Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Dolutegravir (DTG, Tivicay)  
(Last updated April 27, 2017; last reviewed April 27, 2017)

For additional information see Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

**Formulations**

**Tablet:** 10 mg, 25 mg, and 50 mg

**Fixed-Dose Combination Tablet:**
- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

**Dosing Recommendations**

**Neonate/Infant Dose:**
- Not approved for use in neonates/infants

**Children Weighing ≥30 to <40 kg:**
- Not Food and Drug Administration-approved for use in children weighing <30 kg.
- A clinical trial in antiretroviral (ARV) treatment-experienced (but integrase strand inhibitor [INSTI]-naive) children weighing <30 kg is underway (see text).

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Dose* (mg/day)</th>
<th>Dosing Frequency</th>
<th>Tablet Size (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;40</td>
<td>35</td>
<td>Once daily</td>
<td>One 10-mg tablet plus one 25-mg tablet</td>
</tr>
</tbody>
</table>

* These doses are for children who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not being treated with UGT1A1/CYP3A inducers

**Note:** Dolutegravir 10-mg and 25-mg tablets may be available in the retail pharmacy. If not available, when ordering dolutegravir 10-mg or 25-mg tablets, have the pharmacy contact their drug wholesaler and tell the drug wholesaler to order directly from the GSK distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

**Selected Adverse Events**

- Insomnia
- Headache
- Hypersensitivity reactions including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported rarely.

**Special Instructions**

- May be taken without regard to meals
- 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
- In patients who have difficulty swallowing tablets whole, 10-, 25-, and 50-mg tablets may be either split into halves followed by immediate ingestion of both halves of the tablet, or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.¹
- The efficacy of 50-mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).

**Metabolism/Elimination**

- UGT1A1 and cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of lack of data, dolutegravir is not recommended in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and slightly increases measured
serum creatinine, but does not affect glomerular filtration.

- Dosing in patients with renal impairment: No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment or in INSTI-experienced patients with mild or moderate renal impairment.

- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min) because dolutegravir concentrations will be decreased (the cause of this decrease is unknown).

**Drug Interactions** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- **Metabolism:** Dolutegravir is a UGT1A1 and cytochrome 3 (CYP3) A substrate and may require dosage adjustments when administered with UGT1A1 or CYP3A-modulating medications. Because etravirine significantly reduces plasma concentrations of dolutegravir, dolutegravir should not be administered with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteracts this effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data.

- Before dolutegravir is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions.

**Major Toxicities**

- **More common:** Insomnia and headache

- **Less common (more severe):** Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, neuropsychiatric symptoms.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10), and the Stanford University HIV Drug Resistance database offers a discussion of integrase strand transfer inhibitor (INSTI) mutations.
The efficacy of 50-mg dolutegravir twice daily is reduced in patients with INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance mutations: T66A, L74I/M, E138A/K/T, G140SA/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

**Pediatric Use**

**Approval**

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other antiretroviral drugs for children weighing at least 30 kg and who are treatment-naive or treatment-experienced but integrase strand transfer inhibitor (INSTI)-naive.

**Efficacy and Pharmacokinetics**

IMPAACT P1093 is an ongoing open-label trial of children with HIV with the plan to enroll down to age 4 weeks. FDA approval of dolutegravir down to age 12 years/40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents. Intensive pharmacokinetic (PK) evaluations were performed on the first 10 participants (9 weighing ≥40 kg and receiving 50 mg, 1 weighing 37 kg and receiving 35 mg) and resulted in exposures comparable to those seen in adults receiving 50 mg once daily. Nine of 10 participants achieved HIV RNA concentration <400 copies/mL at week 4 (optimal background therapy was added 5 to 10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% had achieved HIV RNA concentration <50 copies/mL. No safety or tolerability concerns were identified. By week 144, 39% and 30% had achieved HIV RNA concentrations <400 and <50 copies/mL, respectively. All who experienced virologic failure were nonadherent. In addition, a younger cohort of children aged ≥6 to <12 years are undergoing PK and longer-term follow-up in P1093, with those weighing ≥30 to <40 kg receiving the 35-mg dose and those weighing ≥40 kg using the 50-mg dose. At 48 weeks, data from 23 participants have demonstrated a favorable safety profile, adequate PK, and virologic efficacy with HIV RNA concentration of <50 copies/mL achieved in 74% (17/23).

This has led to FDA approval of the lower-strength tablets for children with HIV as young as 6 years and with body weight as low as 30 kg. The European Medicines Agency has approved the lower-strength tablets for children aged ≥6 years weighing ≥15 kg based on population PK modelling and simulation analyses. These analyses support a dose of 20 mg for children weighing 15 to <20 kg and 25 mg for those weighing 20 to <30 kg. An oral pediatric granule formulation and a dispersible tablet are also being studied, though the granule formulation will be replaced by the dispersible tablet. Doses for younger children are also under investigation in P1093.

### Pharmacokinetics of Dolutegravir in Adult and Pediatric Studies

<table>
<thead>
<tr>
<th>Population of Study</th>
<th>Weight (kg)</th>
<th>Dose (mg/day)</th>
<th>Tablet Size (mg)</th>
<th>Dosing Frequency</th>
<th>Dose for Lowest Weight Band (mg/kg)</th>
<th>Trough Plasma Concentrationa mcg/mLb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with Prior INSTI Treatment</td>
<td>&gt;40</td>
<td>100</td>
<td>50</td>
<td>Twice daily</td>
<td>2.5</td>
<td>2.12 (47)</td>
</tr>
<tr>
<td>Adults without Prior INSTI Treatment</td>
<td>≥40</td>
<td>50</td>
<td>50</td>
<td>Once daily</td>
<td>1.25</td>
<td>1.11 (46)</td>
</tr>
<tr>
<td>Children without Prior INSTI Treatment (N = 14)</td>
<td>≥40</td>
<td>50</td>
<td>50</td>
<td>Once daily</td>
<td>1.25</td>
<td>0.99 (66)</td>
</tr>
<tr>
<td>Children without Prior INSTI Treatment (N = 3)</td>
<td>30 to &lt;40</td>
<td>35</td>
<td>10 plus 25</td>
<td>Once daily</td>
<td>1.17</td>
<td>1.33 (93)</td>
</tr>
</tbody>
</table>


Geometric mean (percent coefficient of variation)

Note: Recommendations for 100 mg/day are for adults in special circumstances using 50 mg twice daily (see product label or text above).
In patients who have difficulty swallowing tablets whole, 10-, 25-, and 50-mg tablets may be either split into halves followed by immediate ingestion of both halves of the tablet or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed immediately. Crushing and mixing 10-, 25-, and 50-mg tablets would not be expected to adversely impact the product’s pharmaceutical quality, and therefore, would not be expected to alter the intended clinical effect. This conclusion is based on the physicochemical and PK characteristics of the active ingredient, and the in vitro dissolution behavior of the 10-, 25-, and 50-mg tablets in water. In healthy adults, crushed tablets resulted in slightly higher exposures.

References