## Details

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Tivicay*</td>
</tr>
<tr>
<td>Class</td>
<td>Integrase Inhibitor</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>441.36</td>
</tr>
<tr>
<td>Structure</td>
<td><img src="image" alt="Dolutegravir Structure" /></td>
</tr>
</tbody>
</table>

## Summary of Key Pharmacokinetic Parameters

### Linearity/non-linearity
Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Non-linear exposure of dolutegravir was observed following 50 mg twice daily compared with 50 mg once daily in HIV-1–infected subjects and was attributed to the use of metabolic inducers in the background antiretroviral regimen of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

### Steady state
~5 days

### Plasma half life
~14 h

### Cmax
3.67 µg/ml (50 mg once daily, determined from population PK analyses in HIV+ subjects)  
4.15 µg/ml (50 mg twice daily, determined from population PK analyses in HIV+ subjects)

### Cmin
1.11 µg/ml (50 mg once daily, determined from population PK analyses in HIV+ subjects)  
2.12 µg/ml (50 mg twice daily, determined from population PK analyses in HIV+ subjects)

### AUC
53.6 µg.h/ml (50 mg once daily, determined from population PK analyses in HIV+ subjects)  
75.1 µg.h/ml (50 mg twice daily, determined from population PK analyses in HIV+ subjects)

### Bioavailability
Not determined.

### Absorption
Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir AUC by 33%, 41%, and 66%; increased Cmax by 46%, 52%, and 67%; and prolonged Tmax to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

### Protein Binding
≥98.9%

### Volume of Distribution
17.4 L (50 mg once daily, determined from population PK analyses in HIV+ subjects)

### CSF:Plasma ratio
In 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (range: 4-232 ng/mL) 2 to 6 h post dose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

### Semen:Plasma ratio
<7% of blood plasma exposure (and below the protein adjusted IC90) \(^1\)

### Renal Clearance
31% of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (<1% of the dose)
Renal Impairment

In a trial comparing 8 subjects with severe renal impairment (CrCl <30 mL/min) with 8 matched healthy controls, AUC, Cmax, and C24 of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. Population pharmacokinetic analysis indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir.

No dosage adjustment is necessary for treatment-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment.

Hepatic Impairment

Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50 mg dose was similar between the 2 groups.

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B).

The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment.

Metabolism and Distribution

Metabolised by Primarily glucuronidation via UGT1A1 with some contribution from CYP3A. Also a substrate of UGT1A3, UGT1A9, in vitro.

Inducer of Does not induce CYP1A2, CYP2B6, or CYP3A4

Inhibitor of In vitro inhibitor of OCT2 (IC50 = 1.93 μM)

Transported by BCRP and P-gp

References

Unless otherwise stated (see below), information is from:

Tivicay Summary of Product Characteristics, Viiv Healthcare UK Ltd.

Tivicay US Prescribing Information, Viiv Healthcare.