Saquinavir (SQV, Invirase)

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<table>
<tr><th colspan="2">Formulations</th></tr>
<tr><td colspan="2">Capsules: 200 mg

Tablets: 500 mg

For additional information, see Drugs@FDA.</td></tr>
<tr><th>Dosing Recommendations</th><th>Selected Adverse Events</th></tr>
<tr><td rowspan="4">Pediatric Dose

• Not approved for use in infants, children, and adolescents aged <16 years.

Adolescent and Adult Dose

• Saquinavir should only be used in combination with ritonavir.

• Saquinavir 1000 mg plus ritonavir 100 mg twice daily</td><td>• Gastrointestinal intolerance, nausea, diarrhea

• Elevated transaminases

• Hyperlipidemia

• Hyperglycemia

• Fat maldistribution

• PR interval prolongation, QT interval prolongation, and ventricular tachycardia (Torsades de Pointes)</td></tr>
<tr><th>Special Instructions</th></tr>
<tr><td>• 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; saquinavir is contraindicated in patients with a prolonged QT interval.</td></tr>
<tr><th>Metabolism/Elimination</th></tr>
<tr><td>• Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor

• 90% metabolized in the liver

• Use saquinavir with caution in patients who have hepatic impairment; no dose adjustment recommended.</td></tr>
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Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker.

- Saquinavir is both a substrate and inhibitor of the cytochrome P 450 3A4 (CYP3A4) system. Potential exists for multiple drug interactions. Saquinavir **should not be coadministered** with

drugs that are highly dependent on CYP3A clearance, especially in cases where elevated plasma concentrations of the coadministered drug can cause serious 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, lipid abnormalities
- *Less common (more severe):* Exacerbation of chronic liver disease, lipodystrophy
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, pancreatitis, and elevation in serum transaminases. Saquinavir administered with ritonavir can lead to prolonged QT and/or PR intervals with potential for heart block and ventricular tachycardia (Torsades de Pointes).

Resistance

The International AIDS Society–USA maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Saquinavir is not approved for use in children or adolescents aged <16 years.[1]

Efficacy

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors and other protease inhibitors in children with HIV.[2-9] Saquinavir/ritonavir (SQV/r) and a dual-protease inhibitor saquinavir/lopinavir/ritonavir regimen were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications; these regimens **are no longer recommended.**

Pharmacokinetics

Pharmacokinetic (PK) data from children who received SQV/r showed prohibitively low exposure in children younger than 2 years.[10] In children aged ≥2 years, a dose of saquinavir 50 mg/kg twice daily in combination with ritonavir and lopinavir/ritonavir resulted in steady-state plasma trough concentrations (C_{trough}) similar to those seen adults.[9,11] No clinical trials have collected data on the efficacy of saquinavir doses <50 mg/kg in children.

Toxicity

In healthy adult volunteers, SQV/r dose and exposure were associated with increases in both QT and PR intervals.[1,12] Rare cases of Torsades de Pointes and complete heart block have been reported in postmarketing surveillance. SQV/r **is not recommended** for adolescent and adult 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 atrioventricular block, or the use of other drugs that prolong QT interval. An electrocardiogram (EKG) is recommended before initiation of therapy with saquinavir and repeat EKGs should be considered during therapy.

Steady-state saquinavir exposures observed in one pediatric trial (NV20911) were substantially higher than those seen in historical data from adults with QT and PR prolongation.[1,12] Although no EKG abnormalities have been reported among the small number of subjects in pediatric trials, pediatric PK/pharmacodynamics modeling suggests that reducing the saquinavir dose in order to minimize the risk of QT prolongation would decrease saquinavir efficacy in children. Pediatric saquinavir dose recommendations that were both reliably effective and below the thresholds of concern for QT and PR prolongation were not determined.

References

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