1.10**	**4.57**	**0.89**
Q1	4.47	3.39	1.29	0.91	1.68	0.80
Q3	13.00	6.27	1.76	1.18	20.00	1.04
Min	**2.56**	**0.47**	0.82	0.78	**1.46**	0.45
Max	**37.00**	**12.00**	3.89	2.01	**27.00**	3.97

*n=3 containing Q148 pathway
Q1, lower quartile; Q3, upper quartile

Adapted from Nichols G, et al. HIV11 2012. Abstract O232

IN TREATMENT-EXPERIENCED PATIENTS, DTG DEMONSTRATES EFFICACY FOR A MAJORITY OF INI-RESISTANT PATIENTS

- **Day 8 efficacy:** DTG was associated with significant reductions from baseline in HIV-1 RNA; change from baseline: −1.43 $\log_{10}$ c/mL HIV-1 RNA (95% CI: −1.52 to −1.34; *P*<0.001)[1]



*Week 48 population (N=114) included those subjects who had the opportunity to reach Week 48 at time of data cut-off

Adapted from:
1. Nichols G, et al. HIV11 2012. Abstract O232
2. . Nichols G, et al. IAS 2013. Poster TULBPE19

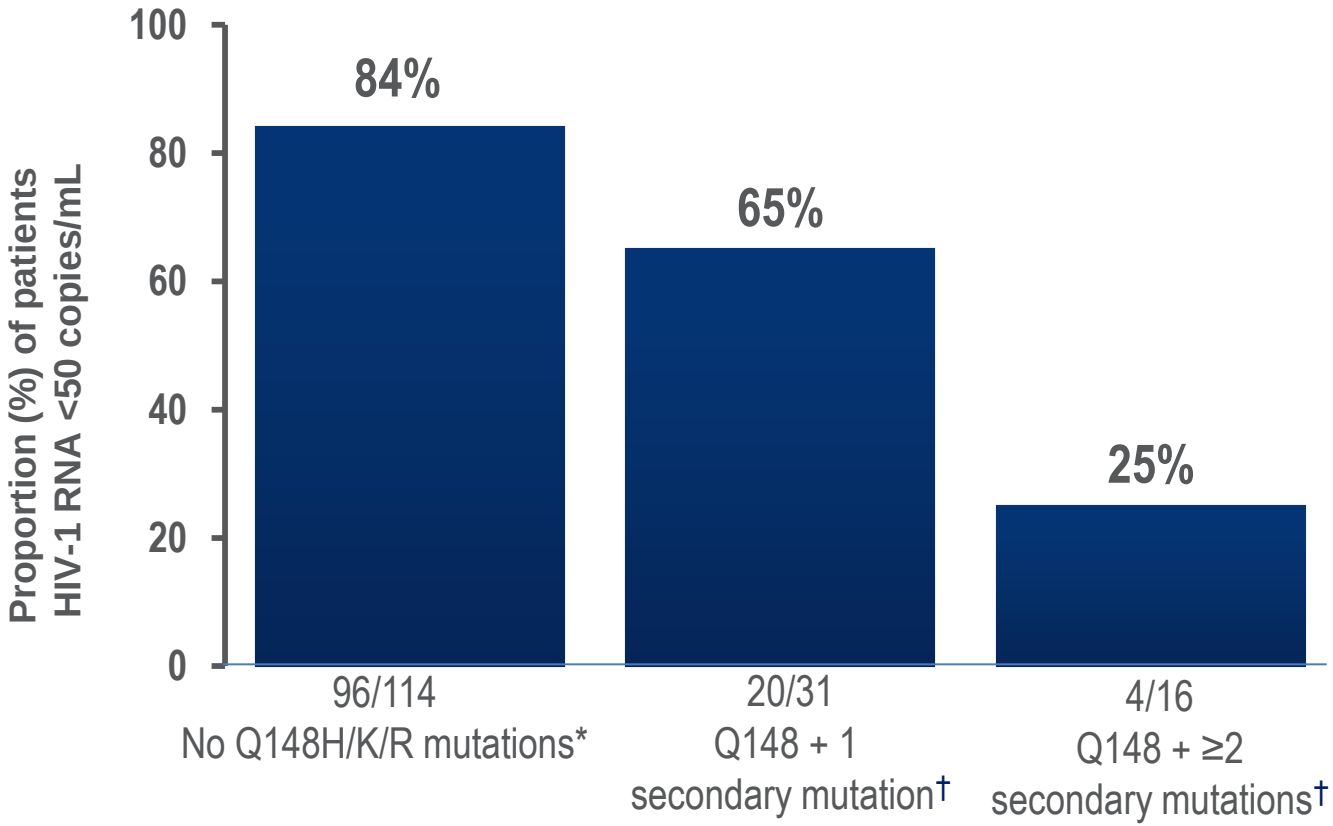
VIROLOGIC SUCCESS AT WEEK 24 AND WEEK 48 (SNAPSHOT, ITT-E)

Subjects, n (%)*	Week 24 DTG 50 mg BID (N=183)	Week 48 DTG 50 mg BID (N=114)†
Virologic success‡	126 (69)	64 (56)
Virologic non-response	50 (27)	44 (39)
No virologic data at cut-off	7 (4)	6 (5)
Discontinued due to AE or death	5 (3)	5 (4)
Discontinued for other reasons	2 (1)	1 (<1)

*Snapshot outcome; †Week 48 population (N=114) included those subjects who had the opportunity to reach Week 48 at time of data cut-off
‡Defined as HIV-1 RNA <50 c/mL

Adapted from Nichols G, et al. IAS 2013. Poster TULBPE19

RESPONSE RATES TO DTG WERE SIGNIFICANTLY REDUCED WITH INCREASING BASELINE INTEGRASE RESISTANCE



Virologic outcome population (n=161)

Week 24 snapshot analysis

*Y143, N155, T66, E92 or historical resistance evidence only

† Key secondary mutations were G140A/C/S, L741, and E138A/K/T

Adapted from Nichols G, et al. IAS 2013. Poster TULBPE19

TREATMENT-EMERGENT INI RESISTANCE WITH DTG AT TIME OF PROTOCOL-DEFINED VIROLOGIC FAILURE

37% of patients with protocol-defined virologic failure had Q148 + ≥2 secondary mutations at the time of failure

	Baseline (N=183), (n%)	At time of protocol-defined virologic failure (n=35), (n%)
INI mutations		
Q148 + ≥ 2 mutations	21 (11%)	13 (37%)
Q148 + 1 mutation	32 (17%)	7 (20%
≥ 2 primary mutations	8 (4%)*	2 (6%)†

- PDVF was detected in 19% (35/183) of patients
- Majority (87% - 13/15) of patients with treatment-emergent INI genotypic resistance at PDVF harboured Q148 mutations at baseline or historic

*4 patients with Q148 + ≥2 mutations with T66 or Y143 mutations

†2 patients with Q148 +≥2 mutations with N155, E92, Y143 or T66 mutations

Adapted from Vavro CL et al. Poster presented at International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies. 2013

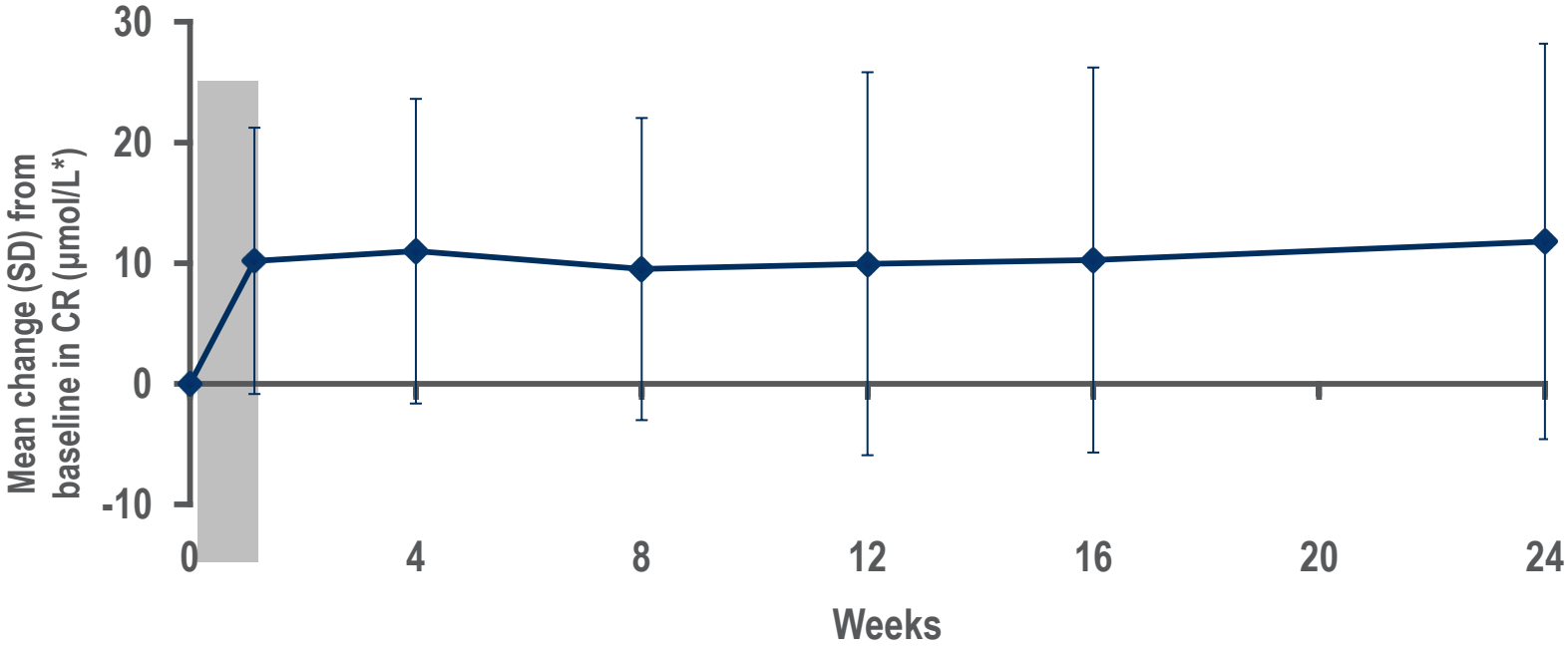
DTG WAS WELL TOLERATED WHEN PRESCRIBED TWICE-DAILY

Event, n (%)	DTG 50 mg BID (N=183)
Drug-related (most common ≥5%)	50 (27)
Nausea	11 (6)
Diarrhoea	10 (5)
Headache	9 (5)
AEs leading to withdrawal	6 (3)
Any serious AE	31 (17)
Fatal*	1 (<1)
Any drug-related serious AE	2 (1)
Hyperbilirubinaemia, elevated ALT, drug eruption†	1 (<1)
Syncope‡	1 (<1)

*Progressive multifocal leukoencephalopathy (fatality post-withdrawal, unrelated to drug)
†Subject on DRV + ETR; ‡Grade 2
ALT, alanine aminotransferase

Adapted from Nichols G, et al. IAS 2013. Poster TULBPE19

SMALL INCREASES IN SERUM CREATININE OCCURRED IN THE FIRST WEEK AND REMAINED STABLE OVER 24 WEEKS



- As previously described,[1] a small initial increase in serum creatinine via inhibition of the renal transporter OCT2 was observed by Week 2[2]
- Serum creatinine levels then remained stable through to Week 24

*10 µmol/L = 0.11 mg/dL
CR, creatinine; OCT2, organic cation transporter 2; SD, standard deviation

1. Koteff J, et al. *Br J Clin Pharmacol* 2013;75:990–6
2. Nichols G, et al. HIV11 2012. Abstract O232

VIKING-3: CONCLUSIONS

- **In treatment-experienced patients, TIVICAY demonstrated efficacy for a majority (56%) of INI-resistant patients[1]**
  - Mean decrease of 1.4 $\log_{10}$ HIV-1 RNA c/mL after 7 days of functional monotherapy
  - 69% (126/183) at Week 24 and 56% (64/114) at Week 48 achieved HIV-1 RNA <50 c/mL with OBR
- **Response rates to TIVICAY were significantly reduced with increasing baseline integrase resistance**
  - DTG 50 mg BID was well tolerated despite advanced disease status
  - Withdrawals due to AEs were infrequent

Nichols G, et al. IAS 2013.Poster TULBPE19

ABBREVIATIONS

- AE, adverse event
- ALT, alanine aminotransferase
- ART, antiretroviral therapy
- ARV, antiretroviral
- BID, twice daily
- c/mL, copies/mL
- CDC, Centers for Disease Control
- CR, creatinine
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- ENF, enfuvirtide
- ETR, etravirine
- EVG, elvitegravir
- FC, fold change
- HIV, human immunodeficiency virus
- INI, integrase inhibitor
- IQR, interquartile range
- ITT-E, intent-to-treat-exposed
- MVC, maraviroc
- NNRTI, non-nucleoside reverse transcriptase inhibitors
- NRTI, nucleoside reverse transcriptase inhibitor
- OBR, optimised background regimen
- OCT2, organic cation transporter 2
- OSS, overall susceptibility score
- PI, protease inhibitor
- PSS, phenotypic sensitivity score
- QD, once daily
- RAL, raltegravir
- RNA, ribonucleic acid
- SD, standard deviation

Indication(s): Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents aged 12 years and older and weighing at least 40 kg.

Succinct safety information:

Contraindications: Coadministration with dofetilide. Hypersensitivity to dolutegravir or to any of the excipients. **Warnings and Precautions**: Integrase class resistance of particular concern: The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring . Hypersensitivity reactions: Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect agents should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop. Immune Reactivation Syndrome: An inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Drug interactions: Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. Metformin concentrations may be increased by dolutegravir. Patients should be monitored during therapy and a dose adjustment of metformin may be required. Osteonecrosis: Although the aetiology is considered to be multifactorial, cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. **Undesirable effects:** Very common: Headache, nausea, diarrhoea. Common: Insomnia, abnormal dreams, dizziness, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort, rash, pruritus, fatigue, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations, creatine phosphokinase (CPK) elevations.

Dosage and administration: Adults: Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class: The recommended dose of dolutegravir is 50 mg (one tablet) orally once daily. Tivicay should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected): The recommended dose of dolutegravir is 50 mg (one tablet) twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern. Co-administration of Tivicay with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Adolescents aged 12 and above: In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily. Method of administration: Oral use. Tivicay can be taken with or without food . In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations).

For full information please refer to MOH approved Prescribing Information