



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Saquinavir (SQV, Invirase) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Capsules: 200 mg

Tablets: 500 mg

Dosing Recommendations

Neonate and Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children and adolescents aged <16 years.

Investigational Doses in Treatment-Experienced Children:

- Saquinavir must be boosted with ritonavir.

Aged <2 Years:

- No dose has been determined.

Aged ≥2 Years (Conditional Dosing Based on Limited Data; See Text):

Weight (kg)	Dose Saquinavir plus Ritonavir
5 to <15 kg	saquinavir 50 mg/kg plus ritonavir 3 mg/kg, both twice daily
15 to <40 kg	saquinavir 50 mg/kg plus ritonavir 2.5 mg/kg, both twice daily
≥40 kg	saquinavir 50 mg/kg plus ritonavir 100 mg, both twice daily

Adolescent (Aged ≥16 years) and Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg, both twice daily.

Cobicistat is not interchangeable with ritonavir to increase systemic exposure of saquinavir. Saquinavir is not recommended for use in combination with cobicistat.

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Increased bleeding episodes in patients with hemophilia
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (torsades de pointes) have been reported.

Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram is recommended and saquinavir is contraindicated in patients with a prolonged QT interval.

Metabolism/Elimination

- Cytochrome P (CYP) 450 3A4 and inhibitor, 90% metabolized in the liver.
- Use in patients with hepatic impairment: use with caution.

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/>)

- Saquinavir is both a substrate and inhibitor of the CYP3A4 system. Potential exists for multiple drug

interactions. Co-administration of saquinavir is contraindicated with drugs that are highly dependent on CYP3A clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, lipodystrophy.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and ventricular tachycardia (torsades de pointes).

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see 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 each mutation (see <http://hivdb.stanford.edu/DR/>).

Pediatric Use

Approval

Saquinavir is not Food and Drug Administration-approved for use in children or adolescents aged <16 years.

Efficacy

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors in HIV-infected children.¹⁻⁶ Saquinavir plus lopinavir/ritonavir (LPV/r) were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications. Because dual PI therapy is no longer recommended in adult or pediatric guidelines, the Panel does not recommend the use of saquinavir in combination with LPV/r.^{1,3-9}

Pharmacokinetics

Studies suggest that saquinavir should not be used without boosting by ritonavir. A pharmacokinetic analysis of 5 children aged <2 years and 13 children aged 2 to 5 years using a dose of 50 mg/kg twice daily with ritonavir boosting demonstrated that drug exposure was lower in children aged <2 years whereas drug exposure was adequate in those aged 2 to 5 years.¹⁰ For this reason, saquinavir should not be administered to children aged <2 years. In children aged ≥2 years, a dose of 50 mg/kg twice daily (maximum dose = 1000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 to <15 kg) or 2.5 mg/kg twice daily (patients weighing 15–40 kg) resulted in area under the curve and steady-state trough plasma concentration (C_{trough}) values similar to those in older children^{7,8} and adults.

In a study of 50 Thai children, saquinavir/ritonavir in combination with lopinavir was initiated as second-line therapy based on extensive NRTI resistance (saquinavir was dosed at 50 mg/m² body surface area and ritonavir-boosted lopinavir was dosed at 230/57.5 mg/m² body surface area, all twice daily). After 96 weeks, 74% of the children achieved an undetectable plasma RNA load at <50 copies/mL. Therapeutic drug monitoring was used to establish adequate minimum plasma concentration (C_{min}) values and to aid with alterations in drug dosage based upon toxicity. Most C_{min} values for saquinavir were above the desired trough value of 0.1 mg/L. The average C_{min} throughout 96 weeks for saquinavir was 1.37 mg/L, and when saquinavir doses were adjusted, most were decreased by an average of 21% (8 mg/kg).^{7,8}

Toxicity

In a healthy adult volunteer study, ritonavir-boosted saquinavir use was associated with increases in both QT and PR intervals.^{11,12} Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Saquinavir/ritonavir is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular (AV) block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval. An electrocardiogram is recommended before initiation of therapy with saquinavir and should be considered during therapy.

References

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