

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS
(PREPARATIONS) - 1986**

This medicine can be sold under doctor's prescription only

**STOCRIN[®] 600 mg
Tablets**

Each tablet contains:
Efavirenz 600 mg

For a list of inactive ingredients please refer to section 6.1 "What **STOCRIN** contains". See also section 2.8 "Important information about some of the ingredients of **STOCRIN**".

Read all of this leaflet carefully before you start using this medicine.

- This leaflet contains concise information about **STOCRIN**. If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their ailment seems similar to yours.

1. WHAT STOCRIN IS INTENDED FOR?

STOCRIN, in combination with other antiretroviral medicines, is used for the treatment of patients suffering from human immunodeficiency virus (HIV-1) infection.

Therapeutic group: **STOCRIN**, which contains the active substance efavirenz, belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an antiretroviral medicine that fights human immunodeficiency virus (HIV) infection by reducing the amount of the virus in blood.

2. BEFORE USING STOCRIN

2.1 Do not use the medicine:

- **if you are sensitive (allergic)** to efavirenz or any of the other ingredients of this medicine (listed in section 6). Contact your doctor or pharmacist for advice.
- **if you have severe liver disease.**
- **if you have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.**
- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.
- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.
- **if you are pregnant or breast-feeding (see section 2.6 "Pregnancy, breast-feeding and fertility").**
- **if you are currently taking any of the following medicines (see also section 2.4 "Taking other medicines"):**
 - **astemizole or terfenadine** (used to treat allergy symptoms)
 - **bepidil** (used to treat heart disease)
 - **cisapride** (used to treat heartburn)
 - **ergot alkaloids** (for example, ergotamine, dihydroergotamine, ergonovine, and methylegonovine) (used to treat migraine and cluster headaches)
 - **midazolam or triazolam** (used to help you sleep)
 - **pimozide, imipramine, amitriptyline or clomipramine** (used to treat certain mental conditions)
 - **St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)

- **flecainide, metoprolol** (used to treat irregular heart beat)
- **certain antibiotics** (macrolides, fluoroquinolones, imidazole)
- **triazole antifungal agents**
- certain **antimalarial treatments**
- **methadone** (used to treat opiate addiction)
- **elbasvir/grazoprevir**

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with **STOCRIN** could create the potential for serious and/or life-threatening side-effects or stop **STOCRIN** from working properly.

2.2 Special warnings concerning use of STOCRIN

Talk to your doctor before taking **STOCRIN**.

- **STOCRIN must be taken with other medicines that act against the HIV virus.** If **STOCRIN** is started because your current treatment has not prevented the virus from multiplying, another medicine you have not taken before must be started at the same time.
- **You can still pass on HIV** when taking this medicine, although the risk is lowered by effective antiretroviral therapy. It is important to take precautions to avoid infecting other people through sexual contact or blood transfer. Discuss with your doctor the precautions needed to avoid infecting other people. This medicine is not a cure for HIV infection and you may continue to develop infections or other illnesses associated with HIV disease.
- You must remain under the care of your doctor while taking **STOCRIN**.
- **Tell your doctor:**
 - **if you have a history of mental illness**, including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts (see section 4, "POSSIBLE SIDE EFFECTS").
 - **if you have a history of convulsions (fits or seizures)** or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your doctor may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking **STOCRIN**. Your doctor may give you a different anticonvulsant.
 - **if you have a history of liver disease, including active chronic hepatitis.** Patients with chronic hepatitis B or C and treated with combination antiretroviral agents have a higher risk for severe and potentially life-threatening liver problems. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine. **If you have severe liver disease, do not take STOCRIN** (see Section 2.1, "Do not Take **STOCRIN**").
 - **if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.**
- **Once you start taking STOCRIN, look out for:**
 - **signs of dizziness, difficulty sleeping, drowsiness, difficulty concentrating or abnormal dreaming.** These side effects may start in the first 1 or 2 days of treatment and usually go away after the first 2 to 4 weeks.
 - **signs of confusion, slow thoughts and physical movement, and delusions (false beliefs) or hallucinations (seeing or hearing things that others do not see or hear).** These side effects may occur months to years after beginning Stocrin therapy. If you notice any symptoms, please inform your doctor.
 - **any signs of skin rash.** If you see any signs of a severe rash with blistering or fever, stop taking **STOCRIN** and tell your doctor at once. If you had a rash while taking another NNRTI, you may be at a higher risk of getting a rash with **STOCRIN**.
 - **any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms

are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **changes in body fat.** Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.
- **bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

2.3 Children and Adolescents

STOCRIN 600 mg tablets are not intended for children weighing less than 40 kg.

2.4 Interactions with other medicines

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, you should inform the attending doctor or pharmacist.

You must not take STOCRIN with certain medicines. These are listed under section 2.1, "Do not use the medicine". They include some common medicines and a herbal remedy (St. John's wort) which can cause serious interactions.

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

STOCRIN may interact with other medicines, including herbal preparations such as Ginkgo biloba extracts. As a result, the amounts of **STOCRIN** or other medicines in your blood may be affected. This may stop the medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels. **It is important to tell your doctor or pharmacist if you are taking any of the following:**

- **Other medicines used for HIV infection:**
 - protease inhibitors: darunavir, indinavir, lopinavir/ritonavir, ritonavir, ritonavir boosted atazanavir, saquinavir or fosamprenavir/saquinavir. Your doctor may consider giving you an alternative medicine or changing the dose of the protease inhibitors.
 - maraviroc
 - Do not take a combination medicine which contains efavirenz, emtricitabine and tenofovir, which is currently known as Atripla without consulting with your doctor, since it contains efavirenz, the active ingredient of **STOCRIN**.
- **Medicines used to treat infection with the hepatitis C virus:** boceprevir, telaprevir, simeprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir /voxilaprevir.
- **Medicines used to treat bacterial infections, including tuberculosis and AIDS-related mycobacterium avium complex:** clarithromycin, rifabutin, rifampicin. Your doctor may consider changing your dose or giving you an alternative antibiotic. **If you weigh 50 kg or more do not take rifampicin with efavirenz. Talk to your doctor before taking rifampicin with efavirenz.**
- **Medicines used to treat fungal infections (antifungals):**
 - voriconazole. **STOCRIN** may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of **STOCRIN** in your blood. **As the 600 mg tablet is the only dose form available in the local marketplace, the recommended dose adjustments for co-administration of efavirenz and voriconazole are not possible.**
 - itraconazole. **STOCRIN** may reduce the amount of itraconazole in your blood.

- posaconazole. **STOCRIN** may reduce the amount of posaconazole in your blood.
- **Medicines used to treat malaria:**
 - artemether/lumefantrine: **STOCRIN** may reduce the amount of artemether/lumefantrine in your blood.
 - atovaquone/proguanil: **STOCRIN** may reduce the amount of atovaquone/proguanil in your blood.
- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. **STOCRIN** can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make **STOCRIN** less likely to work. Your doctor may need to consider giving you a different anticonvulsant.
- **Medicines used to lower blood fats (also called statins):** atorvastatin, pravastatin, simvastatin. **STOCRIN** can reduce the amount of statins in your blood. Your doctor will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- **Methadone** (a medicine used to treat opiate addiction): your doctor may recommend an alternative treatment.
- **Sertraline** (a medicine used to treat depression): your doctor may need to change your dose of sertraline.
- **Bupropion** (a medicine used to treat depression or to help you stop smoking): your doctor may need to change your dose of bupropion.
- **Diltiazem or similar medicines (called calcium channel blockers which are medicines typically used for high blood pressure or heart problems):** when you start taking **STOCRIN**, your doctor may need to adjust your dose of the calcium channel blocker.
- **Immunosuppressants such as cyclosporine, sirolimus, or tacrolimus** (medicines used to prevent organ transplant rejection): when you start or stop taking **STOCRIN**, your doctor will closely monitor your plasma levels of the immunosuppressant and may need to adjust its dose.
- **Hormonal contraceptive, such as birth control pills, an injected contraceptive (for example, Depo-Provera), or a contraceptive implant (for example, Implanon):** you must also use a reliable barrier method of contraception (see section 2.6, “Pregnancy, breast-feeding and fertility”). **STOCRIN** may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking **STOCRIN** while using a contraceptive implant, although it has not been established that the **STOCRIN** therapy caused the contraceptive to fail.
- **Warfarin or acenocoumarol** (medicines used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin or acenocoumarol.
- **Ginkgo biloba extracts** (herbal preparation).
- **Medicines that impact heart rhythm:**
 - **Medicines used to treat heart rhythm problems** such as flecainide or metoprolol.
 - **Medicines used to treat depression** such as imipramine, amitriptyline or clomipramine.
 - **Antibiotics**, including the following types: macrolides, fluoroquinolones or imidazole.

2.5 Taking STOCRIN with food and drink

Taking **STOCRIN** on an empty stomach may reduce the undesirable effects. Grapefruit juice should be avoided when taking **STOCRIN**.

2.6 Pregnancy, breast-feeding and fertility

Women should not get pregnant during treatment with STOCRIN and for 12 weeks thereafter. Your doctor may require you to take a pregnancy test to ensure you are not pregnant before starting treatment with **STOCRIN**.

If you could get pregnant while receiving STOCRIN you need to use a reliable form of barrier contraception (for example, a condom) with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection). Efavirenz may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures, as above, for 12 weeks after you stop taking **STOCRIN**.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take **STOCRIN** only if you and your doctor decide it is clearly needed. Ask your doctor or pharmacist for advice before taking any medicine.

Serious birth defects have been seen in unborn animals and in the babies of women treated with efavirenz or a combination medicine containing efavirenz, emtricitabine and tenofovir during pregnancy. If you have taken **STOCRIN** or the combination tablet containing efavirenz, emtricitabine, and tenofovir during your

pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child.

You should not breast feed your baby if you are taking **STOCRIN**.

2.7 Driving and using machines

STOCRIN contains efavirenz and may cause dizziness, impaired concentration, and drowsiness.

If you are affected, do not drive and do not use any tools or machines.

2.8 Important information about some of the ingredients of STOCRIN

STOCRIN contains 249.6 mg of lactose monohydrate in each 600-mg daily dose.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW SHOULD YOU USE STOCRIN?

Always take **STOCRIN** exactly as your doctor has told you.

You should check with your doctor or pharmacist if you are not sure. Your doctor will give you instructions for proper dosing.

- **STOCRIN** is for oral use. **STOCRIN** is recommended to be taken on an empty stomach preferably at bedtime. This may make some side effects (for example, dizziness, drowsiness) less troublesome. An empty stomach is commonly defined as 1 hour before or 2 hours after a meal.
- It is recommended that the tablet be swallowed whole with water.
- **STOCRIN** must be taken every day.
- **STOCRIN** should never be used alone to treat HIV. **STOCRIN** must always be taken in combination with other anti-HIV medicines.
- No information is available regarding splitting/crushing/chewing of **STOCRIN** tablets.

The usually recommended dosage is:

Adults: The dose for adults is 600 mg once daily.

Children and adolescents:

- The dose for children 3 years of age and older weighing 40 kg or more is 600 mg once daily. This medicine was not evaluated in children below 3 years.

If you have accidentally taken a higher dose than you should

If you take too much **STOCRIN** contact your doctor or nearest emergency department for advice. Keep the medicine container with you so that you can easily describe what you have taken.

If you have taken an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you.

If you forget to take STOCRIN

Try not to miss a dose. **If you do miss a dose**, take the next dose as soon as possible, but do not take a double dose to make up for a forgotten dose. If you need help in planning the best times to take your medicine, ask your doctor or pharmacist.

If you stop taking STOCRIN

When your STOCRIN supply starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

How can you contribute to the success of the treatment?

Complete the full course of treatment as instructed by the doctor.

Even if there is an improvement in your health, do not discontinue use of this medicine before consulting your doctor.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further question on the use of this product, ask your doctor or pharmacist.

4. SIDE EFFECTS

Like all medicines, **STOCRIN** can cause side effects, in some of the users.

Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by **STOCRIN** or by other medicines that you are taking at the same time, or by the HIV disease itself.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The most notable unwanted effects reported with **STOCRIN** in combination with other anti-HIV medicines are skin rash and nervous system symptoms.

You should consult your doctor if you have a rash, since some rashes may be serious; however, most cases of rash disappear without any change to your treatment with **STOCRIN**. Rash was more common in children than in adults treated with **STOCRIN**.

The nervous system symptoms tend to occur when treatment is first started, but generally decrease in the first few weeks. In one study, nervous system symptoms often occurred during the first 1-3 hours after taking a dose. If you are affected your doctor may suggest that you take **STOCRIN** at bedtime and on an empty stomach. Some patients have more serious symptoms that may affect mood or the ability to think clearly. Some patients have actually committed suicide. These problems tend to occur more often in those who have a history of mental illness. In addition, some nervous system symptoms (e.g. confusion, slow thoughts and physical movement, and delusions [false beliefs] or hallucinations [seeing or hearing things that others do not see or hear]) may occur months to years after beginning Stocrin therapy. Always notify your doctor immediately if you have these symptoms or any side effects while taking **STOCRIN**.

Tell your doctor if you notice any of the following side effects:

Very common side effects (affects more than 1 user in 10)

- skin rash

Common side effects (affects 1 to 10 users in 100)

- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with coordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling anxious, feeling depressed

Tests may show:

- increased liver enzymes in the blood
- increased triglycerides (fatty acids) in the blood

Uncommon side effects (affects 1 to 10 users in 1,000)

- nervousness, forgetfulness, confusion, fitting (seizures), abnormal thoughts
- blurred vision
- a feeling of spinning or tilting (vertigo)
- pain in the abdomen (stomach) caused by inflammation of the pancreas
- allergic reaction (hypersensitivity) that may cause severe skin reactions (erythema multiforme, Stevens-Johnson syndrome)
- yellow skin or eyes, itching, or pain in the abdomen (stomach) caused by inflammation of the liver
- breast enlargement in males
- angry behaviour, mood being affected, seeing or hearing things that are not really there (hallucinations), mania (mental condition characterised by episodes of overactivity, elation or irritability), paranoia, suicidal thoughts, catatonia (condition in which the patient is rendered motionless and speechless for a period)
- whistling, ringing or other persistent noise in the ears
- tremor (shaking)
- flushing

Tests may show:

- increased cholesterol in the blood

Rare side effects (affects 1 to 10 users in 10,000)

- itchy rash caused by a reaction to sunlight
- liver failure, in some cases leading to death or liver transplant, has occurred with efavirenz. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease.
- unexplained feelings of distress not associated with hallucinations, but it may be difficult to think clearly or sensibly
- suicide

If a side effect appears, if any of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor. Side effects can be reported to the Ministry of Health by using the link "Adverse Drug Reactions Report" at the home page of the Ministry of Health's web site (www.health.gov.il) which refers to the online side effects reporting form, or by using the link: <https://sideeffects.health.gov.il>

5. HOW TO STORE STOCRIN?

Avoid Poisoning! This medicine, as all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor!

Do not use **STOCRIN** after the expiry date (exp. date) which is stated on pack. The expiry date refers to the last day of the indicated month.

Storage conditions: Store this medicine below 30°C. Do not use this medicine for more than 30 days after the bottle is first opened.

Medicines should not be disposed of via wastewater or household waste. Ask the pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient **STOCRIN** also contains:

The other ingredients of the tablet core are:

Lactose monohydrate, microcrystalline cellulose, Croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate.

The film coating contains:

Opadry® yellow (Hypromellose, Titanium Dioxide, Macrogol 400, Iron Oxide Yellow), Carnauba Wax.

STOCRIN 600 mg Tablets contain lactose:

Each tablet of **STOCRIN** 600 mg contains 249.6 mg lactose monohydrate (see also section 2.8, "Important Information about some of the ingredients of **STOCRIN**").

What STOCRIN looks like and contents of the pack

STOCRIN tablets are yellow, capsule-shaped, debossed with "225" on one side and plain on the other.

Pack size: 30 tablets per pack.

Manufacturer:

Merck Sharp & Dohme B.V., Haarlem, The Netherlands.

License holder:

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

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