PRODUCT INFORMATION

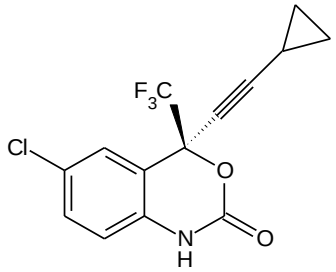
STOCRIN®
(efavirenz)

Tablets and Oral Solution

NAME OF THE MEDICINE

Efavirenz is chemically described as (S) -6- chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

Its empirical formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



CAS Registry Number: 154598-52-4

DESCRIPTION

STOCRIN is a non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1).

Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 μg/mL).

STOCRIN is available as tablets for oral administration. Each STOCRIN tablet contains 50, 200, 300 or 600 mg of efavirenz. STOCRIN is also available as an oral solution containing 30 mg efavirenz per mL.

Each tablet contains the following inactive ingredients: croscarmellose sodium, cellulose - microcrystalline, sodium lauryl sulfate, hyprolose, lactose monohydrate and magnesium stearate. The film coating contains the following inactive ingredients and dyes: hypromellose, titanium dioxide, macrogol 400 and carnauba wax. In addition the 50 mg, 200 mg and 600mg tablets contain iron oxide yellow CI 77492. The 300mg tablets are printed with purple ink, Opacode WB NS-78-10013-N [ARTG No. 4603]. The 50 mg, 200 mg and 600 mg tablets are not printed with ink. The oral solution contains the following inactive ingredients: medium chain triglycerides, benzoic acid and strawberry / mint flavour [ARTG# 4326].

PHARMACOLOGY

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. HIV-2 RT and human cellular DNA

polymerases α, β, γ and δ are not inhibited by concentrations of efavirenz well in excess of those achieved clinically.

Pharmacodynamics

In vitro HIV Susceptibility
The clinical significance of *in vitro* susceptibility of HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90-95% inhibitory concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1.7 to $\leq$ 25nM. Efavirenz potency against variants with mutations of S48T, V108I, V179D, Y181C, P236L or variants with amino acid substitutions in the protease gene was similar to that seen against wild type. Modest resistance (less than 9-fold) was observed against variants containing the mutations A98G, K101E, V106A, Y188C or G190A. The point mutations which led to the highest apparent resistance to efavirenz inhibition *in vitro* were L100I (17 to 22-fold resistance) and K103N (18 to 33-fold resistance). The following multiple base-pair mutated variants which encode RTs with one or more amino acid substitutions showed increased resistance to efavirenz *in vitro* with respect to wild type: S48T+G190S (97-fold), Y181C+K103N (133-fold), G190A+K103N (130-fold), Y188L (140 to 500-fold), K101E+K103N (500-fold), and L100I+K103N (>1000-fold).

Efavirenz demonstrated synergistic activity in cell culture in combination with the nucleoside analogue reverse transcriptase inhibitors (NRTIs), zidovudine (ZDV) or didanosine (ddI), or the protease inhibitor (PI), indinavir.

Cardiac Electrophysiology
The effect of STOCRIN on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see PRECAUTIONS).

Drug Resistance
The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine-to-isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT.

K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz.

Cross Resistance to Other Antiviral Agents

Cross resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical trials who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

The potential for cross resistance between efavirenz and protease inhibitors is low because of the different enzyme targets involved. The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action.

Pharmacokinetic Properties

Absorption

Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in Cmax and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3-5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6-7 days.

In HIV-infected patients at steady state, mean Cmax, mean Cmin, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving STOCRIN 600 mg once daily, steady-state Cmax was 12.9 μM, steady-state Cmin was 5.6 μM, and AUC was 184 μM.h.

In uninfected, fasting adult volunteers, the C_{max} and AUC of a 240 mg dose of STOCRIN oral solution were 78% and 97%, respectively, of the values measured when STOCRIN was given as a 200-mg hard capsule.

Effect of Food on Oral Absorption

Capsules

Administration of a single 600-mg dose of efavirenz capsules with a high fat/high caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced fat/normal caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC∞ and a mean increase of 39% and 51% in efavirenz C_{max} , respectively, relative to the exposures achieved when given under fasted conditions (See DOSAGE AND ADMINISTRATION).

Tablets

Administration of a single 600-mg efavirenz tablet with a high fat/high caloric meal

(approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC∞ of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions. (See DOSAGE AND ADMINISTRATION)

Oral Solution
Administration of a single 240mg dose of efavirenz oral solution (30mg/mL) with a high fat/high caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a mean increase of 30% in efavirenz AUC∞ and a mean increase of 43% in efavirenz C_{max} relative to the exposures achieved when given under fasted conditions.

Distribution

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (N=9) who received STOCRIN 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with Ki values (8.5-17μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (Ki values 82-160 μM) only at concentrations well above those achieved clinically.

Efavirenz plasma exposure maybe increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours). The degree of CYP3A4 induction is expected to be similar between a 400-mg and 600-mg dose of efavirenz based on pharmacokinetic interaction studies in which daily 400-mg or 600-mg efavirenz doses in combination with indinavir did not appear to cause any further reduction of indinavir AUC compared to a 200 mg dose of efavirenz.

Elimination

Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40-55 hours after multiple doses. Approximately 14-34% of a radiolabeled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Characteristics in Patients

Hepatic Impairment

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering STOCRIN to patients with liver disease (see PRECAUTIONS).

Renal Impairment

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Gender and Race

Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric Use

Clinical studies of STOCRIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Paediatric Use

The pharmacokinetics of efavirenz in paediatric patients aged ≥3 years were similar to adults.

For paediatric patients aged ≥ 3 years, dosage was calculated on the basis of body size to be equivalent to an adult 600 mg capsule dose, and subsequently further adjusted based on serum concentration in the first two weeks of dosing.

The study therapy may be discontinued for failure to achieve an efavirenz AUC of at least 110 µM.h despite multiple efavirenz dose adjustment /formulation changes.

CLINICAL TRIALS

In the clinical studies described below, the primary efficacy measure was the percent of patients with plasma HIV-RNA <400 copies/mL, using the Roche RT-PCR (Amplicor™) HIV-1 Monitor assay. Using this assay, which has a lower quantification limit of 400 copies/mL, values obtained which were below the limit of quantification were set as 400 copies/mL for analyses of mean change from baseline. HIV-RNA results are also described using an RT-PCR assay with a lower limit of quantification of 50 copies/mL (Ultrasensitive).

In the Non-Completer equals Failure analyses (NC=F) presented in each figure, patients that terminated the study early for any reason or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification (> 400 copies/mL) were considered treatment failures. In the observed data analyses, presented in the tables, patients on treatment with HIV-RNA > 400 copies/mL at the specified time point are considered treatment failures.

Study 006: STOCRIN (efavirenz) + indinavir or STOCRIN + zidovudine + lamivudine versus indinavir + zidovudine + lamivudine in antiretroviral-naive or NRTI-experienced (lamivudine-naive) patients:

Study 006 was a randomised, open-label trial to evaluate the plasma HIV-RNA suppression achieved by STOCRIN in combination with either indinavir (IDV) or with zidovudine (ZDV) + lamivudine (3TC) compared to indinavir plus zidovudine + lamivudine in HIV-infected patients naive to lamivudine, protease inhibitors and NNRTIs. Patients were randomised to one of three treatment regimens: STOCRIN (600 mg once daily) + indinavir (1000 mg every 8 hours) or STOCRIN (600 mg once daily) + zidovudine (300 mg q12h) + lamivudine (150

mg q12h) versus indinavir (800 mg every 8 hours) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Forty-eight week data analyses are presented for 614 patients (mean age 36.3 years [range 18-64], 58% Caucasian, 86% male). Mean baseline CD4 cell count was 342 cells/mm^3, and mean baseline HIV-RNA plasma level was 4.76 log_{10} copies/mL. The NC=F analysis of the percent of patients achieving plasma HIV-RNA levels <400 copies/mL is presented in Figure 1. Other efficacy results are summarised in Table 1.

Figure 1

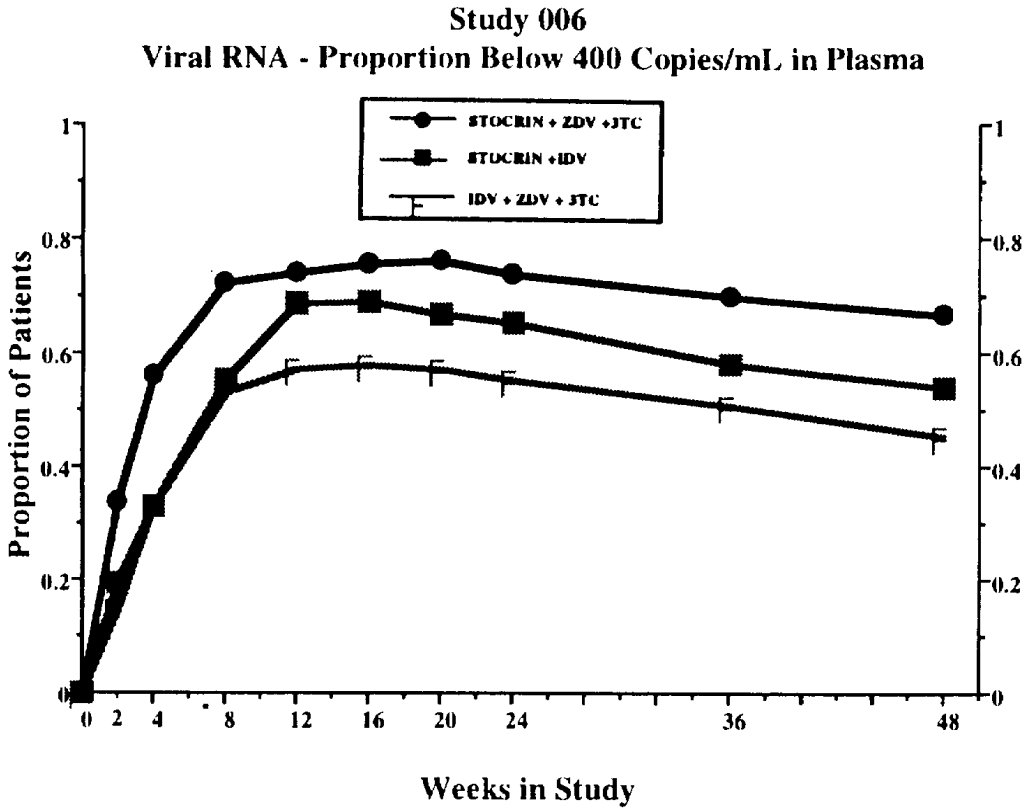


Table 1 Study 006 - Summary of Key Efficacy Results - Week 48

	IDV+ ZDV + 3TC	STOCRIN + IDV	STOCRIN + ZDV + 3TC
Total Patients Randomised	206	206	202
Patients with Plasma HIV-RNA <400 copies/mL			
Observed (n/N)	84.4% (92/109)	85.8% (109/127)	96.9% (126/130)*
(95% CI)	(77.6, 91.2)	(79.8, 91.9)	(94.0, 99.9)
Patients with Plasma HIV-RNA <50 copies/mL Ultrasensitive Assay			
Observed (n/N)	76.9% (83/108)	76.4%(97/127)	90.7% (117/129)*
(95% CI)	(68.9, 84.8)	(69.0, 83.8)	(85.7, 95.7)
NC=F (n/N)	40.4% (82/203)	47.8% (96,/201)	61.6% (117/190)*
(95% CI)	(33.6, 47.1)	(40.9, 54.7)	(54.7, 68.5)
Mean change from Baseline - Log_{10} Transformed Plasma HIV-RNA (SEM)			
Amplicor	-1.67(0.07)**,***	-1.73(0.06)**,***	-1.98(0.05)*,**,***
Ultrasensitive	-1.76(0.10)**,***	-2.08(0.09)**,***,†	-2.32 (0.09) *,**,***
Mean Change from Baseline - CD4 Counts (SEM)	152.60(12.3)***	176.78(11.3)***	187.04(11.8)*, ***

*Statistically significant difference (p≤0.05) between STOCRIN+ZDV+3TC and IDV+ZDV+3TC
**Statistically significant difference (p≤0.05) among treatment groups.
***Statistically significant difference (p≤0.05) from baseline
†Statistically significant difference (p≤0.05) between STOCRIN+IDV and IDV+ZDV+3TC.
CI Confidence Interval
NC=F Non Completer = Failure Analysis

Study 020: Protease Inhibitor + Two NRTIs with/without STOCRIN in NRTI-experienced patients:

Study 020 was a randomised, double-blind, placebo-controlled study in NRTI-experienced, protease inhibitor and NNRTI-naive patients designed to compare quadruple therapy consisting of STOCRIN + indinavir + 2 nucleoside analogue reverse transcriptase inhibitors versus triple therapy consisting of indinavir + 2 NRTIs after 24 weeks of treatment. Patients were randomised to receive either STOCRIN (600 mg once daily) + indinavir (1000mg every 8 hours) + 2 NRTIs or indinavir (800 mg every 8 hours) + 2 NRTIs. Sixty-nine percent of the 327 patients (mean age 38.5 years [range 20-69], 52% Caucasian, 83% male) changed their NRTI regimen at study initiation. Mean baseline CD4 cell count was 328 cells/mm^3 , and mean baseline HIV-RNA plasma level was 4.41 log_{10} copies/mL. The NC=F analysis of the percent of patients achieving plasma HIV-RNA levels <400 copies/mL at 24 weeks is presented in Figure 2. Other efficacy results are summarised in Table 2.

Figure 2

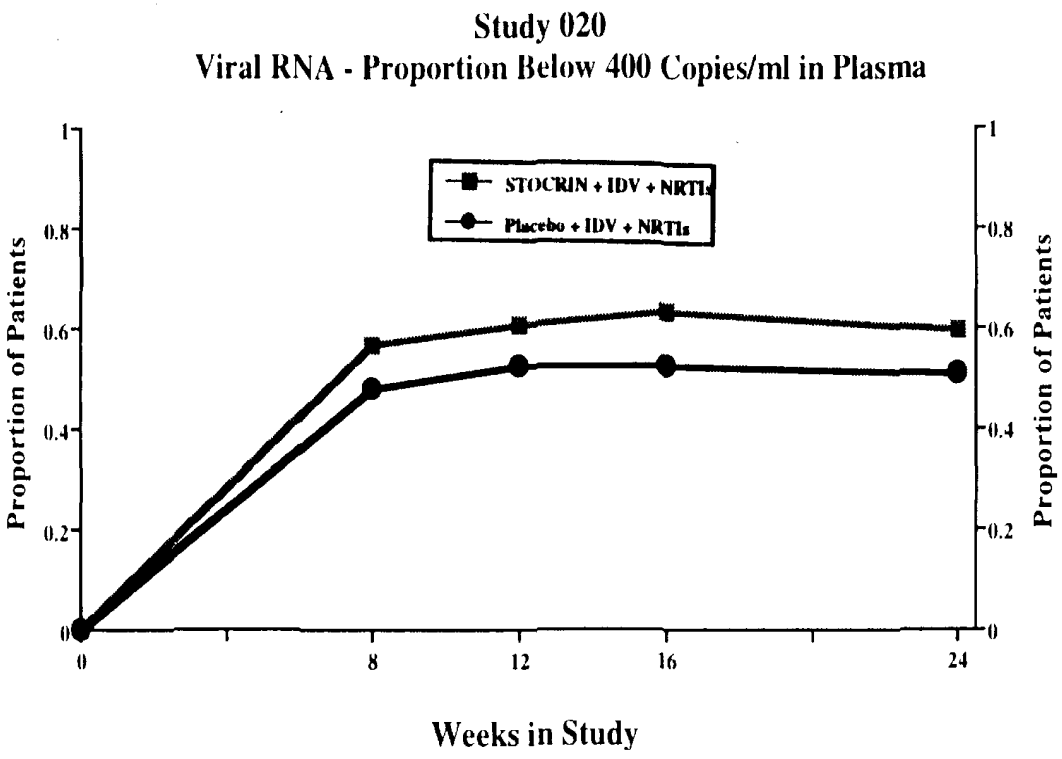


Table 2 Study 020 - Summary of Key Efficacy Results - Week 24

	Indinavir + ZDV + 3TC	**STOCRIN + IDV+ ZDV + 3TC**
Total Patients Randomised	170	157
Patients with Plasma HIV-RNA <400 copies/mL		
Observed (n/N)	65.2% (86/132)	83.0% (93/112)*
(95%CI)	(56.6, 73.7)	(75.6, 90.4)
Patients with Plasma HIV-RNA <50 copies/mL Ultrasensitive Assay		
Observed (n/N)	47.7% (63/132)	68.8% (77/112)*
(95% CI)	(38.8, 56.6)	(59.7, 77.8)
NC=F (n/N)	37.5% (63/168)	49.4% (77/156)*
(95% CI)	(29.9, 45.1)	(41.2, 57.5)
Mean change from Baseline - Log_{10} Transformed Plasma HIV-RNA (SEM)		
Amplicor	-1.12 (0.08)**	–1.45 (0.08)*, **
Ultrasensitive	-1.72 (0.11)**	–2.25 (0.10)*, **
Mean Change from Baseline - CD4 Counts (SEM)		
	77(9.9)**	104 (9.1)*,**

* Statistically significant difference ($p \leq 0.05$) between treatments
**Statistically significant mean change ($p \leq 0.05$) from baseline
CI Confidence interval
NC=F Non Completer = Failure Analysis

Study ACTG 364: STOCRIN in combination with nelfinavir in NRTI-experienced patients:

ACTG 364 was a 48-week double-blind, placebo-controlled study in NRTI-experienced patients, but NNRTI- and protease inhibitor-naïve, who had completed two prior ACTG studies One-hundred and ninety-six HIV-infected patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received NRTIs in combination with STOCRIN (600 mg QD), or nelfinavir (NFV, 750 mg TID), or STOCRIN (600 mg QD) + nelfinavir in a randomised double-blinded manner. Upon entry into the study, all patients were assigned a new open label NRTI regimen, which was dependent on their previous NRTI treatment experience. Overall efficacy results are summarised in Table 3.

Table 3
ACTG 364 - Summary of Key Efficacy Results - Week 48

	NFV + NRTIs	STOCRIN + NRTIs	STOCRIN + NFV + NRTIs
Total Patients Randomised	66	65	65
Patients with Plasma HIV-RNA <500 copies/mL			
Observed (n/N)	48.3% (28/58)*	76.9% (40/52)*,***	82.1% (46/56)*, ††
(95% CI)	(35.4, 61.1)	(65.5, 88.4)	(72.1, 92.2)
NC=F	30.2% (19/63)*	58.1% (36/62)*, ***	70.3%(45/64)*, ††
(95%CI)	(18.8, 41.5)	(45.8, 70.3)	(59.1, 81.5)
Mean change from Baseline - Log_{10} Transformed Plasma HIV-RNA (SEM) †			
Amplicor (Observed)	–0.57 (0.13) **	–0.88 (0.11) **	–0.96(0.11) **
Mean Change from Baseline - CD4 Counts (SEM) †			
	94(13.6)**	114(21.0) **	107(17.9)**

* Statistically significant difference ($p \leq 0.05$) among treatment groups
**Statistically significant difference ($p \leq 0.05$) from baseline
*** Statistically significant difference between NFV and STOCRIN groups ($p \leq 0.05$)
† Analyses exclude follow-up data on patients after termination of randomised treatment
†† Statistically significant difference between groups NFV and STOCRIN + NFV ($p \leq 0.05$)
CI Confidence interval
NC=F Non Completer = Failure Analysis

Use In Children

Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of STOCRIN in combination with didanosine and emtricitabine in antiretroviral-naive and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with STOCRIN. At baseline, median plasma HIV-1 RNA was 5.88 log_{10} copies/mL, median CD4+ cell count was 1144 cells/mm^3, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm^3 and the median increase in CD4+ percentage was 6%.

Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of STOCRIN in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with STOCRIN. At baseline, median plasma HIV 1 RNA was 4.8 log_{10} copies/mL, median CD4+ cell count was 367 cells/mm^3, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week

48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm^3 and the median increase in CD4+ percentage was 13%. In paediatric population <3 years of age the proportions of subjects with viral load suppressed to <400 and <50 c/mL were 50% and 50% respectively.

Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of STOCRIN in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced paediatric patients. One hundred and two patients 3 months to 16 years of age (median 5.7 years) were treated with STOCRIN. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 log_{10} copies/mL, median CD4+ cell count was 755 cells/mm^3, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm^3 and the median increase in CD4+ percentage was 5%. In paediatric population <2 years, the proportions of subjects with viral load suppressed to <400 and <50 c/mL were 38% and 15% respectively.

INDICATIONS

STOCRIN is indicated for use in combination with other antiviral agents for the treatment of HIV-1 infection in adults and children (See CLINICAL TRIALS; Use in Children).

CONTRAINDICATIONS

STOCRIN is contraindicated in patients with clinically significant hypersensitivity to any of its components.

STOCRIN should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot derivatives because competition for CYP3A4 by efavirenz could result in reduction of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events [e.g., cardiac arrhythmias, prolonged sedation or respiratory depression].

Coadministration of STOCRIN with voriconazole is contraindicated. (See INTERACTIONS WITH OTHER MEDICINES).

St. John's wort (*Hypericum perforatum*): Patients on efavirenz should not concomitantly use products containing St. John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of efavirenz. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

PRECAUTIONS

STOCRIN must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when STOCRIN is administered as monotherapy.

When prescribing drugs concomitantly with STOCRIN, physicians should refer to the corresponding manufacturer's Product Information.

If any antiretroviral medication in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications should be restarted at the same

time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral agents is not advisable because of the increased potential for selection of drug-resistant mutant virus.

Coadministration of STOCRIN with combination products that contain efavirenz (e.g., ATRIPLA) is not recommended, unless needed for dose adjustment (eg, with rifampin).

Malformations have been observed in foetuses from efavirenz-treated animals. There are no adequate and well-controlled studies of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, more than 700 pregnancies with first-trimester exposure to STOCRIN as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. Retrospectively in this registry, isolated cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. (see Use in pregnancy). Therefore, pregnancy should be avoided in women receiving STOCRIN. Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives) (see INTERACTIONS WITH OTHER MEDICINES).

QTc Prolongation: QTc prolongation has been observed with the use of efavirenz (see INTERACTIONS WITH OTHER MEDICINES). Consider alternatives to STOCRIN when co-administered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

Psychiatric / Nervous System Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with efavirenz (see ADVERSE EFFECTS). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. There have been reports (approximately 1-2 per thousand STOCRIN-treated patients) of delusions and inappropriate behavior, predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both STOCRIN-treated and control-treated patients. There have also been occasional post-marketing reports of death by suicide, delusions, psychosis-like behaviour, and catatonia although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients who experience these symptoms should contact their doctor immediately because discontinuation of STOCRIN may be required.

Fifty-two percent of patients receiving STOCRIN reported central nervous system and psychiatric symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams and insomnia. In controlled trials, these symptoms were severe in 2.9% of patients receiving STOCRIN 600 mg QD and in 1.3% of patients receiving control regimens. In clinical trials, 2.7% of STOCRIN-treated patients discontinued therapy because of nervous system symptoms. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks. Patients should be informed that these symptoms are likely to improve with continued therapy. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see ADVERSE EFFECTS).

Patients receiving STOCRIN should be alerted to the potential for additive central nervous system effects when STOCRIN is used concomitantly with alcohol or psychoactive drugs.

Patients should be informed that STOCRIN may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Skin Rash: Mild-to-moderate rash has been reported in clinical trials with STOCRIN and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with STOCRIN. The incidence of erythema multiforme or Stevens-Johnson syndrome was 0.14%. STOCRIN should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome). If therapy with STOCRIN is discontinued, consideration should also be given to interrupting therapy with other anti-retroviral agents to avoid development of drug resistant virus (see ADVERSE EFFECTS).

Rash was reported in 59 of 182 paediatric patients (32%) treated with STOCRIN in three clinical trials for a median of 123 weeks. Rash was severe in 6 patients. The median time to onset of rash in paediatric patients was 28 days (range 3-1642 days). Prophylaxis with appropriate antihistamines prior to initiating therapy with STOCRIN in children may be considered.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including STOCRIN. During the initial phase of treatment, a patient whose immune system responds to CART may mount an inflammatory response to indolent or residual opportunistic infections, (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis) which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Special Populations: Efavirenz is not recommended for patients with moderate or severe hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering STOCRIN to patients with hepatic impairment. Patients with mild liver disease may be treated with their normally recommended dose of STOCRIN. Patients should be monitored carefully for adverse events. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.

In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

Patients with underlying liver disease including chronic Hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. A few of the post-marketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

STOCRIN tablets or oral solution have not been adequately evaluated in children below 3 years of age or who weigh less than 13 Kg. Evidence exists indicating that efavirenz may have altered pharmacokinetics in very young children. For this reason, efavirenz tablets or oral solution should not be given to children less than 3 years of age (see DOSAGE AND ADMINISTRATION and USE IN CHILDREN).

Convulsions have been observed rarely in adult and paediatric patients receiving efavirenz, including in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as carbamazepine, phenytoin and phenobarbitone, may require periodic monitoring of plasma levels. Caution must be taken in any patient with a history of seizures.

Voriconazole: STOCRIN must not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations (see: PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

Liver Enzymes: In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with STOCRIN needs to be weighed against the unknown risks of significant liver toxicity (See ADVERSE EFFECTS).

Cholesterol: Monitoring of cholesterol should be considered in patients treated with STOCRIN (see ADVERSE EFFECTS).

Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral & facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsovisceral fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hypergylcaemia and hyperlactataemia. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids & blood glucose. Lipid disorders should be managed as clinically appropriate.

Information for Patients

Patients should be informed that STOCRIN is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of STOCRIN are unknown at this time. Patients should be told that there are currently no data demonstrating that STOCRIN therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take STOCRIN every day as prescribed. STOCRIN must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician.

If therapy with STOCRIN is interrupted for any reason, serious consideration should be given to stopping other antiretroviral agents. Likewise, if any concomitant antiviral therapy is stopped temporarily, therapy with STOCRIN should also be stopped. All antiretroviral agents should be restarted at the same time.

Malformations have been observed in foetuses from efavirenz-treated monkeys that received doses which resulted in plasma drug concentrations similar to those in humans given 600 mg/day (see Use in Pregnancy); therefore, pregnancy should be avoided in women receiving STOCRIN. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives).

STOCRIN may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any prescription or non-prescription medication, or herbal products, particularly St. John's wort.

Effects on Ability to drive and to use machines
Patients should be informed that STOCRIN may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Carcinogenicity/Mutagenicity and Impairment of Fertility
Long-term carcinogenicity studies of efavirenz in rats and mice are in progress.

Efavirenz was not genotoxic in assays for gene mutations (*S. typhimurium, E. coli* and Chinese Hamster Ovary cells) and chromosomal damage (human peripheral blood lymphocytes, Chinese Hamster Ovary cells, and a mouse micronucleus assay).

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm or offspring of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were below those achieved in humans given therapeutic doses of efavirenz.

Use in pregnancy
Pregnancy Category D: Malformations have been observed in 3 of 20 foetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (post-coital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one foetus, microophthalmia was observed in another foetus, and cleft palate was observed in a third foetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those seen in the clinic at the recommended dose, pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives).

Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to, or lower than those achieved in humans given 600 mg QD of efevirenz. Efavirenz produced no reproductive toxicities when

given to pregnant rabbits at doses that produced peak plasma concentrations similar to, and AUC values approximately half of those achieved in humans given 600 mg QD of efavirenz.

Pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Use of adequate contraceptive measures for 12 weeks after discontinuation of STOCRIN is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Efavirenz should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus and there are no other appropriate treatment options. If a woman takes efavirenz during the first trimester of pregnancy or becomes pregnant while taking efavirenz, she should be informed of the potential harm to the foetus.

There are no adequate and well-controlled studies in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, more than 700 pregnancies with first-trimester exposure to STOCRIN as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. In this registry, 4 retrospective reports (ie: after the results of the pregnancy were known) of findings consistent with neural tube defects, including 3 cases of meningomyelocele have been reported. All 4 mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of STOCRIN has not been established, similar defects have been observed in preclinical studies of efavirenz.

Use in lactation
Efavirenz is secreted into the milk of lactating rats and efavirenz also has been shown to pass into human breast milk. The use of STOCRIN in lactating mothers is not recommended. Mothers should be instructed not to breast-feed if they are receiving STOCRIN. It is recommended that HIV-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

Use in children
STOCRIN oral solution should not be used in children less than 3 years of age. Efavirenz has not been studied in paediatric patients below 3 months of age or who weigh less than 3.5 kg (see CLINICAL TRIALS).

The safety, pharmacokinetic profile, and virologic and immunologic responses of STOCRIN (efavirenz) were evaluated in antiretroviral-naive and -experienced HIV-1 infected paediatric patients 3 months to 21 years of age in three open-label clinical trials (see ADVERSE EFFECTS, PHARMACOLOGY, and CLINICAL TRIALS). The type and frequency of adverse reactions in these trials were generally similar to those of adult patients with the exception of a higher frequency of rash, including a higher frequency of Grade 3 or 4 rash, in paediatric patients compared to adults (see PRECAUTIONS and ADVERSE EFFECTS).

Use in the elderly
Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

INTERACTIONS WITH OTHER MEDICINES

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with STOCRIN. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolised by these isozymes may result in altered plasma

concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Although potential interactions with terfenadine, astemizole, cisapride, midazolam triazolam or ergot derivatives have not been studied, STOCRIN should not be administered concurrently with these drugs because competition for CYP3A4 by efavirenz could result in reduction of their metabolism and create the potential for serious and/or life-threatening adverse events (see CONTRAINDICATIONS).

Table 4

Drugs That Should Not Be Coadministered With STOCRIN

Drug Class	**Drugs Within Class Not To Be Coadministered With STOCRIN**
Antihistamines	astemizole, terfenadine
Benzodiazepines	midazolam, triazolam
GI Motility Agents	cisapride
Anti-Migraine	ergot derivatives
Antifungal agents	Voriconazole; itraconazole
Antipsychotic Drugs	pimozide
Calcium channel Blockers	bepridil

Drugs That Require A Dose Adjustment When Coadministered With STOCRIN

Drug Class	**Drugs Within Class Requiring Dose Increase**
Anti-HIV Protease Inhibitor	indinavir (increase dose from 800 mg to 1000 mg every 8 hours) Lopinavir/Ritonavir (increase dose 33.3% from 400/100 mg (3 soft capsules) twice daily to 533/133 mg (4 soft capsules) twice daily

Other Potentially Clinically Significant Drug Interactions With STOCRIN

Anticoagulants: Warfarin/Acenocoumarol	Plasma concentrations and effects potentially increased or decreased by STOCRIN
Anti-HIV Protease Inhibitors: Saquinavir	Plasma concentrations decreased by STOCRIN; should not be used as sole protease inhibitor in combination with STOCRIN
Amprenavir	Plasma concentrations decreased by STOCRIN, clinical significance unknown.

Antimycobacterial Agents Clarithromycin	Plasma concentrations decreased by STOCRIN; clinical significance unknown
Rifabutin	Plasma concentrations decreased and clearance increased by STOCRIN.
Rifampicin	Decreases efavirenz plasma concentrations; (increase dose of STOCRIN from 600 mg to 800 mg once daily)
Oestrogens: Ethinyl Estradiol	Plasma concentrations increased by STOCRIN; clinical significance unknown

Drugs which induce CYP3A4 activity (e.g. phenobarbitone, rifampicin, phenytoin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

QT Prolonging Drugs: There is limited information available on the potential for a pharmacodynamic interaction between STOCRIN and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see PHARMACODYNAMICS). Consider alternatives to STOCRIN when co-administered with a drug with a known risk of Torsade de Pointes.

Concomitant Antiretroviral Agents

Amprenavir: The AUC, Cmax and Cmin of amprenavir (1200 mg every 12 hours) were decreased when given with STOCRIN (600mg once daily) in HIV-infected subjects. While the clinical significance of decreased amprenavir concentrations has not been established, the possibility of this interaction should be taken into consideration before choosing a regimen containing both STOCRIN and amprenavir.

Fosamprenavir calcium: for guidance on coadministration with fosamprenavir and ritonavir, the prescribing information for fosamprenavir calcium should be consulted.

Atazanavir: Coadministration of STOCRIN 600 mg with atazanavir resulted in substantial decreases in atazanavir exposure, necessitating dosage adjustment of atazanavir in combination with ritonavir.

Nelfinavir: The AUC and Cmax of nelfinavir (750 mg every 8 hours) are increased by 20% and 21%, respectively when given with STOCRIN in uninfected volunteers. The combination was generally well tolerated and no dose adjustment is necessary when nelfinavir is administered in combination with STOCRIN.

Indinavir: When indinavir (800 mg every 8 hours) was given with STOCRIN, the indinavir AUC and Cmax were decreased by approximately 31% and 16%, respectively as a result of enzyme induction. The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000mg does not compensate for the increased indinavir metabolism due to efavirenz. No adjustment of the dose of STOCRIN is necessary when given with indinavir.

Maraviroc: Refer to the prescribing information for maraviroc for guidance on coadministration with STOCRIN.

Raltegravir: The AUC, C_{max}, and C_{min} of raltegravir (400 mg single dose) were decreased by 36%, 36%, and 21%, respectively, when given with efavirenz (600 mg once daily) compared to raltegravir alone. The mechanism of the interaction is induction of the UGT1A1 enzyme by efavirenz. No dose adjustment is necessary for raltegravir.

Ritonavir: When STOCRIN 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) was studied in uninfected volunteers, the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when STOCRIN is used in combination with ritonavir.

Saquinavir: When saquinavir soft gelatin capsules (1200 mg every 8 hours) was given with STOCRIN to uninfected volunteers, saquinavir AUC and Cmax were decreased by 62% and 45-50%, respectively. Use of STOCRIN in combination with saquinavir as the sole protease inhibitor is not recommended.

Saquinavir/Ritonavir: No data are available on the potential interactions of STOCRIN with the combination of saquinavir and ritonavir.

Lopinavir/Ritonavir: When used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced subjects, increasing the dose of lopinavir/ritonavir 33.3% from 400/100 mg (3 soft capsules) BID to 533/133 mg (4 soft capsules) BID yielded similar lopinavir plasma concentrations as compared to historical data of lopinavir/ritonavir 400/100 mg BID.

For patients with extensive protease inhibitor experience, or phenotypic or genotypic evidence of significant loss of sensitivity toward lopinavir, dosage increase to 533/133 mg BID should be considered when co-administered with efavirenz.

Boceprevir: When efavirenz (600 mg once daily) was given with boceprevir (800 mg three times daily) the plasma trough concentration of boceprevir was decreased. The clinical outcome of this observed reduction has not been directly assessed.

Telaprevir: Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz. When telaprevir 1125 mg every 8 hours was administered with efavirenz 600 mg once daily, the AUC, C_{max}, and C_{min} of telaprevir were decreased by 18%, 14%, and 25% relative to telaprevir 750 mg every 8 hours administered alone and the AUC, C_{max}, and C_{min} of efavirenz were decreased by 18%, 24%, and 10%. Refer to the prescribing information for telaprevir for guidance on coadministration with STOCRIN.

Simeprevir: Concomitant administration of simeprevir with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz which may result in loss of therapeutic effect of simeprevir. Coadministration of simeprevir with STOCRIN is not recommended. Refer to the product information for simeprevir for more information.

Nucleoside Analogue Reverse Transcriptase Inhibitors: Studies of the interaction between efavirenz and the combination of zidovudine and lamivudine were performed in HIV-infected patients. No clinically significant pharmacokinetic interactions were observed. Specific drug interaction studies have not been performed with STOCRIN and other NRTIs. Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Non-nucleoside Reverse Transcriptase Inhibitors: No studies have been performed with STOCRIN in combination with other NNRTIs.

Antimicrobial Agents

Rifamycins: Rifampicin reduced efavirenz AUC by 26% and Cmax by 20% in 12 uninfected volunteers. The dose of STOCRIN should be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with STOCRIN. In uninfected volunteers, the Cmax and AUC of rifabutin were decreased and rifabutin clearance was increased when rifabutin was given with STOCRIN. The possibility of this interaction should be taken into consideration before choosing a regimen containing both STOCRIN and rifabutin.

Coadministration of STOCRIN with combination products that contain efavirenz (e.g., ATRIPLA) is not recommended, unless needed for dose adjustment (eg, with rifampicin).

Macrolide Antibiotics

Azithromycin: Coadministration of single doses of azithromycin and multiple doses of STOCRIN in uninfected volunteers did not result in any clinically significant pharmacokinetic interaction. No dosage adjustment is necessary when azithromycin is given in combination with STOCRIN.

Clarithromycin: Coadministration of 400 mg of STOCRIN once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and Cmax of clarithromycin decreased 39% and 26%, respectively, while the AUC and Cmax of the clarithromycin hydroxymetabolite were increased 34% and 49%, respectively, when used in combination with STOCRIN. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers, 46% developed rash while receiving STOCRIN and clarithromycin. No dose adjustment of STOCRIN is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

Other macrolide antibiotics, such as erythromycin, have not been studied in combination with STOCRIN.

Antifungal Agents

No clinically significant pharmacokinetic interactions were seen when fluconazole and STOCRIN were coadministered to uninfected volunteers. No dosage adjustment is necessary when the two drugs are used in combination. The potential for drug interactions with STOCRIN and other imidazole antifungals, such as ketoconazole, has not been studied.

Voriconazole: STOCRIN should not be administered concurrently with voriconazole because STOCIN significantly decreases voriconazole plasma concentrations. The steady state AUC

and Cmax of voriconazole decreased by 77% and 61% respectively, while the steady state AUC and Cmax of STOCRIN increased by 44% and 38% respectively. Coadministration of STOCRIN and voriconazole is contraindicated.

Itraconazole: Coadministration of efavirenz (600 mg orally once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady state AUC, Cmax and Cmin of itraconazole. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Posaconazole: Concomitant use of posaconazole and STOCRIN should be avoided unless the benefit to the patient outweighs the risk.

Antimalarial Agents
Concomitant administration of atovaquone/proguanil with efavirenz should be avoided whenever possible.

Artemether/lumefantrine: Coadministration of efavirenz (600 mg once daily) with artemether 20 mg/lumefantrine 120 mg tablets (6 4-tablet doses over 3 days) resulted in a decrease in exposures (AUC) to artemether, dihydroartemisinin (active metabolite of artemether), and lumefantrine by approximately 51%, 46%, and 21%, respectively. Exposure to efavirenz was not significantly affected. Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when STOCRIN and artemether/lumefantrine tablets are coadministered.

Lipid-lowering agents
Coadministration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Cholesterol levels should be periodically monitored. Dosage adjustments of statins may be required.

Other Drug Interactions

Antacids/famotidine: Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz in uninfected volunteers. These data suggest that alteration of gastric pH by other drugs would not be expected to affect efavirenz absorption.

Oral Contraceptives (ethinyl estradiol): Only the ethinyl estradiol component of oral contraceptives has been studied. The AUC following a single dose of 50 μg ethinyl estradiol was increased (37%) by efavirenz. No significant changes were observed in Cmax of ethinyl estradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyl estradiol on efavirenz Cmax or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives.

Immunosuppressants: When an immunosuppressant metabolized by CYP3A4 (eg, ciclosporin, tacrolimus, or sirolimus) is administered with efavirenz, decreased exposure of the immunosuppressant may be expected due to CYP3A4 induction. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.

Anticonvulsants: Carbamazepine: Co-administration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, Cmax and Cmin of carbamazepine decreased by 27%, 20% and 35%, respectively, while the steady-state AUC, Cmax and Cmin of efavirenz

decreased by 36%, 21%, and 47%, respectively. The steady-state AUC, Cmax and Cmin of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data with coadministration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

Other anticonvulsants: No data are available on the potential interactions of efavirenz with phenytoin, phenobarbital, or other anticonvulsants that are substrates of CYP450 isozymes. When efavirenz is administered concomitantly with these agents, there is a potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels should be conducted. Specific interaction studies have not been performed with efavirenz and vigabatrin or gabapentin.

Methadone: Co-administration of efavirenz with methadone has resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Antidepressants: The C_{max}, C_{24} and AUC of sertraline were decreased when given with STOCRIN. The possibility of this interaction should be taken into consideration before choosing a regimen containing both STOCRIN and sertraline. Sertraline dose increases should be guided by clinical response.

Bupropion: Increases in bupropion dose may be necessary when taken in combination with efavirenz and should be guided by clinical response, but should not exceed the maximum recommended dose. No adjustment of efavirenz is required.

Calcium channel blockers: coadministration of efavirenz (600 mg orally once daily) with diltiazem (240 mg orally once daily) in uninfected volunteers decreases the steady state AUC, Cmax and Cmin of diltiazem. Diltiazem dose adjustments should be guided by clinical response (refer to the Product Information for diltiazem).

Although the pharmacokinetic parameters of efavirenz were slightly increased (11%-16%), these changes are not considered clinically significant and, thus, no dosage adjustment is necessary for efavirenz when administered with diltiazem.

No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme (eg: verapamil, felodipine, nifedipine, nicardipine). When efavirenz is administered concomitantly with one of these agents, there is a potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the corresponding Product Information documents for the calcium channel blocker).

Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected volunteers who received STOCRIN. Confirmation of positive screening tests for cannabinoids by a more specific method such as gas chromatography/mass spectrometry is recommended.

ADVERSE EFFECTS

Clinical Trial Information

Efavirenz was generally well tolerated in clinical trials. Efavirenz has been studied in over 9000 patients. In a subset of 1008 patients who received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs in controlled clinical studies, the most frequently reported treatment-related undesirable effects of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). Nausea was reported with a higher frequency in the control groups. The most notable undesirable effects associated with efavirenz are rash, nervous system symptoms and psychiatric symptoms (see PRECAUTIONS).

Other, less frequent, clinically significant treatment-related undesirable effects reported in all clinical trials include: allergic reaction, abnormal coordination, ataxia, confusion, stupor, vertigo, vomiting, diarrhoea, hepatitis, impaired concentration, insomnia, anxiety, abnormal dreams, somnolence, depression, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination, psychosis, and catatonia.

A few cases of pancreatitis have been described although a causal relationship with efavirenz has not been established.

The type and frequency of undesirable effects in children was generally similar to that of adult patients with the exception that rash was reported more frequently in children and was more often of higher grade than in adults.

Skin Rash: In clinical trials, 26% of patients treated with 600 mg STOCRIN experienced new-onset skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with STOCRIN. Grade 3 rash associated with blistering, moist desquamation, or ulceration occurred in less than 1% of patients treated with STOCRIN. The incidence of Grade 4 rash (erythema multiforme or Stevens-Johnson syndrome) was 0.14%. The discontinuation rate for rash in clinical trials was 1.7% (7/413).

Rash was reported in 59 of 182 paediatric patients (32%) treated with STOCRIN in three clinical trials for a median of 123 weeks. Two (1.1%) paediatric patients experienced Grade 3 rash (confluent rash with fever, generalised rash), and four (2.2%) paediatric patients had Grade 4 rash (all erythema multiforme). Five paediatric patients (2.7%) discontinued from the study because of rash. The median time to onset of rash in paediatric patients was 28 days (range 3-1642 days). Prophylaxis with appropriate antihistamines prior to initiating therapy with STOCRIN in children may be considered.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with STOCRIN. In most patients, rash resolves with continuing therapy with STOCRIN within one month. STOCRIN can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when STOCRIN is restarted (see PRECAUTIONS).

Experience with STOCRIN in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with STOCRIN. Nine of these patients developed mild-to-moderate rash while receiving therapy with STOCRIN, and two of these patients discontinued because of rash.

Skin rash was more prevalent in children receiving STOCRIN than in adults.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in some patients treated with efavirenz. The following serious psychiatric events were reported in patients in controlled trials using regimens containing efavirenz (n=1008) and control regimens (n=635): severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), non-fatal suicide attempts (0.4%, 0%), aggressive behaviour (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%) and manic reactions (0.1%, 0%).

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences, with the frequency of each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have been occasional post-marketing reports of death by suicide, delusions psychosis-like behaviour, and catatonia although a causal relationship to the use of efavirenz cannot be determined from these reports.

Nervous System Symptoms: Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration, and abnormal dreaming are frequently reported side effects in patients receiving STOCRIN 600 mg once daily in clinical trials. In controlled clinical trials where 600 mg once daily STOCRIN was administered with other antiretroviral agents, 19.4% of patients experienced nervous system symptoms of moderate-to-severe intensity compared to 9% of patients receiving control regimens. These symptoms were severe in 2.0% of patients receiving STOCRIN 600 mg once daily and in 1.3% of patients receiving control regimens. In clinical trials, 2.1% of patients treated with 600 mg of STOCRIN discontinued therapy because of nervous system symptoms (see PRECAUTIONS).

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. In one clinical study, the monthly prevalence of nervous system symptoms of at least moderate severity between weeks 4 and 48, ranged from 5%-9% in patients treated with regimens containing efavirenz and 3%-5% in patients treated with the control regimen. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see DOSAGE AND ADMINISTRATION). Dose reduction or splitting the daily dose has not been shown to provide benefit and is not recommended.

Drug-related clinical adverse experiences of moderate or severe intensity observed in ≥2% of patients in three controlled clinical trials are presented in Table 5.

Table 5: Percent of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Patients in Studies 006, ACTG 364, or 020

	Study 006 LAM, NNRTI and Protease Inhibitor Naïve Patients			**Study ACTG 364 NRTI-experienced, NNRTI and Protease Inhibitor Naïve Patients**			**Study 020 NRTI-experienced NNRTI and Protease Inhibitor Naïve Patients**	
Adverse Events	Stocrin[2] + ZDV/LAM (N = 412)	Stocrin[2] + Indinavir (N = 415)	Indinavir + ZDV/LAM (N = 401)	Stocrin[2] +Nelfinavir +NRTIs (N = 64)	Stocrin[2] + NRTIs (N = 65)	Nelfinavir + NRTIs (N = 66)	Stocrin[2] +Indinavir + NRTIs (N = 154)	Indinavir + NRTIs (N = 168)
Body as a Whole								
Fatigue (includes asthenia, malaise for 364)	7%	5%	8%	0%	2%	3%	5%	1%
Asthenia	1%	1%	2%	--	--	--	0%	1%

Pain (includes flank & back pain)	1%	1%	5%	13%	6%	17%	4%	3%
Fever	0%	1%	0%	2%	0%	8%	0%	1%
Oedema (includes enlarged/swollen for 364, leg oedema for 006, peripheral oedema for 020)	0%	0%	0%	5%	0%	3%	0%	1%
Cardiovascular System								
Cardiovascular Dysfunction	0%	1%	0%	2%	2%	3%	1%	0%
Central Nervous System								
Dizziness (includes lightheadedness/fainting for 364)	8%	8%	2%	2%	6%	6%	6%	1%
Headache	7%	4%	4%	5%	1%	3%	5%	4%
Insomnia (includes dreams/sleeping problems for 364)	4%	5%	2%	0%	0%	2%	1%	0%
Impaired Concentration	5%	2%	0%	--	--	--	3%	1%
Somnolence	2%	2%	1%	--	--	--	2%	2%
Abnormal Dreaming	2%	1%	0%	--	--	--	2%	1%
Paraesthesia (includes numbness/tingling for 364)	0%	0%	0%	3%	3%	3%	1%	1%
Neurological Dysfunction	--	--	--	0%	0%	3%	--	--
Gastrointestinal System								
Nausea (includes N/V, Vomiting for 364)	10%	6%	22%	2%	6%	2%	10%	8%
Vomiting	5%	3%	12%	--	--	--	5%	5%
Diarrhoea	3%	4%	4%	14%	3%	9%	9%	2%
Abdominal Pain (includes Groin/Pelvic pain for 364)	1%	2%	4%	3%	3%	3%	3%	1%
Dyspepsia	3%	3%	5%	--	--	--	3%	1%
Anorexia	1%	0%	1%	0%	2%	2%	5%	1%
Constipation	0%	0%	2%	2%	0%	0%	1%	0%
Flatulence	0%	1%	2%	--	--	--	0%	1%
Metabolic & Nutritional								
Decreased Weight (includes cachexia/wasting for 364)	--	--	--	2%	0%	2%	2%	1%

Psychiatric								
Nervousness (as agitation/hyperactive for 364)	2%	2%	0%	2%	0%	2%	1%	0%
Depression	2%	1%	0%	3%	0%	5%	2%	0%
Anxiety	1%	3%	0%	--	--	--	2%	1%
Drug Abuse	0%	1%	0%	--	--	--	1%	2%
Respiratory System								
Congestion/Effusion	--	--	--	0%	0%	6%	--	--
Cough	0%	0%	0%	0%	0%	6%	--	--
Dyspnoea	0%	0%	0%	0%	0%	2%	1%	0%
Skin and Appendages								
Rash	13%	20%	7%	9%	5%	6%	10%	6%
Pruritus	0%	1%	1%	0%	2%	5%	2%	1%
Increased Sweating	2%	1%	0%	--	--	--	1%	0%
Urticaria (includes allergic rash/welts/hives for 364)	0%	2%	0%	3%	0%	2%	1%	1%
Erythema/Redness/Inflammation	--	--	--	3%	2%	5%	--	--

Blisters/Ulcerations/Lesions	--	--	--	2%	2%	2%	--	--
Dry Skin	0%	2%	1%	--	--	--	0%	1%
Special Senses								
Taste Perversion	0%	1%	1%	--	--	--	1%	2%
Urinary System								
Haematuria	0%	0%	2%	--	--	--	1%	1%
Renal Calculus	0%	0%	3%	--	--	--	1%	4%
Renal Pain	0%	0%	3%	--	--	--	--	--

[1] Includes adverse events at least possibly related to study drug or of unknown relationship for studies 006 and 020. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

[2] STOCRIN provided as 600 mg QD.

-- = Not Specified.

Assessment of adverse reactions is based on three clinical trials in 182 HIV-1 infected paediatric patients (3 months to 21 years of age) who received STOCRIN (efavirenz) in combination with other antiretroviral agents for a median of 123 weeks. The adverse reactions observed in the three trials were similar to those observed in clinical trials in adults except that rash was more common in paediatric patients (32% for all grades regardless of causality) and more often of higher grade (ie, more severe). Two (1.1%) paediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four (2.2%) paediatric patients had Grade 4 rash (all erythema multiforme). Five paediatric patients (2.7%) discontinued from the study because of rash (see also Use in children).

Adverse clinical experiences of moderate to severe intensity observed in less than 2% of patients receiving STOCRIN in all Phase II/III studies, including the North American expanded access program, and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below by body system:

Body as a Whole: alcohol intolerance, allergic reaction, asthenia, fever, hot flushes, malaise, influenza-like symptoms, pain, peripheral oedema, syncope

Central and Peripheral Nervous System: ataxia, appetite increased, confusion, convulsions, impaired coordination, impotence, libido increased, libido decreased, migraine headaches, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor, vertigo

Gastrointestinal: gastritis, gastroenteritis, gastroesophageal reflux, dry mouth, pancreatitis

Hearing and Vestibular: tinnitus

Cardiovascular: flushing, palpitations, tachycardia, thrombophlebitis

Liver and Biliary System: hepatitis

Metabolic and Nutritional: weight gain, weight loss

Musculoskeletal: arthralgia, myalgia

Psychiatric: aggravated depression, agitation, amnesia, anxiety, apathy, emotional lability, euphoria, hallucination, psychosis

Respiratory: asthma, sinusitis, upper respiratory tract infection

Skin and Appendages: acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria

Special Senses: abnormal vision, diplopia, parosmia, taste perversion

Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral & facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsovisceral fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hypergylcaemia and hyperlactataemia.

LABORATORY TEST FINDINGS

Laboratory Abnormalities:

Liver Enzymes: Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in 3% of 1008 patients treated with 600mg of efavirenz. Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of efavirenz who were seropositive for Hepatitis B and/or C, 7% developed AST levels and 8% developed ALT levels greater than five times the upper limit of the normal range. In 91 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 4% developed ALT elevations to those levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of efavirenz and in 10% of patients seropositive for Hepatitis B or C. In patients treated control regimens, the incidence of GGT elevations to this level was 1.5-2%, irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see PRECAUTIONS).

Lipids: Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving STOCRIN. Increases in non-fasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed in patients treated with efavirenz+ZDV+3TC and of approximately 40% and 35%, in patients treated with efavirenz+IDV. The effects of efavirenz on triglycerides and LDL were not well characterised. The clinical significance of these findings is unknown. (see PRECAUTIONS).

Post-marketing Information

Additional undesirable effects reported in post-marketing surveillance include:

Eye disorders: blurred vision

Gastrointestinal disorders: abdominal pain, pancreatitis

Hepatobiliary disorders: hepatic failure

Nervous system disorders: convulsions, cerebellar co-ordination and balance disturbances, tremor

Psychiatric disorders: neurosis, paranoid reaction

Reproductive system and breast disorders: gynaecomastia

Special Senses: tinnitus

Skin and subcutaneous tissue disorders: pruritus, photoallergic dermatitis, redistribution/accumulation of body fat in areas such as the back of the neck, breasts, abdomen and retroperitoneum, flushing.

A few of the post-marketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

Laboratory abnormalities:
Amylase: Asymptomatic increases in serum amylase levels have been observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients.

DOSAGE AND ADMINISTRATION

STOCRIN should be taken in the fasted state, preferably at bedtime. Food increases the bioavailability of STOCRIN and this may be associated with a higher frequency of side effects.

In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (see ADVERSE EFFECTS).

Concomitant Antiretroviral Therapy: STOCRIN must be given in combination with other antiretroviral medications (see INTERACTIONS WITH OTHER MEDICINES).

Adults:
The recommended dosage of STOCRIN in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily when using the tablets or 24 mL orally once daily when using the oral solution.

Adolescents and children (17 years and under): The recommended dose of STOCRIN in combination with a protease inhibitor and/or NRTIs for patients 17 years of age and under is described in the table below. STOCRIN tablets should only be administered to children who are able to reliably swallow tablets. STOCRIN tablets or oral solution have not been adequately studied in children under the age of 3 years or children weighing less than 13 Kg (see PRECAUTIONS and USE IN CHILDREN).

Paediatric Dose to be Administered Once Daily

Body Weight	**STOCRIN Tablets**	**STOCRIN oral solution (30 mg/mL) Dose (mL)***	
Kg	**Dose (mg)**	**Children 3 to <5 years**	**Adults and children aged 5 years or more**
13 to < 15	200	12	9
15 to < 20	250	13	10
20 to < 25	300	15	12
25 to < 32.5	350	17	15
32.5 to < 40	400	—	17
≥40	600	—	24

* STOCRIN oral solution is less bioavailable than the tablet on a mg per mg basis of efavirenz. The dose recommendations above have been adjusted to take into account the difference in bioavailability.

OVERDOSAGE

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with STOCRIN should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with STOCRIN. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

PRESENTATION AND STORAGE CONDITIONS

TABLETS:
STOCRIN 50 mg, yellow, round shaped tablet debossed with "113" on one side & plain on the other**.** Available in bottles of 30. *

STOCRIN 200 mg, yellow, round shaped tablet debossed with "223" on one side and plain on the other. Available in bottles of 90.

STOCRIN 300mg, white, capsular-shaped tablets, printed with "224" in purple on both sides. Available in bottles* and cartons* of 60.

STOCRIN 600mg, yellow, modified capsular-shaped tablets, debossed with "225" on one side & blank on the other. Available in bottles and cartons* of 30.

Store below 30°C.

STOCRIN 30mg/mL oral solution. Available in bottles containing 180 mL. The solution should be used within one month of first opening the bottle.

Store below 30°C.

*These pack sizes not currently available in Australia.

NAME AND ADDRESS OF THE SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
Level 1, Building A, 26 Talavera Road
Macquarie Park, NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine Schedule 4 (S4).

DATE OF FIRST INCLUSION IN THE AUTRALIAN REGISTER OF THERAPEUTIC GOOD (The ARTG)

28 June 1999

DATE OF MOST RECENT AMENDMENT

3 May 2017