

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIVICAY safely and effectively. See full prescribing information for TIVICAY.

TIVICAY (dolutegravir) Tablets for Oral Use
Initial U.S. Approval: 2013

INDICATIONS AND USAGE

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg. (1)

The following should be considered prior to initiating TIVICAY:

- Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. (12.4)

DOSAGE AND ADMINISTRATION

May be taken without regard to meals. (2)

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance ^a (12.4)	50 mg twice daily

^a Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: (Treatment-naïve or treatment-experienced INSTI-naïve, aged 12 years and older, and weighing at least 40 kg). (2.2)

- The recommended dose is TIVICAY 50 mg once daily.
- If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered, then the dose is TIVICAY 50 mg twice daily.

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg (3)

CONTRAINDICATIONS

Coadministration with dofetilide is contraindicated. (4)

WARNINGS and PRECAUTIONS

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. TIVICAY should not be used in patients who have experienced a previous hypersensitivity reaction to TIVICAY. (5.1)
- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY is recommended in patients with underlying hepatic disease such as hepatitis B or C. (5.2)
- Redistribution/accumulation of body fat and immune reconstitution syndrome have been reported in patients treated with combination antiretroviral therapy. (5.3, 5.4)

ADVERSE REACTIONS

The most common adverse reactions of moderate to severe intensity and incidence $\geq 2\%$ (in those receiving TIVICAY in any one adult trial) are insomnia and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: TIVICAY should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Nursing mothers: Breastfeeding is not recommended due to the potential for HIV transmission. (8.3)
- Pediatric patients: Safety and efficacy of TIVICAY have not been established in pediatric patients younger than 12 years or weighing less than 40 kg, or in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir). (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 TIVICAY[®] is indicated in combination with other antiretroviral agents for the treatment
4 of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years
5 and older and weighing at least 40 kg.

6 The following should be considered prior to initiating treatment with TIVICAY:

- 7 • Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily
8 with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 or more
9 additional INSTI-resistance substitutions, including L74I/M, E138A/D/K/T, G140A/S,
10 Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R [*see Microbiology (12.4)*].

11 **2 DOSAGE AND ADMINISTRATION**

12 TIVICAY tablets may be taken with or without food.

13 **2.1 Adults**

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15 **Table 1. Dosing Recommendations for TIVICAY in Adult Patients**

Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance ^a [<i>see Microbiology (12.4)</i>]	50 mg twice daily

16 ^a Alternative combinations that do not include metabolic inducers should be considered where
17 possible [*see Drug Interactions (7)*].

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19 The safety and efficacy of doses above 50 mg twice daily have not been evaluated.

20 **2.2 Pediatric Patients**

21 Treatment-Naïve or Treatment-Experienced INSTI-Naïve: The recommended dose
22 of TIVICAY in pediatric patients aged 12 years and older and weighing at least 40 kg is 50 mg
23 administered orally once daily.

24 If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered,
25 the recommended dose of TIVICAY is 50 mg twice daily.

26 Safety and efficacy of TIVICAY have not been established in pediatric patients younger
27 than 12 years or weighing less than 40 kg, or in pediatric patients who are INSTI-experienced
28 with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

29 **3 DOSAGE FORMS AND STRENGTHS**

30 TIVICAY 50-mg tablets are yellow, round, film-coated, biconvex tablets debossed with
31 SV 572 on one side and 50 on the other side. Each tablet contains 50 mg of dolutegravir (as
32 dolutegravir sodium) [see Description (11)].

33 **4 CONTRAINDICATIONS**

34 Coadministration of TIVICAY with dofetilide is contraindicated due to the potential for
35 increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events
36 [see Drug Interactions (7)].

37 **5 WARNINGS AND PRECAUTIONS**

38 **5.1 Hypersensitivity Reactions**

39 Hypersensitivity reactions have been reported and were characterized by rash,
40 constitutional findings, and sometimes organ dysfunction, including liver injury. The events were
41 reported in 1% or fewer subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue
42 TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity
43 reactions develop (including, but not limited to, severe rash or rash accompanied by fever,
44 general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or
45 lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing).
46 Clinical status, including liver aminotransferases, should be monitored and appropriate therapy
47 initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of
48 hypersensitivity may result in a life-threatening reaction. TIVICAY should not be used in
49 patients who have experienced a previous hypersensitivity reaction to TIVICAY.

50 **5.2 Effects on Serum Liver Biochemistries in Patients With Hepatitis B or C**
51 **Co-infection**

52 Patients with underlying hepatitis B or C may be at increased risk for worsening or
53 development of transaminase elevations with use of TIVICAY [see Adverse Reactions (6.1)]. In
54 some cases the elevations in transaminases were consistent with immune reconstitution
55 syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was
56 withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for
57 hepatotoxicity during therapy with TIVICAY are recommended in patients with underlying
58 hepatic disease such as hepatitis B or C.

59 **5.3 Fat Redistribution**

60 Redistribution/accumulation of body fat, including central obesity, dorsocervical fat
61 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and
62 “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The
63 mechanism and long-term consequences of these events are currently unknown. A causal
64 relationship has not been established.

65 **5.4 Immune Reconstitution Syndrome**

66 Immune reconstitution syndrome has been reported in patients treated with combination
67 antiretroviral therapy, including TIVICAY. During the initial phase of combination antiretroviral

68 treatment, patients whose immune systems respond may develop an inflammatory response to
69 indolent or residual opportunistic infections (such as *Mycobacterium avium* infection,
70 cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may
71 necessitate further evaluation and treatment.

72 Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré
73 syndrome) have also been reported to occur in the setting of immune reconstitution; however, the
74 time to onset is more variable and can occur many months after initiation of treatment.

75 **6 ADVERSE REACTIONS**

76 The following adverse drug reactions (adverse events assessed as causally related by the
77 investigator or ADRs) are discussed in other sections of the labeling:

- 78 • Hypersensitivity reactions [see *Warnings and Precautions (5.1)*].
- 79 • Effects on serum liver biochemistries in patients with hepatitis B or C co-infection [see
80 *Warnings and Precautions (5.2)*].
- 81 • Fat Redistribution [see *Warnings and Precautions (5.3)*].
- 82 • Immune Reconstitution Syndrome [see *Warnings and Precautions (5.4)*].

83 Because clinical trials are conducted under widely varying conditions, adverse reaction
84 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
85 clinical trials of another drug and may not reflect the rates observed in practice.

86 **6.1 Clinical Trials Experience in Adult Subjects**

87 Treatment-Emergent Adverse Drug Reactions (ADRs): Treatment-Naïve

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

91 In SPRING-2, 822 subjects were randomized and received at least 1 dose of either
92 TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-
93 dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and
94 lamivudine [EPZICOM[®]] or emtricitabine/tenofovir [TRUVADA[®]]). There were 808 subjects
95 included in the efficacy and safety analyses. The rate of adverse events leading to
96 discontinuation was 2% in both treatment arms.

97 In SINGLE, 833 subjects were randomized and received at least 1 dose of either
98 TIVICAY 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or
99 fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA[®]) once daily. The rates of adverse
100 events leading to discontinuation were 2% in subjects receiving TIVICAY 50 mg once daily +
101 EPZICOM and 10% in subjects receiving ATRIPLA once daily.

102 Treatment-emergent ADRs of moderate to severe intensity observed in $\geq 2\%$ of subjects
103 in either treatment arm are provided in Table 2. Side-by-side tabulation is to simplify
104 presentation; direct comparisons across trials should not be made due to differing trial designs.

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Table 2. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and $\geq 2\%$ Frequency in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 Analysis)

System Organ Class/ Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)	TIVICAY 50 mg + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Psychiatric				
Insomnia	<1%	<1%	3%	2%
Abnormal dreams	<1%	<1%	<1%	2%
Nervous System				
Dizziness	<1%	<1%	<1%	5%
Headache	<1%	<1%	2%	2%
Gastrointestinal				
Nausea	1%	1%	<1%	3%
Diarrhea	<1%	<1%	<1%	2%
Skin and Subcutaneous Tissue				
Rash ^a	0	<1%	<1%	6%
Ear and Labyrinth				
Vertigo	0	<1%	0	2%

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^a Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 1% and <1% of subjects receiving TIVICAY and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 3% for TIVICAY and ATRIPLA, respectively. These events were not treatment limiting.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 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 adverse events leading to discontinuation were 2% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent ADR of moderate to severe intensity with $\geq 2\%$ frequency in either treatment group was diarrhea, 1% (5/354) in subjects receiving TIVICAY 50 mg once

125 daily + background regimen and 2% (6/361) in subjects receiving raltegravir 400 mg twice daily
126 + background regimen.

127 *Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced*
128 *Subjects:* In a multicenter, open-label, single-arm trial (ING112574, VIKING-3),
129 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and
130 current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY
131 50 mg twice daily with the current failing background regimen for 7 days and with optimized
132 background therapy from Day 8. The rate of adverse events leading to discontinuation was 3% of
133 subjects at Week 24.

134 Treatment-emergent ADRs in VIKING-3 were generally similar compared with
135 observations with the 50-mg once-daily dose in adult Phase 3 trials.

136 Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-
137 Experienced Trials: The following ADRs occurred in <2% of treatment-naïve or treatment-
138 experienced subjects receiving TIVICAY in a combination regimen in any one trial. These
139 events have been included because of their seriousness and assessment of potential causal
140 relationship.

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

143 *General Disorders:* Fatigue.

144 *Hepatobiliary Disorders:* Hepatitis.

145 *Musculoskeletal Disorders:* Myositis.

146 *Renal and Urinary Disorders:* Renal impairment.

147 *Skin and Subcutaneous Tissue Disorders:* Pruritus.

148 Laboratory Abnormalities: *Treatment-Naïve Subjects:* Selected laboratory
149 abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-
150 grade toxicity in $\geq 2\%$ of subjects are presented in Table 3. The mean change from baseline
151 observed for selected lipid values is presented in Table 4. Side-by-side tabulation is to simplify
152 presentation; direct comparisons across trials should not be made due to differing trial designs.

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154 **Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in**
 155 **SPRING-2 and SINGLE Trials (Week 48 Analysis)**

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)	TIVICAY 50 mg + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
ALT				
Grade 2 (>2.5-5.0 x ULN)	2%	3%	2%	5%
Grade 3 to 4 (>5.1 x ULN)	2%	1%	<1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	3%	3%	2%	3%
Grade 3 to 4 (>5.1 x ULN)	2%	2%	0	2%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	2%	2%	<1%	0
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	0
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	1%	3%	3%	1%
Grade 3 to 4 (>10.0 x ULN)	4%	3%	3%	4%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	5%	5%	7%	4%
Grade 3 (>251 mg/dL)	<1%	1%	1%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	5%	6%	8%	7%
Grade 3 to 4 (>3.1 x ULN)	1%	3%	3%	2%
Total neutrophils				
Grade 2 (0.75-0.99 x 10 ⁹)	3%	3%	2%	4%
Grade 3 to 4 (<0.74 x 10 ⁹)	2%	1%	2%	3%

156 ULN = Upper limit of normal.

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158 **Table 4. Mean Change From Baseline in Fasted Lipid Values in Treatment-Naïve Subjects**
159 **in SPRING-2 and SINGLE Trials (Week 48 Analysis)**

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)	TIVICAY 50 mg + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Cholesterol (mg/dL)	6.7	8.3	17.1	24.0
HDL cholesterol (mg/dL)	2.8	2.6	5.2	7.9
LDL cholesterol (mg/dL)	2.7	2.8	8.5	13.1
Triglycerides (mg/dL)	7.7	9.8	17.7	18.6

160 ^a Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects
161 in each arm in SPRING-2, and in SINGLE: TIVICAY n = 27 and ATRIPLA n = 26). Forty-
162 nine subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment
163 values (prior to starting the agent) were used regardless if they discontinued the agent
164 (SPRING-2: TIVICAY n = 5, raltegravir n = 8; SINGLE: TIVICAY n = 19 and ATRIPLA:
165 n = 17).

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167 *Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects:*
168 Laboratory abnormalities observed in SAILING were generally similar compared with
169 observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

170 *Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced*
171 *Subjects:* The most common treatment-emergent laboratory abnormalities (>5% for Grades 2 to
172 4 combined) were elevated ALT (8%), AST (6%), cholesterol (8%), hyperglycemia (12%), and
173 lipase (8%). Two percent (3/183) of subjects had a Grade 3 to 4, treatment-emergent hematology
174 laboratory abnormality, with neutropenia (1% [2/183]) being the most frequently reported.

175 *Hepatitis B and/or Hepatitis C Virus Co-infection:* In Phase 3 trials, subjects with
176 hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver
177 chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in
178 subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects
179 without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were
180 higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups.
181 Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-
182 infected subjects receiving TIVICAY were observed in 16% vs. 2% with the 50-mg once-daily
183 dose and 8% vs. 7% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with
184 immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the
185 start of therapy with TIVICAY, particularly in the setting where anti-hepatitis therapy was
186 withdrawn [see *Warnings and Precautions (5.2)*].

187 Changes in Serum Creatinine: Dolutegravir has been shown to increase serum
188 creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular

189 function [see *Clinical Pharmacology (12.2)*]. Increases in serum creatinine occurred within the
190 first 4 weeks of treatment and remained stable through 24 to 48 weeks. In treatment-naïve
191 subjects, a mean change from baseline of 0.11 mg/dL (range: -0.60 mg/dL to 0.62 mg/dL) was
192 observed after 48 weeks of treatment. Creatinine increases were comparable by background
193 NRTIs and were similar in treatment-experienced subjects.

194 **6.2 Clinical Trials Experience in Pediatric Subjects**

195 IMPAACT P1093 is an ongoing multi-center, open-label, non-comparative trial of
196 approximately 160 HIV-1-infected pediatric subjects aged 6 weeks to less than 18 years, of
197 which 23 treatment-experienced, INSTI-naïve subjects aged 12 to less than 18 years were
198 enrolled [see *Use in Specific Populations (8.4)*, *Clinical Studies (14.2)*].

199 The adverse reaction profile was similar to that for adults. Grade 2 ADRs reported in at
200 least 1 subject were rash (n = 1), abdominal pain (n = 1), and diarrhea (n = 1). No Grade 3 or 4
201 ADRs were reported. The Grade 3 laboratory abnormalities were elevated total bilirubin and
202 lipase reported in 1 subject each. No Grade 4 laboratory abnormalities were reported. The
203 changes in mean serum creatinine were similar to those observed in adults.

204 **7 DRUG INTERACTIONS**

205 Refer to Table 5 for established and other potentially significant drug-drug interactions.

206 **7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents**

207 In vitro, dolutegravir inhibited the renal organic cation transporter, OCT2 (IC₅₀ = 1.93
208 μM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2.
209 Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 (dofetilide and
210 metformin, Table 5) [see *Contraindications (4)*, *Drug Interactions (7.3)*].

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

218 In drug interaction trials, dolutegravir did not have a clinically relevant effect on the
219 pharmacokinetics of the following drugs: tenofovir, methadone, midazolam, rilpivirine, and oral
220 contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to
221 historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect
222 the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine,
223 fosamprenavir, lopinavir, ritonavir, and telaprevir.

224 **7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir**

225 Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A.

226 Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that

227 induce those enzymes and transporters may decrease dolutegravir plasma concentration and
228 reduce the therapeutic effect of dolutegravir.

229 Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase
230 dolutegravir plasma concentration.

231 Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of
232 etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is
233 expected to be mitigated by atazanavir/ritonavir. (Table 5) [see Drug Interactions (7.3), Clinical
234 Pharmacology (12.3)].

235 Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, telaprevir,
236 prednisone, rifabutin, and omeprazole had no clinically significant effect on the
237 pharmacokinetics of dolutegravir.

238 **7.3 Established and Other Potentially Significant Drug Interactions**

239 Table 5 provides clinical recommendations as a result of drug interactions with
240 TIVICAY. These recommendations are based on either drug interaction trials or predicted
241 interactions due to the expected magnitude of interaction and potential for serious adverse events
242 or loss of efficacy. [See Dosage and Administration (2), Clinical Pharmacology (12.3).]
243

244 **Table 5. Established and Other Potentially Significant Drug Interactions: Alterations in**
245 **Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted**
246 **Interactions** [see Dosage and Administration (2)]

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
<i>HIV-1 Antiviral Agents</i>		
Non-nucleoside reverse transcriptase inhibitor: Etravirine ^a	↓Dolutegravir	TIVICAY should not be used with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz ^a	↓Dolutegravir	A dose adjustment of TIVICAY to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance. ^b

Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Coadministration with nevirapine should be avoided because there are insufficient data to make dosing recommendations.
Protease Inhibitor: Fosamprenavir/ritonavir ^a Tipranavir/ritonavir ^a	↓Dolutegravir	A dose adjustment of TIVICAY to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance. ^b
<i>Other Agents</i>		
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)	↓Dolutegravir	Coadministration with these metabolic inducers should be avoided because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) Cation-containing antacids ^a or laxatives Sucralfate Oral iron supplements Oral calcium supplements Buffered medications	↓Dolutegravir	TIVICAY should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations.
Metformin	↑Metformin	Close monitoring is recommended when starting or stopping TIVICAY and metformin together. A dose adjustment of metformin may be necessary.

Rifampin ^a	↓Dolutegravir	<p>A dose adjustment of TIVICAY to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients.</p> <p>Alternatives to rifampin should be used where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.^b</p>
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247 ^a See *Clinical Pharmacology (12.3) Table 9 for magnitude of interaction.*

248 ^b The lower dolutegravir exposures observed in INSTI-experienced patients (with certain
 249 INSTI-associated resistance substitutions or clinically suspected INSTI resistance [*see*
 250 *Microbiology (12.4)*]) upon coadministration with potent inducers may result in loss of
 251 therapeutic effect and development of resistance to TIVICAY or other coadministered
 252 antiretroviral agents.
 253

254 **8 USE IN SPECIFIC POPULATIONS**

255 **8.1 Pregnancy**

256 Pregnancy Category B. There are no adequate and well-controlled studies in pregnant
 257 women. Because animal reproduction studies are not always predictive of human response, and
 258 dolutegravir was shown to cross the placenta in animal studies, this drug should be used during
 259 pregnancy only if clearly needed.

260 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant
 261 women with HIV exposed to TIVICAY and other antiretroviral agents, an Antiretroviral
 262 Pregnancy Registry has been established. Physicians are encouraged to register patients by
 263 calling 1-800-258-4263.

264 Animal Data: Reproduction studies have been performed in rats and rabbits at doses up
 265 to 27 times the human dose of 50 mg twice daily and have revealed no evidence of impaired
 266 fertility or harm to the fetus due to TIVICAY.

267 Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg/kg daily,
 268 approximately 27 times the 50-mg twice-daily human clinical exposure based on AUC, from
 269 days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or
 270 teratogenicity.

271 Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg/kg daily,
 272 approximately 0.4 times the 50-mg twice-daily human clinical exposure based on AUC, from
 273 days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits,
 274 maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight
 275 gain) was observed at 1,000 mg/kg.

276 **8.3 Nursing Mothers**

277 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers
278 in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1
279 infection. Studies in lactating rats and their offspring indicate that dolutegravir was present in rat
280 milk. It is not known whether dolutegravir is excreted in human milk.

281 Because of both the potential for HIV transmission and the potential for adverse reactions
282 in nursing infants, **mothers should be instructed not to breastfeed if they are receiving**
283 **TIVICAY.**

284 **8.4 Pediatric Use**

285 TIVICAY is not recommended in pediatric patients younger than 12 years or weighing
286 less than 40 kg. Safety and efficacy of TIVICAY have not been established in pediatric patients
287 who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs
288 (raltegravir, elvitegravir).

289 The safety, virologic, and immunologic responses in subjects who received TIVICAY
290 were evaluated in 23 treatment-experienced, INSTI-naïve, HIV-1-infected subjects aged 12 to
291 less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093
292 [see *Adverse Reactions (6.2)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.2)*].
293 Pharmacokinetic parameters, evaluated in 9 subjects weighing ≥ 40 kg receiving 50 mg daily and
294 1 subject (weighing 37 kg) receiving 35 mg once daily, were similar to adults receiving 50 mg
295 once daily. See *Dosage and Administration (2.2)* for dosing recommendations for pediatric
296 patients aged 12 years and older and weighing at least 40 kg. Frequency, type, and severity of
297 adverse drug reactions in pediatric subjects were comparable to those observed in adults [see
298 *Adverse Reactions (6.2)*].

299 **8.5 Geriatric Use**

300 Clinical trials of TIVICAY did not include sufficient numbers of subjects aged 65 and
301 older to determine whether they respond differently from younger subjects. In general, caution
302 should be exercised in the administration of TIVICAY in elderly patients reflecting the greater
303 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other
304 drug therapy [see *Clinical Pharmacology (12.3)*].

305 **8.6 Hepatic Impairment**

306 No clinically important pharmacokinetic differences between subjects with moderate
307 hepatic impairment and matching healthy subjects were observed. No dosage adjustment is
308 necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The
309 effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of
310 dolutegravir has not been studied. Therefore, TIVICAY is not recommended for use in patients
311 with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

312 **8.7 Renal Impairment**

313 Dolutegravir plasma concentrations were decreased in subjects with severe renal
314 impairment compared with those in matched healthy controls. However, no dosage adjustment is
315 necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild,

316 moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-
317 associated resistance substitutions or clinically suspected INSTI resistance) with mild or
318 moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain
319 INSTI-associated resistance substitutions or clinically suspected INSTI resistance [*see*
320 *Microbiology (12.4)*]) with severe renal impairment, as the decrease in dolutegravir
321 concentrations may result in loss of therapeutic effect and development of resistance to
322 TIVICAY or other coadministered antiretroviral agents [*see Clinical Pharmacology (12.3)*].
323 Dolutegravir has not been studied in patients on dialysis.

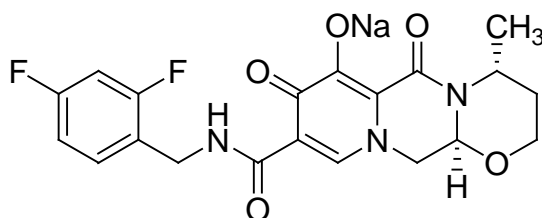
324 **10 OVERDOSAGE**

325 Limited experience with single higher doses (up to 250 mg in healthy subjects) revealed
326 no specific symptoms or signs apart from those listed as adverse reactions. There is no known
327 specific treatment for overdose with TIVICAY. If overdose occurs, the patient should be
328 monitored and standard supportive treatment applied as required. As dolutegravir is highly
329 bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

330 **11 DESCRIPTION**

331 TIVICAY contains dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical
332 name of dolutegravir sodium is sodium (4*R*,12*aS*)-9-[[*(*2,4-difluorophenyl)methyl]carbamoyl]-
333 4-methyl-6,8-dioxo-3,4,6,8,12,12*a*-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-
334 olate. The empirical formula is C₂₀H₁₈F₂N₃NaO₅ and the molecular weight is 441.36 g/mol. It
335 has the following structural formula:

336



337

338

339 Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

340 Each film-coated tablet of TIVICAY for oral administration contains 52.6 mg of
341 dolutegravir sodium, which is equivalent to 50 mg dolutegravir free acid, and the following
342 inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch
343 glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients
344 iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

345 **12 CLINICAL PHARMACOLOGY**

346 **12.1 Mechanism of Action**

347 Dolutegravir is an HIV-1 antiviral agent [*see Microbiology (12.4)*].

348 **12.2 Pharmacodynamics**

349 In a randomized, dose-ranging trial, HIV-1-infected subjects treated with dolutegravir
350 monotherapy demonstrated rapid and dose-dependent antiviral activity with mean declines from
351 baseline to Day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 log₁₀ for dolutegravir 2 mg, 10 mg, and
352 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the
353 last dose in the 50-mg group.

354 **Effects on Electrocardiogram:** In a randomized, placebo-controlled, cross-over trial,
355 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg
356 suspension (exposures approximately 3-fold of the 50-mg once-daily dose at steady state), and
357 moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo
358 adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for
359 dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). TIVICAY did not prolong the QTc
360 interval over 24 hours postdose.

361 **Effects on Renal Function:** The effect of dolutegravir on renal function was evaluated
362 in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects
363 (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily
364 (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as
365 determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14
366 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice
367 daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual
368 glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal
369 plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with
370 the placebo.

371 **12.3 Pharmacokinetics**

372 The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult
373 subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar
374 between healthy subjects and HIV-1–infected subjects. The non-linear exposure of dolutegravir
375 following 50 mg twice daily compared with 50 mg once daily in HIV-1–infected subjects
376 (Table 6) was attributed to the use of metabolic inducers in the background antiretroviral
377 regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials. TIVICAY was
378 administered without regard to food in these trials.

379

380 **Table 6. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1–**
381 **Infected Adults**

Parameter	50 mg Once Daily Geometric Mean ^a (%CV)	50 mg Twice Daily Geometric Mean ^b (%CV)
AUC ₍₀₋₂₄₎ (mcg.h/mL)	53.6 (27)	75.1 (35)
C _{max} (mcg/mL)	3.67 (20)	4.15 (29)
C _{min} (mcg/mL)	1.11 (46)	2.12 (47)

382 ^a Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

383 ^b Based on population pharmacokinetic analyses using data from VIKING (ING112961) and
384 VIKING-3.

385

386 Absorption: Following oral administration of dolutegravir, peak plasma concentrations
387 were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is
388 achieved within approximately 5 days with average accumulation ratios for AUC, C_{\max} , and $C_{24\text{ h}}$
389 ranging from 1.2 to 1.5.

390 Dolutegravir plasma concentrations increased in a less than dose-proportional manner
391 above 50 mg. Dolutegravir is a P-glycoprotein substrate in vitro. The absolute bioavailability of
392 dolutegravir has not been established.

393 Effects of Food on Oral Absorption: TIVICAY may be taken with or without food.
394 Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-,
395 moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased
396 C_{\max} by 46%, 52%, and 67%; and prolonged T_{\max} to 3, 4, and 5 hours from 2 hours under fasted
397 conditions, respectively.

398 Distribution: Dolutegravir is highly bound ($\geq 98.9\%$) to human plasma proteins based on
399 in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent
400 volume of distribution (V_d/F) following 50-mg once-daily administration is estimated at 17.4 L
401 based on a population pharmacokinetic analysis.

402 Cerebrospinal Fluid (CSF): In 11 treatment-naïve subjects on dolutegravir 50 mg
403 daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL
404 (range: 4 ng/mL to 232 ng/mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical
405 relevance of this finding has not been established.

406 Metabolism and Elimination: Dolutegravir is primarily metabolized via UGT1A1 with
407 some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total
408 oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted
409 in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite
410 formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-
411 dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (<1% of
412 the dose).

413 Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance
414 (CL/F) of 1.0 L/h based on population pharmacokinetic analyses.

415 Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy
416 subject trials, subjects with UGT1A1 ($n = 7$) genotypes conferring poor dolutegravir metabolism
417 had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with
418 genotypes associated with normal metabolism via UGT1A1 ($n = 41$).

419 Specific Populations: Hepatic Impairment: Dolutegravir is primarily metabolized and
420 eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-
421 Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg
422 dose was similar between the 2 groups. No dosage adjustment is necessary for patients with mild

423 to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic
424 impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.
425 Therefore, TIVICAY is not recommended for use in patients with severe hepatic impairment.

426 **HBV/HCV Co-infection:** Population analyses using pooled pharmacokinetic data
427 from adult trials indicated no clinically relevant effect of HCV co-infection on the
428 pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

429 **Renal Impairment:** Renal clearance of unchanged drug is a minor pathway of
430 elimination for dolutegravir. In a trial comparing 8 subjects with severe renal impairment (CrCl
431 <30 mL/min) with 8 matched healthy controls, AUC, C_{max}, and C₂₄ of dolutegravir were
432 decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy
433 subjects. The cause of this decrease is unknown. Population pharmacokinetic analysis using data
434 from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no
435 clinically relevant effect on the exposure of dolutegravir. No dosage adjustment is necessary for
436 treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or
437 severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated
438 resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal
439 impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated
440 resistance substitutions or clinically suspected INSTI resistance [*see Microbiology (12.4)*]) with
441 severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of
442 therapeutic effect and development of resistance to TIVICAY or other coadministered
443 antiretroviral agents. Dolutegravir has not been studied in patients requiring dialysis.

444 **Gender:** Population analyses using pooled pharmacokinetic data from adult trials
445 indicated gender had no clinically relevant effect on the exposure of dolutegravir.

446 **Race:** Population analyses using pooled pharmacokinetic data from adult trials
447 indicated race had no clinically relevant effect on the pharmacokinetics of dolutegravir.

448 **Geriatric Patients:** Population analyses using pooled pharmacokinetic data from adult
449 trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

450 **Pediatric Patients:** The pharmacokinetics of dolutegravir in HIV-1–infected children
451 (n = 10) aged 12 to less than 18 years were similar to those observed in HIV-1–infected adults
452 who received dolutegravir 50 mg once daily (Table 7) [*see Clinical Studies (14.2)*].
453

454 **Table 7. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects**

Age/Weight	Dose of TIVICAY ^a	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		C _{max} (mcg/mL) (n = 10)	AUC ₍₀₋₂₄₎ (mcg.h/mL) (n = 10)	C ₂₄ (mcg/mL) (n = 10)
12 to <18 years and ≥40 kg ^a	50 mg once daily	3.49 (38)	46 (43)	0.90 (59)

455 ^a One subject weighing 37 kg received TIVICAY 35 mg once daily.

456

457 **Drug Interactions:** Drug interaction trials were performed with TIVICAY and other
458 drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions.
459 As dolutegravir is not expected to affect the pharmacokinetics of other drugs dependent on
460 hepatic metabolism (Table 8) [see *Drug Interactions (7.1)*], the primary focus of these drug
461 interaction trials was to evaluate the effect of coadministered drug on dolutegravir (Table 9).

462 Dosing or regimen recommendations as a result of established and other potentially
463 significant drug-drug interactions with TIVICAY are provided in Table 5 [see *Dosage and*
464 *Administration (2.1), Drug Interactions (7.3)*].

465

466 **Table 8. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered**
467 **Drugs**

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Dolutegravir No Effect = 1.00		
			C _{max}	AUC	C _τ or C ₂₄
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

468

469 **Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of**
470 **Dolutegravir**

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Coadministered Drugs No Effect = 1.00		
			C _{max}	AUC	C _r or C ₂₄
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg /100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Antacid (Maalox [®]) Simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (Maalox [®]) 2 hrs after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Multivitamin (One-A-Day [®]) Simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin ^a 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin ^b 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)

Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Telaprevir 750 mg every 8 hours	50 mg once daily	15	1.18 (1.11 to 1.26)	1.25 (1.19 to 1.31)	1.40 (1.29 to 1.51)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)

471 ^a Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with
472 dolutegravir 50 mg twice daily.

473 ^b Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with
474 dolutegravir 50 mg once daily.

475

476 **12.4 Microbiology**

477 Mechanism of Action: Dolutegravir inhibits HIV integrase by binding to the integrase
478 active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA)
479 integration which is essential for the HIV replication cycle. Strand transfer biochemical assays
480 using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC₅₀ values of
481 2.7 nM and 12.6 nM.

482 Antiviral Activity in Cell Culture: Dolutegravir exhibited antiviral activity against
483 laboratory strains of wild-type HIV-1 with mean EC₅₀ values of 0.5 nM (0.21 ng/mL) to 2.1 nM
484 (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir
485 exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC₅₀ of
486 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical
487 isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1
488 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with
489 EC₅₀ values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC₅₀ values against 3
490 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

491 Antiviral Activity in Combination With Other Antiviral Agents: The antiviral activity
492 of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside
493 reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse
494 transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir
495 or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide.
496 Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse
497 transcriptase inhibitor, adefovir, or with the antiviral, ribavirin.

498 Resistance: Cell Culture: Dolutegravir-resistant viruses were selected in cell culture
499 starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q,
500 G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased
501 susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or

502 Q148H substitutions selected for additional substitutions in integrase that conferred decreased
503 susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase
504 substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing
505 both G140S and Q148H selected for L74M, E92Q, and N155H.

506 *Treatment-Naïve Subjects:* No subjects in the dolutegravir 50-mg once-daily
507 treatment arms of treatment-naïve trials SPRING-2 and SINGLE had a detectable decrease in
508 susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 6 with
509 HIV-1 RNA >400 copies/mL at failure or last visit through Week 48 and having resistance data).
510 One additional subject in SINGLE with 275 copies/mL HIV-1 RNA had a treatment-emergent
511 INSTI-resistance substitution (E157Q/P) detected at Week 24, but no corresponding decrease in
512 dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background
513 regimen was isolated in the dolutegravir arm in either the SPRING-2 or SINGLE trials.

514 *Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects:* In
515 SAILING, viruses from 5 of 15 subjects in the dolutegravir arm with post-baseline resistance
516 data had evidence of treatment-emergent integrase substitutions (1 subject each with L74I/M,
517 Q95Q/L, or V151V/I, and 2 subjects with R263K). However, none of these subjects' isolates had
518 detectable phenotypic decreases in susceptibility to either dolutegravir or raltegravir. In the
519 comparator raltegravir arm, 9 of 32 subjects with post-baseline resistance data had evidence of
520 emergent INSTI-resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R,
521 Q148H/R, V151I, N155H, E157E/Q, and G163G/R) and raltegravir phenotypic resistance.

522 *Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced*
523 *Subjects:* VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized
524 background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir
525 or raltegravir) containing regimen.

526 Response by Baseline Genotype: Of the 183 subjects with baseline data, 30%
527 harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance
528 substitutions (T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R and N155H) at baseline, but had
529 historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of
530 elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at
531 screening.

532 Response rates by baseline genotype were analyzed using a subset of subjects who had
533 reached Week 24, as well as those who discontinued or rebounded before Week 24 (n = 124)
534 (Table 10). The response rate at Week 24 for subjects with only historic evidence of INSTI-
535 resistance at baseline was 75% (33/44). The response rate at Week 24 to dolutegravir-containing
536 regimens was 36% (13/36) when Q148 substitutions were present at baseline; Q148 was always
537 present with additional INSTI-resistance substitutions. Diminished virologic responses (25%
538 [7/28]) were observed when ≥ 3 of the following INSTI-resistance substitutions were present at
539 baseline: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, Q148H/R, E157Q, G163E/K/Q/R/S, or
540 G193E/R.

541

542 **Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an**
543 **Integrase Strand Transfer Inhibitor in VIKING-3**

Baseline Genotype	Response at Week 24 (<50 copies/mL) Subset N = 124
Overall Response	64% (79/124)
N155H without a Q148 substitution	80% (16/20)
Y143C/H/R without a Q148 substitution	56% (10/18)
Q148H/R + G140A/S without additional INSTI-resistance substitutions	56% (10/18)
Q148H/R + ≥2 INSTI-resistance substitutions ^{a,b}	18% (3/17)

544 ^a INSTI-resistance substitutions include L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q,
545 G163E/K/Q/R/S, or G193E/R.

546 ^b The most common pathway with Q148H/R + ≥2 INSTI-resistance substitutions had
547 Q148+G140+E138 substitutions (n = 12).

548

549 **Response by Baseline Phenotype:** Response rates by baseline phenotype were
550 analyzed using a subset of subjects who had reached Week 24, as well as those who discontinued
551 or rebounded before Week 24 (n = 120) (See Table 11). These baseline phenotypic groups are
552 based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical
553 susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the
554 likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-
555 resistant patients.

556

557 **Table 11. Response by Baseline Dolutegravir Phenotype (Fold-Change From Reference) in**
558 **Subjects With Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3**

Baseline Dolutegravir Phenotype (Fold-Change From Reference)	Response at Week 24 (<50 copies/mL) Subset N = 120
Overall Response	63% (75/120)
<3-fold change	72% (63/87)
3- <10-fold change	42% (10/24)
≥10-fold change	22% (2/9)

559

560 **Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance:** There were
561 40 subjects on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA >400
562 copies/mL at Week 24, the failure timepoint, or the last timepoint on trial who were included in
563 the Week 24 resistance analysis set. In the Week 24 resistance analysis set, 45% (18/40) of the
564 subjects had treatment-emergent INSTI-resistance substitutions in their isolates. The most
565 common treatment-emergent INSTI-resistance substitution was T97A. Other frequently
566 emergent INSTI-resistance substitutions included E138K or A, G140S or A, or Q148H or R or

567 K; substitutions at Q148 were detected in subjects with changes documented at or prior to
568 enrollment in the trial. Substitutions L74M, E92Q, Y143H or C, S147G, V151A, M154I, and
569 N155H each emerged in 1 or 2 subjects' isolates. At failure, the median dolutegravir fold-change
570 from reference was 23-fold (range: 0.92 to 209) for isolates with emergent INSTI-resistance
571 substitutions (n = 18).

572 Resistance to one or more background drugs in the dolutegravir twice-daily regimen also
573 emerged in 30% (12/40) of the subjects in the Week 24 resistance analysis set.

574 Cross-Resistance: Site-Directed Integrase Strand Transfer Inhibitor-Resistant
575 Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60
576 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or
577 more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-
578 resistance substitutions T66K, I151L, and S153Y conferred a >2-fold decrease in dolutegravir
579 susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions
580 T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H,
581 T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a >2-fold decrease in
582 dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants,
583 combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred
584 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed
585 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

586 Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains:
587 Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-
588 resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

589 **13 NONCLINICAL TOXICOLOGY**

590 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

591 Carcinogenesis: Two-year carcinogenicity studies in mice and rats were conducted with
592 dolutegravir. Mice were administered doses of up to 500 mg/kg, and rats were administered
593 doses of up to 50 mg/kg. In mice, no significant increases in the incidence of drug-related
594 neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures
595 approximately 14-fold higher than those in humans at the recommended dose of 50 mg twice
596 daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the
597 highest dose tested, resulting in dolutegravir AUC exposures 10-fold and 15-fold higher in males
598 and females, respectively, than those in human at the recommended dose of 50 mg twice daily.

599 Mutagenesis: Dolutegravir was not genotoxic in the bacterial reverse mutation assay,
600 mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

601 Impairment of Fertility: In a study conducted in rats, there were no effects on mating or
602 fertility with dolutegravir up to 1,000 mg/kg/day. This dose is associated with an exposure that is
603 approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg
604 twice daily.

605 **14 CLINICAL STUDIES**

606 The efficacy of TIVICAY is based on analyses of data from 2 trials, SPRING-2
607 (ING113086) and SINGLE (ING114467), in treatment-naïve, HIV-1-infected subjects
608 (n = 1,641); one trial, SAILING (ING111762), in treatment-experienced, INSTI-naïve
609 HIV-1-infected subjects (n = 715); and from VIKING-3 (ING112574) trial in INSTI-experienced
610 HIV-1-infected subjects (n = 183). The use of TIVICAY in pediatric patients aged 12 years and
611 older is based on evaluation of safety, pharmacokinetics, and efficacy through 24 weeks in a
612 multi-center, open-label trial in subjects (n = 23) without INSTI resistance.

613 **14.1 Adult Subjects**

614 Treatment-Naïve Subjects: The efficacy of TIVICAY in HIV-1-infected treatment-
615 naïve adults is based on the analyses of 48-week data from 2 randomized, international,
616 multicenter, double-blind, active-controlled trials, SPRING-2 and SINGLE.

617 In SPRING-2, 822 subjects were randomized and received at least 1 dose of either
618 TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-
619 dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or
620 emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and
621 safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-
622 white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had
623 HIV-1 RNA >100,000 copies/mL, 48% had CD4+ cell count <350 cells/mm³, and 39% received
624 EPZICOM; these characteristics were similar between treatment groups.

625 In SINGLE, 833 subjects were randomized and received at least 1 dose of either
626 TIVICAY 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or
627 fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects
628 was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-
629 infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA >100,000
630 copies/mL, and 53% had CD4+ cell count <350 cells/mm³; these characteristics were similar
631 between treatment groups.

632 Week 48 outcomes for SPRING-2 and SINGLE are provided in Table 12. Side-by-side
633 tabulation is to simplify presentation; direct comparisons across trials should not be made due to
634 differing trial designs.

635

636 **Table 12. Virologic Outcomes of Randomized Treatment in SPRING-2 and SINGLE at**
637 **Week 48 (Snapshot Algorithm)**

	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)	TIVICAY 50 mg + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
HIV-1 RNA <50 copies/mL	88%	86%	88%	81%
Treatment difference ^a	2.6% (95% CI: -1.9%, 7.2%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic nonresponse^b	5%	7%	5%	6%
No virologic data at Week 48 window	7%	7%	7%	13%
Reasons				
Discontinued study/study drug due to adverse event or death ^c	2%	1%	2%	10%
Discontinued study/study drug for other reasons ^d	5%	6%	5%	3%
Missing data during window but on study	0	0	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	91%	90%	90%	83%
>100,000	82%	75%	83%	76%
Gender				
Male	89%	86%	88%	82%
Female	84%	82%	85%	75%
Race				
White	88%	86%	90%	84%
Non-white	85%	85%	84%	74%

638 ^a Adjusted for pre-specified stratification factors.

639 ^b Includes subjects who changed BR to new class or changed BR not permitted per protocol or
640 due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued
641 prior to Week 48 for lack or loss of efficacy, and subjects who were HIV-1 RNA
642 ≥50 copies/mL in the Week 48 window.

643 ^c Includes subjects who discontinued due to an adverse event or death at any time point from
644 Day 1 through the Week 48 window if this resulted in no virologic data on treatment during
645 the Week 48 window.

646 ^d Other includes reasons such as withdrew consent, loss to follow-up, moved, and
647 protocol deviation.

648

649 *SPRING-2*: Virologic outcomes were also comparable across baseline characteristics
650 including CD4+ cell count, age, and use of EPZICOM or TRUVADA as NRTI background
651 regimen. The median change in CD4+ cell counts from baseline for both groups was
652 +230 cells/mm³ at 48 weeks.

653 *SINGLE*: Treatment differences were maintained across baseline characteristics
654 including HIV-1 RNA, CD4+ cell count, age, gender, and race.

655 The adjusted mean changes in CD4+ cell counts from baseline were 267 cells/mm³ in the
656 group receiving TIVICAY + EPZICOM and 208 cells/mm³ for the ATRIPLA group at 48 weeks.
657 The adjusted difference between treatment arms and 95% CI was 58.9 cells/mm³ (33.4
658 cells/mm³, 84.4 cells/mm³) (adjusted for pre-specified stratification factors: baseline HIV-1
659 RNA, baseline CD4+ cell count, and multiplicity).

660 Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In
661 the international, multicenter, double-blind trial (SAILING), 719 HIV-1- infected, antiretroviral
662 treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily
663 or raltegravir 400 mg twice daily with investigator selected background regimen consisting of up
664 to 2 agents, including at least 1 fully active agent. There were 715 subjects included in the
665 efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 49%
666 non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS),
667 20% had HIV-1 RNA >100,000 copies/mL, and 72% had CD4+ cell count <350 cells/mm³;
668 these characteristics were similar between treatment groups. All subjects had at least 2-class
669 antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral
670 treatment resistance at baseline. Week 24 outcomes for SAILING are shown in Table 13.
671

672 **Table 13. Virologic Outcomes of Randomized Treatment in SAILING at 24 Weeks**
673 **(Snapshot Algorithm)**

	TIVICAY 50 mg Once Daily + BR ^a (N = 354)	Raltegravir 400 mg Twice Daily + BR ^a (N = 361)
HIV-1 RNA <50 copies/mL	79%	70%
Adjusted ^b treatment difference	9.7% (95% CI: 3.4%, 15.9%)	
Virologic nonresponse	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 reasons ^c	3%	3%
Missing data during window but on study	<1%	<1%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	83%	77%
>50,000 copies/mL	70%	53%
Background regimen		
No darunavir use or use of darunavir with primary PI substitutions	79%	67%
Use of darunavir without primary PI substitutions	80%	81%
Gender		
Male	78%	70%
Female	83%	69%
Race		
White	79%	69%
Non-white	80%	71%

674 ^a BR = Background regimen. Background regimen was restricted to ≤2 antiretroviral treatments
675 with at least 1 fully active agent.

676 ^b Adjusted for pre-specified stratification factors.

677 ^c Other includes reasons such as withdrew consent, loss to follow-up, moved, and
678 protocol deviation.

679

680 Treatment differences were maintained across the baseline characteristics including
681 CD4+ cell count and age.

682 The mean changes in CD4+ cell counts from baseline were 114 cells/mm³ in the group
683 receiving TIVICAY and 106 cells/mm³ in the raltegravir group.

684 Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced
685 Subjects: VIKING-3 examined the effect of TIVICAY 50 mg twice daily over 7 days of

686 functional monotherapy, followed by optimized background therapy with continued treatment of
687 TIVICAY 50 mg twice daily.

688 In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV-1-infected,
689 antiretroviral treatment-experienced adults with virological failure and current or historical
690 evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with
691 the current failing background regimen for 7 days, then received TIVICAY with optimized
692 background therapy from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI
693 resistance at screening and 50 subjects with only historical evidence of resistance (and not at
694 screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white,
695 and 20% had hepatitis B and/or C virus co-infection. Median baseline CD4+ cell count was
696 140 cells/mm³, median duration of prior antiretroviral treatment was 13 years, and 56% were
697 CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79%
698 had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major substitutions; 62% had non-R5 virus.

699 Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 log₁₀
700 (95% CI: 1.3 log₁₀, 1.5 log₁₀). Response at Week 24 was affected by baseline INSTI substitutions
701 [see Microbiology (12.4)].

702 After the functional monotherapy phase, subjects had the opportunity to re-optimize their
703 background regimen when possible. Week 24 virologic outcomes for VIKING-3 are shown in
704 Table 14.

705

706 **Table 14. Virologic Outcomes of Treatment of VIKING-3 at 24 Weeks (Snapshot**
707 **Algorithm)**

	TIVICAY 50 mg Twice Daily + Optimized Background Therapy (N = 114)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data at Week 24	
Reasons	
Discontinued study/study drug due to adverse event or death	4%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category	
Gender	
Male	64%
Female	60%
Race	
White	67%
Non-white	52%

708

709 Subjects harboring virus with Q148 and with additional Q148-associated secondary
710 substitutions also had a reduced response at Week 24 in a stepwise fashion [see Microbiology
711 (12.4)].

712 The median change in CD4+ cell count from baseline was 65 cells/mm³ at Week 24.

713 **14.2 Pediatric Subjects**

714 IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the
715 pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY in combination
716 treatment regimens in HIV-1-infected infants, children, and adolescents.

717 The initial dose-finding stage included intensive pharmacokinetic evaluation in
718 10 INSTI-naïve subjects (aged 12 to 18 years). Dose selection was based upon achieving similar
719 dolutegravir plasma exposure and trough concentration as seen in adults. After dose selection, an
720 additional 13 subjects were enrolled for evaluation of long-term safety, tolerability, and efficacy.

721 These 23 subjects had a mean age of 14 years (range: 12 to 17), were 78% female and
722 52% black. At baseline, mean plasma HIV-1 RNA was 4.3 log₁₀ copies/mL, median CD4+ cell
723 count was 466 cells/mm³ (range: 11 to 1,025), and median CD4+% was 22% (range: 1% to
724 39%). Overall, 17% had baseline plasma HIV-1 RNA >50,000 copies/mL and 39% had a CDC
725 HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI
726 (52%) or 1 PI (78%).

727 At 24 weeks, 70% of subjects treated with TIVICAY once daily (35 mg: n = 4, 50 mg:
728 n = 19) plus optimized background therapy achieved a viral load <50 copies/mL. The median
729 CD4+ cell count (percent) increase from baseline to Week 24 was 63 cells/mm³ (5%).

730 **16 HOW SUPPLIED/STORAGE AND HANDLING**

731 TIVICAY Tablets, 50 mg, are yellow, round, film-coated, biconvex tablets debossed with
732 SV 572 on one side and 50 on the other side.

733 Bottle of 30 tablets with child-resistant closure NDC 49702-228-13.

734 Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [See USP
735 Controlled Room Temperature].

736 **17 PATIENT COUNSELING INFORMATION**

737 *See FDA-approved Patient Labeling (Patient Information).*

738 **Drug Interactions:** TIVICAY should not be coadministered with dofetilide because
739 interactions between these drugs can result in potentially life-threatening adverse events [*see*
740 *Contraindications (4)*].

741 **Hypersensitivity Reactions:** Patients should be advised to immediately contact their
742 healthcare provider if they develop rash. Instruct patients to immediately stop taking TIVICAY
743 and other suspect agents, and seek medical attention if they develop a rash associated with any of
744 the following symptoms, as it may be a sign of a more serious reaction such as severe
745 hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or
746 peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the
747 eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems
748 (e.g., yellowing of the skin or whites of the eyes, dark or tea-colored urine, pale-colored stools or
749 bowel movements, nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on the right
750 side below the ribs). Patients should understand that if hypersensitivity occurs, they will be

751 closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated.
752 Patients should also be told that it is very important that they remain under a physician's care
753 during treatment with TIVICAY [*see Warnings and Precautions (5.1)*].

754 Effects on Serum Liver Biochemistries in Patients With Hepatitis B or C Co-
755 infection: Patients with underlying hepatitis B or C may be at increased risk for worsening or
756 development of transaminase elevations with use of TIVICAY and should be advised that they
757 are recommended to have laboratory testing before and during therapy [*see Warnings and*
758 *Precautions (5.2)*].

759 Fat Redistribution: Patients should be informed that redistribution or accumulation of
760 body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term
761 health effects of these conditions are not known at this time [*see Warnings and Precautions*
762 *(5.3)*].

763 Immune Reconstitution Syndrome: In some patients with advanced HIV infection,
764 signs and symptoms of inflammation from previous infections may occur soon after anti-HIV
765 treatment is started. It is believed that these symptoms are due to an improvement in the body's
766 immune response, enabling the body to fight infections that may have been present with no
767 obvious symptoms. Patients should be advised to inform their healthcare provider immediately
768 of any symptoms of infection [*see Warnings and Precautions (5.4)*].

769 Information About HIV-1 Infection: TIVICAY is not a cure for HIV-1 infection and
770 patients may continue to experience illnesses associated with HIV-1 infection, including
771 opportunistic infections. Patients must remain on continuous HIV therapy to control HIV
772 infection and decrease HIV-related illness. Patients should be told that sustained decreases in
773 plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.
774 Patients should remain under the care of a physician when using TIVICAY.

775 Patients should be informed to take all HIV medications exactly as prescribed.

776 Patients should be advised to avoid doing things that can spread HIV-1 infection to
777 others.

- 778 • **Do not re-use or share needles or other injection equipment.**
- 779 • **Do not share personal items that can have blood or body fluids on them, like**
780 **toothbrushes and razor blades.**
- 781 • Continue to practice safe sex by using a latex or polyurethane condom to lower the chance of
782 sexual contact with semen, vaginal secretions, or blood.
- 783 • Female patients should be advised not to breastfeed because it is not known if TIVICAY can
784 be passed to the baby in your breast milk and whether it could harm the baby. Mothers with
785 HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

786
787 Physicians should instruct their patients to read the Patient Information before starting
788 TIVICAY and to reread it each time the prescription is renewed. Patients should be instructed to
789 inform their physician or pharmacist if they develop any unusual symptom, or if any known
790 symptom persists or worsens.

791 Physicians should instruct their patients that if they miss a dose, they should take it as
792 soon as they remember. If they do not remember until it is within 4 hours of the time for the next
793 dose, they should be instructed to skip the missed dose and go back to the regular schedule.
794 Patients should not double their next dose or take more than the prescribed dose.

795

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797

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799 of ViiV Healthcare. The makers of these brands are not affiliated with and do not endorse ViiV
800 Healthcare or its products.

801

802

803 Manufactured for:



804

805 ViiV Healthcare

806 Research Triangle Park, NC 27709

807

808 by:



809

810 GlaxoSmithKline

811 Research Triangle Park, NC 27709

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815 TVC:XPI

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829 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

830

831

832

Patient Information

833

TIVICAY[®] (TIV-eh-kay)

834

(dolutegravir)

835

Tablets

836

837

838

Read this Patient Information before you start taking TIVICAY and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

839

840

841

842

What is TIVICAY?

843

TIVICAY is a prescription HIV medicine that is used with other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infections in adults and children 12 years of age and older and weighing at least 88 pounds.

844

845

846

847

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

848

It is not known if TIVICAY is safe and effective in children under 12 years of age or who weigh less than 88 pounds.

849

850

851

When used with other HIV-1 medicines to treat HIV-1 infection, TIVICAY

852

may help:

853

- Reduce the amount of HIV-1 in your blood. This is called "viral load".

854

- Increase the number of white blood cells called CD4+ (T) cells in your blood, which help fight off other infections.

855

856

- Reduce the amount of HIV-1 and increase the CD4+ (T) cell in your blood which may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

857

858

859

860

TIVICAY does not cure HIV-1 infection or AIDS. You must stay on continuous HIV-1 therapy to control HIV-1 infection and decrease HIV-related illnesses.

861

862

Avoid doing things that can spread HIV-1 infection to others.

863

- Do not share or re-use needles or other injection equipment.

864

- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

865

- 866 • Do not have any kind of sex without protection. Always practice safe sex by
867 using a latex or polyurethane condom to lower the chance of sexual contact with
868 any body fluids such as semen, vaginal secretions, or blood.

869 Ask your healthcare provider if you have any questions about how to prevent
870 passing HIV to other people.

871

872 **Who should not take TIVICAY?**

873 **Do not take TIVICAY if you take dofetilide. Taking TIVICAY and dofetilide**
874 **can cause side effects that may be life-threatening.**

875

876 **What should I tell my healthcare provider before taking TIVICAY?**

877 **Before you take TIVICAY, tell your healthcare provider if you:**

- 878 • have ever had an allergic reaction to TIVICAY
879 • have or had liver problems, including hepatitis B or C infection
880 • have any other medical condition
881 • are pregnant or plan to become pregnant. It is not known if TIVICAY will harm
882 your unborn baby. Tell your healthcare provider if you become pregnant while
883 taking TIVICAY.

884 **Pregnancy Registry.** There is a pregnancy registry for women who take
885 antiviral medicines during pregnancy. The purpose of the registry is to collect
886 information about the health of you and your baby. Talk to your healthcare
887 provider about how you can take part in this registry.

- 888 • are breastfeeding or plan to breastfeed. **Do not breastfeed if you take**
889 **TIVICAY.**

890 • You should not breastfeed if you have HIV-1 because of the risk of passing
891 HIV-1 to your baby.

892 • It is not known if TIVICAY passes into your breast milk.

893 • Talk to your healthcare provider about the best way to feed your baby.

894

895 **Tell your healthcare provider about the medicines you take,** including
896 prescription and over-the-counter medicines, vitamins, or herbal supplements.

897

898 TIVICAY and other medicines may affect each other causing side effects. TIVICAY
899 may affect the way other medicines work, and other medicines may affect how
900 TIVICAY works.

901 Especially tell your healthcare provider if you take:

- 902 • other HIV-1 medicines including: efavirenz (SUSTIVA[®]), etravirine
903 (INTELENCE[®]), fosamprenavir (LEXIVA[®])/ritonavir (NORVIR[®]), nevirapine
904 (VIRAMUNE[®]), or tipranavir (APTIVUS[®])/ritonavir (NORVIR).
905 • antacids or laxatives that contain aluminum, magnesium or calcium, sucralfate
906 (CARAFATE[®]), iron or calcium supplements, or buffered medicines. TIVICAY
907 should be taken at least 2 hours before or 6 hours after you take these
908 medicines.
909 • anti-seizure medicines:
910 • oxcarbazepine (TRILEPTAL[®])
911 • phenytoin (DILANTIN[®], DILANTIN[®]-125, PHENYTEK[®])
912 • phenobarbital (LUMINAL[®])
913 • carbamazepine (CARBATROL[®], EQUETRO[®], TEGRETOL[®], TEGRETOL[®]-XR,
914 TERIL[®], EPITOL[®])
915 • St. John's wort (*Hypericum perforatum*)
916 • a medicine that contains metformin
917 • rifampin (RIFATER[®], RIFAMATE[®], RIMACTANE[®], RIFADAN[®])

918 Ask your healthcare provider or pharmacist if you are not sure if your medicine is
919 one that is listed above.

920 Know the medicines you take. Keep a list of them to show your healthcare provider
921 and pharmacist when you get a new medicine.

922

923 **How should I take TIVICAY?**

- 924 • Take TIVICAY exactly as your healthcare provider tells you.
925 • Do not change your dose or stop taking TIVICAY without talking with your
926 healthcare provider.
927 • Stay under the care of a healthcare provider while taking TIVICAY.
928 • You can take TIVICAY with or without food.
929 • If you miss a dose of TIVICAY, take it as soon as you remember. If it is within 4
930 hours of your next dose, skip the missed dose and take the next dose at your
931 regular time. Do not take 2 doses at the same time. If you are not sure about
932 your dosing, call your healthcare provider.
933 • If you take too much TIVICAY, call your healthcare provider or go to the nearest
934 hospital emergency room right away.
935 • Do not run out of TIVICAY. The virus in your blood may become resistant to
936 other HIV-1 medicines if TIVICAY is stopped for even a short time. When your
937 supply starts to run low, get more from your healthcare provider or pharmacy.
938

939 **What are the possible side effects of TIVICAY?**

940 **TIVICAY may cause serious side effects, including:**

941 • **Allergic reactions.** Call your healthcare provider right away if you develop a
942 rash with TIVICAY. **Stop taking TIVICAY and get medical help right away if**
943 **you:**

944 • **develop a rash with any of the following signs or symptoms**

- 945 ○ fever
- 946 ○ generally ill feeling
- 947 ○ extreme tiredness
- 948 ○ muscle or joint aches
- 949 ○ blisters or sores in mouth
- 950 ○ blisters or peeling of the skin
- 951 ○ redness or swelling of the eyes
- 952 ○ swelling of the mouth, face, lips, or tongue
- 953 ○ problems breathing

954 • **develop any of the following signs or symptoms of liver problems:**

- 955 ○ yellowing of the skin or whites of the eyes
- 956 ○ dark or tea-colored urine
- 957 ○ pale-colored stools or bowel movements
- 958 ○ nausea or vomiting
- 959 ○ loss of appetite
- 960 ○ pain, aching, or tenderness on the right side below the ribs
- 961 • **Changes in liver tests.** People with a history of hepatitis B or C virus may have
962 an increased risk of developing new or worsening changes in certain liver tests
963 during treatment with TIVICAY. Your healthcare provider may do tests to check
964 your liver function before and during treatment with TIVICAY.
- 965 • **Changes in body fat** can happen in people who take HIV-1 medicines. These
966 changes may include increased amount of fat in the upper back and neck
967 (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat
968 from the legs, arms, and face may also happen. The exact cause and long-term
969 health effects of these problems are not known.
- 970 • **Changes in your immune system (Immune Reconstitution Syndrome)** can
971 happen when you start taking HIV-1 medicines. Your immune system may get
972 stronger and begin to fight infections that have been hidden in your body for a
973 long time. Tell your healthcare provider right away if you start having new
974 symptoms after starting your HIV-1 medicine.

975

976 The most common side effects of TIVICAY include:

- 977 • trouble sleeping
- 978 • headache

979 Tell your healthcare provider about any side effect that bothers you or that does
980 not go away.

981 These are not all the possible side effects of TIVICAY. For more information, ask
982 your healthcare provider or pharmacist.

983

984 Call your doctor for medical advice about side effects. You may report side effects
985 to FDA at 1-800-FDA-1088.

986

987 **How should I store TIVICAY?**

- 988 • Store TIVICAY at room temperature between 68°F to 77°F (20°C to 25°C).

989 **Keep TIVICAY and all medicines out of the reach of children.**

990

991 **General information about TIVICAY**

992 Medicines are sometimes prescribed for purposes other than those listed in a
993 Patient Information leaflet. Do not use TIVICAY for a condition for which it was not
994 prescribed. Do not give TIVICAY to other people, even if they have the same
995 symptoms you have. It may harm them.

996 You can ask your pharmacist or healthcare provider for information about TIVICAY
997 that is written for health professionals.

998 For more information call 1-877-844-8872 or go to www.TIVICAY.com.

999

1000 **What are the ingredients in TIVICAY?**

1001 **Active ingredient:** dolutegravir sodium

1002 **Inactive ingredients:** d-mannitol, microcrystalline cellulose, povidone K29/32,
1003 sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating
1004 contains the inactive ingredients iron oxide yellow, macrogol/PEG, polyvinyl alcohol-
1005 part hydrolyzed, talc, and titanium dioxide.

1006

1007 This Patient Information has been approved by the U.S. Food and Drug
1008 Administration.

1009

1010

1011 Manufactured for:



1012

1013 ViiV Healthcare

1014 Research Triangle Park, NC 27709

1015

1016 by:



1017

1018 GlaxoSmithKline

1019 Research Triangle Park, NC 27709

1020

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1023

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