Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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**Dolutegravir (DTG, Tivicay)**  
(Last updated May 22, 2018; last reviewed May 22, 2018)

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

**Formulations**

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

**Fixed-Dose Combination Tablets:**
- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg plus rilpivirine 25 mg

**Dosing Recommendations**

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

**Pediatric Dose (Weighing <30 kg):**
- Not approved for children weighing <30 kg
- Clinical trials in children with HIV weighing <30 kg are under way (see text).

**Pediatric Dose (Weighing ≥30 kg to <40 kg)**

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

\(^a\) These doses are for children who are treatment-naive or treatment-experienced (but integrase strand transfer inhibitor [INSTI]-naive) and who are not being treated with UGT1A1/CYP3A inducers.

**Note:** Dolutegravir 10-mg and 25-mg tablets may be available in retail pharmacies. If dolutegravir 10-mg or 25-mg tablets must be ordered, have the pharmacy contact their drug wholesaler and tell the drug wholesaler to order directly from the GlaxoSmithKline (GSK) distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

**Selected Adverse Events**

- Insomnia
- Headache
- Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions) especially in patients with a history of psychiatric illness
- 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).
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.
**Metabolism/Elimination**

- UGT1A1 and cytochrome P450 (CYP) 3A substrate. **Drugs that induce these enzymes and transporters may decrease plasma concentrations of dolutegravir.**

**Dolutegravir 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.

**Dolutegravir 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 Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- **Metabolism:** Dolutegravir is a UGT1A1 and cytochrome P450 (CYP) 3A substrate and may require dose 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 counteract this effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data.

- **Atazanavir is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients receiving**
dolutegravir, patients who also received atazanavir had two- to four-fold higher plasma dolutegravir concentrations than those receiving other antiretroviral (ARV) drugs.²

- 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, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note neuropsychiatric adverse effects (AEs) following initiation of dolutegravir-based therapy in adults.³⁴

- **Immune reconstitution inflammatory syndrome (IRIS):** In retrospective observational studies, severe cases of IRIS that required hospitalization appeared to be more frequent in patients presenting with advanced disease and initiating treatment with integrase inhibitors, particularly dolutegravir.⁵⁶ This phenomenon is presumed to be linked to the rapid decline in HIV-1 RNA observed with integrase inhibitor therapy.

- **Rare:** Hepatotoxicity. Two cases of presumed drug-induced liver injury, one requiring liver transplantation, have been reported.⁷⁸

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance database offers a discussion of integrase strand transfer inhibitor (INSTI) mutations.

The efficacy of dolutegravir 50 mg twice daily is reduced in patients with INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

**Pediatric Use**

**Approval**

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other ARV drugs for children weighing ≥30 kg and who are treatment-naive or treatment-experienced but INSTI-naive.⁹

The combination tablet abacavir/dolutegravir/lamivudine (Triumeq) is approved for adolescents weighing ≥40 kg.¹⁰ The combination tablet dolutegravir/rilpivirine (Juluca) is not approved for use in children or adolescents at the time of this review.¹¹

**Efficacy and Pharmacokinetics**

**Aged ≥12 years and Weighing ≥40 kg**

IMPAACT P1093 is an ongoing open-label trial of dolutegravir in children with HIV. FDA approval of dolutegravir for use in children weighing as low as 40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.¹² Intensive pharmacokinetic (PK) evaluations were performed on the first 10 participants, nine of whom weighed ≥40 kg and received dolutegravir 50 mg and one of whom weighed 37 kg and received dolutegravir 35 mg. These doses 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 5–10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% of participants had achieved HIV RNA concentration <50 copies/mL. No safety or tolerability concerns were identified. By Week 144, 39% and 30% of participants had achieved HIV RNA concentrations <400 copies/mL and <50 copies/mL, respectively. All who experienced virologic failure were nonadherent.

Additional long-term safety and efficacy data for this age group comes from a French, retrospective.
multicenter cohort study that evaluated 50 adolescents who initiated dolutegravir-based antiretroviral therapy (ART). Of 17 adolescents who were virologically suppressed at the time of dolutegravir-based treatment, 14 (82%) maintained suppression and three had transient viral rebound prior to re-achieving plasma viral load <50 copies/mL. Of the 33 viremic adolescents initiating dolutegravir, 19 (58%) achieved sustained virologic success. Overall, 66% achieved sustained virologic suppression and 78% had undetectable plasma viral load by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and had more frequently detectable viremia in the 6 months prior to dolutegravir initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued dolutegravir-based treatment because of a significant AE (dizziness and sleep disturbance). 13

**Aged ≥6 to <12 Years and Weighing ≥30 kg to <40 kg**

In addition, a younger cohort of children aged ≥6 to <12 years are undergoing PK and longer-term follow-up in IMPAACT P1093, with those weighing ≥30 kg to <40 kg receiving the 35-mg dose and those weighing ≥40 kg receiving the 50-mg dose. At 48 weeks, data from 23 participants demonstrated a favorable safety profile, adequate PK, and virologic efficacy, with HIV RNA concentrations of <50 copies/mL achieved in 74% (17/23) of participants. 12,14 This has led to FDA approval of the lower-strength tablets for children with HIV as young as age 6 years and weighing as low as 30 kg.

**Aged ≥6 Years, Weighing ≥15 kg to <20 kg or ≥20 kg to <30 kg**

The European Medicines Agency (EMA) approved the lower-strength tablets for children aged ≥6 years and weighing ≥15 kg based on population PK modelling and simulation analyses. 15 The EMA approved doses of 20 mg for children weighing 15 kg to <20 kg and 25 mg doses for those weighing 20 kg to <30 kg. Because the available PK data in these weight bands were minimal and the observed C_{trough} concentrations were lower than expected, the FDA did not approve dosing for children weighing <30 kg. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) agrees with the FDA decision and does not recommend use of dolutegravir in this population at this time.

### Pharmacokinetics of Dolutegravir in Adult and Pediatric Studies (P1093)

<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 Concentration^a mcg/mL^b</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>
<tr>
<td>Children without Prior INSTI Treatment (N = 4)</td>
<td>20 to &lt;30</td>
<td>25</td>
<td>25</td>
<td>Once daily</td>
<td>1.25</td>
<td>0.51 (44)</td>
</tr>
</tbody>
</table>

^a Sources: Dolutegravir [package insert]. Food and Drug Administration. 2016. Available at [http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf)

^b Geometric mean (percent coefficient of variation)

**Note:** Recommendations for 100 mg/day are for adults with documented INSTI-resistance mutations using 50 mg twice daily (see product label or text above).
Aged <6 Years and Not Able to Swallow Tablets

IMPAACT P1093 is also investigating an oral pediatric granule formulation and a dispersible tablet for use in patients aged as young as 4 weeks. Data were recently reported from a cohort of patients aged >2 to <6 years receiving dolutegravir granules. Ten patients with median age of 4 years (range: 2–5 years) received approximately 0.8 mg/kg dolutegravir once daily; background regimens were optimized based on PK assessments that were completed after 5 to 10 days. The geometric mean area under the curve after 24 hours (AUC_{24h}) was 44.7 mg*hour/L and concentration after 24 hours (C_{24h}) was 0.51 mg/L. Although the AUC_{24h} target was achieved, the mean C_{24h} was below the target value for this parameter. HIV-1 RNA levels were <400 copies/mL in 8 out of 10 participants at 4 weeks of treatment. Dolutegravir granules were well-tolerated in this age group and these data provide the basis for evaluating a 5-mg dispersible tablet.\textsuperscript{16} The manufacturer of dolutegravir does not plan to produce the oral pediatric granule formulation.

Simplification of Treatment

Two recently reported trials (SWORD-1 and SWORD-2) in adults supported approval of a dolutegravir 50-mg and a rilpivirine 25-mg fixed-dose combination tablet (Juluca) as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations. The participants were randomized to receive either dolutegravir/rilpivirine or a continuation of their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.\textsuperscript{17} More AEs were reported and led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.\textsuperscript{18} Although dolutegravir/rilpivirine (Juluca) is not approved for use in adolescents, the doses of both dolutegravir and rilpivirine in Juluca are approved for use in adolescents as single drugs. The Panel usually endorses adult formulations for use in adolescents, and this product may be appropriate for selected adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents who may have difficulty adhering to therapy, the Panel does not currently recommend use of Juluca for adolescents and children until more data are available.

Crushing Tablets for Administration

In patients who have difficulty swallowing whole tablets, 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.\textsuperscript{1} 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.\textsuperscript{19}

References


