PRODUCT CIRCULAR
Tablets
STOCRIN®
(efavirenz)

I. THERAPEUTIC CLASS

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

II. INDICATIONS

STOCRIN is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children.

III. DOSAGE AND ADMINISTRATION

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. It is recommended that STOCRIN be taken on an empty stomach.

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 SIDE EFFECTS).

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

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 Table 1. STOCRIN tablets should only be administered to children who are able to reliably swallow tablets. It is recommended that STOCRIN be taken on an empty stomach. STOCRIN tablets have not been

adequately studied in children under the age of 3 years or children weighing less than 13 kg (see PRECAUTIONS and PEDIATRIC USE).

Table 1
Pediatric Dose to be Administered Once Daily

Body Weight kg	STOCRIN Tablets Dose (mg)
13 to < 15	200
15 to < 20	250
20 to < 25	300
25 to < 32.5	350
32.5 to < 40	400
≥ 40	600

IV. CONTRAINDICATIONS

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

STOCRIN is contraindicated with elbasvir/grazoprevir due to the expected significant decreases in elbasvir and grazoprevir plasma concentrations (see DRUG INTERACTIONS). This effect is due to an induction of CYP3A4 by efavirenz and is expected to result in the loss of virologic response of elbasvir/grazoprevir.

STOCRIN must not be administered concurrently with the standard doses of voriconazole because efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations (see DRUG INTERACTIONS; for use of adjusted doses of voriconazole with adjusted doses of efavirenz, see DRUG INTERACTIONS).

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.

V. PRECAUTIONS

STOCRIN must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen.

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

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 (e.g., with rifampin).

Malformations have been observed in fetuses from efavirenz-treated animals (see 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 DRUG INTERACTIONS).

Drug Interactions: Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A4. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A4 or CYP2B6. The prominent effect of efavirenz at steady-state is induction of CYP3A4 and CYP2B6. However, efavirenz has demonstrated CYP3A4 inhibitory effects *in vitro*; therefore, the theoretical potential exists for drug levels to be increased temporarily for agents metabolized by CYP3A4. Caution should be used during the first days of STOCRIN therapy in patients taking a CYP3A4 substrate with both a narrow therapeutic index and the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Caution should be exercised for agents such as ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), midazolam, triazolam, bepridil, cisapride, and pimozide.

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

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 (e.g., Stevens-Johnson syndrome). If therapy with STOCRIN is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of drug-resistant virus (see SIDE EFFECTS).

Rash was reported in 59 of 182 children (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 pediatric patients was 28 days (range 3-1642 days). Prophylaxis with appropriate antihistamines prior to initiating therapy with STOCRIN in children may be considered.

Psychiatric Symptoms: Psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. There have also been occasional post-marketing reports of death by suicide, delusions, psychosis-like behavior, and catatonia although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients should be advised that if they experience these symptoms they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see SIDE EFFECTS).

Nervous System Symptoms: Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see SIDE EFFECTS). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of STOCRIN. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of STOCRIN is warranted.

Seizures: convulsions have been observed rarely in adult and pediatric patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolized by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug

interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see DRUG INTERACTIONS). Caution must be taken in any patient with a history of seizures.

Effect of Food: the administration of STOCRIN with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects. Taking STOCRIN on an empty stomach, preferably at bedtime, can 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, 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 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 from younger patients.

STOCRIN tablets have not been 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 should not be given to children less than 3 years of age (see DOSAGE AND ADMINISTRATION and PEDIATRIC USE).

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 SIDE EFFECTS).

Lipids: Monitoring of lipid levels should be considered in patients treated with STOCRIN (see SIDE EFFECTS).

VI. PREGNANCY

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). Because of the long half-life of efavirenz, 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 fetus 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 fetus.

There are no adequate and well-controlled studies of efavirenz in pregnant women. In post-marketing experience through an antiretroviral pregnancy registry, more than 900 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. In this registry, a small number of cases of neural tube defects, including meningomyelocele, have been reported; most of these reports were retrospective, and causality has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects.

VII. NURSING MOTHERS

Efavirenz is secreted into the milk of lactating rats and efavirenz also has been shown to pass into human breast milk. It is recommended that mothers taking efavirenz do not breast-feed their infants. It is recommended that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

VIII. PEDIATRIC USE

STOCRIN tablets have not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

IX. DRUG INTERACTIONS

Efavirenz is an inducer of CYP3A4 and CYP2B6. Other compounds that are substrates of CYP3A4 or CYP2B6 may have decreased plasma concentrations when coadministered with STOCRIN (see V. PRECAUTIONS – Drug Interactions).

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 coadministered with a drug with a known risk of Torsade de Pointes.

Concomitant Antiretroviral Agents

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

Atazanavir: Co-administration of efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz. Efavirenz decreases atazanavir exposure. Refer to the prescribing information for atazanavir guidance on coadministration with efavirenz.

Indinavir: When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg every 24 hours), the indinavir AUC and C_{trough} were decreased by approximately 31% and 40% respectively. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily) in uninfected volunteers, the indinavir AUC and C_{trough} were decreased on average by 33-46% and 39-57%, respectively (ranges represent diurnal variation), compared to when indinavir was given alone at

the standard dose (800 mg every 8 hours). Similar differences in indinavir AUC and C_{trough} were also observed in HIV-infected subjects who received indinavir (1000 mg every 8 hours) with efavirenz (600 mg once daily) compared to indinavir given alone (800 mg every 8 hours). While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz and indinavir.

When efavirenz 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in uninfected volunteers (n = 14), the indinavir AUC, C_{min}, and C_{max} were decreased by approximately 25%, 50% and 17%, respectively, compared to when indinavir/ritonavir 800/100 mg twice daily were given without efavirenz. The geometric mean C_{min} for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical C_{min} (0.15 mg/l) when indinavir was given alone at 800 mg every 8 hours. The pharmacokinetics of efavirenz given in combination with indinavir/ritonavir were comparable to efavirenz alone (600 mg once daily).

When efavirenz 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in HIV-1 infected patients (n = 6), the pharmacokinetics of indinavir and efavirenz were generally comparable to these uninfected volunteer data.

No adjustment of the dose of efavirenz is necessary when given with indinavir or indinavir/ritonavir. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.

Lopinavir/ritonavir: A significant reduction in the C_{min} of lopinavir was observed when a lopinavir/ritonavir combination was coadministered with efavirenz compared to when the lopinavir/ritonavir combination was administered alone. A dose increase of lopinavir/ritonavir capsules or oral solution to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz. Consult the prescribing information for lopinavir/ritonavir tablets for guidance on coadministration of this formulation with efavirenz.

Darunavir/ritonavir: When STOCRIN (600 mg once daily) is given in combination with darunavir/ritonavir (800/100 mg once daily), suboptimal darunavir C_{min} may result. If STOCRIN is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. Consult the prescribing information for darunavir/ritonavir for guidance on coadministration with STOCRIN.

Maraviroc: The AUC_{12} and C_{max} of maraviroc (100 mg twice daily) are decreased by 45% and 51%, respectively, when given with STOCRIN (600 mg once daily) compared to maraviroc administered alone. 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. The clinical significance of this interaction has not been directly assessed. Currently, no dose adjustment is recommended 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 (1200 mg given 3 times a day, soft gel formulation) was given with STOCRIN, the saquinavir AUC and C_{max} were decreased by 62% and 45-50%, respectively. Use of STOCRIN in combination with saquinavir as the sole protease inhibitor is not recommended.

HCV Antivirals

Boceprevir: When efavirenz (600 mg once daily) was given with boceprevir (800 mg three times daily) the plasma trough concentration of boceprevir was decreased (C_{min} ↓ 44%), which may result in loss of therapeutic effect. This combination should be avoided.

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 and tenofovir disoproxil fumarate (TDF) 300 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 prescribing information for simeprevir for more information.

Elbasvir/grazoprevir: Coadministration of STOCRIN with elbasvir/grazoprevir reduces AUC and C_{max} of elbasvir by 54% and 45%, respectively and AUC and C_{max} of grazoprevir by 83% and 87%, respectively compared to elbasvir/grazoprevir alone. Concomitant administration of STOCRIN with elbasvir/grazoprevir is contraindicated (see CONTRAINDICATIONS) because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and

grazoprevir plasma concentrations caused by CYP3A4 induction. Refer to the prescribing information for elbasvir/grazoprevir for more information.

Sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir: Coadministration of efavirenz with a HCV treatment regimen containing velpatasvir has been shown to decrease velpatasvir exposure. Concomitant administration of sofosbuvir/velpatasvir with STOCRIN decreased velpatasvir AUC, C_{max}, and C_{min} by 53%, 47%, and 57%, respectively, compared with sofosbuvir/velpatasvir alone. Coadministration of STOCRIN with sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended. Refer to the prescribing information for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir for more information.

Antimicrobial Agents

Rifamycins: Rifampin reduced efavirenz AUC by 26% and C_{max} by 20% in 12 uninfected volunteers. The dose of STOCRIN should be increased to 800 mg/day when taken with rifampin in patients weighing 50 kg or more. No dose adjustment of rifampin is recommended when given with STOCRIN. In one study in uninfected volunteers, efavirenz induced a reduction in rifabutin C_{max} and AUC by 32% and 38%, respectively, and increased rifabutin clearance. Rifabutin had no significant effect on the pharmacokinetics of efavirenz. These data suggest that the daily dose of rifabutin should be increased by 50% when administered with efavirenz and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with efavirenz.

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 C_{max} of clarithromycin decreased 39% and 26%, respectively, while the AUC and C_{max} 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.

Antifungal Agents

Voriconazole: Coadministration of efavirenz (400 mg orally once daily) with voriconazole (200 mg orally every 12 hours) in uninfected volunteers resulted in a 2-way interaction. The steady-state AUC and C_{max} of voriconazole decreased by 77% and 61%, respectively, while the steady-state AUC and C_{max} of efavirenz increased by 44% and 38%, respectively. Coadministration of standard doses of efavirenz and voriconazole is contraindicated (see CONTRAINDICATIONS).

Following coadministration of efavirenz (300 mg orally once daily) with voriconazole (300 mg twice daily) in uninfected volunteers, the AUC and C_{max} of voriconazole was decreased by 55% and 36% respectively, compared to voriconazole 200 mg twice daily alone; AUC of efavirenz was equivalent but C_{max} was decreased by 14% compared to efavirenz 600 mg once daily alone.

Following coadministration of efavirenz (300 mg orally once daily) with voriconazole (400 mg twice daily) in uninfected volunteers, the AUC of voriconazole was decreased by 7% and C_{max} was increased by 23% compared to voriconazole 200 mg twice daily alone. These differences were not considered to be clinically significant. The AUC of efavirenz was increased by 17% and C_{max} was equivalent compared to efavirenz 600 mg once daily alone.

When efavirenz is coadministered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg twice daily and the efavirenz dose should be reduced by 50%, i.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.

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, C_{max}, and C_{min} of itraconazole by 39%, 37%, and 44%, respectively, and of hydroxyitraconazole by 37%, 35%, and 43%, respectively, compared to itraconazole administered alone. The pharmacokinetics of efavirenz were not affected. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Posaconazole: Coadministration of STOCRIN (400 mg orally once daily) with posaconazole (400 mg orally twice daily) decreased the AUC and C_{max} of posaconazole by 50% and 45% respectively, compared to posaconazole administered alone. Concomitant use of posaconazole and STOCRIN should be avoided unless the benefit to the patient outweighs the risk.

Antimalarial Agents

Atovaquone and proguanil hydrochloride: Coadministration of efavirenz (600 mg once daily) with atovaquone and proguanil (250/100 mg single dose) reduces the AUC and C_{max} 75% and 44% for atovaquone and the AUC 43% for proguanil via the induction of glucoronidation. 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.

Atorvastatin: Coadministration of efavirenz (600 mg orally once daily) with atorvastatin (10 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of atorvastatin by 43% and 12%, respectively, of 2-hydroxy atorvastatin by 35% and 13%, respectively, of 4-hydroxy atorvastatin by 4% and 47%, respectively, and of total active HMG-CoA reductase inhibitors by 34% and 20%, respectively, compared to atorvastatin administered alone.

Pravastatin: Coadministration of efavirenz (600 mg orally once daily) with pravastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of pravastatin by 40% and 18%, respectively, compared to pravastatin administered alone.

Simvastatin: Coadministration of efavirenz (600 mg orally once daily) with simvastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of simvastatin by 69% and 76%, respectively, of simvastatin acid by 58% and 51%, respectively, of total active HMG-CoA reductase inhibitors by 60% and 62%, respectively, and of total HMG-CoA reductase inhibitors by 60% and 70%, respectively, compared to simvastatin administered alone.

Coadministration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values. No dosage adjustment is necessary for efavirenz.

Anticoagulants

Warfarin/Acenocoumarol: Plasma concentrations and effects potentially increased or decreased by STOCRIN.

Anticonvulsants

Carbamazepine: Coadministration 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, C_{max} and C_{min} of carbamazepine decreased by 27%, 20% and 35%, respectively, while the steady-state AUC, C_{max} and C_{min} of efavirenz decreased by 36%, 21%, and 47%, respectively. The steady-state AUC, C_{max} and C_{min} 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. Clinically significant interactions would not be expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and would be unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.

Other Drug Interactions

Hormonal Contraceptives

Oral: When an oral contraceptive (ethinyl estradiol 0.035 mg/norgestimate 0.25 mg once daily) and efavirenz (600 mg once daily) were coadministered for 14 days, efavirenz had no effect on ethinyl estradiol concentrations but plasma concentrations of norelgestromin and levonorgestrel, active metabolites of norgestimate, were markedly decreased in the presence of efavirenz (64%, 46%, and 82% decrease in norelgestromin AUC, C_{max} and C_{min}, respectively, and 83%, 80%, and 86% decrease in levonorgestrel AUC, C_{max}, and C_{min}, respectively). The clinical significance of these effects is not known. No effect of ethinyl estradiol / norgestimate on efavirenz plasma concentrations was observed.

Injection: Limited information exists regarding efavirenz and injectable hormonal contraception. In a 3-month drug interaction study of depo-medroxyprogesterone acetate (DMPA) and efavirenz, plasma progesterone levels for all subjects remained below 5 ng/mL, consistent with suppression of ovulation.

Implant: Decreased exposure of etonogestrel may be expected due to CYP3A4 induction by efavirenz, and there have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.

Immunosuppressants: When an immunosuppressant metabolized by CYP3A4 (e.g., cyclosporine, 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.

Methadone: In a study of HIV-infected IV drug users, coadministration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Antidepressants: There were no clinically significant effects on pharmacokinetic parameters when paroxetine and efavirenz were coadministered. No dose adjustments are necessary for either efavirenz or paroxetine when these drugs are coadministered. Sertraline did not significantly alter the pharmacokinetics of efavirenz. Efavirenz decreased sertraline C_{max}, C_{24}, and AUC by 28.6-46.3%. The dose of sertraline should be increased when administered with efavirenz to compensate for the induction of sertraline metabolism by efavirenz. Sertraline dose increases should be guided by clinical response. Bupropion (150 mg single dose, sustained release) when given with efavirenz (600 mg once daily) reduced the AUC and C_{max} by 55% and 34% respectively. The AUC of hydroxybupropion was unchanged and the C_{max} was increased via CYP2B6 induction by 50%. Increases in bupropion dose should be guided by clinical response, but should not exceed the maximum recommended dose. No adjustment of efavirenz is required.

Cetirizine: Cetirizine had no clinically significant effect on efavirenz pharmacokinetic parameters. Efavirenz decreased cetirizine C_{max} by 24% but did not alter cetirizine AUC. These changes are not expected to be clinically significant. No dose adjustments are necessary for either efavirenz or cetirizine when these drugs are coadministered.

Lorazepam: Efavirenz increased lorazepam C_{max} and AUC by 16.3% and 7.3%, respectively. The pharmacokinetic interaction of efavirenz on lorazepam is unlikely to be clinically significant. No dose adjustments are necessary for either efavirenz or lorazepam when these drugs are co-administered.

Calcium channel blockers: coadministration of efavirenz (600 mg orally once daily) with diltiazem (240 mg orally once daily) in uninfected volunteers decreased the steady-state AUC, C_{max} , and C_{min} of diltiazem by 69%, 60%, and 63%, respectively; desacetyl diltiazem by 75%, 64%, and 62%, respectively; and N-monodesmethyl diltiazem by 37%, 28%, and 37%, respectively, compared to diltiazem administered alone. Diltiazem dose adjustments should be guided by clinical response (refer to the product circular 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 (e.g., 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 manufacturer's product circular 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.

X. SIDE EFFECTS

Efavirenz was generally well tolerated in clinical trials. Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 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. The administration of STOCRIN with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects (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.

Additional undesirable effects reported in post-marketing surveillance include neurosis, paranoid reaction, cerebellar coordination and balance disturbances, convulsions, pruritus, abdominal pain, blurred vision, flushing, gynecomastia, hepatic failure, photoallergic dermatitis, pancreatitis, redistribution/accumulation of body fat in areas such as the back of the neck, breasts, abdomen, and retroperitoneum, tinnitus, tremor, and encephalopathy.

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.

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.

Rash: In clinical trials, 26% of patients treated with 600 mg of STOCRIN experienced skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment-related in 18% of patients treated with STOCRIN. Severe rash occurred in less than 1% of patients treated with STOCRIN and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was 0.14%.

Rash was reported in 59 of 182 children (32%) treated with efavirenz in three clinical trials for a median of 123 weeks. Rash was severe in 6 patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz 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 discontinued because of rash.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1,008 patients treated with regimens containing efavirenz for an average of 1.6 years and 635 patients treated with control regimens for an average of 1.3 years, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), non-fatal suicide attempts (0.4%, 0%), aggressive behavior (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 also been post-marketing reports of death by suicide, delusions, psychosis-like behavior, 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 daily in clinical trials. In controlled clinical trials where 600 mg 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 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.

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.

Xa. 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 1,008 patients treated with 600 mg 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 these 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 with control regimens, the incidence of GGT elevations to this level was 1.5-2%, regardless 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 efavirenz. Increases from baseline 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-characterized. In clinical trials of various efavirenz-containing

regimens in treatment naïve patients, total cholesterol, HDL-cholesterol, and triglycerides increased over 48 weeks of treatment (21-31%, 23-34%, and 23-49%, respectively). The proportion of patients with a total cholesterol/HDL-cholesterol ratio greater than 5 was unchanged. The magnitude of changes in lipid levels may be influenced by factors such as duration of therapy and other components of the antiretroviral regimen.

XI. CLINICAL PHARMACOLOGY

XIa. Mechanism of Action

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.

XIb. Pharmacokinetics

XIb-1. 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 C_{max} 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 C_{max}, mean C_{min}, 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 C_{max} was 12.9 µM, steady-state C_{min} was 5.6 µM, and AUC was 184 µM• h.

Effect of Food on Oral Absorption

The bioavailability of a single 600-mg dose of efavirenz in uninfected volunteers was increased 22% and 17%, respectively, when given with a meal of high fat or normal composition, relative to the bioavailability of a 600-mg dose given under fasted conditions. It is recommended that STOCRIN be taken on an empty stomach.

XIb-2. 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.

XIb-3. Metabolism

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized 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 (8.5-17 μM) 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 may be 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.

XIb-4. 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.

XIb-5. Characteristics in Patients

Hepatic Impairment

A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) effects efavirenz pharmacokinetics (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.

Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of efavirenz were evaluated in antiretroviral-naive and -experienced HIV-1 infected pediatric patients in three open-label clinical trials (see, PHARMACOKINETICS). 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 pediatric patients (32% for all grades regardless of causality) and more often of higher grade (ie, more severe). Two (1.1%) pediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four (2.2%) pediatric patients had Grade 4 rash (all erythema multiforme) (See SIDE EFFECTS).

XIc. 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 ≤ 25 nM. 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, 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 C_{max} 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 C_{max} 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 characterized 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.

XII. 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.

XIII. STORAGE

STOCRIN tablets should be stored below 30°C.

XIV. AVAILABILITY

STOCRIN is available as:

1. 200 mg x 90 tablets/bottle
2. 600 mg x 30 tablets/bottle

Product Owner:

Merck Sharp & Dohme LLC
126 East Lincoln Ave.
P.O. Box 2000
Rahway, New Jersey 07065
USA

This Package Insert was last revised in May 2022.

MSD