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

The medicine is dispensed with a doctor's prescription only

Eviplera®

Film-coated Tablets

Active ingredients and their quantities in each film-coated tablet:

Emtricitabine 200 mg / Rilpivirine 25 mg (as hydrochloride) / Tenofovir disoproxil 245 mg (as fumarate)

Inactive and allergenic ingredients in the preparation – see section 6 "Further Information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Eviplera contains three active ingredients (emtricitabine, rilpivirine and tenofovir disoproxil) in one tablet intended to treat HIV infection (AIDS).

Each of these active ingredients is known as an antiretroviral

medicine that interferes with the activity of an enzyme (a protein called reverse transcriptase) that is essential for the virus to multiply.

Eviplera reduces the amount of HIV in your body, thus improving the immune system and reducing the risk of developing illnesses linked to HIV infection.

Eviplera is a treatment for HIV infection in adults aged 18 years and over who have not been treated before with other medicines for treatment of HIV and whose viral burden before commencement of treatment does not exceed 100,000 copies per ml, and in certain adults with a viral burden below 50 copies per ml at the beginning of treatment in order to replace a current medicinal anti-HIV treatment.

Therapeutic group

- Emtricitabine, nucleoside reverse transcriptase inhibitors (NRTI)
- Rilpivirine, non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Tenofovir disoproxil, nucleotide reverse transcriptase inhibitors (NtRTI)

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- **You are sensitive (allergic)** to the active ingredients (emtricitabine, rilpivirine, tenofovir disoproxil) or any of the

additional ingredients contained in the medicine. Inform your doctor of this immediately. For a list of the inactive ingredients, see section 6 “Further Information”.

- **If you are taking any of the following medicines:**
  - carbamazepine, oxcarbazepine, phenobarbital and phenytoin (medicines to treat epilepsy and prevent seizures)
  - rifampicin and rifapentine (to treat some bacterial infections such as tuberculosis)
  - omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole (proton pump inhibitors, medicines used to prevent and treat stomach ulcers, heartburn and acid reflux disease [esophageal reflux])

- dexamethasone (a corticosteroid used to treat inflammation and suppress the immune system), whether taken by mouth or administered by injection (except as a single dose treatment).
- products that contain St. John's wort (*Hypericum perforatum*) (a herbal remedy used for conditions of depression and anxiety)

Special warnings regarding use of this medicine

You must make sure to be monitored by your attending doctor while being treated with Eviplera.

This medicine does not cure the HIV infection. While taking Eviplera, you may still develop infections or other illnesses associated with HIV infection.

Before beginning treatment with Eviplera, tell the doctor if:

- You suffered from kidney disease or laboratory tests indicated kidney problems. Eviplera may affect your kidneys. Before and during treatment, your doctor may order blood tests to measure kidney function. Treatment with Eviplera is not recommended if you suffer from moderate to severe kidney disease.

  Eviplera is not usually given with other medicines that can damage your kidneys (see “Drug interactions” section). If

this is unavoidable, your doctor will monitor your kidney function once a week.

- **You have a history of liver disease, including hepatitis.** HIV patients with liver disease (including chronic hepatitis B or C), who are treated with antiretroviral medicines, have a higher risk of severe liver complications that could be fatal. If you suffer from hepatitis B, your doctor will carefully consider the best treatment regimen for you. Two of the active ingredients in Eviplera (tenofovir disoproxil and emtricitabine) show some activity against hepatitis B virus. If you have a history of liver disease or chronic hepatitis B infection, your doctor may conduct blood tests in order to monitor liver function.

If you have hepatitis B infection, liver problems may become worse after treatment with Eviplera is stopped. It is important not to stop taking Eviplera without consulting with your doctor (see section 3 “How should the medicine be used”).

- **Tell your doctor immediately and stop taking Eviplera if you develop a skin rash with the following symptoms: fever, blisters, redness in the eyes and swelling of the face, mouth or body.** This may become severe or potentially life-threatening.

- **Consult with your doctor if you are over 65 years of age.** The medicine has not been tested in a large number of patients over 65 years of age. If you are over 65 years of age and are prescribed Eviplera, your doctor will monitor you carefully.

While taking Eviplera:

During the period in which you start taking Eviplera, look out for the following symptoms:

- Any symptom of inflammation or infection
- Bone problems (manifesting as bone pain that is persistent or worsens and sometimes results in fractures) may also occur due to damage to kidney cells (see section 4 “Side

effects"). Tell your doctor if you have bone pain or fractures.

Tenofovir disoproxil (a component of Eviplera) may also cause loss of bone mass. Overall, the effect of tenofovir disoproxil on long-term bone health and fracture risk in adult patients is uncertain. Tell your doctor if you suffer from osteoporosis. Patients with osteoporosis are at a higher risk for fractures.

If you notice any of these symptoms, tell your doctor immediately.

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular if you are taking:

- **Other medicines containing:**
  - emtricitabine
  - rilpivirine
  - tenofovir disoproxil
  - tenofovir alafenamide
  - any antiviral medicine that contains lamivudine or adefovir dipivoxil

Eviplera may interact with other medicines. As a result, the amounts of Eviplera or of other medicines in your blood may be affected. This may impair the effectiveness of the medicines that you are taking or make side effects worse. In some cases, your doctor may need to adjust your dosage or check your blood levels of the medicine.

- **Medicines that may cause kidney damage,** for example:
  - aminoglycosides (such as streptomycin, neomycin and gentamicin), vancomycin (to treat bacterial infections)
  - foscarnet, ganciclovir, cidofovir (to treat viral infections)
  - amphotericin B, pentamidine (for fungal infections)
  - interleukin-2, also called aldesleukin (to treat cancer)

- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

- **Medicines containing didanosine (to treat HIV infection):** Taking Eviplera with other antiviral medicines that contain didanosine may raise the levels of didanosine in your blood and may reduce your CD4+ cell count. Inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported rarely when medicines containing tenofovir disoproxil and didanosine were taken together. Your doctor will carefully consider whether to treat you with other medicines used for treating HIV infection (see “Other medicines used to treat HIV infection”).

- **Other medicines used to treat HIV infection:** Non-nucleoside reverse transcriptase inhibitors (NNRTIs). Eviplera contains an NNRTI (rilpivirine) and so, Eviplera is not to be combined with other medicines of this type. Your doctor will discuss a different medicine with you if required.
- **Rifabutin:** A medicine to treat some bacterial infections. This medicine may decrease the amount of rilpivirine (one of the ingredients of Eviplera) in your blood. Your doctor may need to give you an additional dose of rilpivirine to treat your HIV infection (see section 3 “How Should the Medicine Be Used?”).

- **Antibiotics to treat bacterial infections,** including tuberculosis, containing:
  - clarithromycin
  - erythromycin

  These medicines may increase the amount of rilpivirine (an active ingredient of Eviplera) in your blood. Your doctor may need to change the dosage of the antibiotic or give you a different antibiotic.
- **Medicines for stomach ulcers, heartburn or acid reflux (esophageal reflux)** such as:
  - antacids (aluminum/magnesium hydroxide or calcium carbonate)

- histamine H_2 antagonists (famotidine, cimetidine, nizatidine or ranitidine)

These medicines may decrease the amount of rilpivirine (an active ingredient of Eviplera) in your blood. If you are taking one of these medicines, your doctor will prescribe you a different medicine to treat stomach ulcers, heartburn or acid reflux, or alternatively, advise you how and when to take this medicine.

- **If you are taking an antacid** (such as medicines containing magnesium or potassium), take it at least 2 hours before or at least 4 hours after taking Eviplera (see section 3 “How Should the Medicine Be Used?”).

- **If you are taking medicines from the histamine H_2 antagonist group** (also used to treat stomach acid or acid reflux disease), take this medicine at least 12 hours before or at least 4 hours after taking Eviplera. Histamine H_2 antagonists can only be taken once a day if you take Eviplera. Histamine H_2 antagonists should not be taken twice a day. Consult with your doctor about an alternative treatment regimen (see section 3 “How Should the Medicine Be Used?”).
- **Methadone,** a medicine used to treat opiate addiction. your doctor may need to change your methadone dosage.

- **Dabigatran etexilate,** a medicine used to treat heart problems. your doctor may need to monitor the levels of this medicine in your blood.

Tell your doctor if you are taking any of the aforementioned medicines. Do not stop treatment without consulting with your doctor.

Use of the medicine and food

Eviplera must be taken with a meal (see section 3 “How Should the Medicine Be Used?”).

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you are pregnant or are planning a pregnancy, consult with a doctor or pharmacist before taking this medicine.

- **Use effective contraception** while taking Eviplera.
- **Tell your doctor immediately if you become pregnant or if you plan to become pregnant.** If you are pregnant, discuss the use of this medicine with your doctor. Your doctor will discuss with you the benefits and risks of taking Eviplera for you and your child.
- **If you have taken Eviplera** during pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose

mothers took NRTIs during pregnancy, the benefit from the protection against the HIV virus outweighed the risk of side effects.

Do not breastfeed during treatment with Eviplera

- This is because the active ingredients in this medicine pass via breast milk to the baby.
- Breastfeeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk. If you are breastfeeding, or thinking about breastfeeding, **you should discuss it with your doctor as soon as possible.**

Driving and operating machinery

Do not drive or operate machinery if you feel tired, sleepy or dizzy after taking the medicine.

Important information about some of the ingredients of the medicine

Eviplera contains lactose, sunset yellow aluminum lake (E110) and sodium.

If you have been told by your doctor that you have sensitivity to some sugars, talk to your doctor before taking this medicine.

Tell your doctor if you have an allergy to **sunset yellow aluminum lake.** This substance, also called E110, could cause allergic reactions.

Sodium – this medicine contains less than 1 mmol (23 mg) of sodium per tablet, that is to say, it is considered essentially “sodium-free”.

3. HOW SHOULD THE MEDICINE BE USED?

Always use the preparation according to the doctor’s instructions.

Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

The usual dosage is generally **one tablet taken once a day by mouth. Take the tablet together with a meal.** Taking

the medicine with a meal is important to get the right levels of active ingredient in your body. A nutritional drink alone does not replace a meal.

Do not exceed the recommended dosage.

Swallow the tablet whole with water.

Do not crush, halve or chew the tablet, as this may affect the release of the medicine into your body.

If your doctor decides to stop the administration of one of the ingredients of Eviplera or change the dosage of Eviplera, you may be given the ingredients emtricitabine, rilpivirine and/or tenofovir disoproxil separately or with other medicines for the treatment of HIV infection.

If you are taking an antacid, such as medicines containing magnesium or potassium, take it at least 2 hours before or at least 4 hours after taking Eviplera.

If you are taking medicines from the histamine H_2 antagonist group, such as famotidine, cimetidine, nizatidine or ranitidine, take it at least 12 hours before or at least 4 hours after taking Eviplera. Histamine H_2 antagonists can only be taken once a day if you take Eviplera. Histamine H_2 antagonists should not be taken twice a day. Consult with your doctor about an alternative treatment regimen.

If you are taking rifabutin, your doctor may need to give you an additional dose of rilpivirine. Take the rilpivirine tablet at the same time you take the Eviplera tablet. Check with the doctor or pharmacist if you are uncertain about how to take it.

If you accidentally take a higher dosage of Eviplera than recommended, you may be at increased risk of experiencing side effects of the medicine (see section 4 “Side Effects”).

If you took a higher dosage than recommended, or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you so that you can easily describe what you have taken.

If you forget to take the medicine

It is very important not to forget to take the dose of Eviplera.

If you do forget a dose:

- **If you remember within 12 hours of the time you usually take Eviplera,** you must take Eviplera as soon as possible. Always take Eviplera with a meal. After that, take the next dose as usual at the planned time.
- **If you remember 12 hours or more after the time you usually take Eviplera,** do not take the forgotten dose. Wait until the next time of administration and then take Eviplera with a meal.

If you vomit less than 4 hours after taking Eviplera, take another tablet with a meal**. If you vomit more than 4 hours after taking Eviplera,** you do not need to take another tablet. Take the next tablet at the usual planned time.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, **do not stop treatment with the medicine without consulting the doctor.** Stopping treatment with Eviplera can seriously affect your response to future treatment.

If Eviplera treatment is stopped for any reason, consult with your doctor before you start taking Eviplera again. Your doctor may consider giving you the ingredients of Eviplera separately if you are having problems or need your dosage adjusted.

When your supply of Eviplera is about to run out, make sure to purchase an additional supply of the medicine. This is extremely important because the amount of virus may start to increase if treatment with the medicine is stopped for even a short time, and it may become harder to treat.

If you suffer from both HIV and hepatitis B infections, it is especially important not to stop your Eviplera treatment without consulting with the doctor first. In some patients, blood tests or symptoms indicated that their hepatitis got worse after stopping emtricitabine or tenofovir disoproxil (two of the three active ingredients of Eviplera). If Eviplera treatment is stopped, your doctor may recommend that you resume hepatitis B treatment. You may need blood tests to check how your liver is working approximately 4 months after stopping treatment with Eviplera. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, even to the extent of being life-threatening.

Tell your doctor immediately about new or unusual symptoms upon stopping treatment with Eviplera, particularly about symptoms associated with hepatitis B infection.

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

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Eviplera may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Possible side effects – tell a doctor immediately

- **Lactic acidosis** (excess lactic acid in the blood). This is a rare but potentially life-threatening side effect of the use of some HIV medicines. Lactic acidosis occurs more in women – particularly if they are overweight, and in people with liver disease. The following signs could indicate lactic acidosis:
  - Deep, rapid breathing
  - Tiredness or drowsiness
  - Nausea, vomiting
  - Abdominal pain

If you think you may have lactic acidosis, tell your doctor immediately.

- **Signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur immediately after treatment of the HIV infection is started. It is thought 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.

  In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may occur after starting to take medicines for the treatment of the 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 consult with your doctor immediately to receive treatment.

If you notice any symptoms of inflammation or infection, tell your doctor immediately.

Additional side effects:

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

- Diarrhea, vomiting, nausea

- Difficulty sleeping (insomnia)
- Dizziness, headache
- Rash
- Feeling week

Laboratory tests may indicate:

- Decreased phosphate levels in the blood
- Increased levels of creatine kinase in the blood that may result in muscle pain and weakness
- Increased levels of cholesterol and/or pancreatic amylase in the blood
- Increased levels of liver enzymes in the blood

If any of the side effects get serious, tell your doctor.

Common side effects – (may occur in up to 1 in 10 users)

- Decreased appetite
- Depression and depressed mood
- Tiredness, feeling sleepy
- Drowsiness
- Pain, abdominal pain or abdominal discomfort, feeling bloated, dry mouth
- Abnormal dreams, sleep disorders
- Problems with digestion resulting in discomfort after meals, flatulence
- Rash (including red spots or blotches sometimes with blistering and swelling of the skin), which may be an allergic

reaction, itching, changes in skin color including dark areas on the skin

- Other allergic reactions, such as wheezing, swelling or feeling dizzy

Laboratory tests may indicate:

- Low white blood cell count (thus making you more prone to infection)
- Low platelet count (blood cells that participate in the blood-clotting process)
- Blood hemoglobin decrease (low red blood cell count)
- Increased fatty acids (triglycerides), bilirubin or glucose in the blood

- Pancreas problems

If any of the side effects get serious, tell your doctor.

Uncommon side effects (may occur in up to 1 in 100 users)

- Anemia (low red blood cell count)
- Pain in the abdomen caused by inflammation of the pancreas
- Breakdown of muscle, muscle pain or weakness
- Swelling of the face, lips, tongue or throat
- Signs or symptoms of inflammation or infection
- Severe skin reactions, including rash accompanied by fever, swelling and liver problems
- Damage to kidney cells

Laboratory tests that could indicate:

- Decreased level of potassium in the blood
- Increased level of creatinine in the blood
- Changes in the urine

If any of the side effects get serious, tell your doctor.

Rare side effects (may occur in up to 1 in 1,000 users)

- Lactic acidosis (see “Possible side effects – tell a doctor immediately”)
- Back pain caused by kidney problems, including kidney failure. Your doctor may do blood tests to make sure that your kidneys are working properly
- Fatty liver

- Yellowing of the skin or the white of the eye, itching or pain in the abdomen caused by inflammation of the liver
- Inflammation of the kidney, passing a lot of urine and feeling thirsty
- Softening of the bones (with bone pain and sometimes resulting in fractures)

The breakdown of muscle, softening of the bones (with bone pain, which sometimes causes bone fractures), muscle pain, muscle weakness and a decreased level of potassium or phosphate in the blood may occur due to damage to kidney cells.

If any of the side effects get serious, tell your doctor.

Other effects that may occur during HIV treatment

Side effects of unknown frequency (effects whose frequency has not been determined):

- **Bone problems.** Some patients taking a combination of antiretroviral medicines such as Eviplera may develop a bone disease called "*osteonecrosis*" (a disease in which bone tissue dies due to a loss of blood supply to the bone). Taking this type of medicine for a long time, taking corticosteroids, consuming alcohol, having a very weak immune system and being overweight may be some of the many risk factors for developing this disease.

  Signs of osteonecrosis:

  - Joint stiffness

- Joint pain (especially of the hip, knee and shoulder)
- Difficulty with movement

If you notice any of these symptoms, consult your doctor.

During HIV therapy, there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to an improvement that occurs in health and life style, and increased levels of lipids in the blood is sometimes linked to the anti-HIV medicines themselves. Your doctor will perform tests to monitor for these changes.

If a side effect occurs, if one 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 clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il/.

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, should be kept 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 the doctor.
- Do not use the medicine after the expiry date (Exp. Date) that appears on the package. The expiry date refers to the last day of that month.
- After first opening, use within 30 days and no later than the expiry date of the preparation.

- **Storage Conditions:**
  - Do not store the medicine at a temperature above 25°C.
  - Store the tablets in the original packaging in order to protect from moisture. Make sure to keep the bottle tightly closed.
- Do not throw away medicines in the regular trash can. Consult with the pharmacist about how to throw away medicines that are no longer needed.

6. FURTHER INFORMATION

In addition to the active ingredients, the medicine also contains:

Tablet core:

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Magnesium Stearate, Povidone, Polysorbate 20.

Film-coating:

Hypromellose, Titanium Dioxide (E171), Lactose Monohydrate, Polyethylene Glycol, Triacetin, Red Iron Oxide (E172), Indigo Carmine (E132) Aluminum Lake, Sunset Yellow (E110) Aluminum Lake.

What the medicine looks like and the contents of the package:

- Eviplera is a purplish-pink, capsule-shaped, film-coated tablet with “GSI” written on one side.
- The tablets come in a plastic bottle with a plastic cap.
- Each bottle contains 30 tablets and a desiccant. Keep the desiccant in the bottle in order to protect the tablets from moisture. Do not swallow the desiccant.

Registration Holder: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

Manufacturer: Janssen Cilag S.P.A., via C. Janssen 04100, Borgo S.Michele, Latina, Italy.

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Registration number of the medicine in the National Drug Registry of the Ministry of Health: 149-30-33766

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