Saquinavir mesylate

Brand Name: Invirase
Drug Class: Protease Inhibitors

Drug Description

Saquinavir is a peptidomimetic protease inhibitor (PI). [1]

HIV/AIDS-Related Uses

Saquinavir mesylate was approved by the FDA on December 6, 1995. Saquinavir was approved by the FDA on November 7, 1997. Both are indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. Saquinavir soft gelatin capsules and saquinavir mesylate tablets and hard gelatin capsules are not bioequivalent. Saquinavir mesylate, marketed as Invirase, must be combined with ritonavir to provide plasma saquinavir levels at least equal to those achieved with saquinavir, formerly marketed in the United States as Fortovase.[2] [3] [4]

Because of a decline in clinical demand for Fortovase, this formulation was discontinued by the manufacturer on February 15, 2006. Saquinavir mesylate, now the preferred formulation, will continue to be available. Saquinavir mesylate offers distinct advantages over the saquinavir soft gelatin formulation, including a lower pill burden, smaller pill size, easier storage requirements, and improved gastrointestinal tolerance.[5]

Pharmacology

Saquinavir is a structural analogue of the HIV Phe-Pro protease cleavage site and is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. Saquinavir is active in both acutely and chronically infected cells; chronically infected cells are not affected by nucleoside reverse transcriptase inhibitors (NRTIs). While saquinavir does not affect early stages of the HIV replication cycle, it does interfere with the production of infectious virions, limiting further infectious spread of the virus.[6]

Bioavailability of saquinavir mesylate from hard gelatin capsules is low, averaging 4%. The relative bioavailability of saquinavir in liquid-filled soft gelatin capsules is estimated to average 331% that of saquinavir mesylate hard gelatin capsules. This represents a calculated average oral bioavailability from the soft gelatin capsules of 13%. Peak plasma concentrations and area under the concentration-time curve (AUC) of the drug in soft gelatin capsules are about two times higher in HIV-infected patients than in healthy volunteers.[7]

Distribution of the drug into body tissues and fluids (such as cerebrospinal fluid) has not been fully characterized. Saquinavir is about 97% bound to plasma proteins in concentrations up to 30 mcg/ml. The drug is metabolized in the liver to several monohydroxylated and dihydroxylated inactive metabolites. Metabolism is mediated by cytochrome P450 (CYP); the isoenzyme CYP3A4 is involved in more than 90% of this metabolism. Systemic clearance is rapid. Saquinavir is excreted primarily in the feces, both as unchanged drug and as metabolites.[8]

Saquinavir is in FDA Pregnancy Category B. It is not known whether saquinavir crosses the placenta in humans; placental transfer in laboratory animals is less than 5% of maternal plasma concentrations.[9] There are no adequate and well-controlled studies in pregnant women. Saquinavir should be used during pregnancy only when clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including saquinavir. Physicians are encouraged to register patients by calling 1-800-258-4263 or online at http://www.APRegistry.com.[10] It is not known whether saquinavir is secreted in human milk; however, it is secreted in the milk of laboratory rats.[11]

Because saquinavir is metabolized by the liver, the manufacturer recommends that it be used with caution in patients with hepatic insufficiency. Patients with baseline liver function test results higher than five times the upper limit of normal were not included in clinical studies.[12]

HIV isolates with reduced susceptibility to the drug have been recovered from some patients on long-term saquinavir therapy. Genotypic analysis showed that mutations at amino acid positions 48

Saquinavir mesylate

Pharmacology (cont.)

and/or 90 of the HIV protease gene were consistently associated with saquinavir resistance, and mutations at these positions have not been detected in isolates from PI-naive patients.[13]

Cross resistance among PIs has been recognized; saquinavir-resistant isolates from patients on long-term therapy showed resistance to at least one of the following four PIs: indinavir, nelfinavir, ritonavir, and amprenavir.[14] Cross resistance between saquinavir and NRTIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs) is unlikely because these drugs have different target enzymes.[15] In vitro studies indicate that the antiretroviral effects of PIs and some NRTIs or NNRTIs may be additive or synergistic.[16]

Adverse Events/Toxicity

Saquinavir and saquinavir mesylate appear to be well tolerated. In clinical studies, the most frequently reported adverse effects included abdominal discomfort, diarrhea, and nausea. Other reactions include abdominal pain, anxiety, asthenia, buccal mucosa ulceration, constipation, depression, dizziness, dyspepsia, eczema, fatigue, flatulence, headache, insomnia, libido disorder, musculoskeletal pain, numbness in extremities, paresthesia, peripheral neuropathy, rash, taste perversion, verruca, and vomiting.[17] [18]

Body fat accumulation and redistribution, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus have been reported in patients receiving PIs, including saquinavir.[19]

In clinical studies there have been rare reports of serious adverse effects that may be related to treatment with saquinavir or saquinavir mesylate. These rare effects included confusion, ataxia, and weakness; seizures; headache; acute myeloblastic leukemia; hemolytic anemia; thrombocytopenia; thrombocytopenia and intracranial hemorrhage resulting in death; attempted suicide; Stevens-Johnson syndrome; bullous skin eruptions and polyarthritis; severe cutaneous reaction associated with increased liver function test results; isolated elevation of transaminase values; exacerbation of chronic liver disease with elevated liver function tests, jaundice, ascites, and upper left and right quadrant abdominal pain; fatal pancreatitis; intestinal obstruction; portal hypertension; thrombophlebitis; peripheral vasoconstriction; drug fever; nephrolithiasis; and acute renal insufficiency.[20]

Drug and Food Interactions

Presence of food in the gastrointestinal tract can substantially increase the absorption of saquinavir and saquinavir mesylate. Administering saquinavir mesylate hard gelatin capsules with a meal increases absorption 5- to 10-fold compared with administration on an empty stomach.[21] For saquinavir liquid-filled soft gelatin capsules, the mean 12-hour AUC increased from 167 ng(h)/ml under fasting conditions to 1,120 ng(h)/ml when administered with food.[22] Limited data indicate that the bioavailability of saquinavir is increased when the drug is administered with grapefruit juice.[23]

Concomitant use of certain other antiretroviral agents with saquinavir or saquinavir mesylate may significantly increase or decrease saquinavir plasma concentrations.[24] [25] Efavirenz taken with saquinavir results in decreased concentrations of both drugs.[26] The coformulation of lopinavir/ritonavir taken with saquinavir decreases the serum concentration of ritonavir.[27] Delavirdine, indinavir, or nelfinavir taken with saquinavir increases the serum concentration of saquinavir.[28]

Ritonavir taken with saquinavir increases the serum concentration of saquinavir.[29] There have been other studies of the effects of certain antiretrovirals when used with saquinavir boosted with ritonavir. Atazanavir taken with saquinavir boosted with ritonavir increases the serum concentrations of both saquinavir and ritonavir.[30] Fosamprenavir taken with saquinavir boosted with ritonavir decreases the serum concentration of saquinavir.[31]

Metabolism of saquinavir is mediated by the CYP3A4. Drugs that induce this isoenzyme may reduce saquinavir plasma concentrations. Conversely, drugs that inhibit this isoenzyme may increase plasma concentrations of saquinavir.

Saquinavir mesylate

Drug and Food Interactions (cont.)

Saquinavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system, which may create the possibility of serious adverse effects.[32]

Use of saquinavir or saquinavir mesylate with lovastatin or simvastatin is not recommended. Caution should be used when any PIs, including saquinavir, are used concurrently with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The resulting increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.[33] [34]

Use of saquinavir or saquinavir mesylate with St. John's wort (Hypericum perforatum) or products containing St. John's wort may substantially decrease saquinavir concentrations and may lead to loss of virologic response and possible resistance to saquinavir or other PIs.[35] [36]

Saquinavir should not be coadministered with astemizole, cisapride, or terfenadine (no longer available in the United States). Other drugs, including midazolam, triazolam, and ergot derivatives should not be coadministered with saquinavir. Competition for CYP3A4 by saquinavir may inhibit the metabolism of these drugs, which could potentially cause serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation.[37] [38]

Digoxin serum concentrations should be monitored and the dose may need to be reduced.[39]

Saquinavir should not be used with garlic capsules. Garlic capsules have the potential to induce the metabolism of saquinavir, which may result in subtherapeutic saquinavir concentrations.[40]

Saquinavir, when coadministed with methadone, can cause methadone levels to decrease. The dose of methadone may need to be increased.[41]

Combining saquinavir with tipranavir/ritonavir is not recommened, because coadministration results in a decrease in saquinavir levels.[42]

Caution is advised if omeprazole or another proton pump inhibitor is taken concomitantly with saquinavir. Coadministration causes saquinavir concentrations to increase significantly. Close monitoring is advised.[43]

Coadministration of certain other drugs with saquinavir or saquinavir mesylate may cause an increase or decrease in plasma concentrations of saquinavir or of the coadministered drug. The manufacturer recommends caution when the following drugs are used concomitantly with saquinavir: calcium channel blockers, carbamazepine, clarithromycin, clindamycin, dapsone, dexamethasone, ketoconazole, phenobarbital, phenytoin, quinidine, rifabutin, and sildenafil.[44] [45]

Contraindications

Saquinavir and saquinavir mesylate are contraindicated in patients with clinically significant hypersensitivity to the drugs or any components in the formulations. Caution should be used when administering saquinavir or saquinavir mesylate to patients with impaired hepatic function or hemophilia.[46]

Concomitant use of unboosted saquinavir or saquinavir mesylate with rifampin results in reduced plasma concentrations of saquinavir and is contraindicated.[47]

Recent data from a 28-day Phase I clinical trial of saquinavir/ritonavir 1,000 mg/100 mg twice daily and rifampin 600 mg once daily showed significant hepatocellular toxicity in nearly 40% of patients. Transaminase elevations of up to 20 times the upper limit of normal were noted. Following drug discontinuation, clinical symptoms abated and liver function tests began returning to normal in all affected patients. Based on these data, the manufacturer recommends that rifampin should not be administered to patients taking ritonavir-boosted saquinavir as part of combination antiretroviral therapy.[48]

Clinical Trials

For information on clinical trials that involve Saquinavir mesylate, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the

Saquinavir mesylate

Clinical Trials (cont.)

Search box, enter: Saquinavir mesylate AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[49]

Dosage Form: Saquinavir mesylate: Tablets containing saquinavir 500 mg; hard gelatin capsules containing saquinavir 200 mg.[50]

Saquinavir: Soft gelatin capsules containing saquinavir 200 mg; this formulation was discontinued on February 15, 2006, because of decreased clinical demand and is currently unavailable in the United States.[51]

Saquinavir and saquinavir mesylate are not bioequivalent and cannot be used interchangeably. The recommended dose of saquinavir mesylate is 1,000 mg (taken as either two 500-mg tablets or five 200-mg capsules) coadministered with 100 mg of ritonavir twice a day.[52] Saquinavir mesylate is now the preferred formulation; the manufacturer encourages physicians to refrain from starting their patients on saquinavir soft gelatin capsule treatment and to discuss appropriate alternative treatment regimens for patients currently taking saquinavir soft gelatin capsules.[53] The recommended dose of saquinavir is 1,200 mg (taken as six 200-mg capsules) three times a day or 1,000 mg (taken as five 200-mg capsules) coadministered with 100 mg of ritonavir two times a day.[54]

Both saquinavir and saquinavir mesylate should be taken with a meal or within 2 hours after a full meal.[55]

Storage: Saquinavir mesylate: Store at 15 C to 30 C (59 F to 86 F) in a tightly closed bottle.[56]

Chemistry

CAS Name: Saquinavir mesylate:(S)-N-[(alphaS)-alpha-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro-2(1H)-isoquinolyl]-1 hydroxyethyl)phenethyl)-2-quinaldamidosuccinamide monomethanesulfonate (salt)[57]

CAS Number: Saquinavir mesylate: 149845-06-7[58]

Molecular formula: Saquinavir mesylate: C38-H50-N6-O5.C-H4-O3-S[59]

Saquinavir mesylate: C61.07%, H7.10%, N10.96%, O16.69%, S4.18%[60]

Molecular weight: Saquinavir mesylate: 766.96[61]

Physical Description: Saquinavir mesylate: white to off-white, very fine powder.[62]

Solubility: Saquinavir mesylate: aqueous solubility of 2.22 mg/ml at 25 C.[63]

Other Names

Ro 31-8959/003 (Saquinavir mesylate)[64]

Saquinavir monomethanesulfonate (Saquinavir mesylate)[65]

Saquinavir mesylate[66]

SQV[67]

Further Reading

Dragsted UB, Gerstoft J, Pedersen C, Peters B, Duran A, Obel N, Castagna A, Cahn P, Clumeck N, Bruun JN, Benetucci J, Hill A, Cassetti I, Vernazza P, Youle M, Fox Z, Lundgren JD; MaxCmin1 Trial Group. Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin1 Trial. J Infect Dis. 2003 Sep 1;188(5):635-42.

Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, Mata R, Gomez-Vera J, Alarcon A, Pachon J. Once-daily saquinavir-sgc plus low-dose ritonavir (1200/100 mg) in combination with efavirenz: pharmacokinetics and efficacy in HIV-infected patients with prior antiretroviral therapy. J Acquir Immune Defic Syndr. 2003 Feb 1;32(2):240-2.

O'Brien WA 3rd. Saquinavir/Ritonavir: its evolution and current treatment role. AIDS Read. 2006 Jan;16(1):28-44; discussion 43.

Saquinavir mesylate

Further Reading (cont.)

Ribera E, Azuaje C, Lopez RM, Domingo P, Soriano A, Pou L, Sanchez P, Mallolas J, Sambea MA, Falco V, Ocana I, Lopez-Colomes JL, Gatell JM, Pahissa A. Once-daily regimen of saquinavir, ritonavir, didanosine, and lamivudine in HIV-infected patients with standard tuberculosis therapy (TBQD Study). J Acquir Immune Defic Syndr. 2005 Nov 1;40(3):317-23.

Vithayasai V, Moyle GJ, Supajatura V, Wattanatchariya N, Kanshana S, Sirichthaporn P, Dabtham K, Somburanasin P, Chantawuttinan T, Hill AM, Hawkins D. Safety and efficacy of saquinavir soft-gelatin capsules + zidovudine + optional lamivudine in pregnancy and prevention of vertical HIV transmission. J Acquir Immune Defic Syndr 2002 Aug 1;30(4):410-2.

Manufacturer Information

Saquinavir mesylate
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

Invirase
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

Saquinavir mesylate

1. AHFS Drug Information - 2007; p. 676

2. AHFS Drug Information - 2007; p. 667

3. FDA - Office of AIDS and Special Health Issues - List Serve Announcement - New Dosing Regimens for Invirase and Fortovase (saquinavir). December 29, 2003, p. 10. Available at: http://www.fda.gov/medwatch/SAFETY/2003/03DEC_PI/Invirase_PI.pdf. Accessed 07/18/07.

4. FDA - Discontinuation of Fortovase (saquinavir) in the United States [Dear Health Care Professional Letter]. New Jersey: Roche Pharmaceuticals; May 2005 - Available at: http://www.fda.gov/cder/drug/shortages/fortovase_hcp.pdf. Accessed 07/18/07.

5. FDA - Discontinuation of Fortovase (saquinavir) in the United States [Dear Health Care Professional Letter]. New Jersey: Roche Pharmaceuticals; May 2005 - Available at: http://www.fda.gov/cder/drug/shortages/fortovase_hcp.pdf. Accessed 07/18/07.

6. AHFS Drug Information - 2007; p. 674

7. AHFS Drug Information - 2007; p. 676

8. AHFS Drug Information - 2007; p. 676

9. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, pp. 21-2. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

10. AHFS Drug Information - 2007; p. 671

11. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 22. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

12. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 11. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

13. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 3. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

14. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 3. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

15. AHFS Drug Information - 2007; p. 675

16. AHFS Drug Information - 2007; p. 673

17. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 22. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

18. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 29. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

19. AHFS Drug Information - 2007; pp. 669-70

20. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 23. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

21. AHFS Drug Information - 2007; pp. 675-6

22. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 5. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

23. AHFS Drug Information - 2007; p. 676

24. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 13. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

25. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 13. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

26. FDA - Invirase Prescribing Information, 07/11/07, p. 17. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

27. FDA - Invirase Prescribing Information, 07/11/07, p. 18. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

28. FDA - Invirase Prescribing Information, 07/11/07, pp. 17-8. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

29. FDA - Invirase Prescribing Information, 07/11/07, p. 18. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

30. FDA - Invirase Prescribing Information, 07/11/07, p. 17. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

31. FDA - Invirase Prescribing Information, 07/11/07, p. 18. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

32. AHFS Drug Information - 2007; p. 674

33. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 10. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

34. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 11. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

35. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 15. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

36. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 11. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

37. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 9. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

38. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 10. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

39. FDA - Recent Updates to Invirase package insert [press release], June 11, 2008. Available at: http://www.fda.gov/oashi/aids/listserve/listserve2008.html#61108. Accessed 06/11/08.

40. FDA - Recent Updates to Invirase package insert [press release], June 11, 2008. Available at: http://www.fda.gov/oashi/aids/listserve/listserve2008.html#61108. Accessed 06/11/08.

41. FDA - Recent Updates to Invirase package insert [press release], June 11, 2008. Available at: http://www.fda.gov/oashi/aids/listserve/listserve2008.html#61108. Accessed 06/11/08.

42. FDA - Recent Updates to Invirase package insert [press release], June 11, 2008. Available at: http://www.fda.gov/oashi/aids/listserve/listserve2008.html#61108. Accessed 06/11/08.

43. FDA - Recent Updates to Invirase package insert [press release], June 11, 2008. Available at: http://www.fda.gov/oashi/aids/listserve/listserve2008.html#61108. Accessed 06/11/08.

44. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, pp. 13-5. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

45. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, pp. 10-2. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

46. AHFS Drug Information - 2007; p. 670

47. FDA - Invirase Prescribing Information, 07/11/07, p. 20. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

48. Hoffmann-LaRoche, Inc. - Saquinavir-Rifampin Interaction [Dear Health Care Provider Letter]. New Jersey: Hoffman-La Roche; February 2005, p. 1 - Available at: http://www.rocheusa.com/products/invirase/Invirase_DrLetter.pdf. Accessed 07/18/07.

49. AHFS Drug Information - 2007; p. 676

50. Roche Pharmaceuticals - Invirase Prescribing Information, September 2005, p. 1. Available at: http://www.rocheusa.com/products/invirase/pi.pdf. Accessed 07/18/07.

51. FDA - Discontinuation of Fortovase (saquinavir) in the United States [Dear Health Care Professional Letter]. New Jersey: Roche Pharmaceuticals; May 2005 - Available at: http://www.fda.gov/cder/drug/shortages/fortovase_hcp.pdf. Accessed 07/18/07.

52. Roche Pharmaceuticals - Invirase Prescribing Information, September 2005, p. 31. Available at: http://www.rocheusa.com/products/invirase/pi.pdf. Accessed 07/18/07.

53. FDA - Discontinuation of Fortovase (saquinavir) in the United States [Dear Health Care Professional Letter]. New Jersey: Roche Pharmaceuticals; May 2005 - Available at: http://www.fda.gov/cder/drug/shortages/fortovase_hcp.pdf. Accessed 07/18/07.

54. Roche Pharmaceuticals - Fortovase Prescribing Information, December 2003, p. 29. Available at: http://www.rocheusa.com/products/fortovase/pi.pdf. Accessed 07/18/07.

55. FDA - Invirase Prescribing Information, 07/11/07, p. 28. Available at: http://www.fda.gov/cder/foi/label/2007/020628s025, 021785s004lbl.pdf. Accessed 07/18/07.

56. AHFS Drug Information - 2007; p. 676

57. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 07/18/07.

58. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 07/18/07.

59. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 07/18/07.

60. Calculation. -

61. Merck Index - 2006; p. 1444

62. Roche Pharmaceuticals - Invirase Prescribing Information, September 2005, p. 2. Available at: http://www.rocheusa.com/products/invirase/pi.pdf. Accessed 07/18/07.

63. AHFS Drug Information - 2005; p. 672

64. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 07/18/07.

65. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 07/18/07.

66. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 07/18/07.

67. Antivir Ther - 2004 Jun;9(3):423-9