NEW ZEALAND DATA SHEET

1 PRODUCT NAME

STOCRIN® 50 mg tablet

STOCRIN® 200 mg tablet

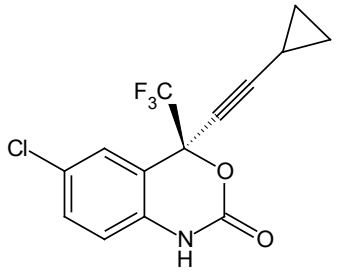
STOCRIN® 600 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

STOCRIN is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

STOCRIN 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:



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

Active Ingredients

STOCRIN 50 mg tablet:
Each tablet contains 50 mg of efavirenz.

STOCRIN 200 mg tablet:
Each tablet contains 200 mg of efavirenz.

STOCRIN 600 mg tablet:
Each tablet contains 600 mg of efavirenz.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

STOCRIN 50 mg tablet
A yellow round shaped tablet engraved with “113” on one side and plain on the other.

STOCRIN 200 mg tablet
A yellow round shaped tablet engraved with “223” on one side and plain on the other.

STOCRIN 600 mg tablet
A yellow modified capsular shaped tablet with “225” engraved on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of 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. STOCRIN may be taken with or without food, as desired.

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 section 4.8).

Concomitant Antiretroviral Therapy: STOCRIN must be given in combination with other antiretroviral medications (see section 4.5).

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. STOCRIN may be taken with or without food, as desired. STOCRIN tablets have not been adequately studied in children under the age of 3 years or children weighing less than 13 kg (see section 4.4).

Table 1: Paediatric 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

4.3 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 section 4.5). 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 should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot derivatives because competition for CYP3A4 by STOCRIN could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events [e.g., cardiac arrhythmias, prolonged sedation or respiratory depression].

STOCRIN is contraindicated in pregnancy (see section 4.4).

STOCRIN must not be administered concurrently with the standard doses of voriconazole because STOCRIN significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases STOCRIN plasma concentrations (see section 4.5; for use of adjusted doses of voriconazole with adjusted doses of efavirenz, see 4.5).

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.

4.4 Special warnings and precautions for use

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 medicines concomitantly with STOCRIN, physicians should refer to the corresponding manufacturer's data sheet.

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 medicine-resistant mutant virus.

Co-administration 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 foetuses from STOCRIN-treated animals (see section 4.6); therefore, pregnancy should be avoided in women receiving STOCRIN. (See section 4.3.) Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives) (see section 4.6 and 4.5).

<u>QTc Prolongation</u>

QTc prolongation has been observed with the use of efavirenz (see section 4.5). 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.

<u>Skin Rash</u>

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 anti-retroviral agents to avoid development of medicine resistant virus (see section 4.8).

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 paediatric patients was 27 days (range 3 - 1504 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 STOCRIN. Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. There have also been post-marketing reports of death by suicide, delusions, psychosis-like behaviour, and catatonia although a causal relationship to the use of STOCRIN 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 STOCRIN, and if so, to determine whether the risks of continued therapy outweigh the benefits (see section 4.8).

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 STOCRIN 600 mg daily in clinical studies (see section 4.8). 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 paediatric patients receiving STOCRIN, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a medicine interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with STOCRIN (see section 4.5). Caution must be taken in any patient with a history of seizures.

Effect of Food

The administration of STOCRIN with food may increase STOCRIN 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 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 STOCRIN 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 STOCRIN have not been studied in patients with renal insufficiency; however, less than 1% of a STOCRIN dose is excreted unchanged in the urine, so the impact of renal impairment on STOCRIN 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 tablets should not be given to children less than 3 years of age (see section 4.2).

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 section 4.8.)

4.5 Interaction with other medicines and other forms of interaction

STOCRIN is an inducer of CYP3A4 and CYP2B6. Other compounds that are substrates of CYP3A4 or CYP2B6 may have decreased plasma concentrations when co-administered with STOCRIN.

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. 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 co-administration with fosamprenavir and ritonavir, the prescribing information for fosamprenavir calcium should be consulted.

Atazanavir: Efavirenz decreases atazanavir exposure. Refer to the prescribing information for atazanavir guidance on co-administration with efavirenz.

Indinavir: When indinavir at an increased dose (1000 mg every 8 hours) was given with STOCRIN (600 mg once daily) in uninfected volunteers, the indinavir AUC and C_{trough} were decreased by approximately 33-46% and 39-57%, respectively compared to when indinavir was given alone at the standard dose (800 mg every 8 hours).

Similar differences in indinavir AUC and C_{max} were also observed in HIV-infected subjects who received indinavir (1000 mg every 8 hours) with STOCRIN (600 mg once daily) compared to indinavir given alone (800 mg every 8 hours). The optimal dose of indinavir, when given in combination with STOCRIN, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to STOCRIN.

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.

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 co-administration with STOCRIN. (Maraviroc is not currently available in New Zealand.)

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 (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.

<u>HCV Antivirals</u>

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%) 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 data sheet 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 section 4.3) 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 STOCRIN 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 50kg or more. No dose adjustment of rifampin is recommended when given with STOCRIN. In one study in uninfected volunteers, STOCRIN 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 STOCRIN. These data suggest that the daily dose of rifabutin should be increased by 50% when administered with STOCRIN and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with STOCRIN.

Clarithromycin: Co-administration 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 STOCRIN 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: Co-administration of STOCRIN (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 STOCRIN increased by 44% and 38%, respectively. Co-administration of standard doses of STOCRIN and voriconazole is contraindicated (see section 4.3).

Following co-administration 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 co-administration 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 co-administered 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: co-administration 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: Co-administration 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

Co-administration of STOCRIN 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: Co-administration of STOCRIN (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: Co-administration of STOCRIN (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: Co-administration of STOCRIN (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.

Co-administration of STOCRIN with atorvastatin, pravastatin, or simvastatin did not affect STOCRIN AUC or C_{max} values. No dosage adjustment is necessary for STOCRIN.

Anticoagulants

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

Anticonvulsants

Carbamazepine: Co-administration of STOCRIN (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 STOCRIN 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 co-administration 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 STOCRIN with phenytoin, phenobarbital, or other anticonvulsants that are substrates of CYP450 isozymes. When STOCRIN 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 STOCRIN 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 STOCRIN.

Other Medicine 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 co-administered 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 STOCRIN plasma concentrations was observed.

Injection: Limited information exists regarding efavirenz and injectable hormonal contraception. In a 3 month medicine 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 (eg, 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, co-administration of STOCRIN 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.

Anti-depressants: There were no clinically significant effects on pharmacokinetic parameters

when paroxetine and STOCRIN were co-administered. No dose adjustments are necessary for either STOCRIN or paroxetine when these medicines are co-administered. Sertraline did not significantly alter the pharmacokinetics of STOCRIN. STOCRIN decreased sertraline C_{max}, C_{24}, and AUC by 28.6 - 46.3%. The dose of sertraline should be increased when administered with STOCRIN to compensate for the induction of sertraline metabolism by STOCRIN. 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 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 in required.

Cetirizine: Cetirizine had no clinically significant effect on STOCRIN pharmacokinetic parameters. STOCRIN 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 STOCRIN or cetirizine when these medicines are co-administered.

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

Calcium channel blockers: co-administration 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 data sheet 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 manufacturer's data sheet for the calcium channel blocker).

Cannabinoid Test Interaction: STOCRIN 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy should be avoided in women treated with STOCRIN. 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 STOCRIN. STOCRIN 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 STOCRIN during the first trimester of pregnancy or becomes pregnant while taking STOCRIN, she should be informed of the potential harm to the foetus.

There are no adequate and well-controlled studies of STOCRIN in pregnant women. In post-marketing experience through an antiretroviral pregnancy registry, more than 900 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, 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.

Breast-feeding

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 STOCRIN 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.

Fertility

STOCRIN 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 STOCRIN was not affected. As a result of the rapid clearance of STOCRIN in rats, systemic medicine exposures achieved at the doses used in these studies were equivalent to or below those achieved in humans given therapeutic doses of STOCRIN.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

STOCRIN was generally well tolerated in clinical trials. STOCRIN has been studied in over 9,000 patients. In a subset of 1,008 patients who received 600 mg STOCRIN 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 STOCRIN are rash,

nervous system symptoms and psychiatric symptoms. The administration of STOCRIN with food may increase STOCRIN exposure and may lead to an increase in the frequency of undesirable effects (see section 4.4).

Other, less frequent, clinically significant treatment-related undesirable effects reported in all clinical trials include: allergic reaction, abnormal co-ordination, 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 co-ordination and balance disturbances, convulsions, pruritus, abdominal pain, blurred vision, flushing, gynaecomastia, 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 characterised 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 STOCRIN 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 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 section 4.4).

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 STOCRIN. In controlled trials of 1,008 patients treated with regimens containing STOCRIN 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 STOCRIN 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 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 a 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 behaviour, and catatonia although a causal relationship to the use of STOCRIN 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 STOCRIN 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 section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit and is not recommended.

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 STOCRIN. Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of STOCRIN 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 STOCRIN 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 STOCRIN may reflect enzyme induction not associated with liver toxicity (see section 4.4).

Lipids: Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving STOCRIN. Increases from baseline in non-fasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed in patients treated with STOCRIN+ZDV+3TC and of approximately 40% and 35%, in patients treated with STOCRIN+IDV. The effects of STOCRIN on triglycerides and LDL were not well-characterised. In another study, increases from baseline in total cholesterol, HDL-cholesterol, fasting LDL-cholesterol, and fasting triglycerides of 21%, 24%, 18%, and 23%, respectively, were observed in patients treated with STOCRIN+ZDV+3TC for 48 weeks. The clinical significance of these findings is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 medicine. There is no specific antidote for overdose with STOCRIN. Since STOCRIN is highly protein bound, dialysis is unlikely to significantly remove the medicine from blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use. Non-nucleoside reverse transcriptase inhibitors. ATC code: J05A G03

Mechanism of Action

STOCRIN is a selective non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1). STOCRIN 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 STOCRIN well in excess of those achieved clinically.

5.2 Pharmacokinetic properties

Absorption

Peak STOCRIN 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 STOCRIN 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. STOCRIN can be administered with or without food.

Distribution

STOCRIN 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 STOCRIN in plasma.

Metabolism

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that STOCRIN 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 STOCRIN metabolism. *In vitro* studies have shown that STOCRIN inhibited P450 isozymes 2C9, 2C19, and 3A4 with Ki values (8.5-17μM) in the range of observed STOCRIN plasma concentrations. In *in vitro* studies, STOCRIN did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (Ki values 82-160 μM) only at concentrations well above those achieved clinically.

STOCRIN 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.

STOCRIN 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 STOCRIN based on pharmacokinetic interaction studies in which daily 400 mg or 600 mg STOCRIN doses in combination with indinavir did not appear to cause any further reduction of indinavir AUC compared to a 200 mg dose of STOCRIN.

Elimination

STOCRIN 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 radiolabelled dose of STOCRIN was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged STOCRIN.

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 section 4.4).

Renal Impairment

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

Gender and Race

Pharmacokinetics of STOCRIN 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

STOCRIN has not been studied in paediatric patients below 3 months of age or who weigh less than 3.5 kg. The safety, pharmacokinetic profile, and virologic and immunologic responses of 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 section 4.8). 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 section 4.4 and 4.8).

5.3 Preclinical safety data

Animal Toxicology

Chronic Toxicity

Minimal to moderate biliary hyperplasia was observed in the livers of cynomolgus monkeys given STOCRIN for 2 years at doses resulting in mean plasma AUC values approximately 2- or 9-fold greater than those in patients given 600 mg/day. One monkey with moderate biliary hyperplasia also had slight cholestasis. The biliary hyperplasia regressed upon cessation of dosing. At the end of the 2 year treatment period, 9/10 monkeys receiving the highest dose of STOCRIN had minimal to moderate biliary hyperplasia. Following a 26-week treatment-free recovery period, 3/5 monkeys that had previously received the highest dose did not have biliary hyperplasia. The remaining two monkeys in the recovery group had minimal biliary hyperplasia.

Minimal to slight thyroid follicular cell hypertrophy occurred in cynomolgus monkeys given STOCRIN for 2 years at doses resulting in mean plasma AUC values approximately 2- or 9-fold greater than those in patients given 600 mg/day. This change resulted from increased thyroxine clearance secondary to hepatic enzyme induction. This finding is not judged to pose a risk to patients given STOCRIN since chronic treatment with other known enzyme inducers is not associated with clinical hypothyroidism, goitre, or thyroid neoplasia.

Non-sustained convulsions were observed in cynomolgus monkeys receiving STOCRIN for ≥1 year, at doses yielding plasma STOCRIN concentrations 4- to 13-fold greater than the plasma concentrations in humans given 600 mg/day. There were no STOCRIN-related microscopic changes in the CNS of these monkeys.

Carcinogenesis

Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice but not in male mice. There was no increase in the rate of any tumour in male mice or in male or female rats given STOCRIN. The hepatic tumours are thought likely to be due to the enzyme-inducing effect of STOCRIN; however, the cause of the increased pulmonary tumours and their relevance to humans is unknown.

Mutagenesis

STOCRIN was not mutagenic or genotoxic in *in vitro* and *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese Hamster Ovary cells, chromosomal aberration assays in human peripheral blood lymphocytes or Chinese Hamster Ovary cells, and an *in vivo* mouse bone marrow micronucleus assay.

Development

Malformations have been observed in 3 of 20 foetuses/newborns from STOCRIN-treated cynomolgus monkeys in an ongoing developmental toxicity study. The pregnant monkeys were dosed with STOCRIN 60 mg/kg/day, a dose resulting in plasma medicine concentrations similar to those in humans given 600 mg/day. Anencephaly and unilateral

anophthalmia with secondary enlargement of the tongue were observed in one foetus, microophthalmia was observed in another foetus, and cleft palate was observed in a third foetus (see section 4.4).

No malformations were observed in foetuses from STOCRIN-treated rats; however, an increase in foetal resorptions was observed in rats given 200 mg/kg/day. The peak plasma concentrations and AUC values in pregnant female rats at this dose of STOCRIN were equivalent to those achieved in humans given 600 mg of STOCRIN once daily. STOCRIN was not teratogenic or embryotoxic when given to pregnant rabbits at 75 mg/kg/day, a dose that produced peak plasma concentrations similar to, and AUC values approximately half of those achieved in humans given 600 mg of STOCRIN once daily.

STOCRIN has been shown to cross the placenta in rats, rabbits, and cynomolgus monkeys. In these animals, foetal blood concentrations of STOCRIN were similar to maternal STOCRIN concentrations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulphate, hydroxypropyl cellulose, lactose monohydrate and magnesium stearate. The film-coating contains the following inactive ingredients and dyes: hypromellose (E464), titanium dioxide (E171) and macrogol 400, and carnauba wax. In addition, the 50 mg, 200 mg, and 600 mg tablets contain yellow iron oxide (E172). The 50 mg, 200 mg and 600 mg tablets are not printed with ink.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

STOCRIN should be stored at or below 30°C (86°F).

6.5 Nature and contents of container

STOCRIN 50 mg and 600 mg tablets are available in HDPE bottles containing 30 tablets each.

STOCRIN 200 mg tablets are available in HDPE bottles containing 90 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Merck Sharp & Dohme (New Zealand) Limited
P O Box 99 851
Newmarket
Auckland
NEW ZEALAND
Tel: 0800 500 673

9 DATE OF FIRST APPROVAL

5 October 2006

10 DATE OF REVISION OF THE TEXT

24 February 2023

RCN: 000024479

SUMMARY TABLE OF CHANGES

Sections Revised	Summary of Change
10	Update to copyright statement