Saquinavir Soft-Gel Capsule
An Updated Review of its Use in the Management of HIV Infection

David P. Figgitt and Greg L. Plosker

Various sections of the manuscript reviewed by:
D.J. Burger, Department of Clinical Pharmacy, University Hospital Nijmegen, Nijmegen, Netherlands; P. Carey, Department of GU Medicine, Royal Liverpool University Hospital, Liverpool, England; C.C.J. Carpenter, Brown University School of Medicine, Providence, Rhode Island, USA; N. Clumeck, Division of Infectious Diseases, Saint-Pierre University Hospital, Brussels, Belgium; B. Conway, Department of Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada; M.J. Gill, Southern Alberta Clinic, Calgary, Alberta, Canada; V. Joly, Xavier-Bichat Medical School, Hôpital Bichat-Claude Bernard, Paris, France; A. Lazzarin, Divisione di Malattie Infettive, IRCCS, Ospedale San Raffaele, Milan, Italy.

Data Selection
Sources: Medical literature published in any language since 1998 on Saquinavir, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.
Search strategy: Medline search terms were ‘Saquinavir’ or ‘RO 31 8959’ or ‘soft-gel capsule’ or ‘soft-gel formulation’. EMBASE search terms were ‘Saquinavir’ or ‘soft-gel capsule’ or ‘soft-gel formulation’. AdisBase search terms were ‘Saquinavir’ or ‘RO-318959’ or ‘soft-gel capsule’ or ‘soft-gel formulation’. Searches were last updated 21 July 2000.
Selection: Studies in patients with HIV infection who received saquinavir soft-gel capsule. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.
Index terms: Saquinavir soft-gel capsule, HIV infection, pharmacodynamics, pharmacokinetics, therapeutic use, adverse events, dosage and administration.

Contents
Summary .......................................................... 482
1. Introduction .................................................. 486
2. Overview of Pharmacodynamic Properties ................. 487
   2.1 Mechanism of Action .................................. 487
   2.2 Antiviral Activity ..................................... 487
      2.2.1 Saquinavir Alone .................................. 487
      2.2.2 Saquinavir in Combination with Other Agents ... 488
   2.3 Resistance ................................................. 488
      2.3.1 Saquinavir Alone .................................. 489
      2.3.2 Saquinavir in Combination with Other Agents ... 489
   2.4 Cross Resistance ......................................... 490
3. Overview of Pharmacokinetic Properties .................... 490
   3.1 Absorption and Distribution ........................... 490
   3.2 Metabolism and Elimination .......................... 492
   3.3 Drug Interactions ........................................ 492
Saquinavir is a potent and highly selective HIV protease inhibitor. Initially formulated as a hard-gel capsule (HGC), saquinavir was the first protease inhibitor available commercially for the treatment of patients with HIV infection.

The limited oral bioavailability of saquinavir HGC has been improved significantly with the introduction of a soft-gel capsule (SGC) formulation. Saquinavir SGC displays greater than dose-proportional pharmacokinetics and mean area under the plasma concentration-time curve (AUC) values are 8- to 10-fold higher with saquinavir SGC 1200mg 3 times daily than with the HGC formulation 600mg 3 times daily, the recommended dosages of the 2 formulations. In combination with other protease inhibitors (particularly "low dose" ritonavir), the oral bioavailability of saquinavir (as either the HGC or SGC formulation) is markedly increased, allowing for reduced dosing frequency and/or dosage. The efficacy and tolerability of once- or twice-daily saquinavir SGC/"low dose" ritonavir combinations are currently being evaluated in patients with HIV infection.

Data (up to 48 weeks) from noncomparative and comparative clinical trials evaluating saquinavir SGC-containing combination regimens in adult patients with HIV infection, support and strengthen the clinical efficacy profile of the drug that was demonstrated in initial trials. In antiretroviral therapy–naïve and –experienced patients, saquinavir SGC combined with ≥2 nucleoside reverse transcriptase inhibitors (NRTIs), or nelfinavir, or nelfinavir plus 2 NRTIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs), markedly improved immunological and virological surrogate markers (increased mean CD4+ cell counts and decreased mean plasma HIV RNA levels) of HIV infection. Saquinavir SGC demonstrated a trend to greater antiviral efficacy (measured by improvements in surrogate markers) than the HGC formulation (not statistically significant); a significantly greater proportion of patients treated with saquinavir SGC had plasma HIV RNA levels <400 copies/ml than patients receiving the HGC formulation. In the first direct comparison of 2 protease inhibitors, saquinavir SGC plus 2 NRTIs demonstrated similar antiviral efficacy to indinavir plus 2 NRTIs in patients with HIV infection (almost all of whom were antiretroviral therapy–naïve); at 24 weeks, a significantly greater increase in CD4+ cell count from baseline was obtained in the saquinavir SGC group compared with the indinavir group, although this difference was not apparent at week 32. Triple therapy with