Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Saquinavir (SQV, Invirase) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Hard-gel capsules: 200 mg

Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- Not approved for use in children.

Investigational doses in treatment-experienced children:

- SQV must be boosted with ritonavir (RTV):

Aged <2 years:

- No dose has been determined.

Aged ≥2 years (conditional dosing based on limited data, see text):

Weight (kg)	Dose SQV + RTV
5–<15 kg	SQV 50 mg/kg + RTV 3 mg/kg, both twice daily
15–40 kg	SQV 50 mg/kg + RTV 2.5 mg/kg, both twice daily
≥40 kg	SQV 50 mg/kg + RTV 100 mg, both twice daily

Aged ≥7 years in combination with lopinavir/ritonavir (LPV/r) for salvage therapy (conditional dosing based on limited data, see text):

- SQV 750 mg/m^2 (max 1600 mg) or SQV 50 mg/kg have been used in combination with LPV/r, both twice daily.

Adolescent (aged ≥16 years)/adult dose:

SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

- SQV 1000 mg + RTV 100 mg, both twice daily.
- SQV 1000 mg + LPV/r 400/100 mg, both twice daily.

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible 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 (ECG) is recommended and SQV is not recommended in patients with a prolonged QT interval.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate 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*)***:***

- *Metabolism:* Saquinavir is both a substrate and inhibitor of the CYP3A4 system, and there is potential for numerous drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing 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 torsades de pointes.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/SQV.html).

Pediatric Use: Saquinavir is not Food and Drug Administration (FDA)-approved for use in children. Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors (PIs) in HIV-infected children.[1-6] Initial studies suggest that saquinavir should not be used without boosting by ritonavir or lopinavir/ritonavir. A pharmacokinetic (PK) analysis of 5 children aged younger than 2 years and 13 children aged 2 to 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir demonstrated that drug exposure was lower in children younger than age 2 years whereas drug exposure was adequate in those ages 2 to 5 years.[7] For this reason, saquinavir should not be given to children younger than age 2 years until an appropriate dose is identified. 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 – <15 kg) or 2.5 mg/kg twice daily (patients weighing 15 – 40 kg) resulted in area under the curve and steady state trough concentration (C_{trough}) values similar to those in older children[8, 9] and adults. Because there is no pediatric formulation, in one study saquinavir was formulated by breaking open the 200-mg hard-gel capsules and mixing capsule contents with sugar syrup, jam, or baby formula. Sorbitol syrup was used for patients with diabetes or glucose intolerance.[7]

Both saquinavir/ritonavir and saquinavir/lopinavir/ritonavir regimens are promising for salvage therapy in children.[1, 3-6, 8-10] In a study evaluating the addition of saquinavir (750 mg/m^2 of body surface area every 12 hours, maximum dose 1600 mg) to a regimen containing lopinavir/ritonavir dosed at 400/100 mg/m^2 of body surface area twice daily (for patients not concurrently taking a non-nucleoside reverse transcriptase inhibitor [NNRTI]) or lopinavir/ritonavir 480/120 mg/m^2 of body surface area twice daily for patients concurrently administered an NNRTI, 18 subjects (median age 14.2 years, range 7.7–17.6 years) were enrolled. The addition of saquinavir at these doses was well tolerated and did not appear to alter lopinavir PKs. Saquinavir dosing was adjusted in four patients (decreased in three, increased in one).[10]

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance. In this group, saquinavir was dosed at 50 mg/m^2 of body surface area and lopinavir/ritonavir was dosed at 230/57.5 mg/m^2 of body surface area, all twice daily. After 96 weeks of

treatment, 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). Median total cholesterol and high-density lipoprotein values increased significantly through 96 weeks from 144 to 196 mg/dL and from 44 to 57 mg/dL, respectively.[8, 9]

In a healthy adult volunteer study, saquinavir/ritonavir use was associated with increases in both QT and PR intervals.[11] The degree of QT prolongation was greater than that seen with some other boosted PIs. 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 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.

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