# Data Sheet

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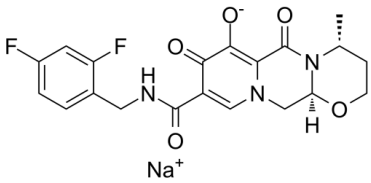
| **Product Name:** | Dolutegravir (sodium) |
| **Cat. No.:** | CS-3496 |
| **CAS No.:** | 1051375-19-9 |
| **Molecular Formula:** | C20H18F2N3NaO5 |
| **Molecular Weight:** | 441.36 |
| **Target:** | HIV; HIV Integrase |
| **Pathway:** | Anti-infection; Metabolic Enzyme/Protease |
| **Solubility:** | DMSO : ≥ 4.5 mg/mL (10.20 mM); H2O : < 0.1 mg/mL (insoluble) |



## BIOLOGICAL ACTIVITY:

Dolutegravir sodium (S/GSK1349572 sodium) is a highly potent and orally bioavailable **HIV integrase strand transfer** inhibitor with an **$IC_{50}$** of 2.7 nM for HIV-1 integrase-catalyzed strand transfer. Dolutegravir sodium (S/GSK1349572 sodium) inhibits HIV-1 viral replication with an $IC_{50}$ of 0.51 nM in peripheral blood mononuclear cells. Dolutegravir sodium (S/GSK1349572 sodium) retains a high potency against the HIV-1 Y143R, N155H, and G140S/Q148H mutants ($EC_{50}$=3.6-5.8 nM)[1][2]. IC50 & Target: IC50: 2.7 nM (HIV-1 integrase)[1] **In Vitro:** The $EC_{50}$ of Dolutegravir (S/GSK1349572) against HIV-1 is 0.51 nM in PBMCs, 0.71 nM in MT-4 cells, and 2.2 nM in the PHIV assay, which uses a pseudotyped self-inactivating virus. The 50% cytotoxic concentrations ($CC_{50}$) for Dolutegravir in proliferating IM-9, U-937, MT-4, and Molt-4 cells are 4.8, 7.0, 14, and 15 μM, respectively. In unstimulated and stimulated PBMCs, the $CC_{50}$ are 189 μM and 52 μM, respectively. Based on the $EC_{50}$ of Dolutegravir against HIV-1 in PBMCs (i.e., 0.51 nM), this translates to a cell-based therapeutic index of at least 9,400[1]. **In Vivo:** Following a single intravenous (IV) administration of Dolutegravir, the plasma clearance is low in rats (0.23 mL/min/kg) and monkeys (2.12 mL/min/kg). The half-lives in the rat and monkey are similar, approximately 6 h, and the steady-state volume of distribution ($V_{SS}$) is low. Following oral administration, Dolutegravir is rapidly absorbed with a high oral bioavailability when administered as a solution to fasted male rats and a single monkey (75.6 and 87.0%, respectively). Dolutegravir exposure ($C_{max}$ and AUC) increased with increasing dose following oral administration of a suspension to non-fasted rats up to 250 mg/kg and non-fasted monkeys up to 50 mg/kg, although the increase is less than proportional[2].

## PROTOCOL (Extracted from published papers and Only for reference)

**Cell Assay:** Dolutegravir (S/GSK1349572) is dissolved in stock solutions, and then diluted with appropriate media before use[1].[1]In vitro growth inhibition (cytotoxicity) studies are conducted with S/GSK1349572 (0.16, 0.8, 4, and 20 nM) in proliferating human leukemic and lymphomic cell lines (IM-9, U-937, MT-4, and Molt-4) as well as in stimulated and unstimulated human PBMCs. ATP levels are quantified by using the CellTiter-Glo luciferase reagent to measure the ability of a compound to inhibit cell growth as an indicator of the compound's potential for cytotoxicity[1]. **Animal Administration:** Dolutegravir (S/GSK1349572) is formulated as a solution in N,N-dimethylacetamide and diluted with 50 mM N-methylglucamine in 3% mannitol (intravenous)[2]. ;Dolutegravir (S/GSK1349572) is formulated as a solution in D:Solutol:50 mM N-methylglucamine in 3% mannitol (1:1:8, v:w:v) (orally administered to fasted rats and monkeys)[2]. ;Dolutegravir (S/GSK1349572) is formulated as a suspension in 0.5% hydroxypropyl methylcellulose (HPMC)/0.1% polyoxyethylene sorbitan monooleate (Tween 80) (orally administered to non-fasted rats and monkeys)[2].[2]For rat and monkey PK studies, Dolutegravir is administered as the free acid or the sodium salt. All doses are presented in terms of the free acid. Dolutegravir is administered by intravenous (IV) short-term (within 2 min) bolus (1 mg/kg) to three male rats and two male monkeys. For single oral administration, Dolutegravir as a solution (5 mg/kg) is administered to three fasted male rats and two fasted male monkeys. Dolutegravir is administered as single oral doses of 5, 50, 100, and 250 mg/kg to non-fasted male rats (n=2/dose level) and 3, 10, and 50 mg/kg to non-fasted female monkeys. For intravenous administration, blood samples are collected from rats (0.2 mL via jugular vein cannula) and monkeys (approximately 0.2 or 0.5 mL via saphenous vein in a hindlimb) into $Na_2$EDTA-treated syringes at

0.083, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h. For oral administration, samples are collected at 0.25 (rats only), 0.5, 1, 2, 4, 6 [rats (solution and suspension) and monkey (solution only)], 8, and 24 h. Following collection, the blood is immediately put on wet ice and then centrifuged within an hour at 1740 g for 10 min at 4°C to obtain plasma. All samples are stored at approximately -20°C or colder prior to analysis by using a method based on protein precipitation and LC-MS/MS analysis.

## References:


[1]. Kobayashi M, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother. 2011 Feb;55(2):813-21.

[2]. Hare S, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). Mol Pharmacol. 2011 Oct;80(4):565-72.

[3]. Moss L, et al. The comparative disposition and metabolism of dolutegravir, a potent HIV-1 integrase inhibitor, in mice, rats, and monkeys. Xenobiotica. 2015 Jan;45(1):60-70.


## CAIndexNames:

2H-Pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide, N-[(2,4-difluorophenyl)methyl]-3,4,6,8,12,12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-, sodium salt (1:1), (4R,12aS)-

## SMILES:

O=C(C1=CN(C2=C([O-])C1=O)C[C@]3([H])OCC[C@@H](C)N3C2=O)NCC4=CC=C(F)C=C4F.[Na+]




Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA