Saquinavir Soft-Gel Capsule Formulation
A Review of its Use in Patients with HIV Infection

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Summary

Saquinavir is an HIV protease inhibitor which, formulated as a hard-gel capsule (HGC), was the first drug of its class to become available for the treatment of patients with HIV infection.

Despite the beneficial effects that saquinavir HGC-containing combination regimens have shown in the treatment of patients with HIV infection, the HGC formulation has limited oral bioavailability and has shown only modest antiviral activity in vivo. To overcome this limitation (with the aim of improving antiviral efficacy), a soft-gel capsule (SGC) formulation of the drug has been developed. At the recommended dosage of 1200mg 3 times daily, the SGC formulation of saquinavir achieves plasma concentrations >8 times higher than those in patients receiving saquinavir HGC 600mg 3 times daily.

Initial results of trials evaluating the therapeutic efficacy of saquinavir SGC-containing combination therapy in patients with moderate to advanced HIV infection are promising. In patients who were previously antiretroviral therapy–naive or –experienced, short term (≤36 weeks) treatment with saquinavir SGC in combination with ≥2 nucleoside reverse transcriptase inhibitors (NRTIs), or nelfinavir, or 2 NRTIs plus nelfinavir led to marked improvements in virological and immunological markers of HIV disease. In comparative trials, saquinavir SGC showed improved antiviral activity compared with the HGC formulation in terms of reducing viral load. Furthermore, saquinavir SGC in combination with 2 NRTIs was as effective as indinavir plus 2 NRTIs in antiretroviral-naive or -experienced patients. Available data suggest that saquinavir SGC-containing combination therapy may be of greatest benefit in patients naive to previous antiretroviral therapy.

The SGC formulation of saquinavir appears to be generally well tolerated by adults with HIV infection. Gastrointestinal adverse events, notably diarrhoea, abdominal discomfort, nausea and dyspepsia, are the most common adverse events occurring during treatment with the drug.

Initial results of several trials that used surrogate markers to assess treatment efficacy indicate that the SGC formulation of saquinavir, administered in combination with other antiretroviral drugs, is an effective and well-tolerated treatment for patients with moderate or advanced HIV infection. Although further data are required before definitive conclusions can be drawn regarding the comparative efficacy and tolerability of the SGC and HGC formulations, it appears likely that the SGC formulation will replace the conventional formulation as a component of combination regimens for the treatment of patients with HIV infection.

Rationale for Developing a Soft-Gel Formulation

Because the hard-gel capsule (HGC) formulation of saquinavir HGC has low oral bioavailability, as a result of limited absorption and extensive first-pass metabolism, its therapeutic efficacy is less than optimal. To address this problem, saquinavir has been reformulated as a soft-gel capsule (SGC) which provides greater systemic exposure to the drug.

Overview of Pharmacodynamic Properties

Saquinavir is a selective inhibitor of HIV protease and a transition-state mimetic of the phenylalanine-proline (Phe-Pro) peptide cleavage site. Its antiviral activity is achieved by competitive inhibition of HIV protease-mediated cleavage of gag and gag-pol polyproteins, thus preventing post-translational viral processing. At therapeutic concentrations, saquinavir does not appear to inhibit the activity of mammalian proteases.

In vitro, saquinavir shows activity against HIV-1, including zidovudine-resistant strains; concentrations required to produce 50% inhibition of various